

Update from DDW: Part 2



Alan Franciscus, Editor-in-Chief

Part 2 will focus on information presented on hepatitis C and veterans at the DDW 2004 Conference.

It is estimated that 5 to 10% of the veteran population is infected with hepatitis C (HCV). In many ways the Veterans Administration health care system has been at the forefront of research, screening, treatment and disease management. As the veteran population with HCV ages, HCV disease progression will increase proportionately. This increase in disease progression among veterans will have a dramatic impact on the future burden of care in the VA health care system.

HCV PREVALENCE AMONG VETERANS

It is well known that the veteran population has a higher prevalence of HCV than the general population. J. Dominitz and colleagues conducted a study of 3863 randomly selected patients at 20 VA Medical Centers to estimate the prevalence HCV antibodies among veterans. Of the original 3863 patients, only 1288 were included in the study. The remaining patients refused to participate, could not be contacted or could not have blood drawn.

The authors reported a 4% HCV prevalence rate in their study, but, after controlling for many factors, estimated that 5.4% of the general veteran population in the United States is infected with hepatitis C. Sixty-three percent of all patients and 100% of those positive for HCV reported blood transfusions, intravenous drug use, drug snorting, tattoos, incarceration, or more than 15 sexual partners, which is consistent with risk factors found in the general population. The authors stated that "the VA system should start to prepare for the increasing burden of care since HCV positive patients will progress on to more serious disease progression over time."

HCV SCREENING AND REFERRAL

In a study to determine the effectiveness of screening and referral in a large urban Veterans Medical Center, H. Groom and colleagues conducted a retrospective review of all patients tested for hepatitis C from 1/1/00 through 12/31/01. Six hundred and eighty-one patients were identified of whom 670 received confirmatory HCV RNA (viral load) testing. Seventy-eight percent (520 patients) tested positive for HCV RNA and

22% (150 patients) tested negative.

Of the 520 patients that tested HCV RNA positive, 83% (430 patients) were referred to specialty care in the hepatitis C clinic. The remaining 17% (90 patients) were neither referred nor scheduled. Eighty-nine percent of the patients (382 patients) referred to a specialty clinic attended at least one appointment; eleven percent (48 patients) did not attend any referral appointments. The authors found that the average time between diagnosis and scheduled appointment was 63 days, with 21% of patients having had a scheduled follow-up more than 6 months after diagnosis. A total of 33% (124 patients) of these patients received interferon drug-based therapy over 3.5 years during the study follow-up. Of the original 124 patients, 109 patients completed therapy and 39.4% (36) patients in the group achieved a sustained virological response (SVR).

In an effort to increase the number of patients seeking medical care, the authors recommended that patient referrals after screening



IN THIS ISSUE

HCV Therapy for African Americans.....	2
HealthWise: Herbs and Hepatitis C — Part 2.....	3

continued on page 4

HCV Therapy for African Americans



Liz Highleyman

The rate of hepatitis C among African Americans is estimated to be 2-3 times higher than the rate among whites. Several recent studies have examined the manifestations of hepatitis C in different racial/ethnic groups, as well as differences in response to HCV therapy.

Various retrospective studies have suggested that blacks do not respond as well as whites to interferon-based therapy. But not all studies have reached this conclusion. For example, Richard Sterling and colleagues reported in the May 2004 issue of the *American Journal of Gastroenterology* that in a retrospective analysis of 59 Virginia prison inmates, blacks and whites with genotype 1 HCV treated with standard interferon plus ribavirin achieved similar sustained virological response (SVR) rates (29% vs 33%). The authors concluded that—at least in a correctional setting where directly observed therapy ensures excellent adherence—blacks respond about as well as whites.

Most past HCV treatment research has included relatively small numbers of African Americans. Recently, however, two prospective studies designed to include adequate representation of blacks also concluded that people of African descent do not respond as well as whites.

