

December
2002

Volume 5
Issue 12

HCV Advocate

A monthly newsletter of the Hepatitis C Support Project
www.hcvadvocate.org

What Did We Learn From AASLD ? Part 1

By Alan Franciscus
Editor-in-Chief

The 53rd annual meeting of the American Association for the Study of Liver Diseases was held in Boston Massachusetts from November 1st thru November 5th. In attendance were over 4000 hepatologists and hepatology health professionals from all around the world to exchange the latest liver disease research, discuss treatment outcomes and interact with their colleagues. This is known to be the premier meeting in the science and practice of hepatology where the cutting edge in the study and treatment of liver and biliary disease is defined.

In Part I, we are going to recap the highlights of the conference as they relate to the natural history of hepatitis C. In this article you will learn some new information regarding the rate of disease progression and whether it is the same throughout life, the effect of fat in the liver (steatosis) as well as the effect that alcohol has on the rates of viral eradication. This article will close with some very interesting data on the treatment of hepatitis C in patients awaiting liver transplantation, which is going to become more and more important as patients are diagnosed with advanced liver disease and as hepatitis C awareness increases. In Part II (next month) you will learn what is new from a treatment standpoint which will include both promising treatments on the horizon as well as those currently or soon to be available.

Firstly, from a Twin Biopsy Study in the United Kingdom (abstract #607), researchers looked at risk factors for the progression of fibrosis. The study found that the following were risk factors: fibrosis score on first biopsy, age at first biopsy, necroinflammatory score, iron on biopsy and mean

duration of infection with the first two factors being the most important determinants of fibrosis progression. The researchers also determined which factors were NOT predictive of progression of fibrosis and these included: HCV genotype, route of transmission, gender (M/F), alcohol intake (less than 6/week in the majority of patients), ALT levels (both mean and peak), steatosis on biopsy or prior HBV infection. The researchers of this study concluded that fibrosis is not linear (does not

See AASLD on page 8

FDA Panel Votes To Approve Pegasys/Copegus

By Alan Franciscus
Editor-in-Chief

On November 14, 2002 the US Food and Drug Administration drug advisory panel voted unanimously (11 to 0 vote) to recommend to the FDA that they approve Pegasys (pegylated alpha 2a) and Copegus (Roche's ribavirin) for the treatment of hepatitis C. Pegasys and ribavirin is more effective than approved treatments for the treatment hepatitis C based upon data presented at the advisory

See FDA Panel page 5

In This Issue:

Depression & HCV.....page 2
Organ Donation.....page 4
California Unity Rally.....page 9

Depression and Hepatitis C-

Part II - The Association Between Depression/Fatigue and HCV

By Alan Franciscus

Editor-in-Chief

Patients with chronic hepatitis C infection frequently report fatigue, lassitude (lethargy, exhaustion and sluggishness), depression, and a perceived inability to function effectively. There have been studies that have shown that patients with hepatitis C exhibit low quality-of-life scores that are completely independent of disease severity, meaning that a patient may have debilitating fatigue or depression that has an impact on their overall feeling of well being and productivity and in fact have no or minimal liver damage. As a person with hepatitis C who is constantly struggling with debilitating fatigue and depression, I decided to research the medical data on the association between hepatitis C and depression and, to be honest, I am totally baffled by the results!

When discussing this correlation, it is important to differentiate between psychological responses to the knowledge that one has been infected with hepatitis C and the direct effects of the virus itself. Knowledge that one has contracted a serious infection such as hepatitis C, with its implications for future health and actions, is a major life stressor and will create emotional stress in most, and a psychiatric disorder in many. This is suggested by one small study (Rodger et al 1999) which compared 15 patients who were aware of their hepatitis C status with 19 patients who were not aware. Those who were unaware of their status reported higher (i.e. better) values on all of the eight scales that make up the SF-36, a commonly used generic measure of quality of life.

Hepatitis C is a major cause of liver disease. Liver disease, like most serious illnesses, is itself associated with fatigue via a variety of mechanisms. Hence, an association may not be due to any direct affect of the virus, but be a by-product of the consequences of hepatic disease.

