Part 5: Recent Insights into HCV Virology and Treatment of Chronic Hepatitis C

Release Date: September 1, 2002.
Termination Date: September 1, 2003.
Part 5 Publication Date: November 29, 2002.

Estimated time to complete this five-part newsletter and monograph series: 2.5 hours. This five-part newsletter and monograph series has been planned and produced as an independent CME activity in accordance with the ACCME Essential Areas and Policies. Please see Part 1 for CME information and instructions, learning objectives, content development information, survey methodology, and a list of contributors and their disclosures.

Download Parts 1–4 @ www.projectsinknowledge.com

Projects In Knowledge gratefully acknowledges the unrestricted educational grant provided by Schering Hepatitis Innovations in support of this independent CME activity.
Addendum

Please note: On December 3, 2002, after this material was printed, the FDA approved pegylated interferon alfa-2a/ribavirin combination therapy for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not been previously treated with interferon alfa.
Dear Colleague:

Now in its sixth year, The Clinician's Companion series has long served as a valuable resource on hepatitis C for practicing gastroenterologists. We trust that you are finding the current series, The Clinician's Companion VI, to be as informative and practical as in years past. Representing the fifth part of the The Clinician's Companion VI, this monograph provides in-depth coverage of some of the most important issues in hepatitis C today, including:

- The latest updates on HCV virology are leading to development of novel anti-HCV treatment strategies
- The increasing efficacy of treatment and the NIH consensus statement are opening the doors to treatment for a broader range of patients
- Individualized treatment with peginterferon/ribavirin according to predictors and early determinations of response
- Improved adherence through use of adjunctive therapies to manage side effects of peginterferon and ribavirin
- Management of the increasing number of HCV-infected patients with advanced liver disease or hepatocellular carcinoma

Here you will find not only the latest data, but also a discussion of their implications for clinical practice and practical strategies for implementing the latest management approaches. As described in Part 1, content for this series was developed at a meeting that featured expert presentations, panel discussions, case studies, and recommendations gathered via survey from a nationwide panel of leading hepatologists, gastroenterologists, and other specialists engaged in research or treatment of hepatitis C. Let recommendations from our expert faculty and panel of nearly 200 contributors guide you through some of the difficult challenges that face physicians treating hepatitis C today.

If you missed any of the Tx Reporters™ that comprised Parts 1 through 4 of this series, you can now find them at http://www.projectsinknowledge.com/Init/G/1571/index.html#news. Please refer to Part 1 for CME information, as well as details on the expert panel of contributors and development of the content for this series. We hope you find this monograph, and the entire Clinician's Companion VI series, helpful and informative.

Sincerely,

Willis C. Maddrey, MD
Co-Chair
University of Texas Southwestern Medical Center at Dallas
Dallas, Texas

Eugene R. Schiff, MD
Co-Chair
University of Miami School of Medicine
Miami, Florida

ACKNOWLEDGMENT
Co-chairs Willis C. Maddrey, MD, and Eugene R. Schiff, MD, and Projects In Knowledge gratefully acknowledge the contributions of the following persons in guiding the expert consensus development process and in creating the content of The Clinician's Companion VI: Expert Perspectives on Contemporary Clinical Issues in Hepatitis C:

Nezam H. Afdhal, MD
Harvey J. Alter, MD
Bruce R. Bacon, MD
Robert S. Brown, Jr, MD, MPH
Robert L. Carithers, Jr, MD
Massimo Colombo, MD
Robert G. Gish, MD
John B. Gross, Jr, MD
Ira M. Jacobson, MD
Barbara H. McGovern, MD
John G. McHutchison, MD
David R. Nelson, MD
Thierry M. Poynard, MD, PhD
Charles L. Raison, MD
Stuart C. Ray, MD
Donald C. Rockey, MD
Angelo Sangiovanni, MD
Mark S. Sulkowski, MD
Myron J. Tong, PhD, MD
Teresa L. Wright, MD

E-mail: gastro@projectsinknowledge.com
THE CLINICIAN’S COMPANION VI:
Expert Perspectives on Contemporary Clinical Issues in Hepatitis C

PART 5: Recent Insights into
HCV Virology and Treatment of Chronic Hepatitis C

TABLE OF CONTENTS

I. Perspectives of HCV and Virology Frontiers at the NIH .................. 2
II. HCV Virology and the Effects of Treatment .......................... 6
III. Impact of HIV on the Natural History of Hepatitis C ............... 8
IV. NIH Draft Consensus Statement on Hepatitis C:
Conclusions and Controversies ..................................... 10
V. A New Look at à la Carte Therapy ..................................... 13
VI. Side-Effect Management ............................................. 16
VII. Maintenance Therapy in Combination Treatment Nonresponders .. 19
VIII. Future Drug Development ........................................... 21
IX. Update on Hepatocellular Carcinoma ................................ 24
X. Liver Transplantation .................................................. 28
XI. Conclusions ......................................................... 31

Co-chairs: Willis C. Maddrey, MD, Eugene R. Schiff, MD
Editor: Lauren A. Cerruto
Education Development: Dr. Deborah Teplow, Jo Hannah Villanueva, MD, and Jane Perrotta
Production Editor: Kim Spino

CME Information
Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education
to provide continuing medical education for physicians.
Projects In Knowledge designates this educational activity for a maximum of 2.5 category 1 credits
toward the AMA Physician’s Recognition Award. Each physician should claim only those hours of
credit that he/she actually spent on the educational activity.

Copyright © 2002, Projects In Knowledge, Inc. All rights reserved.
Introduction

At The Clinician’s Companion VI Development Meeting, co-chair Willis C. Maddrey, MD, interviewed renowned hepatitis researcher, Harvey J. Alter, MD. Dr. Alter is currently Chief of Infectious Diseases and Associate Director for Research in the Department of Transfusion Medicine at the National Institutes of Health (NIH) in Bethesda, Md. Dr. Alter has held academic appointments at Georgetown University School of Medicine, where in 1967, residents and students recognized him with an award for teaching excellence in hematology. Dr. Alter serves as an associate or guest editor for a number of hepatitis journals, and has authored over 270 publications. Among numerous other awards, he is the recipient of the prestigious Albert Lasker Award for Clinical Medical Research, a Distinguished Service Medal from the US Public Health Service, an NIH Directors Award, the Karl Landsteiner Award (the highest scientific award given by The American Association of Blood Banks), and a Scientific Achievement Award from the Hepatitis Foundation International. He has been elected to the National Academy of Sciences, the Institute of Medicine, and the Association of American Physicians, and he is a Master of the American College of Physicians.

A Serendipitous Start

DR. MADDREY: You have had a truly distinguished career. Of all of your accomplishments, the three that I believe are most important are your roles in the discovery of both hepatitis B and hepatitis C, and in ensuring the safety of the blood supply. Let’s start from the beginning. When you finished your training, what got you interested in being a hepatitis virologist?

DR. ALTER: My whole life has been total chance, serendipity. Although I’ve studied hepatitis throughout my career, I didn’t start out as a virologist or hematologist. I was trained as a hematologist and was working as a clinical associate in the NIH blood bank in the early 1960s, trying to figure out why people had reactions to transfusions. We already knew about febrile reactions due to antibodies to red and white cells and were looking for evidence of immune reactions to plasma proteins. I was using agar gel diffusion to see if people who had been multitransfused developed precipitating antibodies to proteins from their blood donors. Richard Aster, MD, who is now a world-famous hematologist, was in the blood bank at that time. He told me about a talk he’d heard by Baruch Blumberg, MD, PhD, who was a geneticist at the NIH looking for protein polymorphisms in a similar agar gel system. The beauty of the NIH is that you can just walk over to people’s labs and establish rapid collaborations. I spoke with Dr. Blumberg, we defined mutual interests, and within a day, we had a collaboration that was ultimately to change my entire career path.

In doing these agar gel diffusions, we discovered a system of inherited differences in lipoproteins. We had been running tests on a variety of serum samples from all over the world that Dr. Blumberg had in his freezers. When we stained the precipitin lines related to this lipoprotein polymorphism, they always stained blue with lipid stains. Then, one day, as we were looking for additional polymorphisms, one precipitin line failed to stain blue but stained red with a protein counterstain. This particular precipitin line turned out to be due to a reaction between the serum of a multitransfused hemophiliac and that of an Australian aborigine—which is why we named it the “Australia antigen.” That little red line in the early ’60s was a very serendipitous observation that would prove to be the beginning of hepatitis B, and eventually of non-A/non-B and hepatitis C. However, at the time, it seemed like a relatively inconsequential finding.

As we continued to run tests, we found that in a normal population, one in 1000 were positive for Australia antigen, but when we tested a group of leukemia patients, 10% were positive. So, we thought this might be a leukemia-associated antigen, which is how we described it in our first publication.1,2

Dr. Blumberg hypothesized that the Australia antigen was an inherited trait that might predispose to leukemia. Based on those assumptions, Dr. Blumberg, who was by this time at the Institute for Cancer Research in Philadelphia, tested patients with Down’s syndrome, since they have an inherited susceptibility to leukemia. Sure enough, 10% of the Down’s syndrome patients had the Australia antigen, a prevalence similar to what we found in patients with leukemia. Although this could have been an “Aha, we’ve got it” experience, Dr. Blumberg then did something that I give him great credit for: He looked at Down’s syndrome patients in different settings. Among Down’s syndrome patients in large institutions, 30% were positive for Australia antigen. In smaller institutions, it was about 10%, and among those who were never in an institution, it was near zero. Moreover, the prevalence of the antigen among Down’s syndrome patients at birth was zero.
This was the first clue that one was not dealing with an inherited condition, but rather an infectious disease, the prevalence of which varied according to conditions of overcrowding and ready routes of disease spread.

Subsequently, a technician in Dr. Blumberg’s lab got jaundiced from an episode of acute hepatitis. She had been serving as an Australia-antigen-negative control, but at the time she became sick, she tested positive. A further look at the Down’s syndrome patients found that those who had the antigen were more likely to have elevated alanine aminotransferase (ALT) levels. This led to intensive investigations of patients with hepatitis, and it became clear that the Australia antigen was really a hepatitis virus marker, ultimately shown to be the hepatitis B surface antigen.

In the midst of this, Dr. Blumberg was moving from the NIH to Philadelphia and asked me to come work with him, but I didn’t because I wanted to finish my clinical training in internal medicine and hematology. When I left the early story, Australia antigen was still considered a leukemia antigen, and I figured I’d never come back to it. However, when I did come back to the NIH in 1969, the association between the antigen and hepatitis B had been made and I got back into the picture. So that is the very serendipitous way that I became involved with hepatitis.

From Non-A/Non-B Hepatitis to Hepatitis C

DR. MADDREY: Tell us about non-A/non-B hepatitis. Was finding it a matter of subtraction or did you become proactively interested in another virus?

DR. ALTER: It really was subtraction. We were doing prospective studies of posttransfusion hepatitis, trying to see how often it occurred and what caused it. My impetus was to determine what we could do to the donor supply to reduce the risk, if there was a risk.

Before 1970, when we began these prospective studies, we found that a third of patients who underwent open-heart surgery got hepatitis, which was an astounding number. The reason the rate was so high was that, during open-heart surgery, they were transfusing 17 units of blood per case, and half the blood was from paid donors. This was the first prospective study of transfusion-associated hepatitis, and we were picking up anicteric cases. No one anticipated that such a high proportion of hepatitis cases would be anicteric and that the overall incidence would be so high. John Walsh, MD, who was at the NIH at that time, had just found that there was an increased risk of hepatitis from paid blood donors—the risk was about 50% when using paid donors versus 7% with blood from only unpaid donors. So, in 1970, I did perhaps the most important thing I have ever done. Paul Holland, MD, Paul Schmidt, MD, and I decided to stop allowing the transfusion of blood from paid donors. We introduced an all-volunteer donor system, and we introduced the first-generation test for hepatitis B antigen. This resulted in a precipitous fall in the rate of posttransfusion hepatitis transmission—a nearly 80% reduction. Nothing that’s been done since then has had a similar impact on the safety of the blood supply.

Retrospectively, we found that the decline in transmission was affected less by the hepatitis B testing than by the elimination of payment for blood donation. Later, when we went back to stored sera with a more sensitive hepatitis B test, we found that even before there were any donor screening hepatitis tests, only about 20% of the total hepatitis cases were due to hepatitis B and hence that the vast majority of cases were due to some non-B agent. As testing for hepatitis B improved over the years, posttransfusion hepatitis B virtually disappeared, but 10% of multitransfused patients continued to get non-B hepatitis.

In 1975, Steve Feinstein, MD, Al Kapikian, MD, and Robert Purcell, MD, discovered the hepatitis A virus. We immediately tested the stored samples of blood from patients with non-B hepatitis using the new test for hepatitis A virus. Of the 19 cases we tested initially, not one was due to hepatitis A virus.4 Bob Purcell, who, unlike me, was a virologist, said, “We can’t call it hepatitis C because, first, we haven’t proved that it is due to an infectious agent, and second, we don’t know how many agents it might be. So let’s be careful and call it non-A/non-B hepatitis.” Shortly after that, we confirmed in chimpanzee transmission studies that non-A/non-B was due to a transmissible agent,4 presumably a virus, and clinically we showed that non-A/non-B was the predominant cause of posttransfusion hepatitis.4 In the late ‘70s and early ‘80s, we tried every technique then known and could not find this virus. There was no detectable antigen or antibody, so “non-A/non-B hepatitis” existed as a clinical entity that could be diagnosed only by serologic exclusion of other known hepatitis agents.

Working with the group of J. Hoofnagel, MD, we showed that non-A/non-B was not just a transaminitis, as many people thought, but was a clinically significant hepatitis. Our studies showed that 20% of people infected with non-A/non-B hepatitis developed cirrhosis.7 As a result, non-A/non-B became an important clinical entity, but we still couldn’t find a test for it. The rates of posttransfusion hepatitis continued to decrease during this time because we were giving less blood and asking better questions of donors, so that by 1980, we had settled at about a 5% to 6% transmission rate.

DR. MADDREY: How did you arrive at the idea that you ought to discard blood that had an elevated ALT level?

DR. ALTER: We introduced the ALT test in 1981. A retrospective study of our stored samples showed that if you got blood from at least one donor who had an elevated ALT level, you were about three to four times more likely to get hepatitis than if you received only
blood with a normal ALT level. However, when we actually started testing for ALT in 1981, it had no apparent impact on transmission rates.

