



VA Hepatitis C Research Symposium
October 1-2, 2001
Leesburg, Virginia

Summary Report

INTRODUCTION

The Department of Veterans Affairs (VA), the nation's leader in screening, testing, and caring for persons infected with the hepatitis C virus (HCV), convened the first VA Hepatitis C Research Symposium on October 1-2, 2001, in Leesburg, Virginia. With this meeting, VA sought to broaden its HCV-related research and to initiate collaborative HCV-related research with other government agencies and industry, in order to improve the quality of health care for veterans with HCV infection. VA's goal is to provide the best in diagnostics and therapies for this chronic viral infection, and to develop preventive measures to protect veterans and other vulnerable populations from becoming infected with HCV.

To address these goals, VA invited HCV experts from within the VA system and other federal agencies as well as from universities and companies in the private sector to attend its October conference. "VA is rich in some resources needed to understand this virus," said VA's Lawrence Deyton in welcoming participants to the conference, "For example, VA is developing a comprehensive case registry that will track clinical and laboratory encounters of all VA HCV patients." He urged attendees to identify specific research needs and to develop a wide-ranging research agenda through which to fulfill this agenda.

HCV DISEASE EXPERIENCE AT VA

The VA system provides health care to more than 3.7 million veterans, and its hospitals are affiliated with more than 100 medical schools. Within this nationwide health care system, VA physicians and allied personnel are faced with caring for more than 80,000 veterans known to be infected with HCV and others whose infections have not yet been identified. In 2000, VA physicians initiated antiviral therapy for more than 4,500 veterans with HCV disease.

The affected VA population not only is large but is also ethnically diverse, according to Dr. Leonard Seeff, emeritus Chief of Gastroenterology and Hepatology at VA, Professor of Medicine at Georgetown University and a scientist at the National Institute of Diabetes and Digestive and Kidney Diseases. According to Dr. Seeff, VA investigators are involved in various aspects of hepatitis C research, including management of several large databases, running research laboratories for the study of HCV, and development of collaborative clinical research programs between VAs and universities.

These factors help to make VA "a unique resource for conducting clinical and basic research" on HCV. There are populations with HCV disease that are overly represented in the VA Healthcare system, according to Dr. Teresa Wright, who directed the Center for Excellence in Hepatitis C Research and Education at the San Francisco VA from 1998

VA Background

- ⊙ VA – largest integrated health care system in US
- ⊙ Over 25 million veterans in US.
- ⊙ In FY 2000:
 - Over 3.7 million persons received VA health care (4.7 million from '94 to '00)
 - Over 670,000 admissions
 - 37.6 million out patient visits

to 2001 and now heads one of four VA Hepatitis C Resource Centers. These populations include patients with comorbidities, such as co-infection with HIV, active substance abuse and psychiatric disease as well over representation of ethnic minority populations. “This is a disease of the under-served.”

Logistic Regression Model for HCV in Veterans

	<u>Adjusted OR</u> <u>(95% CI)</u>
History of IDU	21.7 (12.0-40.4)
H/o tattoo	2.9 (1.7-5.1)
Blood transfusion before 1992	2.2 (1.2-3.9)
H/o Incarceration >48 hours	2.6 (1.5-4.3)
Combat job as a medical worker	2.7 (1.5-4.3)
Number of opposite sex partners	1.6 (0.9-2.8)
Sex with a prostitute	0.5 (0.3-0.8)

Briggs et al. Hepatology In Press

DEMOGRAPHICS OF HCV DISEASE

The VA was involved in hepatitis C research even before the identification of the virus. Dr. Seeff conducted some of the initial research studies of veterans undergoing blood transfusion, when HCV was still unnamed and uncharacterized. Diagnosis was difficult, with little information available to the clinician other than clinical signs and elevation of serum ALT level. From following veterans after needle-stick exposures, investigators became convinced that this form of hepatitis is transmissible through exposure to contaminated blood. Other epidemiologic studies indicated an elevated risk of developing HCV infection among veterans with a history of substance abuse disease, including injection drugs and alcohol.

HCV in the VA

Long-Term Follow-Up Studies

- ⊙ Yellow fever vaccine hepatitis study, (NCI) 1984/5
- ⊙ Natural history of TAH (NHLBI), 1987-1993
- ⊙ Natural history of TAH (NHLBI), 1993-2001
- ⊙ Natural history of hepatitis among military recruits (NCI, NIAID, NHLBI), 1993-2001
- ⊙ Natural history of hepatitis among injection drug users (NIDA), 2000-2001

With this demographic picture emerging over the course of several decades, VA officials came to recognize that HCV has a disproportionate impact on some veterans. On March 17, 1999, a national survey (Hepatitis C Screening Day) was conducted during which some 70,000 veterans already slated for blood drawing provided blood specimens for hepatitis C testing and limited demographic and risk factor information. The point prevalence of HCV antibody positivity among veterans tested that day was 6.6 per cent. This singular effort typifies the comprehensive and systematic means available within the VA system for investigating diseases. The VA Healthcare System (VAHCS) can also draw on a diverse HCV-infected population of veterans for large epidemiological studies in which blood samples are needed for analysis studies as well as for evaluation of new therapeutic products.

Studies subsequent to Hepatitis C Screening Day have revised the estimated prevalence of HCV in the overall VA population down to 2.6 per cent, according to mathematical models developed by Dr. Jason Dominitz of the VA Puget Sound Health Care System. He heads a national prevalence study underway at 20 VA centers, a study aimed at refining the estimate of prevalence and defining risk factors for infection. Regardless of the

VA Cooperative Study #488

- ⊙ “Prevalence of HCV in Veterans”
- ⊙ Population-based, 2 staged, cluster sampled, cross-sectional design
- ⊙ 20 sites selected at random
- ⊙ 200 vets randomly selected/site
- ⊙ Local phlebotomist

actual prevalence of infection, it appears that the HCV infection rate may be higher among veterans that utilize VA medical facilities than in the general U.S. population. Rick Weidman, President of Vietnam Veterans of America, advocated that research defining the reasons for this increased prevalence, and in particular, identifying risk factors for infection specific to veterans, must be a goal of a VA HCV research program.