Despite much medical research in this area, the etiology (the study of the cause of the disease) of these symptoms remains unidentified. The symptoms of fatigue and depression do not appear to be associated with the extent of hepatitis, the occurrence of autoimmune disorders or cirrhosis, or a history of intravenous drug usage. As in other viral infections and chronic liver disease, some studies have described increased production of cytokines, especially of the pro-inflammatory cytokines interleukin-1, IL-6 and tumor necrosis factor in patients with hepatitis B and C. In particular, these studies have found increased pro-inflamma-

tory cytokine levels and increased pro-inflammatory cytokine production by the liver. Pro-inflammatory cytokines, produced in the framework of infections have been described to induce a non-specific behavioral syndrome referred to as 'sickness behavior.' This syndrome comprises anhedonia (inability to experience pleasure in normally pleasurable acts), anorexia, fatigue, diminished activity, weakness, inability to concentrate, sleep disturbance and impaired cognition. Moreover, pro-inflammatory cytokines may stimulate the release of corticotrophin releasing hormone (CRH) and cortisol, thus inducing a hyperactivity of the hypothalmo-pituitary-adrenal axis comparable to that depicted in patients with major depression. Furthermore, major depression has also been related with increased levels of pro-inflammatory cytokines (including IL-1).

For this reason it is probable that depression and fatigue in the framework of viral hepatitis are associated with sickness behavior and with the endocrine changes brought forth by the pro-inflammatory cytokines, but this conclusion is far from solid. Reduced production of pro-inflammatory cytokines by peripheral monocytes of patients with chronic viral hepatitis has also been described. Finally one study by Gershon et al 1998 looked at levels of pro-inflammatory cytokines and fatigue in chronic hepatitis C patients and found increased levels of IL-1, IL-6 and TNF but no relationship with fatigue. Therefore the hypothesis that pro-inflammatory cytokines are related to depression and/or fatigue is not conclusive.

The consequences of psychological disturbances on the fatigue experienced by patients with hepatitis C has not been clearly examined. Thus, it is a real clinical challenge to not only characterize the presence and intensity of fatigue but also determine the association of fatigue with the comorbidities that are present in most chronic illnesses, such as the fear and anxiety of illness, nervousness about transmitting the virus to others and the prospect of future complications, and death. The question is really this: Does the debilitating fatigue that many patients with hepatitis C experience trigger the depression? Is the fatigue experienced by patients infected with hepatitis C truly more severe than that in patients with liver diseases not related to hepatitis C infection and non-hepatic chronic systemic illnesses? Lastly, what is the association of fatigue with psychological disturbances which occur

See Depression on page 3

Depression

Continued from page 2

frequently in this group of patients given their past or current history of alcohol and substance abuse?

There are many various methodologies for speaking to the question of the relationship between fatigue and/or depression and infection. The weakest design is the simple case series, in which a series of patients known to have hepatitis C infection are examined or questioned for the presence of fatigue or depression. This design is capable of numerous biases including and not limited to the fact that the more clinically severe cases are represented, the patients are aware of their diagnosis and therefore it is impossible to separate the psychological impact of the diagnosis from the direct effects of the infection plus case series without controls are difficult to understand. Additionally the particular modes of acquisition of hepatitis C (for example drug use) may cause significant perplexing effect and in fact could be an alternative explanation for an observed association between hepatitis C and depression.

Two other designs are considered of better-quality. One uses surveys in which patients have their exposure status (i.e. hepatitis C status) assessed independently of knowledge of their symptoms or clinical status. An example would be an assessment of hepatitis C status determined in patients presenting with fatigue and depression. However, perplexing effects are still a problem in this type of study as there would be an inclination to focus the study on substance misuse populations. A more suitable study may be done through a blood donor program in which symptoms and hepatitis C status are evaluated independently and from random samples of the population. A study such as this has already been conducted (Hoofnagle, 1997) which actually showed no differences in fatigue and depression between hepatitis C positive and negative blood donors.

Additionally a study by Johnson et al 1998 of drug users, which evaluated subjects for depression and hepatitis C status concurrently showed no important differences in levels of depression between those found to be hepatitis C positive versus those that were negative. To top this off there were two studies, Dale et al 1991 and Mawle et al 1995 on patients with chronic fatigue syndrome in which hepatitis status was evaluated retrospectively thus avoiding perplexing results due to psychological impact of the diagnosis of hepatitis C. Neither study reported any relationship.

