NIH CONSENSUS DEVELOPMENT CONFERENCE ON MANAGEMENT OF HEPATITIS C

Program and Abstracts

(Online Edition)

NIH Consensus Development Conference
March 24–26, 1997

Natcher Conference Center
National Institutes of Health
Bethesda, Maryland

Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases and the NIH Office of Medical Applications of Research. The conference is cosponsored by the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, and the National Institute on Drug Abuse of the National Institutes of Health; and the Centers for Disease Control and Prevention.

Continuing Education Sponsorship by
National Institutes of Health
Office of Education

Contents

III. Epidemiology and Spread of Hepatitis C

IV. Therapy of Hepatitis C

Introduction to the NIH Consensus Development Conference on Management of Hepatitis C

The hepatitis C virus (HCV) is a major cause of both acute and chronic hepatitis in the United States. Hepatitis C, previously known as "non-A, non-B hepatitis," affects between one and two percent of Americans, and chronic infection with HCV is probably the single most important cause of chronic liver disease, cirrhosis, and liver cancer in the Western world. Not all cases of hepatitis C are severe or progressive. Many patients are asymptomatic and are only diagnosed when they are found to have abnormal liver tests following a blood donation or routine evaluation for another problem. Yet, chronic hepatitis C can be insidious and slowly progressive and lead to cirrhosis and liver failure after years or decades of infection.

At present, there are no specific means of prevention of hepatitis C, and the only therapy of proven benefit is alpha interferon. Interferon treatment, however, is far from satisfactory. Therapy is expensive, often poorly tolerated, and results in a favorable long-term response in only a minority of patients. Given the uncertainties regarding hepatitis C, patients with this disease and their doctors face difficult decisions.

To address the most important and controversial clinical issues in hepatitis C, the NIH has organized this $2^{1}/_{2}$-day conference to bring together national and international experts in the fields of virology, epidemiology, natural history, prevention, and therapy of hepatitis C, as well as representatives from the public.

Following $1^{1}/_{2}$ days of presentations and audience discussion, an independent, non-Federal consensus panel will weigh the scientific evidence and write a draft statement that it will present to the audience on the third day. The consensus statement will address the following key questions:

- What is the natural history of hepatitis C?
- What is the most appropriate approach to diagnose and monitor patients?
- What recommendations can be made to patients to prevent transmission?
- Which patients should be treated?
- What is the most effective approach to therapy?
- What are the most important areas for future research on hepatitis C?

On the final day of the meeting, the conference and panel chairperson, D. W. Powell, M.D., Professor and Chairman, Department of Internal Medicine, University of Texas Medical Branch at Galveston, will read the draft statement to the conference audience and invite comments and questions. A press conference will follow to allow the panel and chairperson to respond to questions from media representatives.

CAFETERIA

The cafeteria is located on the lobby level and is open daily from 7:00 a.m. to 3:00 p.m.

GENERAL INFORMATION

Conference sessions will be held in the Natcher Conference Center (Building 45), NIH, 9000 Rockville Pike, Bethesda, Maryland. Sessions will run from 8:30 a.m. to 5:30 p.m. on Monday, 8 a.m. to 12:30 p.m. on Tuesday, and 9 to 11 a.m. on Wednesday.

CONTINUING EDUCATION CREDIT

The purpose of this Consensus Development Conference is to evaluate current efforts to diagnose, treat, and manage patients with hepatitis C.

The conference will (1) present in open, public sessions state-of-the-art information regarding diagnostic techniques, therapeutic approaches, and patient management, (2) prepare a statement in response to the six specific questions, and (3) inform the biomedical research and clinical practice communities and the general public of the conclusions and recommendations of the panel.

The National Institutes of Health is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

The National Institutes of Health designates this educational activity for a maximum of 15 hours in category I credit toward the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he or she actually spent in the educational activity.

SPONSORS

The primary sponsors of this conference are the National Institute of Diabetes and Digestive and Kidney Diseases and the NIH Office of Medical Applications of Research. The conference is cosponsored by the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, and the National Institute on Drug Abuse of the National Institutes of Health; and the Centers for Disease Control and Prevention. This is the 105th Consensus Development Conference held by the NIH since the establishment of the Consensus Development Program in 1977.

Agenda

Monday, March 24, 1997

8:30 a.m.	Welcome and Introduction	Phillip Gorden Director National Institute of Diabetes and Digestive and Kidney Diseases
8:35 a.m.	Charge to Panel	John H. Ferguson Director Office of Medical Applications of Research
8:45 a.m.	Conference Issues	D. W. Powell Conference and Panel Chairperson
	I. Natural History of Hepatitis C	
9:00 a.m.	Hepatitis C Virus: An Introduction	Robert H. Purcell
9:20 a.m.	Hepatitis C: The Clinical Spectrum of Disease	Jay H. Hoofnagle
9:40 a.m.	Natural History of Hepatitis C	Leonard B. Seeff
10:00 a.m.	Blood Donors With Hepatitis C	Harvey J. Alter
10:20 a.m.	Discussion	
10:50 a.m.	Hepatitis C and Hepatocellular Carcinoma	Adrian M. Di Bisceglie
11:10 a.m.	Hepatitis C and Alcohol	Eugene R. Schiff
11:30 a.m.	Discussion	
12:00 noon	Lunch	
	II. Diagnosis of Hepatitis C	
1:00 p.m.	Diagnostic Tests for Hepatitis C	David Gretch
1:20 p.m.	Diagnosis of Hepatitis C	Anna Lok
1:40 p.m.	Role of Liver Biopsy	Robert P. Perrillo
2:00 p.m.	Discussion	

Monday, March 24, 1997 (continued)

	III. Epidemiology and Spread of Hepatitis C	
2:30 p.m.	Epidemiology of Hepatitis C	Miriam J. Alter
2:50 p.m.	Sexual and Perinatal Spread of Hepatitis C Virus Infection	Jules L. Dienstag
3:10 p.m.	Discussion	
	IV. Therapy of Hepatitis C	
3:40 p.m.	Therapy of Hepatitis C: Overview	Karen L. Lindsay
4:00 p.m.	Management of Hepatitis C: A National Survey of Gastroenterologists and Hepatologists	James Everhart
4:20 p.m.	Therapy of Hepatitis C: Interferon Alfa-2b	Robert L. Carithers, Jr.
4:40 p.m.	Discussion	
5:30 p.m.	Adjournment until Tuesday	

Tuesday, March 25, 1997

8:00 a.m.	Therapy of Hepatitis C With Interferon Alfa-2a	William M. Lee
8:15 a.m.	Interferon Alfa-n1 Trials	Geoffrey C. Farrell
8:30 a.m.	Consensus Interferon Trials	Emmet B. Keeffe
8:45 a.m.	Ribavirin Treatment Alone or in Combination With Interferon	Olle Reichard
9:00 a.m.	Side Effects of Interferon Alpha in Viral Hepatitis	Geoffrey Dusheiko
9:15 a.m.	Discussion	
9:40 a.m.	Predictive Factors for a Beneficial Response	Gary L. Davis
10:00 a.m	Treatment of Patients With Cirrhosis	Solko W. Schalm
10:15 a.m.	Treatment of Patients With Normal ALT Levels	Patrick Marcellin

Tuesday, March 25, 1997 (continued)

10:30 a.m.	Retreatment With Interferon	Alfredo Alberti
10:50 a.m.	Other Options for Treatment of Hepatitis C	Herbert L. Bonkovsky
11:10 a.m.	Cost-Effectiveness Analysis	Raymond S. Koff
11:30 a.m.	Discussion	
12:30 p.m.	Adjournment	