The prevalence of infection in veterans differs considerably from that in recent military recruits and those on active duty in military service, according to Dr. Roger Gibson of the Department of Defense (DoD). A 1997 study indicated very low rates of infection among recent recruits, but higher rates in Vietnam era military personnel, and higher rates still in retirees. With a prevalence of infection in active duty personnel that is lower than that observed in the civilian population, DoD officials decided against a general HCV screening program for new recruits and active duty military. Instead, they conduct a targeted, risk-based screening program, of individuals who are older than 35 years on discharge from active duty, as well as of individuals who are considered at increased risk because of use of illicit drugs or who are at increased risk for being infected with HIV.

Results of Serological Survey

Military Personnel in 1997	Prevalence (Unadjusted)	Number Tested	95% Confidence Interval
⊙Active Duty	0.48%	10,000	(0.3 to 0.6%)
⊙Recruits	0.10%	2,000	(0.0 to 0.4%)
⊙Reservists (age adjusted)	0.54%	2,000	(0.3 to 1.0%)
⊙Vietnam era (still on active duty)	1.0%	1,000	(0.5 to 1.8%)
⊙Retirees (mean age 45 years)	1.7%	2,000	(1.2 to 2.4%)

Dr. Miriam Alter of the Centers for Disease Control and Prevention (CDC) in Atlanta described some of the programs in place to determine the epidemiology of HCV in the general U.S. population. Surveillance data indicate that the number of new HCV infections sharply declined to about 40,000 cases per year during the 1990s from a high of 240,000 cases per year in the 1980s. This decline was mostly due to a decrease in cases associated with injection drug use, for reasons that are unclear. However, public health officials remain concerned about the large number of individuals carrying the virus chronically, some of whom have been infected for several decades, as well as those who are becoming newly infected. Dr. Alter also noted that the risk factors for HCV in this population overlap those of the comparable VA population, and include being injection drug users, recipients of blood transfusions (before HCV screening was instituted), and those engaging in sex with multiple partners. Practices such as tattooing and body piercing have not been associated with HCV infection in the general population. Whether VA populations are uniquely at risk for HCV from these or other exposures needs to be evaluated.

Closer scrutiny of HCV demographics leads epidemiologists to discern ever more complex and poorly-understood patterns of infection. Dr. Henry Francis of the National Institute on Drug Abuse stated that epidemiologic data are often inaccurate in describing HCV rates among drug abusers. For example, there are important regional differences in drug abuse behaviors, differences which will in turn

Drug User Profile

⊙Trouble never travels alone

- ⊙60% male, 45% white, 53% employed, 43% completed high school
- ⊙40% HIV+ or AIDS
- ⊙30% TB skin test positive
- ⊙80-90% Hep C+, 40% Hep B+, 60% ETOH
- ⊙STDs 0 to 80%, Females > Males
- ⊙Data is known for IDUs (10% of DU population) only

influence prevalence and incidence of HCV. An estimated 16 million individuals are considered illicit drug users, more than one-third of them being regular users. Of the illicit drug users, about 10 percent are users of injection drugs. HCV infection rates are extremely high in those with a current or past history of injection drug use, with most individuals becoming infected within the first 18 months after they begin this practice.

According to Dr. Francis, these demographics are further complicated because individuals who use illicit drugs frequently also use alcohol and tobacco. Moreover, other segments of the population, such as adolescents, need to be included when developing a comprehensive picture of illicit drug use. For example, there are new trends in non-prescribed drug use, including a recent surge in use of anabolic steroids through injection, which might in turn place an individual at increased risk of HCV. "HCV almost never occurs alone, and there are drug interactions, mental health problems, and other conditions to take into account," stated Dr. Francis. Drug users who are HCV-infected are 60 percent male, 45 percent white, and about 50 percent employed, he noted. Some members of this infected population readily adhere to therapeutic drug regimens, whereas others fail to do so, in part due to ongoing use of illicit drugs, but also due to their difficulties with establishment figures, including law officers.

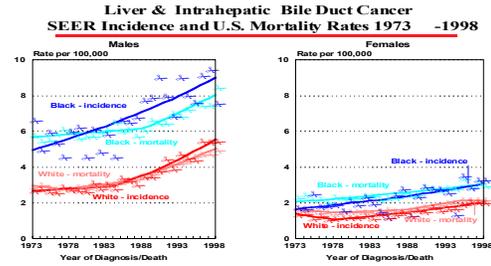
Alcoholism is also a complicating feature for many individuals who are infected with HCV, according to Dr. Diane Lucas of the National Institute on Alcohol Abuse and Alcoholism. Important questions include whether HCV acts synergistically with alcohol to damage the liver, whether heavy drinking enhances one's susceptibility to the virus, and whether a particular threshold consumption of alcohol is critical to the progression of HCV disease. Alcoholics with HCV infection tend to have poorer clinical outcomes than do non-alcoholics. Moreover, virus-infected alcoholics also typically have greater inflammation of the liver and an increased risk for developing hepatocellular carcinoma, said Dr. Timothy Morgan of the VA Long Beach Health Care System. Despite such observations, the mechanism by which alcohol contributes to the liver injury is unknown.

HCV and Alcohol

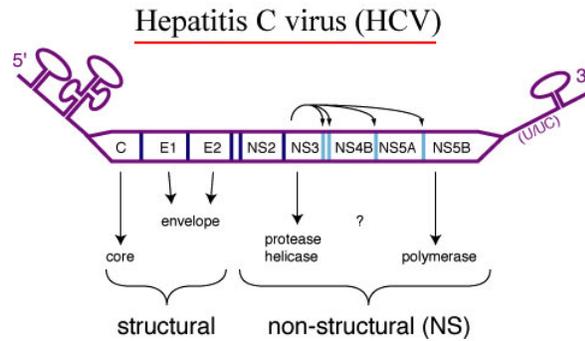
- ⊙ HCV + alcohol is common
- ⊙ Alcohol accelerates progression of HCV liver disease:
 - Greater hepatic inflammation
 - More rapid progression of fibrosis
 - Higher incidence of hepatocellular carcinoma
- ⊙ Alcohol may increase HCV viral load
- ⊙ Alcohol decreases response to interferon
- ⊙ Unanswered questions

CLINICAL EXPERIENCE, NATURAL HISTORY, AND BIOLOGY OF HCV

An estimated 70 percent of HCV infections persist after acute infection, although the acute phase is rarely identified, according to Dr. Seeff. Long-standing infection places individuals at risk for complications of liver disease including portal hypertension and hepatocellular carcinoma, according to Dr. John Cole of the National Cancer Institute. Many factors appear to affect the progression of disease in the chronic phase, including ethnicity, gender, age at infection, in some studies the source of infection, and alcohol consumption. Among young women, for instance, the rate of progression of disease is slow, as it also appears to be among some drug abusers. Investigators now believe there is an appreciable degree of spontaneous recovery from infection, in the range of 25-45 percent, according to Dr. Seeff. The high rate of persistence has led HCV experts to hypothesize that there are inherent properties of the virus that render it capable of escaping a protective human immune response. These findings suggest that development of a vaccine will prove challenging.