On the other hand, there have been some studies using this design that have showed quite the contrary in favor of a relationship between hepatitis and depression and/or fatigue. Rivera and Colleagues 1997 found that patients

with fibromyalgia, a diagnosis associated with generalized fatigue and myalgia were more likely to occur in hepatitis C positive patients than rheumatoid controls (15.2% versus 5.3%). There are also further studies done on patients with known hepatitis C. For example, Sherman and Colleagues 1999 found that patients with known hepatitis C reported a worse quality of life, more depression and more fatigue than normal controls. In a study by Foster et al. 1998, SF-36 scores including physical symptoms and functioning plus fatigue were compared between a group of patients with hepatitis B and a group of patients with hepatitis C. The results were worse in the hepatitis C group but this could be due to differences in other factors including gender. Barkhuizen et al. 1999 reported that in hepatology outpatients, fatigue was found in 67% of hepatitis C positive patients compared to 44% in hepatitis C negative patients. Singh et al 1997 reported that patients with liver disease due to hepatitis C had more symptoms, fatigue and depression than those with end stage liver disease from other causes although quality of life scores did not differ.

Other studies have shown that the relationship maybe more complicated. In a study by Weaver et al. 2000 on hemophilia patients there were no differences in mean fatigue levels between patients without hepatitis C virus as compared to those that were HCV positive including those chronically infected (HCV RNA positive). Goulding et al 1998, Barhuizen et al. 1999 and Cacoub et al. further showed that the only difference observed between patients that were HCV RNA positive versus those that were HVC RNA negative was that in the HCV RNA positive group, more patients met the criteria for chronic fatigue syndrome which may reflect the increased rate of myalgia type symptoms seen in patients chronically infected with hepatitis C. Very similar results were duplicated by Goh et al. 1999 who looked at a well-researched Irish HCV cohort. Although fatigue was considerably increased in the hepatitis C patients compared to controls there was no difference between those who were HCV RNA positive and those who were HCV RNA negative which suggests that active viral replication is not closely related with fatigue. Lastly Taruschio et al. 1996 and Zickmund et al. 1999 studied the reasons why patients who are aware they have hepatitis C may have increased rates of psychological distress, sometimes with anxiety more dominant than depression. These include fears of the future, risk of cirrhosis and liver cancer, concerns about transmitting the virus to relatives, worries about complications

Organ Donation

By Lucinda K. Porter, RN, CCRC

The first successful liver transplant worldwide was performed by Thomas Starzl, M.D. in 1967 at the University of Colorado Health Services Center, Denver, Colorado. A new chapter in medicine began with that event. In 1989, the first successful living-related liver transplant in the United States was performed by Christoph Broelsch at the University of Chicago Medical Center.

Liver transplantation is an aspect of liver disease that can be uncomfortable to discuss. Statistically, most people with chronic hepatitis C virus (HCV) will never have progressive liver disease to an extent that organ transplantation will be necessary. However, for those who have advanced cirrhosis, liver transplantation is a viable and life-sparing option. HCV-cirrhosis is the most common single reason for liver transplantation and accounts for approximately 1000 liver transplants annually (Web MD). Unfortunately, post-transplant recurrence of HCV is nearly universal.

Donated organs originate from two sources – cadavers and living donors. The liver has the ability to regenerate and in a matter of weeks a donated segment will grow into a fully functioning liver. Living donation has risks involved and is not to be entered into casually.

The organization that facilitates the distribution of cadaver organs is the United Network for Organ Sharing (UNOS). The following information is from their website (www.unos.org):

- 17,329 patients waiting on the liver transplant list
- 5107 livers recovered from cadavers in 2001

- 504 living donor livers in 2001
- 1975 patients died in 2001 waiting for an organ
- Adult survival rate – 1 year – 86.9%; 34 months – 81.1%
- Longest surviving living related donor recipient – 11/27/89 (still alive)
- Longest living adult recipient – 26 years and 8 months; 37 year old transplanted 4/9/74

HealthWise

There are some myths circulating about organ donation. The common Internet story about people who wake up in the bathtub without their kidneys is an urban legend and patently false. Also untrue is that wealthy and famous people are moved to the top of the transplant list. Many do not realize that people with chronic hepatitis C virus infection can donate their organs.