Wednesday, March 26, 1997

9:00 a.m.	Presentation of the Consensus Statement	D. W. Powell Conference and Panel Chairperson
9:30 a.m.	Discussion	
11:00 a.m.	Panel Meets in Executive Session	
1:00 p.m.	Press Conference	
2:00 p.m.	Adjournment	

Panel

Panel and Conference Chairperson:
D. W. Powell, M.D.
Professor and Chairman
Department of Internal Medicine
The University of Texas Medical Branch at Galveston
Galveston, Texas

Barbara Z. Abramson
Consumer Representative
Boston, Massachusetts

John A. Balint, M.D., F.R.C.P.
Professor of Medicine
Center for Medical Ethics
Albany Medical College
Albany, New York

Steven Belle, Ph.D.
Assistant Professor
Department of Epidemiology
University of Pittsburgh
Pittsburgh, Pennsylvania

Joseph R. Bloomer, M.D.
Professor of Medicine
Director, UAB Liver Center
Department of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Andrew K. Diehl, M.D., M.Sc.
Professor and Chief
Division of General Medicine
Department of Medicine
University of Texas Health Science Center at San Antonio
San Antonio, Texas

James T. Frakes, M.D., M.S.
Clinical Professor of Medicine
Division of Gastroenterology
University of Illinois
College of Medicine at Rockford
Director, Digestive Disease Unit
Saint Anthony Medical Center
Rockford, Illinois

Guadalupe Garcia-Tsao, M.D.
Associate Professor
Department of Medicine
Yale University School of Medicine
New Haven, Connecticut

Edward W. Hook, M.D.
Henry B. Mulholland Professor
Department of Internal Medicine
University of Virginia
School of Medicine
Charlottesville, Virginia

Jeanne M. Lusher, M.D.
Marion I. Barnhart Hemostasis Research
Professor and Professor of Pediatrics
Hematology-Oncology Division
Wayne State University School of Medicine and Children's Hospital of Michigan
Detroit, Michigan

Mark A. Popovsky, M.D.
Chief Executive Officer and
Chief Medical Officer
American Red Cross, New England Region
Associate Professor of Pathology
Harvard Medical School and Beth Israel Hospital
Boston, Massachusetts

Linda Rabeneck, M.D., M.P.H.
Associate Professor
Department of Medicine
Baylor College of Medicine
Houston, Texas

Ann L. B. Williams, M.B.B.S.
Associate Clinical Professor
Division of Gastroenterology and Nutrition
George Washington University
Washington, DC

Speakers

Alfredo Alberti, M.D.
Department of Clinical and Experimental Medicine
University of Padova
Padova, Italy

Harvey J. Alter, M.D.
Chief, Infectious Disease Section
Department of Transfusion Medicine
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland

Miriam J. Alter, M.D., Ph.D.
Chief, Epidemiology Section
Hepatitis Branch
Centers for Disease Control and Prevention
Atlanta, Georgia

Herbert L. Bonkovsky, M.D.
Director, Division of Digestive Disease and Nutrition
Department of Medicine
University of Massachusetts Medical Center
Worcester, Massachusetts

Robert L. Carithers, Jr., M.D.
Professor of Medicine
Division of Hepatology
Department of Medicine
University of Washington Medical Center
Seattle, Washington

Gary L. Davis, M.D.
Professor of Medicine
Director, Section of Hepatobiliary Diseases
Department of Medicine
University of Florida
Gainesville, Florida

Adrian Di Bisceglie, M.D.
Professor of Internal Medicine
Division of Administration
St. Louis University School of Medicine
St. Louis, Missouri

Jules L. Dienstag, M.D.
Associate Professor of Medicine
Harvard Medical School
Physician
Massachusetts General Hospital
Boston, Massachusetts

Geoffrey Dusheiko, M.D.
Professor
Division of Hepatology
Department of Medicine
Royal Free Hospital
London, England

James Everhart, M.D., M.P.H.
Chief, Epidemiology and Clinical Trials Branch
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Geoffrey C. Farrell, M.D., F.R.A.C.P.
Robert W. Storr Professor of Hepatic Medicine
Division of Gastroenterology and Hepatology
Department of Medicine
The University of Sydney
Westmead, Australia

David Gretch, M.D., Ph.D.
Assistant Professor of Laboratory Medicine
Director of Viral Hepatitis Laboratory
c/o Pacific Medical Center
Seattle, Washington

Jay H. Hoofnagle, M.D.
Director, Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Emmet B. Keeffe, M.D.
Professor of Medicine
Division of Gastroenterology
Department of Medicine
Stanford University
School of Medicine
Palo Alto, California

Raymond S. Koff, M.D.
Chairman
Department of Medicine
University of Massachusetts Medical School
Framingham, Massachusetts

William M. Lee, M.D.
Professor
Division of Liver
Department of Internal Medicine
University of Texas
Southwestern Medical Center
Dallas, Texas

Karen L. Lindsay, M.D.
Associate Professor of Clinical Medicine
Department of Medicine
University of Southern California
School of Medicine
Los Angeles, California

Anna Lok, M.D.
Professor
Department of Internal Medicine
Division of Gastroenterology
University of Michigan Medical Center
Ann Arbor, Michigan

Patrick Marcellin, M.D., Ph.D.
Service d'Hepatologie et Unite de Reserches de
Physiopathologie Hepatique (INSERM U-24)
Hopital Beaujon
Universite Paris VII
Clichy, France

Robert P. Perrillo, M.D.
Section Head, Gastroenterology and
Hepatology
Department of Internal Medicine
Ochsner Clinic
New Orleans, Louisiana

Robert H. Purcell, M.D.
Head, Hepatitis Section
Laboratory of Infectious Diseases
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Olle Reichard, M.D., Ph.D.
Department of Infectious Diseases
Karolinska Institute
Danderyd Hospital
Danderyd, Sweden

Solko W. Schalm, M.D.
Professor of Medicine and Hepatology
Division of Hepatology
Department of Hepatogastroenterology and
Internal Medicine
Erasmus University Hospital Dijkzigt
Rotterdam, The Netherlands

Eugene R. Schiff, M.D.
Director, Center for Liver Diseases
Chief, Division of Hepatology
University of Miami School of Medicine
Miami, Florida

Leonard B. Seeff, M.D.
Chief, Gastroenterology and Hepatology
Veterans Affairs Medical Center
Professor of Medicine
Georgetown University School of Medicine
Washington, DC

Planning Committee

Chairperson: Tommie Sue Tralka
Director, Clinical Trials Program
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Harvey J. Alter, M.D.
Chief, Infectious Disease Section
Department of Transfusion Medicine
Warren G. Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland

Miriam J. Alter, Ph.D.
Chief, Epidemiology Section
Hepatitis Branch
Centers for Disease Control and Prevention
Atlanta, Georgia

Elsa A. Bray
Program Analyst
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Leslie Curtis
Science Writer
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

James Everhart, M.D., M.P.H.
Chief, Epidemiology and Clinical Trials Branch
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Stephen M. Feinstone, M.D.
Chief, Laboratory of Hepatitis Viruses
Division of Viral Products
Center for Biologics Evaluation and Research
Food and Drug Administration
Bethesda, Maryland

John H. Ferguson, M.D.
Director
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Janet S. Gress
Clinical Reviewer
Division of Clinical Trials
Food and Drug Administration
Rockville, Maryland

William H. Hall
Director of Communications
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Jay H. Hoofnagle, M.D.
Director, Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Leslye D. Johnson, Ph.D.
Chief, Enteric and Hepatic Diseases
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Thomas F. Kresina, Ph.D.
Director, Liver Diseases Program
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Karen L. Lindsay, M.D.
Associate Professor of Clinical Medicine
Department of Medicine
University of Southern California
School of Medicine
Los Angeles, California