Currently available treatments for hepatitis C, including the combination of PEG-interferon and ribavirin, are only about 40-50 percent effective. Patient outcomes appear to depend in part on characteristics of the population being treated, including the ethnicity of the individual, and partly on characteristics of the virus, including viral genotype. The HCV virus itself contains a single-stranded RNA molecule of 9.5 kilobases that encodes a single open reading frame from which is produced a set of structural proteins, including core and envelope, and non-structural proteins, including protease (NS3), helicase, polymerase (NS5B), and NS5A. The function of the NS5A is under investigation, but according to Dr. Jeffrey Glenn of Palo Alto VA and Stanford University, this protein appears to be important in membrane association of the virus during replication. Little is known about how the virus replicates in host cells, how its structural proteins are assembled into new viral particles along host cell membranes, and how other HCV genes may contribute to these processes. These are currently areas of active investigation.



While individuals who become persistently infected with HCV are unable to mount an immune response that is adequate to clear the virus, they do develop a partial immune response, according to Dr. Kyong-Mi Chang of the VA Medical Center and University of Pennsylvania in Philadelphia. Little is known about why the immune response so often fails to protect against infection. Nor is it clear why certain individuals such as young

women clear the virus with a higher frequency than do others. T cell responses appear to be higher among individuals who recover from infection than in those who do not, whereas antibody responses that are observed during the acute phase of infection typically do not confer protective immunity. Variations in viral type and sequence may also contribute to the development of persistent infection.

Although researchers are studying HCV infection and immune responses in several non-human primates, such as chimpanzees, tree shrews, and tamarin monkeys, investigators would like to have alternative animal species such as rodents available for study. The absence of such models represent a critical unmet need for investigating the immune response to HCV and vaccine development.

Studies of immune responses to HCV infection in chimpanzees, although limited, offer a valuable opportunity to study the acute phase, according to Dr. Stewart Cooper of the San Francisco VA Medical Center. In one study involving six chimpanzees, two animals that showed strong, multi-specific T-cell cytotoxic responses resolved their infections, whereas the T cell response patterns were limited and delayed in those with persistent infection. There was no correlation between the humoral immune response and viral clearance. In those with viral persistence, antiviral antibodies developed slowly as infection shifted from the acute to the chronic phase.

The value of having better animal models for studying HCV was one of several critical research needs set forth in 1997 during a National Institutes of Health (NIH) consensus development conference devoted to HCV disease management issues. Dr. Leslye Johnson of the National Institute of Allergy and Infectious Diseases (NIAID) outlined the comprehensive HCV-related research agenda of the institute. Participants at that conference cited the need for better access to HCV-infected patient cohorts and appropriate specimens, she said, noting that forthcoming collaborations between NIH and VA investigators represent an important approach to meeting this need. Plans call for updating the findings from that 1997 consensus development effort at a meeting scheduled for June 2002.

Investigative Approaches

- ⊙ Study the immune response in hosts with different clinical & virological outcomes
- ⊙ Examine the virus relative to outcome and immune response
- ⊙ Examine potential viral interference with normal host cellular pathways (e.g. IFN response, apoptosis, immune induction & maintenance)

Comparison of Human and Chimpanzee Immune Response to HCV Infection

Vigor of CD8+T cell responses distinguishes chimpanzee and perhaps human responders.

Plasticity of CTL responses in chimpanzee and human responders can be remarkable – perhaps able to “accommodate” HCV variants.

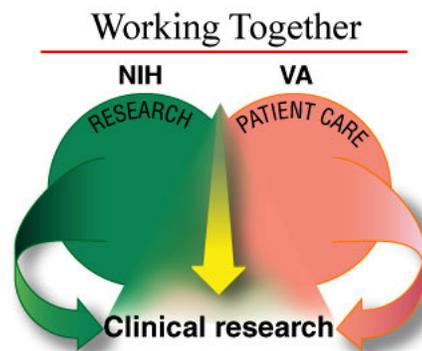
Breadth of CTL responses in responders manifests at 2 levels:

1. Targeting multiple epitopes in the HCV polyprotein.
2. Multiple T cell clones targeting single epitopes.

Delineation of CTL epitopes targeted by responders may reveal regions whose range of variants remain antigenic for inducible T cell receptors.

Many HCV-specific CTL share regulatory receptors with NK cells.

Important to understand determinants of control over virus-specific T cell responses in the liver.



Interferon is the principal biologic used as a therapeutic agent for managing patients with HCV infection. One multicenter clinical trial, HALT-C, was described by Dr. Jay Hoofnagle of the National Institute of Diabetes and Digestive and Kidney Diseases. The goal of this study, which will enroll 1,200 patients, is to evaluate the long-term benefits of PEG-interferon as suppressive therapy in patients who have failed to respond to a finite course of PEG-interferon plus ribavirin.

HALT-C Trial

- ⊙ "Hepatitis C Long-Term Antiviral Trial Against Cirrhosis: HALT-C"
- ⊙ 10 Clinical Centers, Virology Testing Center and Data Center (NERI)
- ⊙ Will enroll 1200 patients with hepatitis C who have advanced fibrosis and who have failed to respond to therapy with interferon
- ⊙ All will be retreated: combination therapy for 6 mo.
- ⊙ Patients who remain viremic will be randomized to either long-term therapy with pegylated interferon or no treatment for the ensuing 3.5 years
- ⊙ Outcome: Prevention of cirrhosis or its complications

HCV-infected patients being treated with ribavirin frequently develop hemolytic anemia. In such patients, particularly if they are symptomatic, anemia can be treated with erythropoietin (EPO), which sometimes permits continued high-dose antiviral therapy, according to Dr. Norbert Bräu of the Bronx VA Medical Center. He suggested conducting a systematic study to determine whether HCV patients could tolerate doses of ribavirin above the FDA recommended doses, if they simultaneously receive EPO.