HIV came along in 1985, and we thought it would be a surrogate marker for hepatitis agents because of common risk factors, but testing for HIV had no impact on non-A/non-B transmission rates that we could measure. Our prospective studies indicated that testing for anti-HBc might serve as a surrogate marker for the agent of non-A/non-B hepatitis and that the receipt of anti-HBc positive blood increased hepatitis risk three-to-fourfold. Based on this and similar findings in a parallel prospective study sponsored by the National Heart, Lung, and Blood Institute (NHLBI), the nation adopted routine anti-HBc testing of donors in 1987. We then showed that testing for anticore antibody, as well as other changes in donor demographics, decreased the rate of non-A/non-B transmission from 6% to about 4% by 1989. In 1987, I told blood banks to adopt the HBcAb test “because we can’t find a test for non-A/non-B, and it may never come.” Just as I was saying this, Michael Houghton, PhD, and coworkers cloned the hepatitis C virus in 1989. Then the first-generation test for hepatitis C antibodies was introduced, and that made another major inroad, decreasing posttransfusion rate of non-A/non-B transmission from 6% to about 4% as other changes in donor demographics, decreased the rate of non-A/non-B transmission from 6% to about 4% by 1989. In 1987, I told blood banks to adopt the HBcAb test “because we can’t find a test for non-A/non-B, and it may never come.” Just as I was saying this, Michael Houghton, PhD, and coworkers cloned the hepatitis C virus in 1989. Then the first-generation test for hepatitis C antibodies was introduced, and that made another major inroad, decreasing posttransfusion rate of non-A/non-B transmission from 6% to about 4% by 1989. In 1987, I told blood banks to adopt the HBcAb test “because we can’t find a test for non-A/non-B, and it may never come.”

The impact of the HCV testing has been incredible. Prior to the introduction of this test, there were 111 cases of hepatitis per day in the United States from transfusion alone—about 60,000 cases per year. From 1990, when testing was introduced, until now—that’s 12 years times 60,000 cases—you could say that 750,000 cases of hepatitis C have been prevented.

Is the Blood Supply Truly Safe?

DR. MADDREY: Is there anything else in blood that causes hepatitis or might cause hepatitis by mutating over the next years?

DR. ALTER: I think the blood supply is very safe from hepatitis viruses, though there is the lingering concern that there may be a non-A, non-B, non-C hepatitis agent. While hepatitis agents are no longer a great concern to the blood supply, other infectious agents still represent threats including bacteria that contaminate platelets stored at room temperature; Trypanosoma cruzi, the cause of Chagas disease; malarial parasites; Babesia; parvovirus B-19; and most recently, West Nile Virus. Of course, our greatest concern is that a new AIDS-like agent will emerge.

In the future, to prevent transmission of viral and nonviral agents, we’re probably going to do preemptive inactivation. By using nucleic acid cross-linking agents such as psoralen and ultraviolet light, you can kill infectious agents you don’t even know exist, as long as they have nucleic acids. I’m hoping we’re going to go that way, and then we’ll stop worrying so much about testing.

Even since hepatitis C was identified, there have been cases of cryptogenic cirrhosis, fulminant hepatitis, and hepatitis-associated aplastic anemia that aren’t explained. None of the agents so far has provided an explanation, including hepatitis G, hepatitis GBV-C, TTv, and SEN. I wonder whether these illnesses represent cryptogenic forms of known agents, nonviral toxic effects, or autoimmune diseases. Most of the time, with fulminant hepatitis, you can’t identify an infectious agent. I think those cases are mostly due to hepatotoxicity rather than viruses, but I don’t know for sure.

A Closer Look at the Hepatitis C Virus

DR. MADDREY: Where do you think HCV came from?

DR. ALTER: Nobody knows where it came from. Hepatitis was described by Hippocrates, and there were epidemics of jaundice in ancient Greece and in the Bible, but those were probably hepatitis A. Serum hepatitis was first reported in the 1850s in Germany among Bremen shipyard workers. These workers were vaccinated with smallpox vaccine that had been diluted with human lymph. In 1942, yellow fever vaccine stabilized with human serum may have infected about 333,000 US Army personnel with hepatitis B.

Hepatitis C is a largely asymptomatic disease, so you can’t pin down when it first occurred. We’ve recently done a viral genetics study with Yasuhito Tanaka, MD, who is visiting my lab. Dr. Tanaka, using molecular clocking techniques and our stored post-transfusion samples, predicted that HCV genotype 1 emerged in the United States around 1910, and in Japan about 30 years earlier. However, 1910 isn’t when hepatitis C first appeared—it’s when genotype 1 diverged from some common ancestor. So it was probably around at least since then.

In the United States, hepatitis C didn’t begin to spread widely until the late 1960s and early 1970s, during Vietnam and at a time when the rate of injection drug use was high. In Japan, it spread in the 1930s and early 1940s, when it is believed that Japanese soldiers used amphetamines as a stimulant before going to battle, first in China, and then in World War II. So, at least one of the ways it was spread was by shared amphetamine use, although it was probably also spread through immunizations. The Japanese have always maintained that they have a higher rate of HCC [hepatocellular carcinoma] because hepatitis C was introduced and spread at an earlier time there,
and that the United States will see a similar increased incidence in the next 2 to 3 decades. Based on these molecular clocking studies, this may be true. In fact, our rates of HCC are already going up.

Prospects for an HCV Vaccine

DR. MADDREY: You’ve worked with Dr. Purcell and Dr. Houghton, whose laboratories are working on HCV vaccines. What are the prospects for an HCV vaccine and what are the barriers?

DR. ALTER: One clear barrier to development of a vaccine is that this virus is so diverse. There are variations by single or double nucleotide changes in everybody. Each person has a swarm of hepatitis C viruses, called quasispecies, so no one is infected with one virus. The evolution of quasispecies in a single patient is enormous. Within 16 weeks, 20 to 30 new strains develop. Beyond that, there are also large variations in the virus known as subtypes or genotypes that are 30% to 40% different from each other.

DR. MADDREY: Are you hopeful for a vaccine?

DR. ALTER: Yes, I’m hopeful. We now know that spontaneous recovery occurs in about 20% to 25% of adults in the first year of infection—and in maybe 45% of infected children. This shows that there is a natural mechanism to recover from hepatitis C, unlike with HIV. Also, HCV is an RNA virus, so it doesn’t integrate into host DNA. These things make me hopeful that we will develop a vaccine. It may not be a sterilizing vaccine or a totally preventive one, but I think a therapeutic vaccine, at least, is probable.

DR. MADDREY: Frank Chisari, MD, showed beautifully that if you can suppress hepatitis B long enough, you can do some good things to the lymphocytes. I think the same thing could happen with hepatitis C. We really can do a reasonably good job of treating many patients now, since the majority achieve sustained response to peginterferon/ribavirin. “Partial responders” is a term we’re bringing back for many of the remaining patients, if they’ve had a substantial reduction in viral load. Such patients might be candidates for a vaccine that could augment a response. What do you think of that approach?

DR. ALTER: I think that’s the way to go. I’m into this cancer model in which you use immunotherapy in addition to chemotherapy. I think you’re going to need the antiviral agents, and then an immune kick to bring it the rest of the way. DNA vaccines are being looked at now as one way to stimulate T-cell responses.

The Future of Hepatitis C Treatment

DR. MADDREY: We’ve come a long way with peginterferon/ribavirin. What do you think is next? Do you think it’s going to be an immunologic therapy, or do you think that the next drugs that will make a difference will affect some part of the virus, such as an inhibitor of polymerase, protease, or helicase?

DR. ALTER: I think we have to use the HIV model that you’ve worked with Dr. Purcell and Dr. Houghton. To me, the peginterferon/ribavirin combination. Immunotherapy, which will take much longer to develop, will probably be added later.

DR. MADDREY: Dr. Alter, many thanks. We all admire and appreciate your considerable contributions.

REFERENCES

Hepatitis C virus (HCV) is the most common chronic RNA virus affecting humans, with about 170 million infected people worldwide.\(^1\) In the United States, HCV infection accounted for 10,000 to 20,000 deaths per year in 1999, according to estimates from death certificates.\(^2\) Knowledge of HCV virology has increased in recent years, leading to better understanding of current treatment effects and identification of targets for future therapies.

**Life Cycle and Replication**

HCV replicates at an extremely rapid rate: approximately \(10^{11}\) to \(10^{12}\) virions/d. The mechanisms of HCV binding and entry into the cell remain poorly understood but appear to involve the low-density lipoprotein receptor, and possibly the nearly ubiquitous transmembrane protein CD81.\(^3\)-\(^8\) The single-stranded RNA genome of approximately 9600 nucleotides is released into the cell.\(^9\) Viral gene expression is the first step in the intracellular HCV life cycle, and unlike with HIV, it is believed to take place outside the cell nucleus. During this step, the genome is translated into a polyprotein of about 3000 amino acids, including core and envelope proteins, as well as nonstructural proteins involved in viral protein processing and replication, virion assembly, and release.\(^9\) (See Fig. 2.1.)

Proteases cleave the polyprotein into its separate protein components, including an RNA-dependent RNA-polymerase (RdRp). This enzyme makes negative-strand copies of the genome, from which positive-strand copies are again made. The RdRp is error-prone, and incorporates about one error per genome per replication cycle. In an HCV-infected cell, these errors accumulate rapidly, since the RdRp is involved in producing both the negative and positive strands of the HCV RNA. This genomic instability results in the development of a quasispecies—a collection of genetically distinct but related variants—in each infected person. The quasispecies may be dominated by a master sequence that is more fit than the others, whereas less-fit variants most commonly are genetic “dead ends.” However, shifts in selection pressure can change this, resulting in a rapid shift to a new master sequence. As a result, the diversity and pace of change of the quasispecies may be an indicator of pressure applied on the virus by the host.\(^10\)-\(^12\)

Globally, HCV is even more genetically diverse than HIV. This diversity is not evenly distributed across the genome, but rather demonstrates regions of varying evolutionary constraint, which are remarkably consistent among the six major genotypes of HCV (Fig. 2.2). Therefore, this sequence variation is the product of both random mutation and specific selection.

**Latency Versus Eradication**

HCV, with its inherently unstable RNA genome, has no mechanism for virologic latency.\(^13\) It prefersentially infects hepatocytes, which have a life span limited to 6 to 12 months, and therefore the affected cell population tends to die off. In contrast, HIV does have a mechanism for virologic latency, as it primarily infects CD4 cells, which can live for many years, harboring the HIV genome in a stable, integrated DNA form.\(^14\) This provides a reservoir for delayed emergence of highly fit wild-type or drug-resistant variants, even years after their initial genesis. In the absence of this virologic latency, HCV can be eradicated from many persons after prolonged pharmacologic suppression of HCV replication.\(^15\)

HCV has also been detected at low levels in phagocytic cells, but this may represent ingestion of HCV rather than true infection with replication.

**Dynamics of Viremia and Therapeutic Response**

HCV dynamics during interferon-based treatment are complex. About 8 hours after the first dose of therapy, HCV RNA levels begin to decline in virtually all patients. This decline continues in two distinct phases. Depending on the HCV genotype, the first phase is
characterized by a steep, dose-dependent decrease in HCV RNA level, which is observed in nearly all treated patients. This is followed by a second phase, during which the rate of decline varies considerably from one patient to another. Some patients quickly eradicate the virus, others take longer, and still others do not show a continued decline and are ultimately treatment non-responders. It is believed that the first phase represents inhibition of viral replication by interferon and that the second phase is due to death of infected cells. Exposure to anti-HCV therapy (including monotherapy) does not appear to select for treatment-resistant mutations, unlike with HIV therapy. Sustained virologic response (SVR), defined as lack of detectable viremia 6 months following completion of therapy, has become the primary therapeutic endpoint in hepatitis C management. Because HCV RNA is occasionally present at a level below the assay lower limits of detection, two measurements should be made to confirm an SVR. Retrospective analyses of data from large trials have indicated that early virologic response (EVR) to interferon-based therapy is strongly linked to SVR; specifically, SVR is highly unlikely if 12 weeks of treatment with peginterferon/ribavirin did not result in a loss of detectable viremia or a decrease by more than 2 log in the level of viremia (see The Clinician’s Companion VI, Part 2).

Conclusions

Understanding of HCV replication, life cycle, and dynamics during treatment has increased in recent years, leading to new targets for drug development (see Chapter VIII). Error-prone replication and rapid viral turnover result in considerable genomic diversity (a quasispecies) in each HCV-infected person. Fortunately, HCV has no known mechanism for virologic latency. As a result, eradication of HCV infection is possible with prolonged pharmacologic suppression of replication, and is achieved in most patients with currently available therapies. While further refinement of such criteria is warranted, EVR has the potential to be a useful tool in early decisions regarding continuation of therapy.

REFERENCES

III.
IMPACT OF HIV ON THE NATURAL HISTORY OF HEPATITIS C
Barbara H. McGovern, MD

Now that patients with HIV are living longer, there is a new focus on coinfection with hepatitis C virus (HCV) in this population. Due to shared routes of transmission, HIV/HCV coinfection is common, affecting an estimated 100,000 to 400,000 persons in the United States.1 HIV has an important impact on hepatitis C, since it affects diagnosis, levels of viremia, and the natural history.

Effects of HIV Coinfection on Diagnosis and HCV Viremia

HIV infection can complicate the diagnosis of hepatitis C. Approximately 5% of patients with severe immunosuppression have false-negative HCV antibody results when their sera are analyzed with enzyme-linked immunosorbent assay (ELISA).2,3 Thus, confirmatory HCV RNA testing is recommended for high-risk patients with a negative ELISA result.

Levels of HCV RNA rise in the setting of acute HIV seroconversion and increase over time, whereas in monoinfected patients, HCV RNA levels tend to remain relatively stable.4 Furthermore, some studies have shown that HCV RNA levels increase after the initiation of antiretroviral therapy.5,6 Although the level of viremia has not been correlated with an increased risk of liver disease, it is important prognostically, since high viral load is associated with a decreased likelihood of response to treatment.7,8

Effects of HIV Coinfection on Natural History of Hepatitis C

HIV infection modifies the natural history of chronic HCV infection. The risk of chronicity of HCV infection appears to be increased in a setting of HIV infection.3,9,10 One study found the prevalence of viremia to be 76% in HCV-monoinfected patients compared with 91% in HIV/HCV coinfected patients.11

Patients with HIV/HCV coinfection have an increased prevalence of fibrosis and higher necro-inflammatory scores compared with HCV-monoinfected patients, even when matched for other factors predictive of fibrosis, such as age, gender, and history of alcohol use.11,12 Moreover, several studies suggest that HIV infection accelerates the progression from chronic active hepatitis to cirrhosis and end-stage liver disease (ESLD). This was first observed in 1989 when three patients who received blood transfusions in the 1980s went on to develop cirrhosis within 3 years of exposure.13

Rapidly progressive disease and death from ESLD in the setting of HIV/HCV coinfection have been well described in the hemophiliac population.14,15 In 1997, Darby and colleagues16 performed a retrospective analysis of all deaths from ESLD in a United Kingdom registry of hemophiliacs and compared the observed and expected number of deaths in an age-matched population of men. The ratio of observed to expected ESLD deaths was 94-fold higher in HIV/HCV coinfected patients than in the general population. Lesens and colleagues17 demonstrated that the risk of progressive liver disease was higher among patients with both HIV and HCV infection than in HCV-monoinfected patients (odds ratio, 7.4; 95% confidence interval, 2.2–25.5).