There is an organ shortage. Before the year ends, please consider organ donation. Tissue and organs that are needed include the heart, kidneys, pancreas, lungs, liver, intestines, eyes, skin, bone, heart valves and tendons. The process of making your wishes known is very simple - tell your family. Ask your family and friends about their wishes and encourage them to express their wishes to their families. Sign a donor card and carry it with you. A signed donor card is not enough to signal your intent. You must tell your family.

To get your donor card and a free brochure on organ & tissue donation and how to talk to your family about this important decision call 1-800-355-SHARE.

Copyright 2002, Lucinda K. Porter, RN
All Rights Reserved

HCV Advocate

Alan Franciscus.....Founder/Editor-in-Chief
e-mail: sfhepcat@msn.com
Joe Shaw.....Managing Editor
e-mail: joesha@yahoo.com
C.D.Mazoff.....Contributing Editor
Liz Highleyman.....Contributing Editor
Janya H. Maxwell..Contributing Editor
Webmaster: C.D. Mazoff

Back To Life A group dedicated to providing patient education and support.
Orange County.....Carol Craig 949-654-4250

You may contact us at:

**P.O. Box 427037
San Francisco, CA 94142-7037**

The HCV Advocate offers information about various forms of intervention in order to serve our community. By providing information about any form of medication, treatment, therapy or diet we are neither promoting nor recommending use, but simply offering information in the belief that the best decision is an educated one.

Permission to reprint is granted and encouraged with credit to the Hepatitis C Support Project.

Hepatitis C Support Project - A Tides Center Project

FDA Panel

Continued from page 1

meeting from two phase III pivotal combination trials (NV15801 and NV15942). Pegasys has been extensively studied in the treatment of hepatitis C with once-weekly Pegasys 180µg injections and daily ribavirin tablets (Copegus – Roche’s ribavirin) – Rebetol (Schering’s ribavirin is in capsule form and is the only currently available form on ribavirin on the market).

Pegasys study NV15801 was the study published recently in the NEJM (Fried) which showed that Pegasys/Copegus was significantly superior to Rebetron with an overall sustained virological response (SVR) of 53% versus 44% (p=0.001).

Patients with genotype 1 high viral load (HVL) had an overall SVR for Pegasys/Copegus versus Rebetron of 40% and 33% respectively, genotype 1 low viral load (LVL) 52% and 44% respectively, non genotype 1 high viral load (HVL) 70% versus 54% respectively and non genotype 1 low viral load (LVL) 70% versus 68% respectively.

Pegasys/Copegus in this trial was associated with a slightly higher incidence of overall serious adverse events (12% Pegasys/Copegus versus 9% for Rebetron). The incidence and degree of neutropenia and thrombocytopenia

were higher in the Pegasys/Copegus group although the rates of resolution were almost identical to that experienced with Rebetron. Dose modifications were higher in the Pegasys/Copegus group versus Rebetron (32% versus 18%) however the incidence of treatment withdrawals was very similar. It is also interesting to note from the data presented that unlike other forms of interferon dose reductions, due to the pharmacokinetics of the product, Pegasys/Copegus did not show considerable drops in sustained responses.

Roche and the FDA also discussed the results of their second phase III combination trial, referred to as the NV15942, which showed very similar SVR’s to the NV15801. This trial demonstrated that for genotype 2/3, Pegasys/Copegus can be given for a shorter duration of 24 weeks with lower doses of ribavirin (800mg/day). The trial also demonstrated that genotype 1 patients require 48 weeks of treatment and ribavirin dosed 1000mg for patients <75kg and 1200mg for patients >75kg. Both the NV15801 and NV15942 showed impressive results in patients with advanced liver disease with the NV15942 having almost a quarter of the patients in the trial being either cirrhotic or having bridging fibrosis.

The combination of Pegasys and Copegus is expected to be FDA approved for marketing in early December 2002.

Help Us Reach More People with Hepatitis C!
Support us through either a paid subscription or donation.

Yes, I'd like to subscribe.

- \$18 one year—12 issues
- \$9 one year—12 issues (for those with fixed incomes)
- Renewal

Yes, I'd like to donate.

- \$10 \$25 \$100 other

Please make checks payable to:
HCSF/The Tides Center

Name _____

Address _____

City _____

State _____ Zip _____

Please mail form to: **HCV ADVOCATE**
P.O. Box 427037
San Francisco, CA
94142-7037

The Hepatitis C Support Project does not share its mailing list with any individual or organization. All subscribers names and addresses are strictly confidential

Depression

Continued from page 3

and so on.