Another multicenter clinical study, now underway, is focusing on resistance to antiviral therapy among HCV-infected patients, particularly among African Americans. According to Dr. Hoofnagle, VA sites are involved in both this study and the HALT-C trial. Although the response to therapy of HCV-infected African Americans may be lower than in Caucasians, the progress of their disease also seems to be slower than for other HCV-infected population groups, said Dr. Lennox Jeffers of the University of Miami. These differences in response appear to hold true not only for PEG-interferon as a monotherapy but also for PEG-interferon in combination with ribavirin. The absolute difference in treatment response and reasons for these differences, remain to be elucidated. Analyzing the reasons for these differences, whatever their magnitude, is further complicated because these population subgroups tend to be infected by different genotypes of HCV, according to Dr. Jeffers. Moreover, several studies indicate that there are major differences among HCV genotypes in terms of their responses to interferon therapy, added Dr. Ed Bini of the New York Harbor VA Medical Center.

Virahep-C Trial

- ⊙ Study of Resistance to Antiviral Rx in HCV
- ⊙ 400 treatment-naïve patients with hepatitis C: half African-Americans and half Caucasians
- ⊙ Combination therapy for 48 weeks
- ⊙ Evaluation of viral kinetics and responses
- ⊙ Correlation of responses with viral, interferon, immunological and genetic markers
- ⊙ Aim: What is the response rate among African American patients and what are mechanisms for lack of response to antiviral therapy

Other types of complications arise when treating HCV-infected patients who are co-infected with HIV, according to Dr. Lorna Dove of Columbia University. Because there are many more new and effective therapeutic options for HIV-infected individuals now than a decade ago, patients have fewer complicating opportunistic infections, she said. However, this patient population typically receives multiple HIV antiretrovirals, placing them at risk for hepatotoxicity from these agents. In addition, hepatic metabolism of

antiretrovirals may be altered in patients with liver disease, further increasing the potential for toxicities. The management of the individual with coinfection receiving HCV-specific therapy requires careful monitoring for drug-drug interactions and for toxicities. Additional studies of this patient population are warranted.

Proposed Research

- ⊙ Await the results of PEG-Inf/Riba studies
 - ?SVR
 - Tolerance of side effects \Complications
 - Need for Hematological Support
 - Optimal length of therapy in patients with non -1 genotypes and HIV
- ⊙ Determine the predictive value of pre-treatment CD4 or HIV RNA in the era of HAART
- ⊙ More investigation of the in vivo interactions of HCV therapy and HAART

EFFORTS TO DEVELOP DRUGS FOR TREATING HCV DISEASE

During the past decade, researchers in the private sector have been developing and evaluating antiviral regimens for HCV disease. Regimens include interferon as a single agent, or in combination with ribavirin. In July 2001, officials at the Food and Drug Administration (FDA) approved use of Schering Plough's version of a combination of PEG-interferon with ribavirin for treating such patients, according to Dr. Clifford Brass of Schering Plough. PEG-interferon is a polymer-bound version of interferon that is designed to increase its half-life in the body. Schering Plough has supported a number of studies within VA. The company is currently working with VA investigators on weight-based ribavirin dosing regimens and adherence strategies.

Roche Pharmaceuticals is also developing a PEG-interferon for use as a monotherapy as well as in combination with ribavirin, according to Dr. George Harb of Roche Pharmaceuticals. The company is collaborating with VA investigators to evaluate different treatment regimens in among veterans with HCV infection. Veterans under study include those who are co-infected with HIV, those on methadone and those with a history of substance abuse (alcohol and/or injection drugs). His company also is collaborating with several biotechnology companies as they investigate a number of novel approaches to treating this disease.

Collaboration With VA: The Future

- ⊙ HCV/HIV Co-infection
- ⊙ Alcohol impact on HCV therapy
- ⊙ Compliance with HCV therapy
- ⊙ Neuropsychiatric illness and HCV therapy
- ⊙ Comorbid disease burden and HCV therapy
- ⊙ CHC in African Americans

Some properties of HCV represent formidable challenges while others appear to offer opportunities for investigation according to Stephen J. Rossi, Pharm.D, of the San Francisco VA Medical Center. For example, the conserved 5' IRES site in the HCV genome, the virus-encoded protease and helicase, the RNA polymerase, and the envelope protein all represent potential antiviral drug targets. However there are substantial difficulties to overcome in developing and evaluating such products. Examples of these difficulties include the high degree of genetic variability of HCV, the lack of a consistent culture or suitable small animal model system for drug screening and testing, and the

overlap between the site of infection of this virus (the liver) and the site of frequent toxicities.

Drug candidates under investigation include inhibitors of inosine phosphate dehydrogenase (IMPDH) that may block viral replication, drugs that are also potentially immunosuppressive, and that may have adverse effects on P450 metabolism, according to Dr. Rossi. Another drug, levovirin, that is similar to ribavirin may act as an immunomodulatory agent, and yet another candidate drug, a histamine analog, may inhibit phagocytosis and enhance HCV-specific T cells activity against the virus. Yet another approach to anti-HCV drug development entails designing specific ribozymes that potentially disrupt the viral genome. In early phase clinical trial, HCV ribozymes produced no adverse effects but also failed to reduce HCV RNA levels. Another approach involves development of an anti-sense oligonucleotide that targets the HCV genome. One such product in early evaluation has been associated with reduction in HCV RNA levels in a small group of patients. Finally HCV immunoglobulin appears to attenuate HCV infection and might prove useful in specialized populations, such as patients undergoing liver transplantation.

RECOMMENDATIONS FROM WORKSHOPS

During workshop sessions, participants identified the following HCV-related research goals as part of VA efforts to develop a comprehensive program and to harness the VA system's resources for meeting those goals.