Morbidity and mortality from ESLD have also been studied in populations of injection drug users. In a retrospective study of all causes of mortality in patients with HIV infection in 1991, 1996, and 1998, at a Massachusetts hospital, ESLD was found to be the leading cause of death in the 1998 cohort (Fig. 3.1).19

A study of patients at a Houston Veterans Affairs Medical Center found that HIV/HCV-coinfected patients had a similar overall mortality rate, but a higher rate of decompensated liver disease and death due to liver disease compared with persons infected with either virus alone (Table 3.1).20 Access to liver transplantation is also very limited to few sites in the setting of clinical trials.

A recent meta-analysis of eight studies found that the pooled relative risk (RR) for cirrhosis was 2.07 (95% confidence interval [CI], 1.40–3.07), and the RR for decompensated liver disease was 6.14 (95% CI, 2.86–13.20) among HIV/HCV coinfected patients, compared with those who have HCV infection alone.21 A retrospective study found that a history of

![Figure 3.1. Increasing Mortality from ESLD in Patients with HIV.](image)
Survey Findings

The Clinician’s Companion VI survey respondents agreed that HIV/HCV coinfected patients have a higher risk of morbidity related to liver disease, a greater risk of chronic disease, a faster rate of progression to cirrhosis, and a higher risk of mortality from ESLD compared with HIV alone (ratings 4.5–4.6 on a scale of 1 = strongly disagree to 5 = strongly agree). Survey respondents also indicated that they do not avoid treatment of HCV infection in these patients and are generally no less likely to use either peginterferon or ribavirin. In fact, about half said that they manage HCV infection in HIV-coinfected patients no differently from those without HIV infection. Others said they are more likely to treat HCV infection in an HIV-coinfected patient, monitor more aggressively, use growth factors or reduced doses of anti-HCV drugs, refer to or collaborate with an infectious disease specialist, enroll the patient in a clinical trial, and to consider the status of the patient’s HIV infection and antiretroviral drugs.

Conclusions

The Infectious Diseases Society of America and the US Public Health Service jointly recommended that all patients with HIV should have hepatitis C antibody testing. The National Institutes of Health 2002 Consensus Conference on Hepatitis C concurred in its final statement. A trend toward increasing morbidity and mortality from HCV coinfection has occurred in the setting of dramatic declines in mortality from opportunistic diseases in patients with HIV infection. Patients with HIV/HCV coinfection appear to have an accelerated HCV disease course, resulting in an increased risk of cirrhosis, hepatic decompensation, and death compared with persons with HCV infection alone. Moreover, access to liver transplants is generally limited for patients with HIV infection. Early diagnosis and treatment of hepatitis C should be considered, since antiviral therapy for hepatitis C is potentially curative and has the potential to greatly reduce the risk of HCV-related morbidity and mortality in the HIV population.

### Table 3.1. Morbidity and Mortality in HIV/HCV Patients

<table>
<thead>
<tr>
<th>End Events</th>
<th>HIV/HCV Coinfection (n = 166)</th>
<th>HIV Infection Alone (n = 263)</th>
<th>HCV Infection Alone (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decompensated liver disease*</td>
<td>14 (8.4%)</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Total number of deaths†</td>
<td>19 (11.6%)</td>
<td>18 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>Liver disease–related deaths, n/N (%)‡</td>
<td>9/19 (47%)</td>
<td>0/18 (0%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Statistically significant differences between HIV/HCV and HIV alone groups (P < .05).
†Statistically significant differences only between HIV/HCV and HIV alone groups (P ≤ .02).
‡Adapted with permission from Monga H, Rodriguez-Barradas MC, Breaux K, et al. Hepatitis C virus infection–related morbidity and mortality among patients with human immunodeficiency virus infection. Clin Infect Dis. 2001;33:240-247. Published by the University of Chicago. © 2001 by the Infectious Diseases Society of America. All rights reserved.

References

PART 5: RECENT INSIGHTS INTO HCV VIROLOGY AND TREATMENT OF CHRONIC HEPATITIS C

NIH DRAFT CONSENSUS STATEMENT ON HEPATITIS C: CONCLUSIONS AND CONTROVERSIES

The Clinician’s Companion VI Development Meeting was held less than 2 weeks after the 2002 National Institutes of Health (NIH) Consensus Development Conference on the Management of Hepatitis C. A special Clinician’s Companion VI panel convened to discuss selected issues addressed by the 2002 Consensus Statement released at the conclusion of the Consensus Development Conference.1 Discussion, repeated here, focused primarily on the conference’s conclusions with regard to diagnostic testing for hepatitis C virus (HCV) infection, and treatment of those with acute infection and substance abusers. Other issues addressed by the NIH Consensus Statement are discussed elsewhere throughout The Clinician’s Companion VI.

Is There Still a Role for RIBA?

According to the NIH Draft Consensus Statement,1 “The very high sensitivity and specificity of the third-generation EIA [enzyme immunoassays] (sensitivity greater than 99%, specificity 99%) obviate the need for a confirmatory RIBA [recombinant immunoblot assay] in the diagnosis of individual patients, particularly those with risk factors for HCV.” The Draft Consensus Statement also said that “RIBA remains a useful supplemental assay in the setting of large-scale HCV screening of blood products.”2 (This was subsequently replaced in the Final Consensus Statement with the observation that “the immunoblot assay is still useful as a supplemental assay for persons screened in nonclinical settings and in persons with a positive EIA who test negative for HCV RNA.”3)

Dr. Mark Sulkowski commented, “The NIH Statement limited RIBA testing to blood banks, and nonclinical settings, which I think is the appropriate use for that test. The primary limitations of the RIBA are that it tests for many of the same antibodies as the EIA. Furthermore, the RIBA is expensive, and unlike the HCV RNA test, it doesn’t tell you whether the patient has active infection. Consequently, in order to provide appropriate medical care, an HCV RNA test is still necessary even after a positive RIBA. Thus, RIBA is neither efficient nor cost-effective in clinical settings.”

Is Confirmatory HCV RNA Testing Always Necessary for Diagnosis?

The NIH Consensus Statement says, “Acute or chronic HCV infection in a patient with a positive EIA test should be confirmed by a qualitative HCV RNA assay with a lower limit of detection of 50 IU/mL or less (approximately 100 viral genes/mL).”4,5 The NIH Final
Consensus Statement adds that “confirmation may be unnecessary in a patient who has evidence of liver disease and obvious risk factors for HCV.” The panel and a majority of contributors argued the necessity of confirmatory testing in all EIA-positive patients for the following reasons:

- It is necessary to confirm chronic infection, since most patients who have cleared acute infection will test positive for HCV antibodies on EIA. This will allow patients who do not have active infection to avoid unnecessary invasive testing (liver biopsy) and treatment.
- It will identify patients who require further workup for other causes of ALT elevation, in the absence of chronic HCV infection.
- Even if treatment is contraindicated, knowledge of whether the patient has chronic infection will determine the need for future monitoring and follow-up.

Furthermore, Dr. Ian Williams, from the Centers for Disease Control and Prevention, noted that the sensitivity of EIA testing is a lot lower when used to screen low-risk populations. Confirmatory testing is especially important in such cases.

With regard to quantitative HCV RNA testing, Dr. Willis Maddrey, co-chair of The Clinician’s Companion VI, pointed out the need for standardized assays that report HCV RNA levels in international units. He also cited the need for assays with a higher upper limit of detection in light of the move to assess virologic response at week 12 according to whether there has been at least a 2-log decrease in HCV RNA level.

**Treatment of Acute Hepatitis C**

Hepatitis C is rarely recognized in the acute stage, which has made collection of data on early treatment challenging. The final NIH statement concluded, “High SVR rates (83% to 100%) have been reported by small uncontrolled trials with interferon monotherapy. Accordingly, treatment of persons with acute hepatitis C is warranted, but the timing of therapy and the type of regimen to use remains to be determined from future trials.” The statement also reports, “Delays in treatment for 2 to 3 months seem reasonable to identify cases that spontaneously resolve.”

According to Dr. Maddrey, there is general agreement among experts on hepatitis C that acute HCV infection should be treated. However, the optimal regimen and timing of treatment have not been determined due to the difficulty in identifying enough patients with acute infection for prospective studies. In a German study, 44 patients with acute hepatitis C were treated with 5 mIU interferon alfa-2b daily for 4 weeks and then TIW for another 20 weeks. Forty-three patients (98%) had undetectable HCV RNA and normal ALT levels at the end of therapy and 24 weeks later.

Dr. Sulkowski said, “It is important for all healthcare settings to have a mechanism in place to diagnose acute hepatitis C among exposed healthcare workers. The standard screening of hepatitis C antibody at 6 months isn’t adequate any more.” If a patient is HCV RNA positive at 4 weeks, persistent viremia needs to be confirmed on at least one other occasion, according to Dr. Sulkowski. “We need to be careful in interpreting HCV RNA results in the setting of acute exposure,” he said. False-positive PCR results do occur in this context, and clinicians must be aware that acutely infected patients can have transiently undetectable HCV RNA. He also pointed out that many of the patients in the German study were symptomatic, and that it is not clear whether the data apply to patients who are asymptomatic.

The 2002 NIH Consensus Statement’s suggestion that it might be reasonable to wait 2 to 3 months before treating acute hepatitis C was considered controversial. Many of the panelists agreed that such a delay is reasonable. “In my view, you have the luxury to wait a few months to see if the acutely infected patients clear HCV RNA on their own,” said Dr. Sulkowski. He pointed out that the average interval between infection and treatment was 89 days in the German study. On the other hand, he said, the patient should be informed of the potential benefits and risks of treatment and allowed to participate in the decision regarding whether and when to receive treatment. Dr. Bruce Bacon and Dr. Robert Carithers also said they tend to wait 3 to 6 months before treating acute hepatitis C and do not believe that such a delay affects treatment response. All of the panel members emphasized the need to ensure follow-up of these patients so that they are offered treatment after a reasonable time period if they are still viremic. Long-term posttreatment follow-up is also important: Dr. Carithers reported that he has two patients with acute infection who cleared the virus with treatment yet subsequently developed chronic infection.

Dr. Harvey Alter objected to the practice of delaying treatment for several months in patients with acute infection. He argued that HCV-exposed persons, particularly healthcare personnel exposed through needle sticks, were not going to tolerate such a long delay. Dr. Maddrey agreed with this assessment. Moreover, Dr. William Cassidy, a Clinician’s Companion VI contributor, questioned the utility of delaying treatment in African Americans given that they reportedly have a lower rate of spontaneous HCV clearance.

**Treatment of Substance Abusers**

Persons actively abusing injection drugs or alcohol have largely been excluded from clinical trials of hepatitis C treatment. The 2002 NIH Draft Consensus Statement argued, “Recent, albeit limited, experience has demonstrated the feasibility and effectiveness of treating chronic hepatitis C in people who use illicit injection drugs. . . . HCV therapy has been successful
even when the patients have not abstained from continued drug or alcohol use or are on daily methadone.” The final draft retained this statement and a recommendation that “treatment of active injection drug use be considered on a case-by-case basis, and that active injection drug use in and of itself not be used to exclude such patients from antiviral therapy.” Furthermore, the NIH statement notes, “A history of alcohol abuse is not a contraindication to therapy. . . .”

One of the contributors from the Chicago area stated, “We have a large number of substance abuse patients on methadone maintenance. They seem to be highly motivated and are often successfully treated for HCV infection. I see no reason not to treat them aggressively.” This person also called for the inclusion of such patients in general clinical trials on HCV infection.

“I’ve treated several of these patients and I agree with you that they are very motivated and have good outcomes,” said Dr. Bacon.

Another contributor emphasized, “One of the messages that came through [at the NIH meeting] was the need to treat the whole patient. The first and foremost thing is to treat the drug addiction effectively and aggressively, deal with the alcohol abuse and drug addiction, and select those individuals who are compliant with those various regimens as potential candidates for [anti-HCV] therapy.”

“These are very heterogeneous groups,” noted another contributor. He pointed out that methadone maintenance patients “run the full spectrum with respect to candidacy for anti-HCV treatment. So, the mandate is to look at those patients as candidates, which is not the same as saying they should all be treated.”

Survey Findings

On the written survey, contributors to *The Clinician’s Companion VI* were asked to rate their level of agreement with various conclusions from the 2002 NIH Draft Consensus Statement. The results are shown in Figure 4.1. In addition, survey respondents were asked whether the NIH consensus guidelines would change their clinical practice. Fifty-five percent said “no,” 26% said “maybe,” and 19% said “yes.”

Conclusions

Dr. Maddrey concluded *The Clinician’s Companion VI* panel discussion saying, “The NIH consensus statement greatly broadened the horizon, and removed many of the restrictions to treatment, as well as bringing many issues to the fore. Therefore, it should be viewed as an overall positive and hopeful document. One of the reasons for this positivity is that the results of treatment are getting better. When treatment outcomes improve, we will continue to be progressively more liberal in our approach to treatment.”

Figure 4.1. Survey Findings: Agreement with NIH Consensus Statement

How strongly do you agree or disagree with the following statements from the 2002 NIH Draft Consensus Statement?

A. Overall, pegylated interferon plus ribavirin is more effective than standard interferon-ribavirin combination or pegylated interferon alone.

B. Liver biopsy yields information on fibrosis and histology assessment that is not obtainable by any other means.

C. A follow-up qualitative HCV RNA should be performed to confirm the absence of HCV replication in patients with one negative result after positive EIA.

D. SVR rates were similar with both forms of pegylated interferon (alfa-2a and alfa-2b) when used in combination with ribavirin.

E. All patients with chronic hepatitis C are potential candidates for antiviral therapy.

F. Needle and syringe exchange programs and comprehensive risk-modifying educational programs are likely to be useful for decreasing HCV transmission.

G. Treatment of HCV should be performed in conjunction with efforts to treat alcohol abuse or dependence.

H. Efforts should be made to increase availability of the best current treatment to patients who have been ineligible for trials because of injection drug use, alcohol abuse, age, and co-morbid medical and neuropsychiatric conditions.