Anna Lok, M.D.
Professor
Department of Internal Medicine
Division of Gastroenterology
University of Michigan Medical Center
Ann Arbor, Michigan

Paul R. McCurdy, M.D.
Director, Blood Resources Program
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Robert P. Perrillo, M.D.
Section Head, Gastroenterology and Hepatology
Department of Internal Medicine
Ochsner Clinic
New Orleans, Louisiana

D. W. Powell, M.D.
Panel and Conference Chairperson
Professor and Chairman
Department of Internal Medicine
The University of Texas Medical Branch
at Galveston
Galveston, Texas

Robert H. Purcell, M.D.
Head, Hepatitis Section
Laboratory of Infectious Diseases
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Eugene Schiff, M.D.
Director, Center for Liver Diseases
Chief, Division of Hepatology
University of Miami School of Medicine
Miami, Florida

William D. Schwieterman, M.D.
Branch Chief
Center for Biologics Evaluation and Research
Food and Drug Administration
Bethesda, Maryland

Leonard B. Seeff, M.D.
Chief, Gastroenterology and Hepatology
Veterans Affairs Medical Center
Professor of Medicine
Georgetown University School of Medicine
Washington, DC

Charles R. Sherman, Ph.D.
Deputy Director
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Michael H. Stolar, Ph.D.
Senior Vice President
American Gastroenterological Association
Bethesda, Maryland

Alan Trachtenberg, M.D.
Medical Officer
Office of Science Policy and Communications
National Institute on Drug Abuse
Rockville, Maryland

Abstracts

The following abstracts of presentations to the NIH Consensus Development Conference on Management of Hepatitis C were furnished by presenters in advance of the conference. This book is designed for the use of panelists and participants in the conference and as a pertinent reference document for anyone interested in the conference deliberations. We are grateful to the authors who have summarized their materials and made them available in a timely fashion.

Tommie Sue Tralka
Director, Clinical Trials Program
Division of Digestive Diseases and Nutrition
National Institute of Diabetes and Digestive
and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Elsa A. Bray
Program Analyst
Office of Medical Applications
of Research
National Institutes of Health
Bethesda, Maryland

Hepatitis C Virus: An Introduction

Robert H. Purcell, M.D.

History

Hepatitis C was first recognized as a separate disease entity in 1975 when the majority of cases of transfusion-associated hepatitis were found not to be caused by the only two hepatitis viruses recognized at the time, hepatitis A virus and hepatitis B virus. The disease was called "non-A non-B hepatitis," and it was demonstrated to be transmissible to chimpanzees. It was not until 1989, however, that the cloning and sequencing of the viral genome of the non-A non-B hepatitis virus was first reported and the virus was renamed "hepatitis C virus" (HCV). Tests for antibody to HCV quickly followed, and screening for such antibody remains a principal method of diagnosis.

Taxonomy and Nomenclature

Hepatitis C virus shares virological and genetic characteristics with the *Flaviviridae*. Its genomic organization is similar to that of the flaviviruses and pestiviruses and shares slight sequence identity with these viruses, especially the pestiviruses. Each of these groups of viruses comprises a separate genus within the *Flaviviridae*: *flavivirus*, *pestivirus*, and *hepacivirus*.

Properties of the Virion and Genome

Properties of the Virion

Hepatitis C virus is a spherical enveloped virus of approximately 50 nm in diameter. Its buoyant density in sucrose is only 1.06 g/cm^3 but much of the virus in chronically infected individuals appears to be bound to antibody, which imparts a higher density of approximately 1.17 g/cm^3.

Properties of the Genome

The genome of HCV is a single-strand linear RNA of positive sense. It is unsegmented. A 5¢ non-coding (NC) region consists of approximately 340 nucleotides and contains an apparent internal ribosomal entry site (IRES). Immediately downstream is a single large open reading frame (ORF) of approximately 9,000 nucleotides, encoding a large polyprotein precursor of approximately 3,000 amino acids that is cotranslationally or posttranslationally cleaved into separate proteins by a combination of host and viral proteases. A capsid protein, two envelope proteins (E1 and E2), and a small protein of unknown function (P7) are encoded in the 5¢ region of the ORF. At least six nonstructural proteins, including protease, helicase, and RNA polymerase enzymes and regulatory peptides, are arrayed in the 3¢ portion of the ORF. Finally, there is a 3¢ NC region that consists of approximately 50 nucleotides, a polypyrimidine track and a highly conserved terminal sequence of approximately 100 nucleotides.

Genetic Heterogeneity: Types, Subtypes, and Quasispecies

The genome of HCV is highly heterogeneous. The most highly conserved regions of the genome are parts of the 5¢ NC region and the terminal 3¢ NC region. The most highly conserved region of the ORF is the capsid gene. In contrast, the most heterogeneous portions of the genome are the genes encoding the envelope proteins. The 5¢ end of the E2 gene is the most heterogeneous region of all and has been named the "first hypervariable region" (HVR1). A few strains have a second HVR just 3¢ of HVR1. The HVR1 consists of approximately 90 nucleotides (30 amino acids) and is believed to be a major neutralization epitope of HCV: its heterogeneity appears to be the result of selective pressures by the host's humoral immune system.

Based on their genetic heterogeneity, HCV strains can be divided into major groups, called types or genotypes (and provisionally classified as separate species) of the virus (Table 1). Within types, HCV isolates have been grouped into numerous subtypes. Finally, individual isolates consist of heterogeneous populations of the viral genomes that comprise "quasispecies" or "swarms" of closely related but different viruses. Some genotypes of HCV appear to be geographically restricted; others have worldwide distribution. More extensive genetic analysis of HCV has revealed that the hierarchical classification of isolates into types, subtypes, and isolates is somewhat artifactual and the viruses probably exist as a continuum of genetic diversity.

TABLE 1. Genetic Complexity of Hepatitis C Virus

Category	Sequence Identity (%)
Type (Species)	66–69
Subtype	77–80
Isolate	91–95
Quasispecies	>98

Immunity and Resistance to Infection

The consequence of the genetic diversity of HCV is a virus that has the ability to escape the immune surveillance of its host, leading to a high rate (more than 80 percent) of chronic infections and lack of immunity to reinfection in repeatedly exposed individuals. Both chronicity and lack of solid immunity probably result from the emergence of minor populations of the virus quasispecies that vary in sequence, especially in the HVR1. Data supporting this conclusion came from experimental infections of chimpanzees that develop repeated infections with HCV following up to four sequential inoculations with the virus and from observations of natural reinfections of thalassemic children undergoing repeated transfusions of blood.

Similar conclusions can be drawn from attempts to vaccinate chimpanzees with recombinant HCV envelope antigens expressed in eukaryotic cells: the chimpanzees were protected following challenge with 10 chimpanzee infectious doses of the homologous virus but not when rechallenged with 64 chimpanzee infectious doses of a closely related strain of HCV. Attempts to neutralize HCV *in vitro* reveal that neutralizing antibodies were produced by patients in response to infection with HCV but these neutralizing antibodies were of low titer and specific for individual variants of HCV within the quasispecies infecting the individual. The sequence-specific neutralization has been localized to one or more epitopes in the HVR1 of the virus. Thus, it will probably be difficult to develop a broadly protective vaccine against HCV.