In the June 2004 issue of *Hepa-*

tology, Lennox Jeffers and colleagues reported on an open-label study of 78 blacks and 28 non-Hispanic whites, all with genotype 1, receiving HCV treatment for the first time. The characteristics of the two groups were generally similar, but the black group included more men and the black participants were slightly older, somewhat heavier, and slightly more likely to have high viral loads. After 48 weeks of therapy with Pegasys plus ribavirin, 26% of blacks and 39% of whites achieved SVR in an intent-to-treat analysis. This is the highest response rate yet seen in a black population. In a multivariate analysis, black race, age less than 40, lower viral load, and lower baseline ALT levels were significantly associated with SVR.

Side effects were more common in whites, and more whites discontinued therapy due to adverse events. However, about twice as many blacks had their Pegasys dose reduced due to neutropenia (a low level of neutrophils, a type of immune system white blood cell). Because healthy blacks naturally have lower neutrophil levels than healthy whites, neutropenia is a greater concern for black patients. However, studies suggest that neutropenia does not increase the risk of serious infections in blacks being treated for HCV. Paired pre- and post-treatment biopsies revealed that more than 90% in both groups showed improved or stabi-

lized fibrosis progression. Overall, 25% of black subjects showed evidence of improvement, including 22% of patients who did not achieve SVR.

In a second study reported in the May 27, 2004 issue of the *New England Journal of Medicine*, Andrew Muir and colleagues treated 100 black and 100 white subjects (98% in both groups with genotype 1) with Peg-Intron plus ribavirin for 48 weeks. The characteristics of the two groups were similar although, here again, there were more men in the black group and the black patients were slightly older, somewhat heavier, and had been infected with HCV slightly longer. Although adherence was comparable, SVR rates were considerably lower for blacks than whites: 19% vs 52% in an intent-to-treat analysis. In a multivariate regression analysis, only black race was significantly associated with lower response rates.

In contrast to Jeffers' study, side effects were similar in both groups, as were the rates of dose reduction and treatment discontinuation. However, in this trial 10 black patients were initially excluded due to low neutrophil counts. A comparison of pre- and post-treatment liver biopsies from patients who did not achieve SVR revealed that white participants experienced a greater reduction in histological

continued on page 6

HealthWise:

Herbs and Hepatitis C - Part 3 of a 3 Part Series

Lucinda K. Porter, RN, CCRC

The first installment of this three-part series presented an overview on the subject of herbs and hepatitis C virus (HCV) infection. Last month's column suggested guidelines and tools that can be used for making informed choices about the use of herbs. This month's column focuses on a few herbs that may be helpful or problematic for those with liver disease. A list of resources has been provided at the end of this article for those who want more information about herbs.

HCV TREATMENT AND HERBS

There is virtually no research on the safety of herbs and supplements co-administered with pegylated interferon/ribavirin therapy. Because of this, it is common for patients to abstain from milk thistle and herb use while undergoing antiviral therapy. Even commonly used botanicals need to be used with caution. Quite a few herbs can alter laboratory results. Some herbs and supplements can hinder the ability of the blood to clot. For instance, ginger is widely used to relieve nausea. However, patients with gallstones should talk to their healthcare provider prior to using ginger. Additionally, ginger has an anticlotting action and should not be taken if you have reduced blood clotting ability. Interferon therapy and/or cirrhosis can also interfere with blood clotting, so there may be an increased risk if some herbs are used simultaneously under these conditions. Other commonly used herbs, such as chamomile and St. John's Wort carry a warning of potential drug interactions. The rule of thumb is to be informed and talk to your healthcare provider prior to using any botanical product.

At least 16 deaths have been reported in Japan in HCV patients being treated simultaneously with alpha interferon and Xiao Chai Hu Tang (Minor Bupleurum).

MILK THISTLE

Milk thistle, (*Silybum marianum*), is the most commonly used herb for liver problems. A frequently asked question regarding chronic HCV infection concerns the use of this herb. If you are considering taking a milk thistle product, talk to your doctor and find out if it is compatible with other drugs or supplements you are taking. Verify that the supplement is not contraindicated for any other condition you may have (see "A Warning about Milk Thistle and Drug Interactions" below). Do not use milk thistle if you have decompensated cirrhosis.