Whatever it is that is associated with fatigue, it is not the degree of liver damage involved. No correlation between fatigue and measures of liver damage was found by practically every study that considered the matter, including Mahl et al. 1996, Nelles et al 1996, Foster et al. 1998, Poynard et al. 1998, Barkhuizen et al 1999; Goh et al. 1999, Lau et al 1999, Kraus et al 2000, Dwight et al. 2001, with one exception, Desmorat, 1998. It is thought, therefore, that the same factors that would be found in the non-hepatitis C samples, for example gender, increasing age, weight loss etc. are directly related with fatigue in hepatitis C. The summary finding was further shown in Poynard et al 1998 and Lau et al. 1999.

This finding may come as great surprise to many of us who experience the debilitating fatigue associated with hepatitis C on a daily basis. But if we consider other physical illnesses in which fatigue plays a prominent role, nearly all studies fail to show a simple relationship between measures of disease activity and degree of fatigue. Despite the proven lack of relationship in most disease states, depression, illness beliefs, lack of activity and so on have shown a much stronger correlation with primary biliary cirrhosis (Cauch-Dudeck et al.1998), systemic lupus (McKinley et al. 1995 and Wang et al. 1998), HIV (Ferraqndoi et al. 1998) and rheumatic diseases (Wolfe et al. 1996). In summary, to date, until proven otherwise it is assumed that hepatitis C infection is not a significant cause of fatigue.

What about a correlation between depression and hepatitis C? In a study by Pariente et al. 1999, which studied the treatment of interferon alpha in patients with chronic viral hepatitis B and C with or without psychiatric diagnosis before starting interferon alpha therapy, an analysis of the baseline psychiatric diagnosis and the type of virus in 57 subjects from the study found that more patients with HCV (14 out of 39, 36%) had a psychiatric diagnosis at baseline (mostly an anxiety or depressive disorder) compared to patients with hepatitis B (2 out of 18, 11%). In this particular study patients with hepatitis C were more likely to be females (36%) compared to hepatitis B (11%). When the male sample was analyzed for psychopathology the same trend held even though it was not statistically significant (28% in the hepatitis C versus 11% in the hepatitis B group).

All the arguments outlined about the difficulties in determining the extent and nature of the relationship between fatigue and hepatitis C apply equally to depression. Dwight et al. 2001 reported that 28% of those with hepatitis C fulfill criteria for major depression. In this study though all patients knew of their diagnosis and the psychosocial influence of receiving the diagnosis cannot be determined. In addition this study was done in a specialist environment and therefore there could be a bias towards sicker patients being evaluated.

Similarly Birchard, 2000 reported from Ireland that 26% of those with hepatitis C as a result of receiving contaminated blood had 'clinical levels of depression' but truly without controls this is impossible to evaluate. Lee and Colleagues, 1977 reported that over a quarter of patients were depressed but no standardized instruments or definitions were reported. As cited earlier, Johnson et al. 1998 reported that there were no differences in levels of depression in drug users whether they were HCV positive or negative.

Depression is not the only psychiatric disorder. Two abstracts from Taruschio et al. 1996 and Zickmund et al. 1999 report higher levels of anxiety than depression in hepatitis C patients.

Thorough review of the literature to date on hepatitis C and depression has not yielded any comprehensible conclusions. Even though many patients with hepatitis C report that they have extreme fatigue and signs of depression, and physicians that are treating patients with hepatitis C are leaning more to the expertise of psychiatrists, further well controlled studies are needed in this area to determine the role of depression in patients with hepatitis C. All that can be said with confidence is that many patients with advanced hepatitis C and associated liver disease are also disturbed by clinically significant depression and fatigue as reported by Zdilar et al. 2000. In cases where patients have advanced liver disease and perhaps are heading towards transplantation, numerous cases exist, such as the debilitating effects of liver failure, the side effects of treatment, and the knowledge of further complications and even mortality. In such cases it is assumed that there is a causal relationship between some aspect of hepatitis C and fatigue/depression. In patients with hepatitis C infection and either liver disease of lesser severity or no apparent liver dysfunction, it is too premature based upon the data available to date to say whether or not such a relationship exists.