Despite this pessimism, there may be some reason for hope that HCV can be prevented by immunoprophylaxis. Double-blind placebo-controlled trials of normal immune globulin for the prevention of transfusion-associated non-A non-B hepatitis (most of which was hepatitis C) revealed

that, if the globulin was administered prior to transfusion, significant protection against total and icteric non-A non-B hepatitis, as well as chronic disease, could be achieved. Similarly, when plasma units containing antibody to HCV were screened from pools of plasma destined for fractionation into blood products, the resultant lots of intravenous immune globulin were associated with a high incidence of hepatitis C in recipients, in contrast to results obtained with most lots of intravenous immune globulin prepared before anti-HCV positive plasma units were removed. Both of these observations strongly suggest that pooled plasma contains a mixture of antibodies to HCV that is capable of neutralizing diverse HCV strains found in nature. Thus the neutralization epitopes of HCV must be finite in their diversity. If the breadth of this diversity can be mapped it may be possible to construct a polyvalent vaccine that can protect against most if not all HCV variants.

References

1. Bukh J, Miller RH, Purcell RH. Defining the genotypes of hepatitis C virus and their epidemiology. INTER-action 1995;3:10–5.

2. Choo QL, Kuo G, Ralston R, Weiner A, Chien D, Van Nest G, Han J, Berger K, Thudium K, Kuo C, Kansopon J, McFarland J, Tabrizi A, Ching K, Moss B, Cummins LB, Houghton M, Muchmore E. Vaccination of chimpanzees against infection by the hepatitis C virus. Proc Natl Acad Sci U S A 1994;91:1294–8.

3. Conrad ME. Prevention of post-transfusion hepatitis. Lancet 1988;339(2):217.

4. Farci P, Alter HJ, Govindarajan S, Wong DC, Engle R, Lesniewski RR, Mushahwar IK, Desai SM, Miller RH, Ogata N, Purcell RH. Lack of protective immunity against reinfection with hepatitis C virus. Science 1992;258:135–40.

5. Farci P, Shimoda A, Wong D, Cabezon T, De Gioannis D, Strazzera A, Shimizu Y, Shapiro M, Alter HJ, Purcell RH. Prevention of HCV infection in chimpanzees by hyperimmune serum against the hypervariable region 1 of the envelope 2 protein. Proc Natl Acad Sci U S A. In press.

6. Hijikata M, Shimizu YK, Kato H, Iwamoto A, Shih JW, Alter HJ, Purcell RH, Yoshikura H. Equilibrium centrifugation studies of hepatitis C virus: evidence for circulating immune complexes. J Virol 1993;67:1953–8.

7. Houghton M. Hepatitis C virus. In: Fields BN, Knipe DM, Howley PM, eds. Fields Virology, Third Edition. Philadelphia: Lippincott—Raven Publishers 1996:1035–58.

8. Lai ME, Mazzoleni AP, Argiolu F, De Virgilis S, Balestrieri A, Purcell RH, Cao A, Farci P. Hepatitis C virus in multiple episodes of acute hepatitis in polytransfused thalassaemic children. Lancet 1994;343:388–90.

9. Shimizu YK, Feinstone SM, Kohara M, Purcell RH, Yoshikura H. Hepatitis C virus: detection of intracellular virus particles by electron microscopy. Hepatology 1996;23:205–9.

10. Shimizu YK, Igarashi H, Kiyohara T, Cabezon T, Purcell RH, Yoshikura H. A hyperimmune serum against a synthetic peptide corresponding to the hypervariable region 1 of hepatitis C virus can prevent viral infection in cell cultures. Virology 1996;223(2):409–12.

11. Yu MW, Mason BL, Guo ZP, Tankersley DL, Nedjar S, Mitchell FD, Biswas RM. Hepatitis C transmission associated with intravenous immunoglobulins. Lancet 1995;345:1173–4.

Hepatitis C: The Clinical Spectrum of Disease

Jay H. Hoofnagle, M.D.

The hepatitis C virus (HCV) is an important cause of both acute and chronic hepatitis. As with all diseases, the clinical course and outcome of hepatitis C are variable—there is no single natural history of disease, but rather a broad clinical spectrum of disease presentations and outcomes.

In the United States, hepatitis C represents approximately 20 percent of cases of acute hepatitis. The mean incubation period to onset of symptoms is 7 weeks; the range is 3–20 weeks. However, long before onset of symptoms, markers of virus appear in the serum: HCV RNA is detectable within 1–3 weeks of exposure and rises rapidly to levels of 106–108 genomes per ml. After several weeks, serum alanine aminotransferase levels (ALT) begin to rise and shortly thereafter clinical symptoms appear. The severity of the acute illness is variable; virtually all infected patients have a transient elevation in ALT with peak levels greater than tenfold elevated. Yet only a third of patients develop jaundice or symptoms: in the remainder, the disease is anicteric and subclinical. If clinically apparent, the illness generally lasts 2–12 weeks. Acute hepatitis C can result in fulminant hepatitis, but this is quite rare. In cases of acute, self-limited disease, HCV RNA becomes undetectable within a few weeks of onset of symptoms and aminotransferase levels return to normal.

Unfortunately, the majority of patients with acute hepatitis C develop chronic infection; symptoms of acute hepatitis resolve, but ALT levels remain elevated and HCV RNA persists. Indeed, a propensity to chronicity is the most distinguishing characteristic of HCV infection, occurring in at least 85 percent of patients with acute HCV infection. The factors that lead to chronicity in hepatitis C are not well defined. The quasispecies nature of HCV and the tendency of the envelope gene of the virus to mutate rapidly may be key factors, the virus constantly escaping immune recognition by mutations in the antigenic epitopes to which any neutralizing antibody is made. The role of cellular immunity to HCV antigens in explaining why 15 percent of patients clear HCV infection while the majority do not may also be important.

Not all patients who continue to be viremic continue to have raised ALT levels. In most surveys, approximately one-third of patients with chronic HCV infection have *persistently* normal serum ALT levels, and in others ALT levels are only intermittently abnormal. These patients have been referred to as "healthy HCV carriers," but this term is misleading and should be avoided. Liver biopsies in patients with chronic HCV infection with normal ALT levels reveal histological evidence of chronic hepatitis in virtually all patients. Perhaps more appropriate is to say that these patients have mild or subclinical chronic hepatitis C: their prognosis may be excellent.

The majority of patients with chronic HCV infection have raised ALT levels, which can fluctuate widely over time. There is not a very good correlation between the height of the ALT levels and disease severity as judged histologically. Long-term followup studies, however, suggest that most patients with progressive liver disease who develop cirrhosis have prominent ALT elevations; these can, however, be intermittent.

A smaller proportion of patients with chronic HCV infection have clinical symptoms or signs of liver disease. Symptoms in chronic hepatitis C tend to be nonspecific, mild, and intermittent. The most frequent symptom is fatigue, variably described as lethargy, malaise, lack of energy or stamina, and easy fatigability. Often, it is a challenge to determine whether the fatigue is attributable to the liver disease rather than to something else—depression, anxiety over the illness, aging, sleep disturbance, or another medical condition. Other, less frequent symptoms are nausea, poor appetite, muscle aches, arthralgias, feverishness, weakness, and weight loss. Symptoms are rarely incapacitating, but they can cause a decrease in the quality of life. In general, patients with higher ALT levels and

more severe disease histologically are more likely to have symptoms, but marked exceptions exist. Because the symptoms are nonspecific, it is hard to define what percentage of patients with chronic HCV infection are symptomatic; but it is probably less than 20 percent. These are the patients, however, who are most likely to present to a physician for diagnosis and management.