Medical consultants for the Consumers Union recommended the following in the April 2001 issue of *Consumer Reports On Health*:

- Patients should not use milk thistle to replace a conventional treatment for viral hepatitis;
- Patients should not take milk thistle while on a conventional treatment for viral hepatitis;
- Milk thistle is probably safe and no one should be discouraged from taking it if there are no other options;
- Choose a brand that contains silibin and phosphatidyl choline, which may be better absorbed.

There is insufficient research to establish a suggested daily dose of milk thistle. Typical dosages are in the range of 140-420 mg in divided doses, 2-3 times a day, of 70-80% silymarin. See the section "Suggested

Guidelines for Herbal Use" in part 2 of this series for more information on choosing milk thistle and other herbal products.

A WARNING ABOUT MILK THISTLE AND DRUG INTERACTIONS

Raman Venkataramanan and colleagues¹ at the University of Pittsburg reported observations about sily-

continued on page 5

D_{DW}

continued from page 1

should be increased and the waiting time between screening and clinic appointment should be reduced. The authors also stated that improvements in clinical care and treatment options are needed.

ACCESS TO CARE

Why do many so patients fail to access medical care when effective therapeutic options exist? This is a question that Eric W. Dieperink and colleagues sought to answer with specific focus groups in order to develop strategies that would encourage veterans to seek medical care. The authors conducted seven focus groups consisting of patients that were actively in HCV care (2 groups) and patients that did not attend any specialty care appointments (5 groups). The patient characteristics were similar in both groups.

The researchers identified several factors that influence barriers to seeking care, including the lack of patient knowledge regarding HCV care, disease progression and treatment. In addition, the authors found that social stigma was an important factor that prevented patients from seeking medical care. The authors recommended several strategies for improving access to care including flexibility of appointment scheduling, support group availability, and the interest and knowledge of the staff. Additional recommendations included: peer resources to enhance knowledge regarding asymptomatic disease versus active disease; resources that target family and friends to decrease stigma; and decreases in the time from diagnosis to first appointment, which will improve the connection between patient education and test results.

TREATMENT

A. Anantharaju and colleagues released data from a study conducted at an urban VA hospital on the effectiveness of pegylated interferon plus ribavirin combination therapy in veterans with hepatitis C.

This study followed 246 male HCV patients who started pegylated interferon (Peg-Intron and Pegasys) plus ribavirin therapy between May 2001 and April 2004. The pegylated interferons were given at the recommended dose; ribavirin was given at a dose of 11 mg/kg. Pretreatment liver biopsies and genotype tests were obtained. Growth factors were used as needed for cytopenias.

Of the 246 patients who began therapy, 168 patients completed therapy and 141 patients were available for the 24-week post follow up evaluation. The overall sustained virological response (SVR) was 31.2%. A total of 61.3% patients reported side effects—*anemia* (30.5%), *psychiatric disturbances* (19.1%), *thrombocytopenia* (5.1%), *neutropenia* (7.1%), and *hypothyroidism* (8.5%). Approximately 20% stopped therapy due to side effects. The authors concluded that the SVR among veterans is higher when compared to standard interferon and ribavirin, but lower than the large pegylated interferon plus ribavirin clinical registration trials.

The authors also released data on another study examining the use of pegylated interferon plus ribavirin in veterans with compensated cirrhosis. In this study 55 patients were enrolled of whom 31 completed 48 weeks of therapy. The overall SVR was 11.8%. Reported side effects included: *anemia* (28.9%), *psychiatric disturbances* (22.2%), *thrombocytopenia* (15.6%), *neutropenia* (11.1%), and *hypothyroidism* (8.5%). Approximately 20% of the patients did not complete therapy

due to side effects. The authors concluded that treatment with pegylated interferon and ribavirin showed a poor response rate in veterans with compensated cirrhosis compared to HCV patients treated in the general population.