I. The risk of progressive disease at 20 years is now considered to be closer to the estimates from prospective studies (ie, 7%-16%).

J. Adult or pediatric patients with persistently normal or slightly elevated ALT and minimal or no fibrosis on liver biopsy may be reassured of a favorable prognosis and decide to defer antiviral therapy.

K. HCV therapy has been successful in IDUs even when the patients have not been abstinent from continued drug use or are on daily methadone.

*These statements were substantively revised on the final draft.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
<td>4.6</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
<td></td>
<td>4.3</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>G</td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td>J</td>
<td></td>
<td></td>
<td></td>
<td>3.4</td>
</tr>
<tr>
<td>K</td>
<td></td>
<td></td>
<td></td>
<td>3.2</td>
</tr>
</tbody>
</table>

N = 188

Strongly Disagree Agree Strongly Agree
A NEW LOOK AT A LA CARTE THERAPY

Thierry M. Poynard, MD, PhD

An individualized approach to management of hepatitis C virus (HCV) infection using interferon/ribavirin was published in 2000.1 This approach, known as à la carte therapy, involved using the number of prognostic factors to determine the optimal duration of treatment in patients who showed a virologic response at week 24. Since that publication, pegylated interferon has replaced standard interferon as the standard of care for treatment of HCV infection. In addition, new data have become available on factors that predict response to peginterferon/ribavirin, and quantitative HCV RNA assays have allowed for earlier assessments of response. The original recommendations are updated here.

The Original à la Carte Regimen

In studies of standard interferon/ribavirin for treatment of chronic HCV infection, factors that best predicted sustained virologic response (SVR) included genotype 2 or 3 infection and low viral load (ie, <1 million IU/mL).1-3 Mild disease (no fibrosis or only portal fibrosis), age <40 years, and female gender were also independently associated with SVR, but were less predictive than genotype and viral load.1-3

In the 2000 à la carte publication, Poynard et al1 analyzed data from 1744 treatment-naïve patients who were included in trials of 24 or 48 weeks of interferon/ribavirin. They recommended interferon/ribavirin at standard doses as first-line treatment over interferon monotherapy. In addition, they showed that patients with four or five favorable factors responded equally well to 24 or 48 weeks of interferon/ribavirin, whereas those with fewer factors showed better rates of response with 48 weeks of treatment.

Quantitative viral load assessment at 4 or 12 weeks was not predictive enough to be included in those recommendations. Moreover, Poynard et al1 showed that 10% of patients who still had detectable HCV RNA at week 12 would achieve a sustained response with continued therapy. This confirmed the common practice of continuing interferon/ribavirin until at least 24 weeks before discontinuing treatment as a result of nonresponse.

à la Carte Therapy in 2002

Peginterferon/ribavirin has been shown to be more effective than interferon/ribavirin,4,5 and has since become the standard of care. In a multivariate analysis of 240 patients treated with 48 weeks of peginterferon alfa-2b 1.5 µg/kg QW and ribavirin 800 mg/d, the following four factors were identified as predictors of SVR (Poynard T, unpublished data, 2002):

1. Genotype 2 or 3 infection (odds ratio [OR] = 0.11; 95% confidence interval [CI], 0.05–0.26; P < .001)
2. Fibrosis F0–F1, as determined by Fibrotest results (OR = 0.33; 95% CI, 0.16–0.66; P < .001). The Fibrotest, developed by Poynard and colleagues,6,7 consists of a combination of five biochemical markers for fibrosis used as an alternative to liver biopsy in France and other European countries. Degree of fibrosis was less predictive of SVR when determined by biopsy.
3. Low viral load; ie, <1.3 million IU/mL (OR = 0.36; 95% CI, 0.20–0.66; P < .001)
4. Body mass index [BMI] <27 (OR = 0.56; 95% CI, 0.30–1.03; P = .06)

No association was found between SVR and either gender or age. Viral load at 12 weeks was highly predictive of SVR, with a negative predictive value of 100% in patients with a <2-log reduction in serum HCV RNA. Thus, using quantitative HCV RNA testing, it is now possible to determine response as early as week 12, as discussed in Part 2 of this Clinician’s Companion series.

The decision to discontinue treatment in patients with nonresponse should take into account histologic benefits of treatment, as well as virologic endpoints. Poynard et al6 also conducted a pooled analysis of data on fibrosis from 3010 patients who received...
initial treatment for HCV infection, as well as paired liver biopsies, in four randomized trials. Ten different regimens were used in these studies, ranging from 24 weeks of interferon monotherapy to peginterferon alfa-2b/ribavirin combination therapy in various doses. The pooled analysis indicated that each advance in the treatment of HCV infection over the past decade or so has been associated with greater reductions in histologic activity grade (Fig. 5.1A) and fibrosis (Fig. 5.1B) compared with less effective therapies. Patients who achieved a sustained response to treatment had the greatest reduction in fibrosis: The rate of fibrosis progression per year decreased from a median of 0.139 fibrosis units pretreatment to –0.591 posttreatment. However, even treatment nonresponders experienced histologic benefit from treatment: The rate of fibrosis progression per year decreased from 0.135 pretreatment to 0 posttreatment. Moreover, a reversal of cirrhosis was observed in 49% (75/153) of patients with histologically confirmed cirrhosis at baseline.

Logistic regression analysis has shown a relationship between dose per kg of body weight and SVR, with higher SVR rates among those who received >10.6 mg/kg in the registration trial. Weight-based ribavirin dosing is being studied in ongoing prospective trials and currently constitutes off-label use; the US Food and Drug Administration (FDA) has approved a fixed dose of 800 mg/d ribavirin in combination with peginterferon alfa-2b 1.5 µg/kg.

Quantitative HCV RNA measurement should be performed at 12 weeks. Patients with undetectable HCV RNA or a ≥2-log decrease at week 12 should continue treatment. At 24 weeks of treatment, if HCV RNA is then negative, treatment should be considered completed for those who had three or four of the four favorable predictive factors listed above. Treatment should be continued for a total of 48 weeks for those with less than three favorable factors. Patients with a <2-log decrease in HCV RNA level at week 12 or any detectable HCV RNA at week 24 should stop treatment, but maintenance therapy with interferon or peginterferon should be considered, particularly if fibrosis is advanced or progression has been rapid.

Peginterferon alfa-2a/Ribavirin

Peginterferon alfa-2a was approved in October 2002 by the FDA for use as monotherapy. Use of ribavirin in combination with peginterferon alfa-2a currently constitutes off-label use of FDA-approved products. A recently published phase III study reported an SVR rate of 56% in treatment-naive patients treated with peginterferon alfa-2a 180 µg QW plus ribavirin 1000 mg/d for patients ≤75 kg or 1200 mg/d for patients ≥75 kg. Factors that independently predicted SVR in multivariate analysis included HCV genotype other than 1 (OR 3.25, 95% CI 2.09–5.12; P < .001), age ≥40 years (OR 2.60, 95% CI 1.72–3.95; P < .001), and body weight ≥75 kg (OR 1.91, 95% CI 1.27–2.89; P = .002). The ability to predict response at week 12 based on quantitative HCV RNA appears to be true for peginterferon alfa-2a/ribavirin (see *Clinician’s Companion*).
VI, Part 2). In a published study of peginterferon alfa-2a monotherapy, SVR was 39%, and predictors of response included younger age, smaller body-surface area, lower HCV RNA level, higher ALT quotient, absence of bridging fibrosis or cirrhosis, and HCV genotype non-1 infection.10

Survey Findings

Survey respondents were asked to rate the extent to which various prognostic factors predict response to peginterferon/ribavirin based on their own clinical experience. Using a scale of 1 = not at all predictive to 5 = highly predictive, they rated genotype 2/3 infection as most predictive of response (rating 4.8). This was followed by low baseline viral load (rating 3.8), absence of extensive fibrosis (rating 3.8), BMI (rating 3.6), age <40 years (rating 3.5), and female gender (rating 3.3). Virtually none (median 0%, mean 0.3%) of the survey respondents currently uses biochemical markers, such as the Fibrotest to estimate the extent of fibrosis.

Respondents were also asked how long they would treat various HCV-infected patients. Their responses (Table 5.1) indicate that most would treat genotype 1–infected patients for 48 weeks, irrespective of the number of other predictive factors. However, respondents generally do seem to take other predictive factors into account when deciding how long to treat patients with non-1 genotypes.

Table 5.1. Survey Findings: How Predictive Factors Affect Treatment Duration.

<table>
<thead>
<tr>
<th>Patient Description</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 Weeks</td>
</tr>
<tr>
<td>A) Genotype 2, F0, low viral load, BMI &lt;27</td>
<td>95%</td>
</tr>
<tr>
<td>B) Genotype 2, F4, low viral load, BMI &lt;27</td>
<td>44%</td>
</tr>
<tr>
<td>C) Genotype 2, F4, high viral load, BMI &gt;27</td>
<td>26%</td>
</tr>
<tr>
<td>D) Genotype 1, F4, high viral load, BMI &gt;27</td>
<td>0%</td>
</tr>
<tr>
<td>E) Genotype 1, F4, low viral load, BMI &lt;27</td>
<td>1%</td>
</tr>
<tr>
<td>F) Genotype 1, F1, low viral load, and BMI &lt;27</td>
<td>4%</td>
</tr>
</tbody>
</table>

Conclusions

Peginterferon/ribavirin is the current standard of care for HCV-infected patients, offering the greatest opportunity for viral eradication and histologic benefit. The duration of treatment should be individualized based on indicators of response at weeks 12 and 24, and predictive factors, such as genotype, viral load, degree of fibrosis, and BMI. Maintenance therapy with peginterferon or interferon should be considered for nonresponders.

REFERENCES

Outcomes for patients with hepatitis C may be limited by treatment tolerability. Adverse events occur in nearly all patients taking peginterferon/ribavirin combination therapy, and psychiatric and hematologic side effects are among the primary reasons for treatment discontinuation and dose reduction, respectively.1 Aggressive management of these side effects may improve outcomes by helping patients remain on therapeutic doses for a sufficient duration.

Neuropsychiatric Side Effects

Treatment with peginterferon is hampered by a high rate of behavioral side effects, especially depression, anxiety, irritability, fatigue, and cognitive dysfunction. These side effects generally appear late (after the fourth week of treatment) and worsen over time. Fortunately, recent studies demonstrate that interferon-induced psychiatric syndromes can be ameliorated by treatment with antidepressants, and may be prevented or diminished if antidepressant prophylaxis is initiated before starting peginterferon in high-risk patients.

Treatment and Prevention

Antidepressant pretreatment may be indicated for patients with current anxiety or depression at baseline, since such patients are at increased risk for neuropsychiatric side effects of peginterferon.2 If patients develop severe depression during treatment with peginterferon, it may be necessary to stop treatment until the depression is controlled. If the depression is mild to moderate, treatment with an antidepressant and careful monitoring may allow continuation of antiviral therapy. Patients should be informed that it will take 2 to 6 weeks before response to antidepressants can be expected, and 4 to 8 weeks before a full medical response (ie, remission of depressed mood and anxiety) is likely.

The antidepressant that has been best studied for the treatment of interferon-induced depression is the selective serotonin reuptake inhibitor (SSRI) paroxetine. A well-controlled, double-blind study demonstrated that paroxetine, given prior to initiation of high-dose interferon in patients with malignant melanoma, is superior to placebo in preventing the development of major depression and reducing the need for treatment discontinuation.2 A prospective study reported that 79% (11/14) of patients who developed interferon-induced depression were able to complete treatment for hepatitis C with concomitant paroxetine treatment.3 Depression scores declined significantly in all treated patients.3 Case reports and small case series also suggest efficacy for fluoxetine, sertraline, citalopram, and nefazodone.4,6

Since a variety of effective antidepressants are available, antidepressants should be selected by several criteria: drug-drug interactions, side effects, and speed of onset of action (Table 6.1). Venlafaxine, mirtazapine, bupropion, and citalopram have the least risk of drug-drug interactions. Bupropion and mirtazapine are the least likely to produce sexual side effects, and venlafaxine is one of those least likely to cause weight gain. Antidepressant treatment strategies that target both norepinephrine and serotonin (eg, venlafaxine, mirtazapine, or SSRIs plus bupropion or desipramine) may be particularly efficacious, have a more rapid onset of action, and may improve fatigue and pain.7,8 Regardless of which antidepressant is selected, a low initial dose should be used, particularly in patients with anxiety, panic, or somatic side effects. The dose may then be increased to a therapeutic dose (Table 6.1).

In patients receiving interferon, antidepressants appear to be more effective in treating depressed mood, anxiety, and cognitive complaints than in decreasing fatigue.9 Methylphenidate (5–20 mg/d), modafinil (100–400 mg/d), or bupropion (75–300 mg/d) may be of benefit in the treatment of fatigue.

A number of case reports describe manic behavior (including irritability) induced by interferon alfa.12,16 Interferon-induced mania may be worsened by antidepressants, which also are capable of inducing mania.17 Mania is an emergency that requires immediate discontinuation of both interferon alfa and antidepressants. Acute mania is treated with neuroleptics, mood stabilizers, or benzodiazepines, and psychiatric hospitalization is usually indicated.

Survey Findings

For patients with elevated Beck Depression Inventory or Neurotoxicity Rating Scale scores, survey respondents favored pretreatment with an antidepressant and delay of antiviral therapy until depression is stable (rating 4.4 on a scale of 1 = very unlikely course of action to 5 = very likely course of action). They also often refer such patients for psychiatric evaluation or consultation prior to treating hepatitis C virus (HCV) infection (rating 3.9). Survey respondents most frequently prescribe SSRIs over other antidepressants for patients who develop depression during treatment with peginterferon/ribavirin.
Hematologic Side Effects

Use of hematologic growth factors (eg, epoetin, and granulocyte colony-stimulating factor [G-CSF]) is not specifically approved by the US Food and Drug Administration for patients with HCV infection, but is an increasingly common practice to reduce the need for dose reduction or treatment discontinuation due to hematologic side effects. This practice was recently recognized in the National Institutes of Health Consensus Statement, which said that growth factors “may be useful to reduce symptoms and maintain adherence.” However, the statement added that more study is needed to determine effects on SVR rate and optimal doses.