Chronic hepatitis C, whether or not symptoms are present, can lead to cirrhosis and end-stage liver disease. Cirrhosis can develop rapidly, within 1–2 years of exposure, or slowly, within 2–3 decades. In studies with 10–20 years of followup, cirrhosis develops in 20–30 percent of patients. It is unclear whether the remaining patients will eventually develop cirrhosis or not. Thus, chronic hepatitis C probably does not have one typical course; there are probably multiple typical courses, from rapidly progressive to slowly progressive to nonprogressive.

Once cirrhosis develops, the symptoms of end-stage liver disease can appear, such as marked fatigue, muscle weakness and wasting, fluid retention, easy bruisability, upper intestinal hemorrhage, jaundice, dark urine, and itching. Nevertheless, some patients with cirrhosis remain asymptomatic of liver disease until they have major complications of cirrhosis, such as variceal hemorrhage or ascites or they die of an unrelated cause. Hepatitis C ranks with alcoholic liver disease as the most common cause of cirrhosis and the major indication for liver transplantation in the United States. Liver transplantation is the only means of restoring health to patients with end-stage liver disease due to HCV. Recurrent infection of the new graft occurs in almost all patients, but in many cases the recurrent infection is mild. Long-term studies are needed to assess at what rate recurrent hepatitis C leads to recurrence of cirrhosis. At present, long-term survival after liver transplantation for hepatitis C is similar to that for other diagnoses, averaging 65 percent after 5 years.

In many areas of the world, chronic hepatitis C is a major cause of hepatocellular carcinoma (HCC). This tumor occurs largely in patients with long-standing disease, and the majority have cirrhosis. Therapies for HCC are unsatisfactory and focus must be on prevention of development of cirrhosis and early detection of liver cancer.

The spectrum of hepatitis C also includes several nonhepatic manifestations, including arthritis, keratoconjunctivitis sicca, lichen planus, glomerulonephritis, and essential mixed cryoglobulinemia (EMC). EMC is a syndrome marked by varying combinations of fatigue, muscle and joint aches, arthritis, skin rash (hives, purpura, or vasculitis), neuropathy, and glomerulonephritis. Cryoglobulins are found in serum composed of immune complexes of HCV and anti-HCV, immunoglobulins, rheumatoid factor, and complement. Hepatitis C appears to be the most common cause of EMC, a fact that was not appreciated before the availability of serological tests for HCV. Cryoglobulins are detectable in up to one-third of patients with chronic hepatitis C, but the clinical syndrome of EMC occurs in only 1–2 percent of patients. This syndrome can be severe, incapacitating, and even fatal. Resolution of the hepatitis C is followed by resolution of the EMC. Glomerulonephritis can also occur with hepatitis C; it usually represents the renal involvement of HCV-related EMC. Overall, this syndrome might best be called HCV-related systemic vasculitis.

A final clinical manifestation of chronic hepatitis C is porphyria cutanea tarda (PCT). This form of porphyria is found in several forms of chronic liver disease often in association with iron overload. In some parts of the world, hepatitis C is the major underlying cause of PCT. Like other forms, HCV-related PCT can be treated with phlebotomy to deplete the excess iron stores that exacerbate the porphyria.

Thus, there is a wide clinical spectrum to acute and chronic hepatitis C. Simple and reliable systems to stage and grade the severity of chronic hepatitis C are needed. Histological systems such as the histology activity index (HAI) have been developed to categorize chronic hepatitis C for use in clinical studies of natural history and therapy. A possible system which mixes clinical symptoms, serum biochemical tests, and liver histology would be as follows:

Disease activity:	Mild (ALT normal or <2 times upper limit)
	Moderate (ALT 2–5 times upper limit)
	Severe (ALT >5 times upper limit)
Cirrhosis:	Present or absent
Symptoms:	Present or absent

Bibliography

1. Houghton M, Weiner A, Han J, et al. Molecular biology of the hepatitis C viruses: implications for diagnosis, development and control of viral disease. Hepatology 1991;14:381–8.

2. Alter MJ, Mast EE. The epidemiology of viral hepatitis in the United States. Gastroenterol Clin North Am 1994;23:437–55.

3. Alter HJ, Purcell RH, Shih JW, et al. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med 1989;321:1494–500.

4. Farci P, Alter HJ, Wong D, et al. A long-term study of hepatitis C virus replication in non-A, non-B hepatitis. N Engl J Med 1991;325:98–104.

5. Alter HJ, Sanchez-Pescador R, Urdea MS, et al. Evaluation of branched DNA signal amplification for the detection of hepatitis C virus RNA. J Viral Hepatitis 1995;2:121–32.

6. Weiner AJ, Geysen HM, Christopherson C, et al. Evidence for immune selection of hepatitis C virus (HCV) putative envelope glycoprotein variants: potential role in chronic HCV infections. Proc Natl Acad Sci USA 1992;89:3468–72.

7. Shakil AO, Conry-Cantilena C, Alter HJ, et al. Volunteer blood donors with antibody to hepatitis C virus: clinical, biochemical, virologic and histologic features. Ann Intern Med 1995;123:330–7.

8. Alberti A, Morsica G, Chemello L, et al. Hepatitis C viraemia and liver disease in symptom-free individuals with anti-HCV. Lancet 1992;340:697–8.

9. Seeff LB, Buskell-Bales Z, Wright EC, et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. N Engl J Med 1992;327:1906–11.

10. Di Bisceglie AM, Goodman ZD, Ishak KG, Hoofnagle JH, Melpolder JJ, Alter HJ. Long-term clinical and histopathological follow-up of chronic posttransfusion hepatitis. Hepatology 1991;14:969–74.

11. Tong MJ, El-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995;332:1463–6.

12. Detre KM, Belle SH. Liver transplantation for chronic viral hepatitis. Viral Hepatitis Reviews. In press.

13. Colombo M, Kuo G, Choo QL, et al. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. Lancet 1989;2:1006–9.

14. Johnson RJ, Gretch DR, Yamabe H, et al. Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med 1993;328:465–70.

15. Agnello V, Chung RT, Kaplan LM. A role of hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med 1992; 327:1490–5.

16. DeCastro M, Sanchez J, Herrera JF, et al. Hepatitis C virus antibodies and liver disease in patients with porphyria cutanea tarda. Hepatology 1993; 17:551–7.

17. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513–20.

Natural History of Hepatitis C

Leonard B. Seeff, M.D.

Introduction

Of the many perplexing issues regarding viral hepatitis, type C, none is more uncertain and, indeed, more controversial than the matter of its natural history. Knowledge of outcome of the disease is critical in order to provide meaningful information to persons who are chronically infected and in order to make judicious and prudent decisions regarding treatment.

In the course of the last decade of study of what was initially referred to as non-A, non-B (NANB) hepatitis, and then more recently, hepatitis C, it had become clear that the vast majority of persons who develop acute hepatitis C—perhaps over 80 percent—remain infected. The consequence of this is progression in many such individuals from acute to chronic hepatitis, advancement in a proportion of instances to cirrhosis, ending in the development by some of hepatocellular carcinoma (HCC). This sequence has been particularly well-recognized among infected persons in Japan,[1,2] Italy,[3] and Spain.[4] While similar outcomes have been observed among persons infected in the United States, the frequency of termination in end-stage liver disease and particularly HCC has seemed to be less frequent. This has led to two contradictory viewpoints, the first being that all or most chronically infected persons will advance to serious or terminal liver disease if they do not succumb first to another lethal illness, the second holding the position that only a limited proportion of infected persons develop progressive disease, the challenge being to determine which persons will follow this path and the reason or reasons why. Only by conducting appropriate long-term natural history studies is it possible to resolve the conflict.