FIRST SESSION

Workshop 1. Epidemiology (leader: Jason Dominitz)

Health experts recognize that, for particular population groups within the VA system, the risk of HCV infection is particularly high, especially those with substance abuse and psychiatric illness. With that in mind, workshop participants recommend focusing HCV-screening resources on these high-risk individuals. The participants also recommend looking at health care personnel within the VA who are at risk for becoming infected with the virus through needle-stick accidents. Importantly, VA should systematically track HCV infection in these populations to determine critical risk factors and to identify any other associated diseases. Workshop participants developed the following list of research questions and projects:

Research Questions

1. What is the incidence of HCV infection among hemodialysis patients?
2. What is the incidence of HCV infection after accidental blood exposure?
3. What is the most efficient and effective way to detect new cases of HCV in a VA population? Should the VA recommend universal screening or more targeted screening? What are the implications for cost and quality of life?
4. What is the prevalence of HCV infection among high-risk groups, including domiciliary residents, mental health clinic patients, and substance abuse clinic patients?
5. What is the prevalence of HCV among veterans who do not use VA for health care? How often do veterans seek care from the VA primarily due to a new diagnosis of HCV or for HCV-related treatment?
6. What is the association between HCV and other conditions, including non-hepatic malignancy?

Specific Projects

1. A retrospective study of incidence of HCV infection using pre-existing databases (e.g. VISN 20 CHIPS) with substance use as a covariate.
2. A national survey of all employee health offices to audit their experience with HCV seroconversion after needlestick.
3. Central database of HCV positive and HCV negative veterans—via the Emerging Pathogens Initiative or the Hepatitis C registry-- to facilitate epidemiologic research.

Workshop 2. Secondary Prevention
(co-leaders: Kim Hamlett-Berry and Dave Metzger)

To reduce the risk of HCV infection spreading into additional population groups, VA health care workers will need to work with those who are infected to help in identifying others who are at risk for becoming infected, such as needle-sharing and sexual partners. Another goal is to develop approaches for stabilizing disease in individuals who are HCV virus-infected—for example, by determining whether it is essential for alcohol- or other substance users within such cohorts to abstain from drinking or using such drugs. Ordinarily, because such HCV-infected individuals are not considered suitable candidates for receiving anti-viral therapy, the VA will need to determine appropriate strategies for managing such patients. Workshop participants recommend evaluating chronic care models to determine which are applicable to such HCV-infected patient groups. Moreover, they recommend that the VA construct a meaningful patient registry and database. Workshop participants developed the following list of research questions and projects:

Research Questions

1. What are the best practice models to stabilize patients prior to HCV treatment?
 - a. Include practice variations
2. Which patients with substance use disease or mental health diagnoses are HCV treatment candidates (what constitutes “clinically stable” or “treatment-ready”)?
3. What are predictors of treatment adherence?
4. If substance use is a predictor of non-adherence, is any substance use (moderate ETOH, cannabis) equivalent to injection drug use as a predictor?
5. What are models of care for non-treatment candidates?
 - a. Appropriate monitoring
 - b. Health behavior promotion
 - c. Chronic disease management models
 - d. Case management
 - e. Integrated care
 - f. Provider education to reduce arbitrary selection and stigma
 - g. Patient education

Specific Projects

1. Develop Hepatitis C Registry

Workshop 3 Treatment of HCV in Standard VA Populations
(co-leaders: Teresa Wright and Mike Fried)

The VA system is well suited for addressing fundamental questions about how best to treat HCV-infected population groups. Workshop participants recommend designing and conducting a “head-to-head” PEG-interferon-ribavirin combination- comparison clinical trial within VA. To design such a trial, investigators need to determine how many patients will need to be enrolled and what are appropriate end points. Enrollees should be

treatment naïve; criteria for inclusion in the trial will need to be tailored to the needs and characteristics of special population subgroups within the HCV-infected VA cohort; adjunctive therapies should be considered to minimize therapeutic drug reduction adjustments for some of those subgroups; side effects should be carefully monitored; special measures of adherence to the therapeutic protocol, such as electronic monitoring, should be considered; and the trial should take into account non-responder populations. Workshop participants recommended the following list of specific questions and projects:

Research Questions

1. How do pegylated interferon-alpha 2a + ribavirin and pegylated interferon-alfa 2b + ribavirin compare in treating naïve patients?
2. What strategy should be employed in patients who fail treatment with interferon-alfa 2b and ribavirin?
3. What is the role of growth factors in an overall treatment strategy?

Specific Projects

1. A head-to-head study between pegylated interferon-alpha 2a (at 180 ug/wk) + ribavirin (1000/1200 mg/d) and pegylated interferon-alfa 2b (at 1.5 ug/kg/wk) + ribavirin (1000/1200 mg/d) in genotype 1 naïve patients treated for one year.
 - a. Primary endpoints: SVR
 - b. Secondary endpoints: QOL, cost-effectiveness, side-effects (quantitative measures including depression, drug use, relapse rate), adherence (measured using pill counts and electronic caps)
 - c. Conduct a “real-world” study
 - d. Use a standard definition for exclusion for depression, eg BDI > 10
 - e. Measure HCV RNA at pre, wk 4, 12, 24, 48, 60, 72
 - f. Sample size should be calculated based on non-equivalency assumptions
2. Conduct a retreatment study after failure of interferon-alfa 2b + ribavirin with a similar study design as the naïve study.
3. Conduct a study of the role of erythropoietin and GCSF, including:
 - a. Dose reductions of ribavirin versus erythropoietin when Hgb < 10.
 - b. Racial differences in anemia, leukopenia/neutropenia and response to growth factors.

Workshop 4 HIV/HCV Co-infection (co-leaders: Paul Volberding and Michael Rigsby)

In developing research programs for HIV/HCV co-infection, VA officials will necessarily be facing situations in which health care needs are very much blended with research efforts. Hence, workshop participants urged the VA to broaden the availability of treatments for those within this population group while making an explicit effort to learn more about their specific treatment needs and responses, particularly among African Americans who are co-infected with these two viruses. An important question to address is why treatments lack efficacy in some of these subgroups, raising the related question as to whether treating HCV with interferon interferes with HIV treatment regimens.