Hemolytic Anemia

Hemoglobin usually declines 2 to 4 g/dL within the first 4 weeks, although the decreases can also occur later in the treatment course. In patients with normal iron stores, anemia can be treated with epoetin 40,000 U/wk by subcutaneous injection and/or ribavirin dose reduction. Ribavirin discontinuation is recommended if hemoglobin level drops to <8.5 g/dL. If erythropoietin is started before the hemoglobin drops below 12 g/dL, dose reduction or discontinuation of ribavirin can often be avoided. Treatment of ribavirin-induced anemia with epoetin has been shown to result in a greater increase in hemoglobin level compared with standard of care, which included ribavirin dose reduction (mean change, 2.9 versus 0.3 g/dL, *P < .05*). Furthermore, epoetin alfa may allow for administration of closer to recommended doses of ribavirin (926 versus 782 mg/d; *P < .05*) and improved quality of life (Fig. 6.1) in patients who develop anemia due to interferon/ribavirin therapy. There may also be a role for the use of epoetin prior to interferon/ribavirin therapy in patients who are anemic at baseline; however, this strategy has not been adequately studied to date.

Treatment of Neutropenia and Thrombocytopenia

Similarly, clinical experience has shown that the use of G-CSF (filgrastim) in patients who develop neutropenia during interferon-based therapy can maintain more-normal neutrophil counts and allow higher doses of interferon to be administered. For correction of interferon-related neutropenia, G-CSF is generally given at a dose of 300 µg administered subcutaneously once to thrice weekly and then titrated to maintain an absolute neutrophil count >750/mm³. Potential adverse reactions include skin rash, vasculitis, bone pain, myalgias, thrombocytopenia, splenomegaly, leukemoid reaction, and exacerbation of psoriasis.

---

**Table 6.1. Newer Antidepressants: Dosing and Safety.**

<table>
<thead>
<tr>
<th>Antidepressant*</th>
<th>Starting Dose (mg/d)</th>
<th>Therapeutic Dose (mg/d)</th>
<th>Side Effects</th>
<th>CYP450 Enzyme Inhibitory Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1A2</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25–50</td>
<td>50–200</td>
<td>Anxiety, GI complaints, insomnia</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10–20</td>
<td>20–80</td>
<td>sexual problems, sweating, headaches, weight gain</td>
<td>0</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100</td>
<td>100–300</td>
<td>(with long-term use)</td>
<td>0</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10–20</td>
<td>20–80</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Citalopram</td>
<td>20</td>
<td>20–60</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5</td>
<td>75–450</td>
<td>GI complaints, anxiety, sexual problems, sweating, headaches, increased BP (with &gt;150 mg/d)</td>
<td>0</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15–30</td>
<td>15–60</td>
<td>Significant weight gain, somnolence, rare agranulocytosis, no sexual side effects, sexual side effects, sleep promoting</td>
<td>0</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>50</td>
<td>300–600</td>
<td>Somnolence, nausea, dizziness, very rare fatal liver failure (1 in 300,000), low rate of sexual side effects, sleep promoting</td>
<td>0</td>
</tr>
<tr>
<td>Bupropion†</td>
<td>75</td>
<td>300–450</td>
<td>Anxiety, GI upset, potential for increased seizure risk with HIV protease inhibitors, no sexual side effects</td>
<td>0</td>
</tr>
</tbody>
</table>

*Avoid TCAs (amitriptyline, nortriptyline, desipramine, imipramine) and MAOIs, which have a high risk of lethality in overdose, which may occur as a result of interactions with other drugs. †May interact with drugs that affect CYP450 2B6.

---

**Figure 6.1. Improvements in Quality of Life: Epoetin Versus Standard of Care for Anemia.**

![Figure 6.1. Improvements in Quality of Life: Epoetin Versus Standard of Care for Anemia.](image-url)
With the exception of patients with cirrhosis, thrombocytopenia is rarely a problem in patients receiving combination therapy for HCV infection. However, some, particularly those with significant liver disease, may require dose reduction or treatment discontinuation. Interleukin-11 (IL-11) is used in cancer patients to treat thrombocytopenia and is being investigated in HCV-infected patients.

Survey Findings

Among all of their patients treated with peginterferon/ribavirin, survey respondents said they used epoetin in a mean of 12.7% (median, 10%) and G-CSF in a mean of 8.8% (median, 5%). Using a scale of 1 = never to 5 = always, they said they were most likely to use epoetin in HIV-infected patients with symptomatic anemia (rating 3.8) and high-risk patients (eg, stable cardiac disease) with hemoglobin <12 g/dL (rating 3.7). They also may use it in addition to (rating 3.5) or instead of (rating 3.4) dose reduction in patients with hemoglobin <10 g/dL.

Conclusions

Psychiatric and hematologic side effects are the most likely to interfere with treatment of hepatitis C. However, with aggressive management of these adverse effects, successful treatment outcomes are usually possible. Co-morbid psychiatric disorders and psychiatric side effects are common in HCV-infected patients, especially while on peginterferon therapy. Close mental-health follow-up and careful selection of appropriate antidepressants and other adjunctive therapies are key management strategies. For patients who develop anemia during treatment for hepatitis C, a clinical trial has shown that epoetin alfa significantly increases hemoglobin levels and allows patients to receive higher doses of ribavirin than would be possible with traditional management of anemia. Clinical experience suggests that G-CSF can be used safely and effectively to prevent dose reduction due to neutropenia.

REFERENCES

Despite high rates of sustained response to peginterferon/ribavirin (the most effective available therapy for hepatitis C), at least 45% of patients with advanced fibrosis are still virologic nonresponders. Current studies suggest a possible role for maintenance therapy in hepatitis C virus (HCV)-infected patients with advanced fibrosis or cirrhosis. Maintenance therapy can be defined as treatment that is continued regardless of the virologic or biochemical response. The goals of maintenance therapy are (1) to prevent progression of fibrosis and development of cirrhosis, and (2) to prevent liver failure and hepatocellular carcinoma (HCC).

Rationale for Maintenance Therapy

The development of cirrhosis is a critical event in the natural history of HCV infection because the predominant morbidity and mortality from this disease are related to cirrhosis complications. Decompensated liver disease and HCC are seen only in the presence of cirrhosis. Therefore, every attempt should be made to prevent cirrhosis in high-risk individuals or to delay the onset of the complications of cirrhosis.

Although the primary goal of antiviral therapy is sustained viral eradication, recent studies have elucidated that the secondary goals of preventing progressive fibrosis or liver cancer can be achieved even in nonresponders. Two large studies in Western European patients have shown a significantly decreased risk of HCC, and increased survival in cirrhotics who did not have a sustained response with interferon monotherapy. In one study, Serfaty et al actually showed a survival benefit associated with interferon in 103 cirrhosis patients. This type of secondary-response benefit from interferon monotherapy again highlights the importance of treating patients with well-compensated cirrhosis. Ikeda et al also showed a marked reduction in HCC development in patients treated with interferon, particularly those with either a complete sustained response or a partial response with normalization of alanine aminotransferase (ALT) level posttherapy.

Interferon has also been shown to have a beneficial effect on liver fibrosis. In a study of 185 interferon-treated patients and 102 HCV-infected control patients with serial liver biopsies, treated patients experienced significantly lower rates of progression after treatment versus pretreatment regardless of whether their HCV viral load had decreased. Significantly fewer treated patients compared with controls showed disease progression and significantly more showed disease regression. Modeling in this study suggested that interferon may alter the natural history of HCV infection.

In the only published, controlled trial of maintenance therapy, Shiffman et al demonstrated that continuing interferon for 2 years in nonresponders stabilized fibrosis and reduced inflammation on serial biopsies. In this study, patients who had failed to achieve a sustained virologic response to interferon/ribavirin, but who had nonetheless shown a histologic response (improvement by ≥2 points on Knodell Histologic Activity Index) were randomized to either stop therapy or receive maintenance interferon 3 mIU TIW for approximately 2 years. Among patients who were randomized to stop therapy, inflammation increased to baseline levels, whereas patients who continued on interferon as maintenance therapy experienced continued reductions in inflammation. Similar results were seen in terms of fibrosis scores, which decreased from 2.5 at baseline to 1.7 after 30 months of maintenance therapy, but rose from 2.2 at baseline to 2.4 at month 30 in the group that discontinued therapy. Limitations of this study are that patients were not selected for maintenance therapy based on degree of fibrosis and only patients who had already exhibited some histologic response to initial treatment were enrolled.

Lifestyle Modification and Adjuvant Therapy

Risk factors for progressive fibrosis include age ≥40 years at acquisition of HCV infection, presence of bridging fibrosis on biopsy, increased body weight with hepatic steatosis, excess hepatic iron, alcohol consumption >25 g/d, and immunosuppression. Simple lifestyle changes with promotion of weight loss, therapy for steatosis, cessation of alcohol consumption, and reduction of hepatic iron should be recommended to at-risk patients. Controlled studies are necessary to see if there is a long-term benefit from these therapies.

Adjuvant therapy with antifibrotics or cytoprotective agents has not been well studied in preventing HCV disease progression, but has been shown to have a role in other forms of progressive liver disease. Agents like colchicine and ursodeoxycholic acid have no direct antiviral activity, and few data are available on their role for long-term therapy in patients with cirrhosis.
and HCV infection. The antioxidant vitamin E has shown some benefit in reducing ALT levels in patients with HCV infection.8

New and Ongoing Maintenance Therapy Studies

Several studies have started to evaluate maintenance therapy with pegylated interferons, including the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) trial, which is sponsored by the National Institutes of Health, and Colchicine vs PegIntron Long-Term (COPILOT), which is sponsored by Schering Hepatitis Innovations. These studies will evaluate the effect of 4 years of treatment with a pegylated interferon on the progression of fibrosis and the development of HCC and liver decompensation. Both HALT-C and COPILOT plan to recruit large numbers of patients and measure similar endpoints.

In HALT-C, interferon nonresponders with Ishak stage 3 to 6 fibrosis are initially treated with peginterferon alfa-2a plus ribavirin for 6 months with the goal of viral eradication, and nonresponders are then randomized to long-term peginterferon alfa-2a maintenance therapy or placebo. Preliminary results from the first phase of this study are described in The Clinician’s Companion VI, Part 1. Results of the subsequent maintenance phase are not yet available.

In COPILOT, 800 patients with an Ishak fibrosis score >3, and who were nonresponders to interferon monotherapy, interferon/ribavirin, or peginterferon/ribavirin are randomized to either colchicine 0.6 mg BID or peginterferon alfa-2b 0.5 µg/kg QW for 4 years. Primary endpoints include death or transplant, variceal bleed, increase in Child-Pugh-Turcotte (CPT) score >2, and HCC. Secondary endpoints include histology, fibrosis markers, and quality of life. Currently almost 400 patients have been enrolled.

Baseline demographics on the first 296 patients are as follows: Mean age is approximately 50 years, 68% are male, 12% are African American, and 88% are infected with genotype 1. Approximately 62% have high viral load (>850,000 IU or 2 million copies/mL) as assessed by the Roche Amplicor assay. Ninety-five percent have been infected for >20 years. All of the patients have been infected for >20 years. All of the patients were previously treated with interferon/ribavirin and/or peginterferon/ribavirin, and about half were also treated with interferon monotherapy.

Preliminary data at 1 year of follow-up indicate a nonsignificant reduction in ALT level with both treatments. Colchicine has had no effect on viral load. Over the first 48 weeks, about 90% of peginterferon-treated patients have had at least a 1-log reduction in viral load (P = .06 versus baseline). There is also a trend toward a lower rate of clinical events with peginterferon (3% versus 10% with colchicine; Table 7.1). Discontinuation due to adverse effects has occurred in 11% of the colchicine group and 8% of the peginterferon group. The rate of serious adverse events is 1.4% with colchicine and 2.5% with peginterferon. Few hematologic side effects have been observed.9

### Table 7.1. COPILOT Study: Primary Endpoints

<table>
<thead>
<tr>
<th>Condition</th>
<th>Colchicine (n = 140)</th>
<th>PEG IFN alfa-2b (n = 156)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver transplant</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>2*</td>
</tr>
<tr>
<td>CPT &gt;2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Variceal bleed</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>HCC</td>
<td>1</td>
<td>2*</td>
</tr>
</tbody>
</table>

*AVA

1HCC and liver failure within 2 weeks

A third study, Evaluation of PegIntron in Control of Hepatitis C Cirrhosis (EPIC), also supported by Schering Hepatitis Innovations) is evaluating histologic and clinical endpoints in nonresponders re-treated with either peginterferon alfa-2b maintenance therapy or placebo. In addition, the Antifibrotic Efficacy of Gamma Interferon Study (AEGIS) is evaluating histologic and clinical endpoints with 1 year of interferon alfa-1b 100 or 200 µg TIW versus placebo in interferon nonresponders with Ishak scores ≥4.

Survey Findings

According to survey respondents, evidence most strongly supports the hypothesis that maintenance therapy improves histology (rating 3.9 on a scale of 1 = no evidence to 5 = very strong evidence). Respondents also believe that maintenance reduces the risk of HCC (rating 3.5), prevents hepatic decompensation (rating 3.3), and can cause regression or reversal of cirrhosis (rating 3.3). Survey respondents said that they are likely to use peginterferon maintenance therapy for peginterferon/ribavirin nonresponders with bridging fibrosis or compensated cirrhosis (Fig. 7.1). They indicated that an average of 28% of such patients in their practices have been treated with maintenance therapy. The most influential factors (scale of 1 = not influential to 5 = highly influential) in their decision to use maintenance therapy are baseline histology (rating 4.4), tolerability of previous therapy (rating 4.1), and the presence of co-morbidities.

### Figure 7.1. Survey Findings: Candidates for Maintenance Therapy

How likely are you to use peginterferon maintenance therapy for each of the following:

A. Peginterferon/ribavirin nonresponders with bridging fibrosis or compensated cirrhosis
B. No patients until more studies are completed
Conclusions

HCV-infected patients with advanced fibrosis or cirrhosis who do not achieve a sustained response to the best available therapies should be considered for maintenance therapy trials. The goal of maintenance therapy is to prevent cirrhosis and its complications. Preliminary results from the COPILOT study indicate that both colchicine and low-dose peginterferon alfa-2b are well tolerated and reduce ALT levels. Peginterferon alfa-2b maintenance therapy also reduced viral load and clinical events. Final results from the HALT-C, COPILOT, EPIC, and AEGIS studies should define the role of maintenance therapy with pegylated interferons and interferon gamma in HCV-infected patients.

REFERENCES

9. Afdhal NH, Freilich B, Block M, Levine R, Brass C. Comparison of therapy with Peg-Intron 0.5 mcg/kg versus colchicine 0.6 mg BID in 250 patients with cirrhosis and HCV: interim data from COPILOT [abstract 595]. Hepatology. 2002;36:312A.