Needle Exchange

By Alan Franciscus
Editor-in-Chief

State laws prohibiting syringe sales without a prescription, or possession of a syringe for the purpose of injecting illegal drugs, have made sterile syringes hard to come by and led to substantial sharing and the spread of incurable diseases at epidemic levels. In minority populations that are subjected to considerable police presence, injectors avoid carrying syringes for more than a minimal period of time, in order to avoid arrest, but thereby causing needle sharing to occur with even greater regularity. An African American drug injector is almost five times as likely to be diagnosed with HIV as a white drug injector, and a Latino drug injector is more than three times more likely.

Needle exchange programs, which increase the availability of sterile syringes, are an important practice for reducing HIV infection and other blood-borne diseases, such as hepatitis B and C, among the most rapidly growing population of HIV infection, injection drug users and their often unknowing sexual partners and children. Most needle exchange programs operate on a one-for-one exchange so they also reduce the occurrence of infected needles in playgrounds, streets and trash receptacles—protecting children, sanitation workers and others from needle sticks.

Needle exchanges have been operating legally and illegally in the United States since at least 1988. In the last decade, much has changed - from a beginning of a few lone individuals exchanging on the streets, there are now at least 113 programs in 80 cities and 32 states around the country, and over 17 million syringes were exchanged in 1997 (the last official survey on needle exchange). While the debate in Washington has been fairly inactive, steps forward on the state level have been made in many areas. In fact, 68 out of 113 of the needle exchanges participating in the 1997 survey were either legal or illegal but put up with by local officials.

Extensive studies by the nation's leading public health and scientific agencies have shown that needle exchange programs do not raise the regularity of drug use and do not increase the number of new drug injectors. Additionally, needle exchange programs involving drug counseling and drug treatment program referrals increase the possibility of really reducing drug abuse.

The policy of the American Medical Association is to encourage needle exchange programs. The decision that supported this policy statement acknowledged that syringe exchange programs reduce occurrences of HIV infection and that a harmful price due to these exchange programs has not been detected. However, the AMA is only one

part of the equation. The implementation of the medical science is presently limited by legal barriers that were established before the era of HIV/AIDS.

The first Needle Exchange Program was developed in Amsterdam, in the Netherlands in 1984 by a drug user's advocacy group called the Junkie Union whose goal was to avoid an epidemic of hepatitis B when an inner-city pharmacist intended to put an end to selling syringes to injection drug users. The first person to hand out drug injection equipment openly in the US was Jon Parker, in New Haven, CT and Boston, MA in November 1986. The first US Needle Exchange Program to make available all-inclusive services was established in Tacoma, WA in 1988.

The Canadian experience with Needle Exchange Programs has been significantly different from that in the US. As early as 1989, the Canadian federal government offered to co-fund comprehensive pilot injection drug user HIV prevention programs that included Needle Exchange Programs. By February 1993, a total of 28 Canadian cities had active Needle Exchange Programs. While some Canadian community and neighborhood groups have been against Needle Exchange Programs, the debate has generally been less politically charged than in the US. The fact is that pilot needle exchange programs run within a comprehensive approach to drug use that combines education, counseling, law enforcement, and associations to other services, including drug treatment, has helped diminish community resistance. In Britain, pharmacies and more than 250 agencies distribute clean needles. Before 1987, 60 percent of injecting drug users regularly shared needles, now the figure in Britain is about 10 percent. Additionally, three Catholic agencies sponsor needle exchanges in Australia. According to David Waterford of the Adelaide Diocesan AIDS Council, Southern Australia (with 55 exchange programs for a population of 1.2 million) has reported no new HIV infections resultant from needle sharing over the past three years.

Tremendous scientific evidence has revealed that needle exchange programs, and pharmacy syringe accessibility, reduce the spread of disease without increasing the use of drugs; on the other hand, laws prohibiting syringe distribution, and police actions against needle exchange programs, increase the spread of HIV and cause needless deaths. Yet infectious diseases are now seen as a weapon in the war on drugs, and some elected officials have stated outright that they see the risk of AIDS as a useful warning to the use of drugs. Drug warriors say they are fighting "for the children," but current rulings are killing children with infected needles. As of June 1997, more than half of all children born with AIDS were the children of drug injectors or their sexual partners.