Such studies have been difficult to perform for the following reasons: (1) most persons who develop *acute* hepatitis C do so in the complete absence of symptoms, thus frustrating the ability to accurately determine onset and hence duration of disease; (2) the total lack or paucity of symptoms at onset of the illness hinders the ability to recognize the full disease spectrum, the focus then being on those with the more severe forms of the illness; (3) the lack of symptoms associated with the acute illness precludes the opportunity to select a noninfected control group to perform appropriate case-control followup studies; (4) treatment is now commonplace which has the clear potential of altering the natural history of the disease; and (5) the extremely slow rate of progression of the disease, ranging from 2 to 4 decades, makes it a daunting task for any investigator to embark on the necessary long-term studies. Consequently, most data on natural history have come from relatively short-term followup studies starting with disease onset, from studies that begin with already established chronic liver disease, or from retrospective studies. These approaches tend to focus attention on the more severe form of the disease while neglecting the milder cases that may not come to attention, thus creating potential outcome bias.

Prospective Studies Beginning from Disease Onset

Five prospective studies have been reported from the United States and Europe involving persons with transfusion-associated NANB hepatitis, predominantly but not exclusively due to hepatitis C virus (HCV) infection.[5–9] The mean duration of followup was 8–15 years. About 10 percent of study subjects were reported in followup to have clinical symptoms, histologic cirrhosis was noted in 15–20 percent, and HCC was identified in two of the studies (0.7 percent and 1.3 percent, respectively). Mortality ranged from 1.6–6.0 percent. These studies, with somewhat small numbers and relatively short durations of followup, demonstrated an unequivocal but modest frequency of mortality and morbidity over their limited time courses.

More benign data come from a study reported from Ireland of HCV-infection following receipt of HCV-contaminated immunoglobulin products.[10,11] A followup of 232 infected persons over a 17-year period showed that about one-quarter had mild fatigue, none were jaundiced or had hepatosplenomegaly, and about 60 percent had modest enzyme abnormalities. Liver biopsies revealed the presence of chronic hepatitis, mostly mild, in the majority of instances, only 2.4 percent of them showing early cirrhosis and 1.8 percent showing severe fibrosis. The authors concluded from these data that there was minimal evidence of progressive disease.

Followup Studies Beginning with Already Established Chronic Liver Disease

Among three such studies with mean followup periods of 9–15 years, cirrhosis was reported to develop in 8 percent, 30 percent, and 42 percent, and HCC in 15 percent and 19 percent.[12–14] The high frequency of cirrhosis and HCC was noted in the two studies from Japan.[12,13] It is of more than passing interest that this strikingly high frequency of HCC among persons infected in Japan may not be replicated once they move to other countries. In a recent examination of records in Hawaii over a 25-year period seeking information on HCC among descendants of Japanese immigrants, 28 HCC cases were identified, 24 of which had sera available for serologic evaluation.[15] Fifteen of the 24 had hepatitis B virus markers, while *none* had HCV markers. This implies that there is either an extremely low prevalence of HCV in Hawaii, or that another factor—cultural, nutritional, environmental—exists in Japan that helps promote carcinogenesis among HCV carriers residing in that country.

Two other important studies must be considered in the context of evaluating the natural history of those with already existing chronic hepatitis C. In one from Japan, involving a followup of transfusion-associated *chronic* NANB/C hepatitis cases, HCC development was found to be common.[16] Attempting to establish the rate of progression by extending information back to the time of initial infection based on transfusion histories, the investigators estimated that chronic hepatitis emerges after 10 years, cirrhosis after 21.2 years, and HCC after 29 years. In three cases, the interval even exceeded 50 years. In a similar study from the United States, involving an initial and followup evaluation of 131 transfusion-associated cases of chronic hepatitis C, initial evaluation revealed fatigue among 67.2 percent, hepatomegaly among 67.9 percent, histologically-defined "chronic active hepatitis" in 22.9 percent, and HCC in 5.3 percent.[17] During the followup period of 3.9 years, an additional 5.3 percent developed HCC, and 15.3 percent died. Emulating the Japanese study, the investigators estimated that, following acute infection, chronic hepatitis could be identified 13.7$\pm$10.9 years later, chronic active hepatitis 18.4$\pm$11.2 years later, cirrhosis 20.6$\pm$10.1 years later, and HCC, 28.3$\pm$11.5 years later. These studies demonstrated two important points: (1) serious outcomes are common in studies that begin with already established endstage or near-endstage chronic liver disease; and (2) the rate of progression is exceptionally slow, serious sequelae generally beginning to emerge only in the third or later decades after initial infection. Therefore, satisfactory information regarding the natural history of chronic hepatitis C can come only from longer-term prospective studies.

The National Heart, Lung, and Blood Institute (NHLBI) Long-Term Followup Study of Transfusion-Associated NANB Hepatitis

A long-term followup study has been in progress during the past 8 years directed at evaluating the sequelae of acute NANB hepatitis that had developed among persons participating in five separate transfusion studies conducted in the United States between 1968 and 1980.[18] In all five studies, hepatitis had been sought by prospective, repetitive serum enzyme monitoring of blood recipients, thus identifying even the entirely subclinical cases. Over 90 percent of these cases were defined as NANB hepatitis, 71 percent of whom were established to be HCV in origin. A total of 568 hepatitis cases were identified and matched with a transfused, non-hepatitis control group (984 subjects) from the same studies, both cohorts then being subjected to long-term followup evaluation.

All-cause mortality after an average of 18 years of followup was approximately 50 percent in both the cases and the controls, indicating no difference between cases and controls. Liver-related mortality, based on death certificate analysis, was 3.2 percent for the cases and 1.5 percent for the controls, a difference that was significant even though the frequency was quite low. Of note is that 71 percent of the study subjects who had died as a consequence of liver disease were found after enrollment to be heavy drinkers, some with hospitalizations for this problem. Evaluation of mortality by life-table analysis at the end of 20 years continued to demonstrate no difference on mortality between cases and controls. Furthermore, no difference in mortality could be found when the analysis was restricted to the HCV-positive cases and their controls.

Morbidity is also being assessed by recalling all living patients to determine their current status clinically, biochemically, serologically, and histologically. Two hundred and five cases and 335 controls were available for analysis, with a subgroup of 146 cases among whom all original (repository) and followup sera were available, permitting paired comparisons. Among the main group, certain marked differences were found between cases and controls. This included the frequency of fatigue and hepatomegaly, both found to be present slightly more commonly among cases than controls, the presence of raised serum enzymes (noted in one-third of cases and 4 percent of controls), and the presence of HCV-related hepatitis serology (anti-HCV and HCV RNA in 53 percent of cases and 6 percent of controls). Focusing on the 146 with available original and followup sera, 104 (71 percent) of them could be shown to have originally developed acute HCV-related transfusion-associated hepatitis. In followup of these individuals, one-half remained HCV RNA-positive in association with biochemical evidence of chronic hepatitis; one-fifth remained HCV RNA-positive but without biochemically defined chronic hepatitis; 15 percent showed anti-HCV alone; and 10 percent appeared to have recovered completely, both biochemically and seologically. Followup of the originally HCV-*negative* cases revealed that 93 percent remained negative, but 19 percent showed chronic hepatitis of undefined etiology.

Liver biopsies revealed the histology of chronic hepatitis alone in 58 percent and of cirrhosis in 28 percent. Correlating the histologic findings with overt clinical evidence of chronic hepatitis, clinical disease could be identified in 5 percent of those with chronic hepatitis alone, but in 70 percent of those with cirrhosis. However, among the latter, only about one-third of those with evident chronic liver disease had clearly advanced or moderately advanced chronic liver disease. Thus, 15–18 years after the initial infection, advanced liver disease could be demonstrated in 5–8 percent of the entire living cohort of NANB hepatitis cases among whom followup could be accomplished, or in 13 percent of those who had been defined biochemically to have chronic hepatitis. These data suggest that, at this juncture in the followup of the transfusion-associated NANB/C hepatitis cases, both mortality and severe morbidity are present, but in relatively low frequency. Moreover, overt morbidity appears confined largely to those with histologically identified cirrhosis. Whether persons with histologically detected chronic hepatitis alone will ultimately advance to cirrhosis and then assume the risks of the cirrhotic group remains to be determined through continued followup.