The 2002 National Institutes of Health Consensus Statement on the Management of Hepatitis C states, “Priority should be given to developing less toxic therapies and molecular-based agents that specifically inhibit viral replication and/or translation of viral RNA.” Such a task requires a clear understanding of the viral life cycle and the pathogenesis of virus-mediated injury. Based on current understanding, specific therapeutic strategies are being developed to target critical steps in this process. Advances in interferon-based treatments and the use of new antiviral, immunomodulating, and antifibrotic agents give cause for optimism in the clinical management of hepatitis C virus (HCV) infections. In the meantime, peginterferon/ribavirin remains the best available treatment and should be considered the standard of care for treatment of chronic HCV infection.

Modified Interferons and Ribavirin

Recent efforts have been directed toward improving the efficacy and tolerability of existing treatments with the development of pegylated interferons and new derivatives of ribavirin. Peginterferon alfa-2b (PegIntron™, Schering Corporation) was approved by the US Food and Drug Administration (FDA) in January 2001 for use as monotherapy and in August 2001 for use in combination with ribavirin. Peginterferon alfa-2a (Pegasys®, Roche Pharmaceuticals) was approved by the FDA in October 2002 for use as monotherapy, and a
pegylated formulation of consensus interferon is in development at InterMune Pharmaceuticals.

Albumin-interferon alpha (Albuferon®, Human Genome Sciences), a new protein created by fusing the gene for interferon alpha with albumin, produces a protein with properties of both interferon alpha and albumin. This protein has the potential to provide a longer-acting therapeutic activity and an improved side-effect profile compared with standard interferon alpha. A phase I trial is currently underway.

Ribavirin is a nucleoside analog with many intrinsic properties that contribute to its antiviral properties. Proposed mechanisms of action include RNA mutagenic activity that increases the replication error rate and reduces viral fitness; immunomodulatory properties (enhanced Th1 response); and inhibition of host enzyme inosine 5'-monophosphate dehydrogenase. Less toxic, more potent derivatives of ribavirin are in development. An L-enantiomer of ribavirin (Levovirin®, ICN Pharmaceuticals, Inc) with similar activity but less toxicity, is in phase I studies. A prodrug of ribavirin (Viramidine®, ICN Pharmaceuticals, Inc) that is converted to ribavirin in the liver should allow for a higher therapeutic index, more favorable tissue distribution, and better safety profile than ribavirin based on preclinical studies. An investigational new drug application was filed for Viramidine in January 2002.

**Viral Life-Cycle Targets**

Since HCV must target a cell-membrane-associated receptor site (eg, low-density lipoprotein receptors) in order to enter the cell, the viral sequences that bind to these sites are potential therapeutic targets. Another alternative that may be effective in preventing hepatocyte infection is to use neutralizing antibodies that bind to circulating HCV. For example, hepatitis C immunoglobulin (Civacir®, Nabi Biopharmaceuticals) consists of polyclonal immunoglobulins enriched with high titer anti-HCV. An 18-patient phase I study of this agent is underway to see if passive transfer of hyper-immune anti-HCV immunoglobulins can prevent or curtail reinfection of newly transplanted liver grafts.

Other targets for drug development include HCV’s protease and helicase (both encoded by the NS3 gene) and RNA-dependent RNA polymerase encoded by the NS5b gene. These genes contribute to specific steps in the viral-replication cycle, and some, such as proteases in HIV infection, have been successfully targeted in other viral diseases. Small-molecule protease inhibitors inhibit hepatitis C NS3-4A protease, a chymotrypsin-like protease with a shallow substrate-binding region that is essential for viral reproduction. Vertex Pharmaceuticals, Inc, in collaboration with Eli Lilly and Company, and Boehringer Ingelheim Pharmaceuticals, Inc, have developed candidate molecules that are in preclinical and early clinical trials. Other small molecule inhibitors are being evaluated in the HCV replicon system.

Antisense approaches rely on nucleic acids designed to specifically bind RNA, forming RNA-DNA (antisense DNA) or RNA-RNA complexes (antisense RNA), leading to termination of mRNA translation, RNA replication, and reverse transcription. Isis Pharmaceuticals, Inc, is testing an antisense oligonucleotide (ISIS 14803) in HCV infection. In a dose-escalation study, ISIS 14803 was well tolerated and resulted in significant reductions (1 log) in plasma HCV RNA levels in two of four patients treated with a high dose (2 mg/kg), and was associated with transient, asymptomatic alanine aminotransferase (ALT) flare. Phase II studies are now underway.

Ribozymes are pieces of RNA that act as enzymes, cleaving RNA at defined sites. Ribozymes can be designed to recognize and bind specific HCV mRNA sequences and to cleave both RNA transcripts and pregenomic RNA. The internal ribosome entry site is an attractive target for ribozymes since disruption of this RNA segment will abrogate translation of the viral polyprotein. A phase II clinical trial using Heptazyme®, (Ribozyme Pharmaceuticals, Inc) demonstrated a reduction in serum HCV RNA in 10% of patients; however, the trial has been stopped to allow review of an animal toxicity concern.

**Immunomodulators**

Host immune responses to HCV infection also represent pathways that could be exploited in attempts to control the infection or resulting liver disease. T cells and natural killer (NK) cells are primarily responsible for clearance of infected hepatocytes. CD8 cells play an important role in secreting interferon gamma (γ), which inhibits intracellular viral replication. In addition, CD8 and NK cells induce apoptosis of infected cells. Interferon, in addition to having direct antiviral activity, also appears to augment the immune response. A number of investigational therapies also seek to augment the immune response to HCV.

Thymalfasin (Zadaxin®, thymosin alpha 1, SciClone Pharmaceuticals International, Ltd) has a number of immunomodulating activities that augment T-cell function. Thymalfasin promotes T-cell differentiation and maturation, increases production of interferon-γ and interleukin (IL)-2 following activation by antigens, and increases NK cell activity. The pattern of enhanced cytokine production suggests that thymalfasin may influence progression to a Th1 type of immune response. It has no direct antiviral activity. Preliminary clinical experience indicates that thymalfasin plus interferon combination therapy is superior to interferon monotherapy (end-of-treatment response 37.1% versus 16.2%; chi-squared = 4.05, P = .04). Large phase III trials are underway.

Histamine dihydrochloride (Ceplene®, previously called Maxamine, Maxim Pharmaceuticals) binds type 2 histamine receptors on phagocytic cells, reduces free radical production, and enhances NK T-cell function.
A phase II study showed benefit in combination with interferon alfa-2b (sustained virologic response in 40% overall and 38% in genotype 1). Side effects were generally mild and included transient flush, headache, hypotension, and tachycardia. They may have a role as adjuvant immunotherapy in combination with other antiviral compounds. Interferon-γ was recently shown to have antiviral activity in the HCV subgenomic replicon, but in a pilot study in the early 1990s had no effect on ALT levels. Active immunization may be possible with HCV recombinant protein or DNA vaccines to try to boost HCV antibodies or T-cell responses. Protective antibody vaccines have been tested in chimpanzees, and “T-cell vaccines” are currently being evaluated in humans with chronic HCV infection. Most of these T-cell immunotherapy strategies aim to boost the viral-specific CD4+ and CD8+ responses, which are closely associated with viral clearance.

Antifibrotic Agents

Cytokines secreted by antigen-stimulated immune cells are important in stopping viral replication and clearing infected cells. However, some of these cytokines also activate hepatic stellate cells and promote fibrosis. Several antifibrotic cytokines are under investigation for control of fibrosis. Interferon γ-1b can inhibit both stellate-cell activation in vitro and collagen deposition. It has shown great clinical promise in treating idiopathic pulmonary fibrosis. Interferon γ-1b is currently under investigation in advanced HCV infection to determine if it can reverse or halt disease progression. A small pilot study in 30 HCV-infected patients showed no change in ALT level and a nonsignificant trend toward less fibrosis. A Chinese study found that 9 months of interferon-γ led to improvements in fibrosis and serologic markers of extracellular matrix without significant side effects in 47 patients with fibrosis due to chronic hepatitis B. Tumor necrosis factor (TNF) alpha is a key cytokine implicated in the progression of the immune-mediated injury that characterizes HCV infection. Anti-TNF treatment has anecdotally improved liver function test results in HCV-infected patients. Clinical trials are in the development phase. Tumor growth factor-β isotypes play a central role in the fibrogenic response to HCV infection. A number of strategies to develop effective therapeutic antagonism are underway, but the use of soluble receptors appears to be the most promising. Multiple other agents are being evaluated for their potential to alter disease progression related to HCV infection, including colchicine, silymarin, pentoxifylline, glycyrrhizin, ursodiol, and antioxidants.

Conclusions

Peginterferon/ribavirin has provided increased efficacy and convenience over previous antiviral regimens used in the treatment of hepatitis C. With this regimen, which is now the standard of care, we can eradicate HCV in more than half of all treated patients. New therapies for hepatitis C will impact treatment options in the next few years. Given the rapid rate of viral replication, the diversity of quasispecies, and the potential for development of treatment resistance, it is likely that interferons, other antiviral agents, and immunomodulators will be used in combination to achieve the greatest efficacy. It is now being recognized that fibrosis is likely a reversible process. As a result, liver-specific antifibrotic agents are also likely to be important future therapies in the management of hepatitis C.

REFERENCES

Hepatocellular carcinoma (HCC) is one of the most serious sequelae of hepatitis C, and its incidence is increasing. Surveillance for HCC is common practice for patients with cirrhosis, but this practice has not been well validated. Surgical resection, liver transplantation, and percutaneous ablation are potentially curative. However, overall survival remains poor, with a life expectancy of only about 6 months, pointing to the need for more aggressive prevention.

Epidemiology and Pathogenesis

Worldwide, more than 500,000 new cases of HCC are diagnosed each year, with consumption of aflatoxin-contaminated food being the most common cause. High incidence rates are also found in countries where hepatitis B virus (HBV) and/or hepatitis C virus (HCV) are endemic. In the United States, where the aflatoxin-related risk is low, HCV infection accounts for one third of all HCC cases. The incidence rate in the United States increased 71% (from 1.4 to 2.4 per 100,000 persons) from the late 1970s to the early 1990s, with a corresponding 46% increase in hospitalization rate and 41% increase in mortality. The incidence of HCC in the United States is expected to peak in the next decade. The HCC risk is particularly high in patients with established cirrhosis, age ≥50 years, alpha-fetoprotein (AFP) level ≥15 ng/mL, male gender, large esophageal varices, and prothrombin <70%.

Development of HCC is a multistep process. In patients with HCV infection, expression of viral proteins stimulates an immune response and triggers chronic inflammation. This causes genetic alterations that interfere with the cell cycle, resulting in clonal cell expansion and transformation, and ultimately lead to angiogenesis and metastasis. Genetic alterations in HCC tumors vary according to HCC risk factor; investigations of genetic mutations in HCCs from persons with HCV infection have found an increased prevalence of microsomal epoxide hydrolase polymorphisms, overexpression of p73 protein, chromosome 11q13 copy gain, and inactivation of p14(ARF).

Natural History

HCC nodes in patients with cirrhosis double at a median of about 6 months (range, 1–20 months). Tumor spread is an early event in the natural history. In a study of 322 patients who underwent curative resection for HCC at a Veterans Hospital in Taiwan, microscopic vascular invasion was observed in 40%, and macrovascular invasion in 2.7% of patients with small (<2 cm) tumors at the time of resection. The incidence was higher in patients with larger tumors, reaching 93% for microvascular and 52% for macrovascular invasion among those with tumors >12 cm.

Tumor characteristics, the patient's general health, and liver function affect the prognosis of a patient with HCC. In an evaluation of the natural history of untreatable HCC in 102 patients, survival rates at 1, 2, and 3 years were 54%, 40%, and 28%, respectively. Multivariate analysis identified performance status 1 to 2, constitutional syndrome, vascular invasion, and extrahepatic spread as predictors of mortality. For patients with at least one of these factors, survival rates at 1, 2, and 3 years were 29%, 16%, and 8%, versus 80%, 65%, and 50%, respectively, for patients with none of these factors. Based on these prognostic factors, the Barcelona Clinic Liver Cancer staging classification divides HCC into early (A), intermediate (B), advanced (C), and end-stage (D) disease (Table 9.1). Dysplasia, irregular regeneration, or atypical macrogeneerative nodules may represent precancerous changes. In addition, there is an increased likelihood of HCC in those with positive immunostaining results for proliferative cell nuclear antigen or silver-stained nucleolar organizer region on liver specimens.

Screening and Diagnosis

Early detection of HCC has been shown to prolong survival in three of four studies. HBV and/or HCV carriers with cirrhosis and noncirrhotic Asian or African HBV carriers who are at high risk of liver cancer as a consequence of concurrent exposure to dietary
### Table 9.1. The Barcelona Clinic Liver Cancer Staging Classification.

<table>
<thead>
<tr>
<th>Staging</th>
<th>Performance Status</th>
<th>Tumor Stage</th>
<th>Child-Pugh</th>
<th>Recommended Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Early</td>
<td>0</td>
<td>Single &lt;5 cm 3 nodes &lt;3 cm</td>
<td>A &amp; B</td>
<td>Surgery</td>
</tr>
<tr>
<td>(B) Intermediate</td>
<td>0</td>
<td>Large/ multinodular</td>
<td>A &amp; B</td>
<td>Palliation or clinical trial</td>
</tr>
<tr>
<td>(C) Advanced</td>
<td>1–2</td>
<td>Vascular invasion extrahepatic spread</td>
<td>A &amp; B</td>
<td>Palliation or clinical trial</td>
</tr>
<tr>
<td>(D) End-stage</td>
<td>3–4</td>
<td>Any of the above</td>
<td>C</td>
<td>Palliation</td>
</tr>
</tbody>
</table>


### Survey Findings

The Clinician’s Companion VI survey respondents said they screen for HCC a median of every 6 months (mean, 7.2 months) in patients with established cirrhosis.

### Treatment

Surgical resection, liver transplantation, and percutaneous ablation are the best options for treatment of HCC and are assumed to improve the natural history of the disease. Optimal candidates for resection are patients with single tumors and otherwise well-preserved liver function. Such patients have a 50% survival rate at 5 years after resection, with the best predictors of survival being the absence of relevant portal hypertension and normal serum bilirubin level (74% survival at 5 years). However, a 3-year recurrence rate of 50% limits the value of resection.

Transplantation, when restricted to patients with single tumors ≤5 cm or up to three nodules ≤3 cm each, provides excellent long-term results (5-year survival rate of 71%–74%), with marginal recurrence rates. Similar results have been reported when the inclusion criteria were extended to include patients with single tumors up to 6.5 cm or up to three nodules ≤4.5 cm each. However, an increasing need for liver transplants has led to longer waiting times. As a result, while waiting for a transplant, more patients with HCC are experiencing progression to stages that contraindicate the procedure. This, in turn, has led to a substantial number of patients excluded from treatment, and to decreased outcomes when assessing transplantation results by intent-to-treat (ITT) analysis (Table 9.2).