AASLD

Continued from page 1

progress at the same rate throughout life) which suggests that patients with higher levels of fibrosis maybe be at a higher risk of fibrosis progression than those with no or low levels of fibrosis. This study has important clinical implications as the current recommendation is to perform a liver biopsy every 4-5 years in untreated patients. Based upon these findings this may need to be modified so that patients with more fibrosis may need to get a biopsy every 2-3 years. Age is also important in that older patients with fibrosis are more likely to be at the higher risk of fibrosis progression. On the other side are patients with no or minimal fibrosis who, based upon this data, probably need a liver biopsy even less often than every 4-5 years.

Secondly, as it relates to hepatitis C and steatosis (fat in the liver), there were some new findings at the AASLD conference. It was concluded by the researchers (abstract # 408) that the following factors are associated with steatosis: fibrosis score and presence of cirrhosis (but not inflammation), BMI (Body Mass Index) average 26.5 for grade 0 and 29.2 for grade 3, HCV RNA levels and HCV genotype 3. It was interesting to note that in this study in a multivariate analysis, alcohol use, cholesterol, triglycerides, and glucose were not associated with steatosis. The fact that HCV genotype and viral load are related to the presence of steatosis suggests that the virus plays a unique role in fat turnover and transport within liver cells. In addition, the fact that steatosis is associated with fibrosis but not inflammation suggests that liver fibrosis occurs by a unique mechanism which is non-inflammatory. In addition to the above mentioned findings, the researchers concluded that achieving an optimum weight may be important in reducing the risk of fibrosis in patients with hepatitis C. Another abstract focusing on steatosis (abstract 416) looked at the difference in steatosis between patients infected with different genotypes (genotype 1 and 3) and further clarified the metabolic association in steatosis. This study provided strong evidence that genotype 3 virus but NOT genotype 1 virus is important in modifying hepatocyte lipid turnover and transport. This information suggests that there are

two different mechanisms for fatty liver in patients with hepatitis C infection. In HCV genotype 3 there is a direct effect of the virus on steatosis and, therefore, eradicating the virus would have a significant impact on the steatosis. On the contrary, steatosis associated with other genotypes is related to metabolic abnormalities including obesity, hyperlipidemia and diabetes. In the non-genotype 3 patients, steatosis needs to be managed through the metabolic abnormalities such as diet, exercise and/or control of diabetes. The eradication of the HCV in these genotypes will not reduce the steatosis.

What we know to date about the potential effects of alcohol on patients with chronic hepatitis C is that during the acute infection, alcohol lowers the likelihood of clearance (either spontaneously or with treatment) since alcohol suppresses the immune system. During chronic infection, alcohol increases the likelihood of abnormal liver enzymes, potentially increases viral load and may increase the development of viral quasispecies. During the decades of chronic disease alcohol has been shown to increase liver inflammation, increase risk of developing cirrhosis as well as increase the risk of developing liver cancer. At AASLD researchers (abstract #888) studied the impact of alcohol use on spontaneous viral clearance on a couple of hundred veterans. The results showed that heavy alcohol use lowered the rate of clearance. Interestingly race and age at time of assessment (not age of infection) were not associated with rates of clearance. The results support the idea that alcohol can negatively influence a person's ability to eradicate HCV after exposure. In this study patients with heavy alcohol use (defined by dependency on alcohol or use of alcohol dependence support services) were 50% less likely to eradicate the virus. This may explain the higher prevalence of HCV among persons with a history of alcohol use/dependency. Unfortunately, this study did not address whether alcohol use that is "not heavy" influences the rate of viral clearance. The researchers also looked at the literature to determine whether alcohol use during anti-HCV

Continued on page 9

California Unity Rally

On January 29, 2003 from Noon until 2:00pm patient and hepatitis C advocates from across California will converge on the capital of California, Sacramento, to voice their concerns about the lack of any sound public health policies around hepatitis C in the state. This will certainly be a day when people affected by hepatitis C will take strong action to advocate for much needed change in California.

This day of 'Silent Vigil and Unity Rally' is spearheaded by Dr. Diana Sylvestre of the O.A.S.I.S. clinic in Oakland, CA. This day will bring together advocates from many diverse groups in California to advocate for changes in laws on hepatitis C, HIV, substance abuse, homelessness, and other issues that affect the underserved in California. "For many of us, it is an inconvenient day at an inconvenient time

at an inconvenient place, but that will be part of its impact," comments Dr. Sylvestre. Sylvestre adds that this day will be a silent memorial to pay respect to those who have died as a result of our current public health policies and will be followed by an hour of individual visits to the offices of the state legislators. "These personal visits," Sylvestre says, "can make an inestimable impression."