Another long-term followup study is also in progress that involves approximately 10,000 young Air Force recruits who were phlebotomized between 1948 and 1954 in the course of the evaluation, at that time, of an outbreak of streptococcal infection. The samples had been stored in deep freeze for

the past 40–45 years. With their rediscovery, the entire group was tested for the presence of HCV markers. A number of positive samples having been identified, a mortality and morbidity study is now in progress, comparing outcome among those who are positive with those selected as negative controls. This represents a unique opportunity to determine outcome among young persons found to be HCV-positive almost 50 years ago. Data will be presented.

Predictive Factors for Outcome of Chronic HCV Infection

If progression of chronic HCV infection is not inevitable, is it possible to identify factors that might help in predicting outcome? Viral factors that have been examined include viral dose, genotype, and the presence of quasispecies, each of which have been identified as having predictive value, although available data are conflicting.[19–24] Host-related factors include age, race, gender, and geographic location. Age may play an important role, the rate of progression appearing to be more rapid as the age at the time of infection rises. Geographic location also may be of importance, perhaps related to cultural or environmental differences. Extraneous influences may consist of co-infection with other viruses, exposure to environmental contaminants, smoking, or concomitant chronic alcoholism. Co-infection with hepatitis B has been reported to increase the severity of chronic hepatitis C and the likelihood of development of HCC.[25] Co-infection with HIV has been shown in hemophiliacs to increase HCV RNA levels[26] and to worsen the course of the disease.[27] Co-infection with hepatitis G was earlier considered likely to play a promoting role in disease progression, but careful studies have recently disproved these views.[28,29] Chronic alcoholism quite clearly enhances disease progression, either because it promotes increased viral replication or because it is an additive liver-damaging factor.[30,31] The use of alcohol should be strongly condemned in persons who have chronic HCV infection.

Summary

It is quite clear that a proportion of persons with chronic HCV infection will advance in time to cirrhosis and progress eventually to terminal chronic liver disease, in some instances after developing HCC. These are the seriously ill patients seen in tertiary care and liver transplant centers. The perception of the frequency of these adverse events depends, in part, on the stage of the disease at the time that followup studies are initiated. If they begin when chronic liver disease has already evolved, the frequency and tempo of progression is found to be high, particularly in some geographic areas such as Japan and Italy. If, however, studies begin with disease onset, serious sequelae seem to be defined less frequently. Current data suggest that during the first two decades after infection, with occasional exceptions, the disease runs an indolent course with relatively low frequencies of mortality and overt morbidity. If cirrhosis has developed during this period, symptomatic disease is more common than is noted when the histology demonstrates chronic hepatitis without cirrhosis. It can be anticipated that future morbidity and liver-related mortality is likely to emerge predominantly from the group that has developed cirrhosis, and this will become apparent as the disease process moves into its third or later decades. Whether progression is enhanced by definable factors is not yet fully established, but it does appear that late age of infection, genotype characteristics, and concomitant alcoholism may play promoting roles. Other promoting factors must continue to be sought. Whether persons with histologic evidence of chronic hepatitis alone at the end of the second decade will ultimately advance to cirrhosis and then assume the increased risks that accompany that lesion needs further evaluation through additional long-term studies. The proportion of cases whose disease remains completely stable is not yet known but might well represent the bulk of cases. The problem at present is that while helpful aggregate data are beginning to emerge, prediction of outcome for the individual case remains difficult to define. Indeed, the need for this information would be reduced if available treatment were more effective, less uncomfortable, and less costly. Continued long-term studies both of natural history and treatment strategies are, therefore, sorely needed. Finally, there is critical need for natural history and treatment studies involving children and adolescents with chronic HCV infection because of the extended life that awaits them.

References

1. Nishioka K, Watanabe J, Furuta S, et al. A high prevalence of the antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. Cancer 1991;67:429–33.

2. Tanaka K, Hirohata T, Koga S, et al. Hepatitis C and hepatitis B in the etiology of hepatocellular carcinoma in the Japanese population. Cancer Res 1991;51:2842–7.

3. Colombo M, Choo QL, Del Ninno E, et al. Prevalence of antibodies to hepatitis C virus in Italian patients with hepatocellular carcinoma. Lancet 1989;2:1006–8.

4. Bruix J, Calvet X, Costa J, et al. Prevalence of antibody to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. Lancet 1989;2:1004–6.

5. Hopf U, Moller B, Kuther D, et al. Long-term followup of posttransfusion and sporadic chronic hepatitis non-A, non-B and frequency of circulating antibodies to hepatitis C virus. J Hepatol 1990;10:69–76.

6. Di Bisceglie AM, Goodman ZD, Ishak, KG, et al. Long-term clinical and histopathological followup of chronic post-transfusion hepatitis. Hepatology 1991;14:969–74.

7. Tremolada F, Casarin C, Alberti A, et al. Long-term followup of non-A, non-B (type C) post-transfusion hepatitis. J Hepatol 1992;16:273–81.

8. Koretz RL, Abbey H, Coleman E, Gitnick G. Non-A, non-B post-transfusion hepatitis: looking back in the second decade. Ann Intern Med 1993;119:110–15.

9. Mattson L, Sonnerborg A, Weiland O. Outcome of acute symptomatic non-A, non-B hepatitis: a 13–year followup study of hepatitis C virus markers. Liver 1993;13:274–8.

10. Crowe J, Doyle C, Fielding JF, et al. Presentation of hepatitis C in a unique uniform cohort 17 years from inoculation (Abstract). Gastroenterology 1995;108:A1054.

11. Power JP, Lawlor E, Davidson F, et al. Hepatitis C viremia in recipients of Irish intravenous anti-D immunoglobulin. Lancet 1994;344:1166–7.

12. Takahashi M, Yamada G, Miyamoto R, et al. Natural course of chronic hepatitis C. Am J Gastroenterol 1993;88:240–3.

13. Yano M, Yatsuhasi H, Inoue O, et al. Epidemiology and long-term prognosis of hepatitis C virus infection in Japan. Gut 1993;34(Suppl):S13–S16.

14. Roberts JM, Searle JW, Cooksley WGE: Histological patterns of prolonged hepatitis C virus infection. Gastroenterol Jpn 1993;28:901–5.

15. Nomura A, Stemmermann GN, Chyou P-H, Tabor E: Hepatitis B and C serologies among Japanese Americans with hepatocellular carcinoma. J Infect Dis 1996;173:1474–6.

16. Kiyosawa K, Sodeyama T, Tanaka E, et al. Interrelationship of blood transfusion non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibidy to hepatitis C virus. Hepatology 1990;12:671–5.

17. Tong MJ, El-Farra NS, Reikes AR, Co RL: Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995;332:1436–66.

18. Seeff LB, Buskell-Bales Z, Wright EC, et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. N Engl J Med 1992;327:1906–11.

19. Gretch D, Corey I, Wilson J, et al. Assessment of hepatitis C virus RNA levels by quantitative competetive RNA polymerase chain reaction: high-titer viremia correlates with advanced stage of disease. J Infect Dis 1994;169:1219–25.