### Table 9.2. ITT Analysis of Transplantation for Early HCC (Spain).

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Waiting period</th>
<th>Drop-out rate</th>
<th>2-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989–1995</td>
<td>50</td>
<td>62 days</td>
<td>0</td>
<td>84%</td>
</tr>
<tr>
<td>1996–1997</td>
<td>37</td>
<td>162 days</td>
<td>8</td>
<td>54%</td>
</tr>
</tbody>
</table>

There are several forms of percutaneous ablation used to treat HCC. Based on early results, the use of interstitial radiofrequency or chemo-embolization to attenuate tumor progression while waiting for a donor (bridge-therapy) is under evaluation in several centers. Percutaneous ethanol injection has a high antitumoral efficacy in small solitary HCC (47% survival rate at 5 years) and a relatively low economic cost, but it shows universal recurrence at 5 years in patients with high AFP levels and those without peritumoral capsule. Thermal ablation by radiofrequency has the advantage of requiring only a single treatment session, and the antitumoral effect does not depend on tissue diffusion. However, its use is contraindicated in tumors with difficult access, with close proximity of blood vessels >3 mm, or with hypervascularization. In a prospective randomized trial, radiofrequency ablation had a therapeutic efficacy similar to ethanol injection (complete response, 90% versus 80%, respectively). In this study, tumor ablation was achieved in fewer treatment sessions (1.2 versus 4.8), but it caused more complications (9.5% versus 0%). Transcatheter arterial chemo-embolization has been applied to patients with inoperable HCC, with mixed results. Only the two most recent of five randomized trials have shown a significant improvement in 2-year survival compared with controls.

#### Survey Findings

Survey respondents rated the appropriateness of treatment for patients with well-compensated cirrhosis and HCC (Fig. 9.1).
**PART 5: RECENT INSIGHTS INTO HCV VIROLOGY AND TREATMENT OF CHRONIC HEPATITIS C**

**Figure 9.1.** Survey Findings: Treatment for HCC.

How appropriate is each option for treating patients with well-compensated cirrhosis and HCC?

A. Resection
B. Liver transplantation
C. Radiofrequency ablation
D. Percutaneous ethanol injection
E. Chemo-embolization
F. Living donor transplantation
G. Microwave coagulation
H. Systemic chemotherapy

![Survey Results](image)

**Prevention**

Substantial reductions in both HCC incidence and mortality have been achieved in areas hyperendemic for HBV through mass vaccination against HBV of all newborns. For patients infected with HCV, secondary prevention of HCC with interferon is under evaluation. A meta-analysis did favor a preventive effect of interferon in HCV-infected patients with cirrhosis (Fig. 9.2).43

**Conclusions**

The incidence of HCC is increasing, resulting in increasing hospitalization and mortality rates. Patients with HCV-related cirrhosis or other risk factors for HCC should undergo abdominal ultrasound and AFP determination every 6 months for surveillance. Diagnosis of HCC in cirrhotic patients with a nodule detected by ultrasound, or patients with AFP elevations and no focal lesions, requires confirmation with triphasic CT scan or dynamic MRI. Surgical resection, liver transplantation, and percutaneous ablation are potentially curative, but only a small proportion of patients are candidates for resection and waiting times for liver transplants are increasing. More aggressive prevention of HCC is needed.

**REFERENCES**


![Reprint of Figure 9.2](image)
Hepatitis C is the most common indication for liver transplantation, both in the United States and in Europe. However, the graft becomes reinfected with hepatitis C virus (HCV) in almost all of those with pretransplantation HCV infection, and may lead to progressive liver injury in the graft. Patient survival is worse among those who undergo liver transplantation for HCV disease than among patients who are HCV negative.1

Identification of variables associated with poor posttransplantation outcome may allow more appropriate selection of patients for transplantation and modification of these variables in patients with HCV disease. Such variables may include donor age, HCV RNA level at the time of transplantation, early posttransplantation recurrence, degree of immunosuppression, and treatment of graft rejection. A second approach to improving outcomes in transplant recipients is to treat HCV infection with antiviral therapy, either before liver transplantation, preemptively early in the post-transplantation period, or once posttransplantation disease is established.

**Disturbing Trends in Liver Transplantation**

The United Network for Organ Sharing has reported some disturbing trends regarding increased need for liver transplantation and its effect on wait-list time in the United States. The number of new registrations per year for liver transplants has more than doubled in the past decade (Fig. 10.1).2 Since the number of transplants performed each year remains relatively stable, the time from registration to transplant has increased from a median of 92 days in 1991 to 817 days in 1998.2 At the end of 2000, 36% of those on the list had been waiting more than 2 years. As of August 9, 2002, there were 17,459 patients awaiting transplants, with only a little more than 5000 transplants being done annually.3 Despite increasing wait times, the death rate decreased from 393.9 per 1000 patient-years at risk in 1991 to 106.4 in 2000.2 This may be a result of improved strategies for managing complications such as portal hypertension in patients awaiting transplantation.

Fibrosis is linearly progressive postransplantation (Fig. 10.2),4 and cirrhosis develops within 5 years of transplantation in 28% of patients.5 The median rate of progression varies considerably (range, 0.01–2.4 fibrosis U/yr; median, 0.56); however, in general, progression rate is faster than before transplantation, and faster than in immunocompetent persons.4 Immunosuppressive regimens associated with progressive liver disease include steroid boluses and OKT3. Once patients have developed cirrhosis of the graft, the probability of decompensation in the first year is about 50%,6 and survival is decreased (Fig. 10.3).5

A major concern is that HCV disease progression in the graft has increased recently so that the probability of developing stage 3/4 fibrosis 3 years after transplantation increased from $<5\%$ from 1985–1989 to 90% from 1996–1997.7 Reasons for this increase in disease progression are under investigation but likely include use of less well-preserved organs (due to the organ shortage) and of more potent immunosuppressive regimens in recent years with rapid tapering of steroid doses and immunological rebound that may lead to progressive disease.4
Treating HCV Infection Before Transplantation

High HCV RNA level at transplantation is associated with more aggressive disease posttransplantation. This observation has led to attempts to reduce HCV RNA levels prior to transplantation. To date, only uncontrolled trials have been reported. These studies show that viral eradication is achievable, but few patients with decompensated liver disease are candidates and toxicity rates are high.

In a single-center study, 91 patients (predominantly genotype 1) awaiting liver transplantation were treated with low-dose interferon (1.5 mIU TIW) and ribavirin (600 mg/d). Interferon was increased to 3 mIU after 2 weeks, and ribavirin was increased by 200 mg/wk up to a dose of 1000 mg/d for patients ≤75 kg or 1200 mg/d for those >75 kg for patients who tolerated initial doses. Growth factors were given as needed. On-treatment clearance of HCV RNA occurred in 38% (35/91), and 22% (20/91) achieved sustained virologic response. Of the nonresponders, 27% developed serious adverse effects. Eight HCV RNA negative patients underwent liver transplantation and all remained virus-free posttransplantation.

Results of pretransplantation antiviral therapy were less encouraging in a sicker population of patients treated with monotherapy or combination therapy. In this study, 32 patients at or near the top of the transplantation waiting list were screened, and 15 enrolled. Three patients were treated with interferon 1 mIU/d, 6 were treated with interferon 3 mIU TIW, and the other 6 were treated with interferon 1 mIU/d plus ribavirin 400 mg BID. On-treatment virologic response occurred in 33%, and 55% had a decrease in viral titer during therapy. Only 2 patients were negative for HCV RNA at the time of transplantation; both experienced posttransplantation recurrence. In the 15 patients treated, there were 23 adverse events, 20 of which were serious. These included 7 cases of thrombocytopenia (platelets <20,000/µL), 4 cases of neutropenia, 3 cases of hepatic encephalopa-thy, 1 case of *Staphylococcus aureus* arthritis, and 1 case of culture-negative empyema that had a fatal outcome. The study was terminated after the second major infection was reported.

Data on the safety and efficacy of peginterferon/ribavirin in the pretransplant setting are unavailable, but it is likely that the risk of cytopenias will be greater with peginterferon based on reports of cytopenias from the registration trials of peginterferon alfa-2a and alfa-2b.

**Treating HCV Infection After Transplantation**

Because of the safety concerns associated with use of interferon-based therapies in patients with decompensated cirrhosis, antiviral therapy is usually reserved until after transplantation. Theoretical benefits of successful treatment of HCV recurrence posttransplantation include clinical improvement and stabilization of disease, and possibly avoidance of the need for retransplantation.

**Interferon/Ribavirin**

Interferon/ribavirin combination therapy has been more successful than either drug alone, but is associated with significant toxicity, especially anemia, in transplant recipients.

In a 1997 study, 21 patients (92% genotype 1) with posttransplantation recurrence of HCV infection were treated with interferon/ribavirin for 6 months followed by ribavirin alone for 6 additional months. Biochemical response occurred in all patients and a virologic response in 48% (10/21) at the end of interferon/ribavirin. During ribavirin monotherapy, ALT remained normal in 94% (17/18) and HCV RNA remained negative in half (5/10). Three patients discontinued therapy due to anemia. No episodes of rejection occurred.

In a more recent study, 450 patients were screened and 49 considered eligible for interferon (3 mIU TIW) and ribavirin (800 mg/d). At the end of treatment, 27% had normalized ALT levels and 25% had cleared HCV RNA. Adverse events included acute myocardial infarction (n = 2), death from multiorgan failure (n = 1), and severe cholestatic hepatitis (n = 1). Mean hemoglobin level decreased from 14 ± 1.6 g/dL at baseline to 12.3 ± 1.6 g/dL at the end of treatment (P = .0001). There were no episodes of rejection.

**Pegylated Interferons**

Pegylated interferons may be superior to standard interferons, and it is likely that peginterferon/ribavirin combination therapy will be necessary to optimize treatment, as is the case in patients with earlier stages of HCV infection.

Lee et al recently presented data on peginterferon alfa-2b 1.5 µg/kg QW plus ribavirin 400 to 600 mg/d...
posttransplantation. Among 30 treatment-naive patients, 30% were HCV RNA negative at 3 months and 27% at 6 months. Among 30 patients who previously were nonresponders to interferon/ribavirin, 18% were HCV RNA negative at 6 months. Even with the low dose of ribavirin used in this study, anemia was a common side effect. Cytopenias and depression were also observed.

In another recent presentation, 28 patients were randomized to treatment with peginterferon alfa-2a 180 µg QW monotherapy versus 28 who were observed without therapy posttransplantation. After 24 weeks of treatment, 44% of treated patients had a ≥2-log reduction in HCV RNA, and 25% had undetectable HCV RNA. Ninety-five percent of treated patients and 81% of untreated patients had one or more side effects, including fatigue, nausea, diarrhea, fever, abdominal pain, and headache. There were no treatment discontinuations due to side effects.14

Survey Findings

Survey respondents sometimes do treat recurrent HCV infection following transplantation (rating 3.3 on a scale of 1 = never to 5 = always), and may also give antiviral therapy to patients awaiting liver transplantation (rating 3.1). They are less likely to give antiviral therapy immediately after transplant as prophylaxis against recurrence (rating 2.3). When treating recurrence, 75% of survey respondents said they use peginterferon alfa-2b/ribavirin, 14% use interferon/ribavirin, 10% use peginterferon monotherapy, and 1% use interferon monotherapy. Doses of peginterferon were generally 1.0 or 1.5 µg/kg. Ribavirin doses varied considerably, from fixed doses of 400 to 1000 mg/d, to weight-based dosing at 10 to 15 mg/kg/d. Durations also varied, with the most common answers being 24 weeks, 48 weeks, or indefinitely.

The decision to treat posttransplantation HCV disease is based primarily on histologic severity (rating 4.4 on a scale of 1 = not at all influential to 5 = very influential), according to survey respondents. They also take into account the degree of renal insufficiency (rating 4.1), the presence of concomitant cytopenia (rating 3.9), the degree of immune deficiency (rating 3.8), and the risk of allograft rejection (rating 3.6).

Conclusions

Hepatitis C-related disease is a major problem both before and after liver transplantation. The incidence of HCV-associated hepatic decompensation is increasing, resulting in a greater demand, and wait, for liver transplants. Following transplantation, HCV reinfection of the graft is nearly universal and results in progressive liver disease that compromises patient and graft survival. Variables associated with disease progression are under investigation. Interferon/ribavirin has some efficacy posttransplantation, but limited efficacy pretransplantation, and is associated with increased risk of toxicity in both settings. While there have been concerns about the potential risk of precipitating allograft rejection with posttransplantation antiviral therapy, most case series have not demonstrated this to be an important problem clinically. New therapies, including pegylated interferons, are under investigation in transplant recipients.

REFERENCES

As described in this five-part *Clinician’s Companion VI* series, remarkable progress has been made in the management of hepatitis C over the past 10 to 15 years. Until 1989, the hepatitis C virus (HCV) had not even been identified, and by 2002, management has become fairly sophisticated. More than half of all treated patients now achieve a sustained virologic response—up from only around 10% with the first available regimen (interferon monotherapy) in 1991. In the past year, since *The Clinician’s Companion V*, progress has consisted largely of nuances in management that improve response rates and tolerability of therapy for more patients. As a result, both physicians and HCV-infected patients can approach the disease with a more hopeful perspective.

One of the great accomplishments in the fields of hematology, internal medicine, and liver disease has been the dramatic improvements that have been made in the safety of the blood supply. In the 1970s, few patients or surgeons appreciated that there was a 30% risk of acquiring hepatitis during coronary artery bypass surgery. Thanks to the tenacity of Harvey J. Alter, MD, and others, the risk of acquiring hepatitis through donated blood is now virtually zero.

Diagnosis and monitoring of hepatitis C has been greatly facilitated by the introduction of HCV RNA assays. These tests confirm with great accuracy the presence of chronic infection. They also allow for more accurate determination of response to treatment than was previously possible with biochemical measures alone. The recent introduction of standardized international units will help to make these tests reproducible and consistent. The ability to quantify the level of HCV RNA with these tests has also led to “early stopping rules” for treatment. With either peginterferon alpha-2b or peginterferon alpha-2a in combination with ribavirin, we can now predict response after only 12 weeks of treatment, with response defined as undetectable HCV RNA or a ≥2-log decrease in HCV RNA. These early stopping rules allow us to discontinue therapy in half the usual time for patients who are nonresponders (unless secondary, histologic benefits warrant continued treatment), and also allow us to provide greater motivation to patients who have early signs of response.