TREATMENT RELATED DEPRESSION AMONG VETERANS

E. Paredez and colleagues presented data on a study to identify trends of psychiatric side effects in patients with a history of significant psychiatric disorders compared to patients without psychiatric disorders.

The study analyzed data from all patients (total of 40 patients) with hepatitis C who finished HCV treatment at the Albuquerque Veterans Administration Medical Center between January 2002 and September 2003. Information, including clinical and psychiatric data in addition to the CES-D scale (Center for Epidemiologic Studies - Depression), was collected at baseline, week 2, 4, 8, 12 and every 6 weeks thereafter. Data collected included the increase in psychiatric medications, completion of planned HCV therapy and sustained virological response rates. The researchers found that more than half of the veterans with or without a psychiatric diagnosis required an addition or increase in psychiatric medication while receiving interferon-based therapy, but that patients with psychiatric diagnoses did not have a worsening of their depression. The authors stated that this may be due to timely interventions and adjustment of their psychiatric medication during treatment. More importantly the authors found that the treatment response rates and the rate of patients that completed therapy were similar between the two groups.

continued on page 6

HERBS

continued from page 3

marin, a compound found in milk thistle. In short, this report raised concerns that silymarin may impair the metabolism of certain drugs when taken together. Further, the potential exists for increased toxicity of co-administered drugs in the presence of silymarin.

The medication levels of the following may increase if taken by people who are also using milk thistle. The source for this list is the Community AIDS Treatment Information Exchange (CATIE). It is not meant to be complete.

- protease inhibitors
- non-nucleoside analogues
- methadone
- heart drugs - Tambacor (flecainide), Rythmol (propafenone)
 - antibiotics - erythromycin, rifampin
 - anti-seizure drugs - carbamazepine (Tegretol)
 - antidepressants - St. John's wort, Zyban/Wellbutrin (bupropion), Paxil (paroxetine), Prozac (fluoxetine), Luvox (fluvoxetine), Serzone (nefazodone), Zoloft (sertraline), Effexor (venlafaxine)
 - antifungals - itraconazole (Sporanox), ketoconazole (Nizoral)
 - gastrointestinal motility agents - Prepulsid (Cisapride)
 - ergot drugs - Ergonovine, Ergomar (ergotamine)
 - anti-psychotics - Clozaril (clozapine), Orap (pimozide)
 - sedatives/sleeping pills - Ambien (zolpidem), Halcion (triazolam), Versed (midazolam)
 - lipid-lowering drugs (statins) - Lescol (fluvastatin), Mevacor (lovastatin), Pravachol (pravastatin) and Zocor (simvastatin), Baycol (cerivastatin)
 - transplant drugs - cyclosporine (Neoral, Sandimmune), ProGraf (tacrolimus)

Milk thistle also has the potential to lower levels of the following drugs:

- anti-parasite drugs - Mepron (atovaquone)
- sedatives/sleeping pills - Ativan (lorazepam)
- hormones - estrogen

SOME HERBS ASSOCIATED WITH LIVER TOXICITY

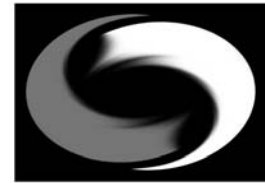
This list is primarily liver specific and by no means exhaustive. The substances on this list are referred to in their oral form only.