Registries and databases could help to address these and other complex questions about unusual immune system responses of patients during various treatment regimens. Workshop participants were especially enthusiastic over the prospect of the VA conducting natural history studies, studying the pathophysiology of co-infection in such patients. Workshop participants recommended the following list of research questions and projects:

Research Questions

1. What is the natural history of HIV/HCV? This could be studied by:
 - a. a cohort study (like the Multi-Center AIDS Cohort Study) with specimen repository, related to a larger “virtual cohort”
 - b. a cohort study of patients with varied levels of immunosuppression to follow liver histology and immunologic characteristics.
 - c. comparing co-infected patients to patients infected w/HCV alone.
2. What are the best systems of care delivery and management strategies? including:
 - a. QOL issues
 - b. Management of side effects
 - c. Effects of education; lifestyle/behavioral changes on disease progression
 - d. Adherence
3. Basic science questions:
 - a. Resistance
 - b. Kinetics of viral replication and clearance
 - c. Mechanisms of fibrosis
 - d. Mitochondrial toxicity
4. Clinical questions:
 - a. Hepatotoxicity
 - b. Transplant
 - c. Role of complementary and alternative medicines
 - d. Hepatocellular carcinoma
 - e. Drug interactions
 - f. Therapeutic Drug Monitoring

Specific Projects

1. Develop a national HIV/HCV working group to write proposals, look for support from NIH and industry, examine issues of transfer of funds.
2. Explore partnering with existing cohorts (e.g. the Veterans with HIV/Aging Cohort)
3. Explore partnering with other health care systems to increase numbers of female patients
4. Examine barriers to enrollment of female patients in VA.

Workshop 5. Host Genetics

(co-leaders: Tim Morgan and Tom O'Brien)

Although genetic traits likely play a role in determining susceptibility to HCV infection, little if anything is understood about the specific genetic determinants that are involved in the course of disease that follows infection and the differences in response to antiviral treatment. Workshop participants recommend using DNA analytic tests to address such questions and suggest that such testing be added to other on-going clinical studies as a

cost-effective approach for doing so. Because tests to address some specific questions about host genetic factors are not now available, the participants recommend that patient specimens be stored for later testing once such specific factors are identified. The participants also urge VA to establish a specimen repository, standardized means for retrieving specimens, and appropriate databases to meet these research needs. A list of specific research questions and projects compiled by workshop attendees includes:

Research Questions

1. What are host determinants of HCV clearance?
2. What are genetic determinants for development of fibrosis?
3. What are genetic determinants for development of HCC?
4. What are genetic determinants of response to therapy, including efficacy and adverse events?

Specific Projects

1. Establish a repository for DNA, cells, and liver tissue
2. Develop a national Host Genetics Working Group.
3. Ease administrative burdens with standardized consent forms and other research procedures.

Workshop 6. Virology

(co-leaders: Harry Greenberg and Curt Hagedorn)

To address molecular-level HCV research needs, workshop participants recommend that the VA build the infrastructure needed for meeting those needs, including production and distribution of reagents such as cell lines for growing virus, viral clones, monoclonal antibodies, and viral peptides. They recommend that VA develop a partnership with NIH to help in producing, storing, and distributing these and other biological materials, including serum and cell repositories. Recommended priority research undertakings include the development of cell lines in which to culture HCV, small animal models in which to study the course of HCV infection, and *in vitro* assays for studying specific HCV functions. Workshop participants recommend that proposals for undertaking such research be peer-reviewed and that VA establish a working committee to oversee efforts to realize these goals. VA should also consider designating a central lab for testing clinical samples and maintaining a related database. The list of specific research questions and projects includes:

Research Needs

1. Develop a permissive cell culture system.
2. Develop a small animal model that recapitulates pathogenesis, oncogenesis, and the immune response.
3. Develop an *in vitro* assay that measures specific functions—membranous association, helicase and protease activity.

Specific Projects

1. Continue basic, peer-reviewed, merit-based research that reaps benefits in patient care.
2. Develop a tissue and specimen bank within the context of a prospective, consented cohort
3. Create a central laboratory for expensive clinical laboratory studies that would generate specimens and centralize data.
4. Catalog existing VA specimen repositories.
5. Develop a database of acute infection patients.
6. Promote industry collaboration by good communication, ease IRB processes, make VA more “nimble” in working with industry in terms of intellectual property
7. Establish a clearinghouse of and for VA investigators—sharing information about research projects needing investigators and investigators looking for opportunities
8. Create a reagent catalog—a “Los Alamos” –like system for HCV
9. Form a VA Hepatitis C Working Group of “catalyzers”.

SECOND SESSION*Workshop 1. Immunopathogenesis*

(co-leaders: *Barbara Rehermann and Stewart Cooper*)

The immunopathogenesis of HCV infection appears to be very complex, and both antibody- and T cell-based reagents will be needed. Workshop participants recommended the establishment of a central laboratory mandated to develop and distribute such reagents. Noting that T cell responses apparently are critical for limiting HCV-mediated pathogenesis, it would be helpful to study these responses in specific patient populations, such as health care personnel infected with the virus through occupational accidents. Another viral feature that will complicate the study of immunopathogenesis is the varying behavior of genotypes of HCV, and the fact that the virus forms quasispecies. The participants recommended that the VA address several infrastructure needs for such research, including the development of databases (in collaboration with NIH for the genetics of these viruses) and establishment of specimen repositories. Specific research questions and projects outlined by participants were:

Research Questions

1. What are the determinants of polarity in the immune response?
2. What determines the response to treatment?
3. Who gets infected and why?
4. What are the determinants of immunity vs. pathogenesis?
5. What is the influence of origin of infection and age of infection?

Specific Projects

1. Establish a needlestick protocol in order to study acute hepatitis, asymptomatic clinical infection, and post-exposure treatment
2. Develop a study of host/environmental factors in disease progression, especially in minority patients, alcohol users, agent orange-exposed, substance abuse patients, and patients following treatment, both with and without viral clearance
3. Study HCV in immunosuppressed patients, especially HIV/HCV co-infection

4. Develop a prospective, consented cohort with specimen storage (a nationwide serum, cell-, cell line, and tissue repository that is longitudinal and linked to clinical data, with standardized criteria) and appropriate consents in place.
5. Develop a study of immune response after transplantation.
6. Study role of quasispecies in the immune response.
7. Study genotype-specific immune response with reagents for genotypes 2 and 3.
8. Develop a central database of ongoing and planned studies to assist VA investigators to participate in or develop studies of interest.
9. Develop "SOPs" to make VA/NIH rules easier to work with; establish an infrastructure for research.
10. Develop a relational database to study and predict outcomes.
11. Develop a database for genetic information.
12. Develop a VA Hepatitis C Working Group.