Pegylated interferon has largely replaced standard interferon, and peginterferon/ribavirin has become the standard of care. We now have over a year’s worth of experience using peginterferon alfa-2b/ribavirin. The regimen approved by the US Food and Drug Administration (FDA) in August 2001, peginterferon alfa-2b 1.5 µg/kg QW plus ribavirin 800 mg/d, produces sustained virologic response (SVR) in 54% of treated patients, including 42% of genotype 1–infected and 82% of genotype 2/3–infected patients. Retrospective analyses showed that SVR was achieved in 61% of those who were prescribed >10.6 mg/kg of ribavirin in combination with 1.5 µg/kg QW peginterferon alfa-2b (off-label use of FDA-approved products), and with 80+80+80 adherence to these doses, SVR was 72%. (As described in Part 2, 80+80+80 adherence = ≥80% of peginterferon dose and ≥80% of ribavirin dose for ≥80% of recommended duration.) Peginterferon alfa-2a 180 µg QW was approved in October 2002 for use as monotherapy; off-label use in combination with ribavirin 1000 mg in patients <75 kg or 1200 mg in patients ≥75 kg produces SVR in 56% of patients overall.

The increasing efficacy of treatment has provided a rationale for offering treatment to a broader range of patients. This was reinforced by the 2002 National Institutes of Health Consensus Development Conference statement, which calls all HCV-infected patients “potential candidates for antiviral therapy.” This statement has further opened the doors for treatment of:

- persons with a history of injection-drug or alcohol use
- patients with neuropsychiatric disorders
- some patients with normal alanine aminotransferase (ALT) levels
- patients with compensated cirrhosis
- children
- those with acute hepatitis C
- HIV-coinfected patients
New data have shown us that treating hepatitis C earlier in the course of disease results in improved treatment outcomes. Treatment of acute hepatitis C has a high rate of success and prevents the development of chronic infection. The optimal dose, duration, and timing of treatment for patients with acute disease has not been determined. Whereas patients with normal ALT levels were often excluded from treatment in the past, some show evidence of advanced disease upon liver biopsy. As a result, more physicians are recognizing the need to biopsy and consider treatment in this population. Similarly, although mild disease was often left untreated, many physicians are now individualizing the decision to treat such patients, especially in light of data showing higher response rates in patients with mild disease than in those with advanced fibrosis or cirrhosis. The decision to treat mild disease should be based on genotype, symptoms, comorbid conditions, age, and patient motivation.

Adherence to treatment clearly has an important impact on treatment outcomes. Rates of treatment discontinuation have been disappointing in clinical practice. Physicians need to take a more aggressive approach to keep patients on treatment. Patients need to be prepared for side effects at the initiation of therapy and should be told that the side effects of interferon can be likened to those of chemotherapy but can also be managed in most cases. When side effects do occur, physicians should take advantage of effective adjunctive therapies, such as antidepressants and growth factors.

The increasing size of the patient population, the need for time-consuming patient education and aggressive side-effect management, and the rising costs of healthcare mean that most physicians in clinical practice can no longer manage these patients without considerable help. Increasing use of a trained support staff (eg, nurse practitioners, physician assistants, nurses, medical assistants, and office personnel) is becoming a necessity in most practices. Support staff can provide invaluable assistance in screening patients, providing instruction and education, monitoring patients and managing side effects, as well as carrying out administrative functions.

We are now facing an epidemic of advanced liver disease secondary to HCV infection, as patients infected decades ago during the peak incidence period reach the late stages of the disease. The incidence of hepatic decompensation and hepatocellular carcinoma (HCC) is increasing, bringing with it an increasing need for liver transplants. Better approaches to screening for HCC are needed, particularly now that treatments are improving. Evidence is accumulating that suggests that earlier treatment of HCV-related disease with interferon-based therapies does prevent HCC, further supporting the growing practice of maintenance therapy for virologic nonresponders.

Great strides have been made in understanding HCV virology, including the viral life cycle. This knowledge is leading to new approaches to drug development, including therapies that target HCV protease, polymerase, and helicase; inhibit cell binding; or deactivate stellate cells to reduce the production of fibrosis. Research needs to continue to focus on the safety and efficacy of treatment in special populations (eg, HIV-coinfected patients), determining the impact of fatty liver on the overall disease and on transplant outcomes, and development of a hepatitis C vaccine. In the meantime, physicians should take full advantage of the remarkable progress we have made in improving the treatment regimens we have today. Tailored therapy, using peginterferon/ribavirin and aggressive promotion of adherence, results in successful treatment outcomes in the majority of patients.
All five parts of *The Clinician’s Companion VI* are available at www.projectsinknowledge.com:

**Part 1:** REPORTER: Emerging Advances: Preliminary Findings from Ongoing Studies of Peginterferon/Ribavirin

**Part 2:** REPORTER: Predicting Response and Promoting Adherence to Peginterferon/Ribavirin

**Part 3:** REPORTER: Mild Disease: To Treat or Not to Treat?

**Part 4:** REPORTER: What Constitutes Treatment Response?

**Part 5:** Monograph: Recent Insights into HCV Virology and Treatment of Chronic Hepatitis C
CME Instructions
This activity comprises five parts sent to you throughout the year. To earn credit, you must read and complete all five parts. To receive documentation of your participation in this five-part CME activity for a total of 2.5 hours of CME credit, please complete the following steps:

1. Read each of the five parts.
2. Complete the CME posttest and evaluation/needs assessment.
3. Mail or fax the posttest and evaluation/needs assessment to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.

CME Certificate
Projects In Knowledge will mail you a certificate of completion for this activity if your score on the posttest is 70% or higher. If your score is lower than 70%, you will be notified by mail and given an opportunity to take the posttest again.

Name

Degrees/Credentials

Mailing Address

City

State

ZIP

Phone

Fax

E-mail

Please indicate your answers below (circle one).

1. Analysis of demographic data from the WIN-R study indicates that African Americans are more likely than Caucasians to have:
   a. Genotype 1 infection  
   b. High viral load  
   c. Fibrosis  
   d. All of the above  
   e. Only a and b

2. Persons weighing >105 kg who were treated with peginterferon alfa-2b 1.5 µg/kg + ribavirin 1400 mg/d in the WIN-R study were significantly more likely than patients who weighed less and received less ribavirin to experience a reduction in their hemoglobin level to <10 g/dL.
   a. True  
   b. False

3. Preliminary analysis of the RENEW study on retreatment of interferon/ribavirin nonresponders suggests that 3.0 µg/kg peginterferon alfa-2b plus weight-based ribavirin:
   a. Is poorly tolerated, resulting in high rates of treatment discontinuation  
   b. Produces on-treatment HCV RNA clearance rates equivalent to standard doses of peginterferon/ribavirin  
   c. Produces on-treatment HCV RNA clearance rates higher than with lower doses (ie, 1.5 or 0.5 µg/kg) of peginterferon and weight-based ribavirin  
   d. None of the above

4. The likelihood of achieving SVR is <4% if at least a 2-log decrease in HCV RNA has not occurred by week 12 of treatment with peginterferon/ribavirin.
   a. True  
   b. False

5. What percentage of patients who do achieve at least a 2-log reduction in HCV RNA during treatment with peginterferon alfa-2a/ribavirin go on to achieve SVR?
   a. 50%  
   b. 65%  
   c. 80%  
   d. 98%

6. Rates of SVR increase with increasing adherence to recommended doses and duration of treatment.
   a. True  
   b. False

7. HCV-infected patients with normal ALT levels:
   a. Are more likely than those with elevated ALT levels to respond to antiviral therapy  
   b. Are less likely than those with elevated ALT levels to respond to antiviral therapy  
   c. Have rates of response to antiviral therapy that are comparable to those in patients with elevated ALT levels
8. Subgroup analysis in the study by Manns et al of peginterferon alfa-2b/ribavirin showed a better response rate among patients with bridging fibrosis or cirrhosis compared with those who had minimal or no fibrosis.
   a. True  
   b. False

9. What percentage of patients relapse at ≥3 years after an SVR to antiviral therapy for HCV infection?
   a. Virtually none  
   b. 1% to 2%  
   c. 3% to 5%  
   d. >5%

10. Patients with compensated cirrhosis who achieve an SVR no longer require screening for HCC.
   a. True  
   b. False

11. Which of the following had the greatest impact on the safety of the blood supply?
   a. The elimination of payment for blood donation
   b. Screening for ALT elevations
   c. Screening for hepatitis B core antigen
   d. Screening for hepatitis C antibodies

12. HCV gene expression takes place:
   a. In the cell nucleus  
   b. In the cytoplasm

13. Fibrosis progresses more rapidly:
   a. In patients with HIV/HCV coinfection versus those with HCV monoinfection
   b. Following liver transplantation versus before transplantation
   c. Both a and b are true
   d. Neither a nor b is true

14. In the 2002 NIH Consensus Statement, which of the following tests is recommended to confirm the HCV diagnosis in patients with HCV antibodies by EIA?
   a. RIBA
   b. Quantitative HCV RNA assay
   c. Qualitative HCV RNA assay
   d. None of the above; positive EIA alone is sufficient to diagnosis hepatitis C

15. Which of the following has not been found to be a predictor of response to peginterferon alfa-2b or alfa-2a, in combination with ribavirin?
   a. Genotype 2/3 infection
   b. Histologically mild disease
   c. Lower body mass index or smaller body surface area
   d. Low viral load
   e. Female gender

16. Which of the following serotonin reuptake inhibitors has the least risk of drug interactions?
   a. Citalopram  
   b. Paroxetine  
   c. Fluoxetine  
   d. Sertraline

17. In the only published controlled trial of maintenance therapy, interferon 3 mIU for 2 years:
   a. Reduced inflammation but not fibrosis  
   b. Reduced fibrosis but not inflammation  
   c. Reduced inflammation and fibrosis  
   d. Reduced neither inflammation nor fibrosis

18. Which of the following is an investigational immunomodulating agent being investigated in combination with interferon in the treatment of hepatitis C?
   a. Colchicine  
   b. Zadaxin® (thymalfasin)
   c. Albuferon® (albumin-interferon alpha)  
   d. Civacir® (hepatitis C immunoglobulin)

19. Five-year survival following resection for HCC is:
   a. 20%  
   b. 35%  
   c. 50%  
   d. 75%

20. Which of the following is false regarding liver transplantation in the United States?
   a. The number of new registrations per year has more than doubled in the past decade  
   b. The number of transplants performed annually remains relatively stable  
   c. Nearly 17,500 patients are currently waiting for liver transplants  
   d. From 1991 to 1998 there was nearly a ninefold increase in waiting time  
   e. Death rates among patients on the waiting list doubled from 1991 to 2000
Instructions
Please complete this Evaluation/Needs Assessment, along with the CME posttest, and either mail or fax back to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.

1. Please rate the extent to which you achieved the learning objectives:

   - Discuss advances and new directions in HCV research, including virology, natural history, treatment, and prevention
   - Examine new NIH consensus guidelines and how they inform clinical decision making
   - Formulate effective, individualized treatment strategies for patients with chronic HCV infection using pegylated interferon/ribavirin combination therapy
   - Use diagnostic procedures, including HCV PCR and liver biopsy in a timely fashion to determine treatment response
   - Promote adherence to anti-HCV therapy by managing side effects and by providing appropriate psychosocial support
   - Develop appropriate management strategies for different patient groups, including patients with HIV/HCV, mild disease, normal ALT levels, advanced liver disease, and hepatocellular carcinoma

2. Please rate the overall value of this enduring material:

3. Is this activity free from commercial bias? Yes ☐ No ☐

   If “no,” please describe .................................................................

4. Do you anticipate making any changes to your practice as a result of this activity?

   Yes ☐ No ☐ Maybe ☐

   If “yes” or “maybe,” please describe ..............................................

5. Please indicate how long it took you to complete Parts 1 through 5, the posttest, and the evaluation ..............................................

6. Please rate the level of the material presented:

   Just Right ☐ Too Advanced ☐ Too Basic ☐

7. For each chapter in The Clinician’s Companion VI (CCVI), please indicate your level of agreement:

   (4 = Strongly Agree; 3 = Agree; 2 = Disagree; 1 = Strongly Disagree)

<table>
<thead>
<tr>
<th>Chapter Details</th>
<th>The material was interesting</th>
<th>The material helps me manage patients with HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCVI, Part 1: The WIN-R Trial: Early Observations on Weight-Based Dosing of Peginterferon alfa-2b/Ribavirin</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>CCVI, Part 1: Treating Interferon/Ribavirin Nonresponders</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>CCVI, Part 2: Predicting Response to Peginterferon/Ribavirin</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>CCVI, Part 2: Promoting Adherence to Treatment</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>CCVI, Part 3: Mild Chronic Hepatitis C (F0–F1): Treatment Issues</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>CCVI, Part 3: Case Studies: an Individualized Approach to Treating Patients with Mild Disease</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
7. continued…

<table>
<thead>
<tr>
<th>The material was interesting</th>
<th>The material helps me manage patients with HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCVI, Part 4: What Constitutes Treatment Response? (Case Studies)</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: I. Perspectives of HCV and Virology Frontiers at the NIH</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5, II. HCV Virology and the Effects of Treatment</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5, III. Impact of HIV on the Natural History of Hepatitis C</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: IV. NIH Draft Consensus Statement on Hepatitis C: Conclusions and Controversies</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: V. A new Look at à la Carte Therapy</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: VI. Side-Effect Management</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: VII. Maintenance Therapy in Combination Treatment Nonresponders</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: VIII. Future Drug Development</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: IX. Update on Hepatocellular Carcinoma</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: X. Liver Transplantation</td>
<td></td>
</tr>
<tr>
<td>CCVI, Part 5: XI. Conclusions</td>
<td></td>
</tr>
</tbody>
</table>

8. Which educational formats do you prefer?

- [ ] Audioconference  - [ ] On-line interactive  - [ ] CD-ROM  - [ ] Videoconference  - [ ] Symposia
- [ ] Printed Enduring Materials  - [ ] Other . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . .

9. Do you currently use the Internet?  Yes [ ]  No [ ]

If “yes,” indicate how you most often use it:
- [ ] E-mail Colleagues  - [ ] E-mail Patients  - [ ] Free On-line CME
- [ ] Fee-based On-line CME  - [ ] Literature Search  - [ ] Listserv Participation
- [ ] Download Slides and Articles for Printing  - [ ] Journal Subscriptions  - [ ] Other . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . .

10. What topics would you like to see discussed in The Clinician’s Companion VII?

.........................................................................................................................................................................

11. Follow-up: As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:

- [ ] Yes, I would be interested in participating in a follow-up survey.
- [ ] No, I’m not interested in participating in a follow-up survey.

Additional comments about this activity:

.........................................................................................................................................................................

Thank you for your participation.