- Blue-green Algae
- Borage (*Borago officinalis*)
- Bupleurum
- Chaparral (*Larrea tridentata*)
- Comfrey (*Symphytum officinale* and *S. uplandicum*)
- Dong Quai (*Angelica polymorpha*)
- Germander (*Teucrium chamaedrys*)
- Jin Bu Huan (*Lycopodium serratum*)
- Kava
- Mistletoe (*Phoradendron leucarpum* and *Viscum album*)
- Pennyroyal (*Mentha pulegium*)
- Sassafras (*Sassafras albidum*)
- Shark Cartilage
- Skullcap (*Scutellaria lateriflora*)
- Valerian

Warning: *Bupleurum is a popular herb used in a variety of traditional Chinese and Japanese medicine mixtures for liver conditions. At least 16 deaths have been reported in Japan in HCV patients being treated simultaneously with alpha interferon and Xiao Chai Hu Tang (Minor Bupleurum).*

EPHEDRA

Although not specifically associated with liver toxicity, products containing ephedrine alkaloids (ephedra) should be avoided. Reports of heart attacks, strokes, seizures, psychosis, and death have been linked



HEPATITIS C SUPPORT PROJECT

Executive Director Editor-in-Chief, HCSP Publications

Alan Franciscus
alanfranciscus@hcvadvocate.org

Managing Editor, Webmaster

C.D. Mazoff, PhD
cdmazoff@hcvadvocate.org

Contributing Authors

Liz Highleyman
Lucinda K. Porter, RN, CCRC

Design and Production

Paula Fener
Blue Kangaroo Design
blueroodesign@aol.com

Contact information:

Hepatitis C Support Project
PO 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.

Reprint permission is granted and encouraged with credit to the Hepatitis C Support Project.

© 2004
Hepatitis C Support Project

continued on page 7

DDW

continued from page 4

THE EVALUATION AND USE OF ANTIDEPRESSANTS IN VETERANS

J. Nelligan and colleagues examined the use of antidepressants for treatment of interferon-induced depression. Four hundred-seventy-eight veterans were enrolled in the study and completed a Beck Depression Inventory-II (BDI-II) test as part of their initial HCV specialty clinic appointment. It was found that, of the 478 veterans enrolled in the study, (31.5%) were taking a psychotropic medication prescribed for depression, anxiety, sleep difficulty, pain, psychotic symptoms, etc. One hundred-thirty-two (27.6%) were taking an antidepressant (mostly SSRIs); 96 patients (20.1%) were taking opioid pain medications and 32 patients (6.7%) were taking other types of pain medication.

According to the completed BDI-II scores, it was found that about 1/3 of the patients had moderate to severe depression of whom 72 (56%) patients were not taking an antidepressant. Furthermore, 57 (44%) patients continued to experience moderate to severe depression despite taking antidepressants. The 260 veterans who were not prescribed antidepressants at the beginning of the trial scored lower (less depression) than those veterans (119) taking an antidepressant (14.2 vs. 19.1, $p < .0001$).

The authors noted that depression was common in this sample group and recommended routine screening for psychiatric illness to facilitate the treatment of depression, which should decrease treatment related side effects, allowing the patient to stay on HCV therapy, thereby increasing treatment response.

**AFRICAN AMERICANS**

continued from page 2

activity and fibrosis scores than blacks.

It is not clear why people of African descent respond less well to HCV treatment, but there are several possible contributing factors. Blacks are more likely than whites (about 90-95% vs 65-75%) to have hard-to-treat genotype 1 HCV, but this was not relevant in these two studies, which included only or mostly individuals with this genotype. Male sex, older age, and heavier weight are also linked to worse treatment outcomes, but these factors were not significantly associated with decreased SVR rates in these studies.

Jeffers and colleagues suggested that differences in the rate of viral clearance may be due to "variations in interferon pharmacokinetics, signal transduction pathways, or immunologic factors." Recent research has shown that interferon does not produce as much HCV suppression within the first 24-48 hours in black patients. It is possible that blacks process interferon differently in their bodies. Or, they may respond differently to interferon. Some studies suggest that blacks have a weaker natural interferon response to HCV, which may explain why they are less likely to spontaneously clear the virus and more likely to develop chronic hepatitis C. Other possible factors include higher testosterone levels in blacks and differences in CD4 and CD8 cell activity and cytokine (intracellular chemical messenger) production. Another hypothesis points to different genetic patterns of HLA molecules, antigens on human cells that influence immune response.