Workshop 2. Alcohol Issues

(co-leaders: Craig McClain and Kenneth Sherman)

Workshop participants agreed that basic assumptions about the influence of alcohol on the course of HCV infection need to be re-examined critically, including the question of whether alcohol consumption itself or associated practices, such as smoking, affect the disease process. If alcohol consumption indeed affects the progress of HCV-related disease, investigators should focus on learning just how it does so and whether relative levels of alcohol consumption make an important difference to disease outcomes. On a practical level, achieving treatment compliance among alcoholics who are infected with this virus is an important challenge, and defining biomarkers and identifying alternative approaches to therapy would be valuable. Throughout such efforts, it will be important for different branches within VA to cooperate, particularly those responsible for psychiatric treatment of veterans, and also for VA and NIH researchers to collaborate. Specifically, participants developed the following list of research questions and projects:

Research Questions

1. Is alcohol consumption associated with the emergence of HCV quasispecies which leads to less interferon responsiveness?
2. Does competitive replication of HCV quasispecies present in alcohol users lead to decreased liver disease progression?
3. Why does viral load vary?
4. What is the role of genetic drift and shift?
5. Are quasispecies altered by changes in alcohol use?
6. What immunologic correlates are there with quasispecies' emergence?
7. What is the impact of alcohol on disease progression?
8. Does alcohol use affect treatment outcomes?
9. How does coinfection with HIV change progression of HCV in the alcohol user?
10. Is the alcohol user at greater or less risk of primary HCV infection and viral persistence?
11. Are biologic effects of alcohol involved in the transmission of HCV to others?
12. What is the impact of street drug use on alcohol-HCV interactions?
13. Does timing of alcohol use determine or have an impact on immune response?
14. How is alcohol use best measured? Are there measures other than self-reporting?

15. What are biologic markers of alcohol use?
16. How can acceptance of alcohol treatment be increased in alcohol users with HCV?
17. How can treatment of HCV be increased in alcohol users?
18. What is the impact of alcohol cessation on treatment?
19. Is there a safe level of alcohol use in HCV disease?
20. Are there drug interactions between interferon-alpha and naltrexone?
21. What are treatment goals in alcoholics?
22. What is the role of complementary and alternative therapies (specifically SAM [S-adenosyl methionine])?

Specific Projects

1. Establish a Hepatitis C registry (that includes data on alcohol use and HCV disease progression).
2. Perform cross-sectional and natural history studies.
3. Continue discussions with NIDA and NIAAA

Workshop 3. Hepatocellular Carcinoma (co-leaders: Chris O'Brien and Adrian DiBisceglie)

Noting that other workshop groups recommend that the VA establish a comprehensive database for HCV patients and related research involving this patient population, participants in this workshop urged that this database include information about HCV patients who develop liver cancer. They also said that different patient screening procedures should be evaluated, and urged VA to conduct clinical trials evaluating agents intended to prevent development of cancers among members of the HCV-infected patient population. To meet clinical trial infrastructure needs, the VA should consider establishing regional treatment centers and a hepatocellular carcinoma (HCC) working group to manage these efforts. The workshop participants' list of specific research questions and projects included:

Research Questions

1. Does screening for HCC prolong survival?
2. Who should be screened and undergo surveillance?
3. What is the role of diagnostic imaging in screening (ultrasound, CT)?
4. How best to diagnose cirrhosis: (especially in HCV patients with platelet counts of < 120K)?
5. What is the role of alpha fetoprotein in screening?
6. What is tumor doubling time in U.S. patients?
7. What is the role of alcohol as an additive risk for HCC in patients with HCV?
8. What is the role of cancer chemoprevention (vitamin E or COX2 inhibitors) for HCC?

Specific Projects

1. Study interventions for cirrhotics: beta blockers, endoscopy for varices, etc.
2. Study screening approaches for HCC with a case control study or a prospective randomized clinical trial, including patients who have been treated with or without viral clearance, and those who are on therapy
3. Couple screening strategy with cancer chemoprevention (vitamin E or COX2 inhibitors) for HCC
4. Establish surveillance strategies for stage III and IV HCV, as well as for patients with clinical cirrhosis
5. Form a national HCC Working Group—hepatologists, oncologists, surgeons, and others who are interested in establishing a treatment consortium.
6. Develop a registry of VA patients with HCC
7. Measure health-associated costs of screening for HCC: cost per life saved, cost per tumor detected.
8. Develop Centers of Excellence for Management of HCC.
9. Develop an electronic clinical reminder for HCV and cirrhosis that promotes HCC screening strategies.

Workshop 4. Natural History

(co-leaders: Leonard Seeff and Harvey Alter)

Several fundamental questions about the natural history of HCV infection need to be addressed, including what accounts for the high rate of persistence of this virus, what occurs as the virus moves from the acute to the persistent phase, and what factors affect clinical outcomes of infection once chronic. There are also questions about appropriate treatment of such infection during the acute phase, including whether a recently published study by a group of clinical investigators in Germany represents an optimal approach to early-phase treatment, and about spontaneous recovery from such infections (observed primarily among children and young women). A database reflecting the clinical experience across the broad VA cohort could be helpful in addressing such questions. Development of a VA-based repository for HCV-related specimens should be considered “mandatory.” Creation of an oversight committee for managing that effort should also be seriously considered. Workshop attendees developed the following list of research questions and projects:

Research Questions

1. Why is there such a high rate of viral persistence?
 - a. What role does hamming distance of viral quasispecifics play?
 - b. What are innate immune mechanisms that protect from chronic infection?
 - c. What defines persistence?
 - d. What defines progression?
2. Is there spontaneous recovery after the infection has persisted for > 1 year?
 - a. How often does spontaneous recovery occur?
3. What determines progression vs. non-progression?
 - a. Is progression linear?
 - b. What factors play a role in development of HCC?

- c. What is the role of age, gender, race, host genetics, source of infection, viral genotype, and other co-factors including ETOH, smoking, diet, environment?
- d. What happens after 20 years of chronic infection?