If you would like more information about the rally, need transportation, or if you would like to submit names to be memorialized at the Vigil, please call O.A.S.I.S. Clinic at 1-800-282-1777 or visit the O.A.S.I.S. web site at www.oasisclinic.org.

AASLD

Continued from page 8

treatment would have a similar effect on the likelihood of clearing the virus. Recent literature states that not only does drinking during antiviral therapy reduce the likelihood of responding, but also that drinking up to the time of starting treatment can also influence response rates. In some research findings published in *J Viral Hepatitis*, 2002 (Tabone, M) the researchers found that a 33% SVR was achieved in non-drinkers compared to a 21% SVR in drinkers of less than 3-5 drinks/day PRE-interferon to a 9% SVR in drinkers of more than 7 drinks/day PRE-interferon. Drinkers who were abstinent for \geq 3 years prior to treatment had SVR's similar to infrequent or non-drinkers.

Lastly there was some very interesting information shared by Dr. Gregory Everson (Abstract 536) on the safety and efficacy of antiviral therapy in patients with advanced liver disease and decompensated cirrhosis awaiting liver transplantation. Safety in this population is a major concern as patients are at a higher risk of bacterial infections, as was reported by Hoofnagle, 1989, as well as the fact that there was a very high rate of adverse events reported in one study of patients awaiting liver transplantation (23 adverse events among 12 patients treated) reported by Crippen et al, *Liver Transplant* 2001. It is important to remember that pre-treatment eradication of the virus may reduce the risk of hepatitis C after

transplantation plus interferon may improve the health of the liver during the waiting period (not a parameter of this study). The researchers developed a LADR (low ascending dose regimen) protocol which consisted of 1.5MU interferon (IFN) TIW (three times a week) plus ribavirin (RBV) 600mg QD. After 2 weeks the interferon was increased to 3MU and then after 4 weeks the RBV is increased by 200mg weekly. Granulocyte Colony Stimulating Factor (GCSF)/erythropoietin (Procrit) were used to keep PMN (polymorphonuclear leukocytes - neutrophils) >800 , Hgb (hemoglobin) >10 . The goal of the escalation is to get patients to IFN 3MU TIW and RBV 1-1.2g/day. Of the 102 patients enrolled into this protocol, 6 were early drop outs. The SVR by genotype was 11% for genotype 1 and 50% for genotype non-1. What was most impressive about this study is that 32 patients in this group were then followed through transplantation (10 patients were HCV RNA negative prior to transplant and 22 patients were HCV RNA positive prior to transplant). Of the 10 patients that were HCV negative prior to transplantation, 100% remained HCV RNA negative after transplantation, whereas all those HCV RNA positive prior to transplant remained positive after transplantation.

Clinical Trials **National Trials**

ROCHE - 866-GO-WINGS
NIH - HALT-C (Cirrhosis)
800-411-1222

Northern California

University of California, Davis
Dr. Rossaro (916) 734-8696
University of San Francisco Medical Center
Stephanie Straley, PA (415) 353-2328
VA Hospital-UCSF
(415) 750-2105
California Pacific Medical Center
(415) 600-1100 or (415) 600-1106
San Francisco General Hospital
Athiana (415) 206-3725
San Francisco
Dr. Cazen (415) 565-6288
Stanford University Hospital
Stanford Liver Research Clinic (650) 724-7057

Quest Medical Research (HIV/HCV Coinfection)
Dr. Lalezari (415) 353-0800
East Bay Liver Clinic
Oakland, CA - Grant Young (510) 208-1777
Dr. John J. Jolley - San Rafael
Contact: Lynn Jolley
(415) 257-3030

Southern California

USC Hepatitis Research Clinic
Dr. Karen Lindsay, Susan Milstein, RN
(323) 442-5550
UC Irvine Medical Center
Dr. John Hoefs, Barbara Walker, RN
(714) 456-7821
VA Medical Center - Long Beach
Dr. Timothy Morgan, Julia Sanborn, RN
(562) 494-5933
Santa Barbara/Ventura Counties
Dr. Kip Lyche (805) 641-6525

HCSP
P.O. Box 427037
San Francisco, CA
94142-7037