While African Americans re-

spond less well to interferon, the news is not all discouraging. Studies also indicate that blacks appear to suffer less HCV-related liver damage. In the June 2004 issue of *Clinical Gastroenterology and Hepatology*, Kester Crosse and colleagues reported that in a retrospective comparison, despite being older and more likely to have genotype 1, black patients had lower ALT levels and lower fibrosis and histological activity scores than whites (7.6 vs 8.7), indicating less liver necrosis (cell death) and inflammation. Sterling's team (see above) also found that blacks had lower mean ALT levels, less piecemeal necrosis, and lower fibrosis scores than whites, although a similar proportion had bridging fibrosis or cirrhosis. And in a retrospective analysis of 355 liver biopsy specimens, T.E. Wiley and colleagues found that African Americans with HCV had lower ALT levels, less liver inflammation, and less cirrhosis than individuals of other racial/ethnic groups. It is not yet clear why this is the case, but because HCV-related liver damage is largely due to the immune system's response rather than the virus itself, the variations in immune activity discussed above could help explain these differences as well.

Clearly, more research is needed on the natural history of hepatitis C and response to treatment in different racial/ethnic groups. These studies highlight the importance of including adequate numbers of African Americans and other non-Caucasian individuals in clinical research. A large National Institutes of Health trial called VIRALHEP-C is currently underway to further explore treatment response in African Americans with chronic hepatitis C.



HERBS

continued from page 5

to the use of ephedrine alkaloids. The FDA has banned the sale of dietary supplements containing ephedrine alkaloids, including ephedra and Ma Huang.

FINAL WORDS

Herbs have been part of the healing arts for centuries. Clearly more research needs to be conducted in this area in order to better understand and incorporate the use of botanical products into current health practices. In the meantime, make informed decisions regarding your health. Your future depends on it.

¹Venkataramanan R, Ramachandran V, Komoroski BJ, et al. Milk thistle, a herbal supplement, decreases the activity of CYP3A4 and uridine diphosphoglucuronosyl transferase in human

hepatocyte cultures. *Drug Metabolism and Disposition* 2000;28(11):1270-1273.

Resources:

- *The American Pharmaceutical Association Practical Guide to Natural Medicines*, by Andrea Peirce
- *The ABC Clinical Guide to Herbs*, edited by Mark Blumenthal, et al at the American Botanical Council
- *ConsumerLab.com's Guide to Buying Vitamins & Supplements: What's Really in the Bottle*, by Tod Cooperman, M.D., William Obermeyer, Ph.D., Denise Webb, R.D., Ph.D.
- *The Green Pharmacy*, by James A. Duke
- *Herbs of Choice*, by James E. Robbers and Varro E. Tyler
- *PDR for Herbal Medicines*, published by the Medical Economics Company
- *Tyler's Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies*, by Stephen Foster and Varro E. Tyler, Ph.D.

- American Botanical Council - 512-926-4900, www.herbalgram.org
- American Herbal Products Association www.ahpa.org
- ConsumerLab.com www.consumerlab.com
- FDA Dietary Supplement website - <http://vm.cfsan.fda.gov/~dms/supplmnt.html>
- HerbMed - www.herbmed.org
- Memorial Sloan-Kettering Cancer Center www.mskcc.org/about/herbs
- National Center for Complementary and Alternative Medicine - 888-644-6226, <http://nccam.nih.gov>
- National Institutes of Health Clinical Trial Information www.clinicaltrials.gov
- National Sanitation Foundation (NFS International) www.nsf.org
- The United States Pharmacopeia - 800-822-8772, www.usp.org
- UC Berkeley Wellness Letter www.wellnessletter.com

©Lucinda Porter, RN and the Hepatitis C Support Project



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

NAME _____

ADDRESS _____

CITY _____

STATE _____ ZIP _____

Please make checks payable to: HCSP/The Tides Center

YES! I'd like to donate

- \$10 \$25
- \$100 other

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

For Living Positively. Being Well.



www.hcvadvocate.org

HCSP

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