Specific Projects

1. Establish a needlestick study with multiple VA medical centers to gather acute phase samples from large numbers of patients
 - a. follow patients longitudinally to study determinants of clearance vs establishment of chronic infection

Workshop 5. Treatment of Special Populations (co-leaders: Doris Strader and Henry "Skip" Francis)

Workshop participants said that they were uncomfortable with the term, "special populations" of HCV-infected patients, pointing out that at many VA centers the majority of patients might fit that definition because of a higher prevalence of infection among individuals who are intravenous drug and/or alcohol users, African Americans, or psychiatric patients. Participants recommended that VA make sure that populations with co-morbidities have access to appropriate treatment. They also recommend that the VA study whether particular patients are at special risk for becoming re-infected with HCV, whether there are unusual side effects to look for among HCV-infected patients in methadone programs, whether abstinence is crucial for efficacy of antiviral interventions, and what effects psychiatric conditions such as depression might have on antiviral therapy outcomes. They also questioned whether current impressions about differences in response to antiviral therapies between African American and other HCV-infected population groups are accurate and, if not, whether this misperception is putting some people at a higher risk for poor outcomes following such therapy. Workshop participants developed the following list of research questions:

Research Questions

1. IV Drug Use
 - a. What outcomes of HCV disease are associated with various models of health care delivery, including psychiatry, primary care, substance abuse treatment?
 - b. What are the virologic, immunologic, and behavioral issues surrounding re-infection of IV drug users?
 - c. What are the best treatment models for methadone maintenance? (side-effect management, dosing requirements when on HCV treatment)
 - d. What period of abstinence should be required before treatment (is absolute abstinence required? Should marijuana use be an exclusion?)
2. Alcohol Use
 - a. How much alcohol is too much?
 - b. How can the impact of alcohol abuse be monitored?
 - c. Is an increase in alcohol use a surrogate marker of other drug use?
 - d. Does current HCV treatment and associated depression lead to alcohol relapse?
 - e. What is the impact of ETOH on immune response to interferon-alpha and other pharmacologic therapies for HCV?

3. Mental Health
 - a. What are predictive factors for the occurrence of mental health problems during HCV treatment?
 - b. What constitutes treatment candidacy in patients with a history of psychiatric illness?
 - i. Depressive disorders
 - ii. Non-depressive disorders
 - c. What is the impact of medication prophylaxis for depression vs an interventional approach?
 - d. What are best practices or tools for perceived psychosocial support?
4. African-American Populations
 - a. What are treatment responses?
 - b. What are VA-specific data on treatment response to current HCV treatment?
 - c. Are there pharmacologic or immune response differences?
 - d. Are there genetic reasons for treatment response differences?
 - e. Are there genetic reasons for differences in liver injury?
 - f. What are reasons for non-response (leukopenia, tolerability, increased risk of adverse events)?
5. Female Veterans
 - a. What is the prevalence of HCV in female veterans?
 - b. What are the access-to-care issues in female veterans?

*Workshop 6. Extra-Hepatic Manifestations
(co-leaders: Vincent Agnello and S. Louis Bridges)*

The prevalence of several conditions now associated with persistent HCV infection, including mixed cryoglobulinemia, other cell tropisms, autoimmunity, arthritis, Sjögren syndrome, and porphyria cutanea are thought to be relatively low, according to workshop participants. It was recommended that VA develop a concerted effort to determine those prevalences and also determine through clinical trials whether antiviral treatments for HCV also are appropriate for treating cryoglobulinemia. Workshop attendees noted there are likely enough numbers of such patients within the VA system for the purpose of designing and conducting such studies, but noted that preliminary epidemiologic studies will be needed before those study designs can be completed. Workshop participants developed the following list of specific research questions and projects:

Research Questions

1. What is the prevalence of extra-hepatic disease associations including mixed cryoglobulinemia, B cell lymphoma, arthritis, Sjögren's syndrome, sialadenitis without Sjögren's syndrome, porphyria cutanea tarda, endocrine disorders?
2. What is the prevalence of autoantibodies (e.g. rheumatoid factor, ANA) and various types of cryoglobulins (immune complexes)?
3. What are immunopathologic mechanisms of membranoproliferative glomerulonephritis without mixed cryoglobulinemia?

Specific Projects

1. Determine the prevalence of extra-hepatic disease manifestations in VA patients with HCV and mixed cryobulinemia, including diabetes mellitus, endocrine dysfunction, and depression.
2. Develop specific criteria for diagnosis of mixed cryoglobulinemia and characterization of cryoglobulins.
3. Perform studies on immunopathogenesis of peripheral neuropathy, glomerulonephritis, B cell clonality in mixed cryoglobulinemia, and other extra-hepatic disease associations established by prevalence studies.
4. Conduct a clinical trial for the treatment of HCV-associated type II cryoglobulinemia mixed cryoglobulinemia syndrome: treat with pegylated interferon for 1 year, followed by treatment with pegylated interferon until sustained virologic response and presence of a monoclonal B cell population in peripheral blood. Maximum treatment of 4 years.
5. Create a repository of blood samples and liver biopsy specimens from patients with mixed cryoglobulinemia and other extra-hepatic disease associations.

CONCLUSIONS

After considering recommendations from the twelve workshops, meeting participants urged VA to set up electronic communications systems that will provide information on its ongoing HCV- research-related developments. They also recommend that VA set up a working group to design a number of clinical and basic research projects and collaborations.

Commenting more generally, Dr. Paul Volberding from the San Francisco VA Medical Center praised the spirit of the meeting and said that it was reminiscent of research planning meetings during the early days of the HIV epidemic.

Dr. Deyton noted that the participants at the October meeting identified important ideas for VA to consider in building its HCV research agenda, noting in particular their agreement over the need for studying the “needle stick” cohort at VA, comparing available antiviral regimens head-to-head, and for identifying markers of disease progression and discerning why some patients fail to benefit from currently available antiviral drugs. Despite logistical barriers, he held that it is critical to let science drive VA efforts to improve the treatment of HCV-infected veterans. He noted the need to capture the energy of participants and the momentum created by the meeting. He urged participants to pursue ideas and contacts initiated at this meeting, and to attend follow-up meetings to pursue the development of a comprehensive VA HCV research portfolio.

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