20. Honda M, Kaneko S, Sakai A, et al. Degree of diversity of hepatitis C virus quasispecies and progression of liver disease. Hepatology 1994;20:1144–51.

21. Farci P, Melpolder JC, Shimoda A, et al. Studies of HCV quasispecies in patients with acute resolving hepatitis compared to those who progress ro chronic hepatitis. Hepatology 1996;24:350A.

22. Tanaka E, Kiyosawa K, Matsushima T, et al. Epidemiology of genotypes of hepatitis C virus in Japanese patients with type C chronic liver disease: a multi-institution analysis. J Gastroenterol Hepatol 1995;10:538–45.

23. Kobayashi M, Tanaka E, Sodeyama E, et al. The natural course of chronic hepatitis C: a comparison between patients with genotypes 1 and 2 hepatitis C viruses. Hepatology 1996;23:695–9.

24. Romeo R, Tommasini MA, Rumi MG, et al. Genotypes in the progression of hepatitis C related cirrhosis and development of hepatocellular carcinoma. Hepatology 1996;24:153A.

25. Chiba T, Matsuzaki Y, Abei M, et al. The role of previous hepatitis B virus infection and heavy smoking in hepatitis C virus-related hepatocellular carcinoma. Am J Gastroenterol 1996;91:119–203.

26. Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. Blood 1994;84:1020–3.

27. Eyster ME, Diamondstone LS, Lien JM, et al. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus. The Multicenter Hemophilia Cohort Study. J Acquir Immun Defic Syndr 1993;6:602–10.

28. Tanaka E, Alter HJ, Nakatsuji Y, et al. Effect of hepatitis G virus infection on chronic hepatitis C. Ann Intern Med 1996;125:740–3.

29. Pawlotsky JM, Roudot-Thoravel F, Pellerin M, et al. GBV-C infection in HCV-infected patients: epidemiological characteristics, influence on HCV infection and response to interferon alfa therapy. Hepatology 1996;24:226A.

30. Oshita M, Hayashi N, Kasahara A, et al. Increased serum hepatitis C virus RNA levels among alcoholic patients with chronic hepatitis C. Hepatology 1994;20:1115–20.

31. Noda K, Yoshihara H, Suzuki K, et al. Progression of type C chronic hepatitis to liver cirrhosis and hepatocellular carcinoma—its relationship to alcohol drinking and the age of transfusion. Alcohol Clin Exp Res 1996;20:95A–100A.

Blood Donors With Hepatitis C

Harvey J. Alter, M.D.

Cloning of the hepatitis C virus (HCV)[1] and the subsequent development of sensitive serologic assays and polymerase chain reaction (PCR) for HCV RNA revealed that this agent was widespread in the donor population, that it accounted for approximately 90 percent of transfusion-transmitted hepatitis and that infection, though generally asymptomatic, could in some cases lead to cirrhosis, hepatocellular carcinoma, and end-stage liver disease.[2,3] The first-generation test for antibody to HCV (anti-HCV) was introduced into donor screening in 1990. At that time, 0.5–0.6 percent of donors were repeatedly reactive for this antibody by enzyme immunoassay (EIA) and approximately 0.3 percent confirmed as positive by a supplemental strip immunoblot assay (SIA, RIBA™). A more sensitive second-generation EIA was introduced in 1992[4] and current data from the American Red Cross show a repeat reactive rate of 0.23 percent and a confirmed reactive rate of 0.16 percent. These tests have been extremely beneficial in the prevention of transfusion-associated hepatitis. An ongoing NIH prospective study of transfusion recipients shows no cases of hepatitis C among approximately 650 recipients followed since second- generation screening was implemented.

These screening assays have uncovered a large population of asymptomatic HCV carriers. It has been estimated that there are more than 1 million such carriers in the United States alone. Further, this virus is globally distributed with anti-HCV rates among donors throughout the world ranging from 0.3–1.5 percent. What is the significance of this infection to these asymptomatic individuals? How were they infected? What is the risk that they will transmit the infection to others by nonparenteral routes? What proportion of antibody-positive individuals have active infection? What proportion have significant liver disease? To address these issues, we initiated a study, in collaboration with the American Red Cross, to investigate risk factors, transmission patterns, viremia rates, and disease manifestations among 248 donors who were confirmed anti-HCV positives, 102 who were indeterminate on the SIA-supplemental assay and 131 who were SIA-negative.[5] When SIA-positives were compared with SIA-negatives, the significant demographic and historical factors were, respectively, as follows: lower age
(37 vs. 44, $p<0.001$), the absence of college education (54 percent vs. 16 percent, $p<0.001$), black race (19 percent vs. 7 percent, $p=0.002$), first time donor status (24 percent vs. 2 percent, $p<0.001$), a history of liver disease (31 percent vs. 5 percent, $p<0.001$), and a history of sexually transmitted disease
(28 percent vs. 10 percent, $p<0.001$).

Risk factor analysis revealed several unexpected findings. When anti-HCV/SIA-positives were compared with SIA-negatives in a logistic regression model, the significant risk factors were, respectively: a history of blood transfusion (27 percent vs. 8 percent, $p<0.001$); intranasal cocaine use (68 percent vs. 11 percent, $p<0.001$); intravenous drug use (42 percent vs. 2 percent, $p=0.001$); sexual promiscuity as defined by a history of STD, sex with a prostitute, or more than 5 partners per year
(53 percent vs. 24 percent, $p=0.002$); and ear piercing among males (30 percent vs. 0 percent, $p<0.05$). A history of tattooing or imprisonment were significant in the univariate analysis, but not in the multivariate analysis because of the close association with intravenous drug use (IVDU). There was no significant association with acupuncture or medically related needle-stick injuries. The high frequency of IVDU was unexpected, since these participants had denied such use at the time of donation. On further questioning, it was revealed that none were currently using drugs, that 74 percent had not used IV drugs since 1980 and, generally, that the donors did not consider this remote drug use important to the safety of their donation. Nonetheless, it is remarkable that almost half of this HCV-infected donor population had used intravenous drugs with shared needles at some point in their life. Just as startling was the high proportion of donors who had snorted cocaine, not only the 68 percent frequency among those who were anti-HCV confirmed positives, but also the 11 percent rate in those

anti-HCV negative. Further questioning of anti-HCV-positive cocaine users revealed that 84 percent shared straws during cocaine use, 44 percent snorted three or more times per day, 29 percent had epistaxis during snorting and 27 percent observed epistaxis in others. We postulate that cocaine snorting with shared devices and associated epistaxis may represent a covert mechanism of viral transmission.

HCV transmission to contacts was measured in 85 sexual partners, 47 children, and 9 parents of SIA-positive donors. Although 9 of 85 (11 percent) sexual partners were anti-HCV positive, 8 had independent parenteral risk factors. Similarly, although 5 of 47 children (11 percent) were anti-HCV positive, in 4, the antibody appeared due to passive transfer from the mother, and in the other there was an established parenteral risk factor. Although 2 of 9 parents were anti-HCV positive, both had known parenteral exposures. Thus in only 1 of 132 contacts (0.7 percent) was anti-HCV positivity unexplained by an independent parenteral risk or by passive transfer of antibody.

HCV RNA by PCR was detected in 86 percent of SIA-positive donors, 3 percent of SIA-indeterminate donors, and none of the SIA-negative donors. Of the three SIA-indeterminate donors who were PCR-positive, two were SIA-positive on a more sensitive third-generation assay. It is important to note that 14 percent of confirmed antibody positives were PCR-negative. This remained true even when the PCR was repeated, and it suggests that approximately 15 percent of HCV-infected individuals recover from their infection. Prospective studies of transfusion recipients reveal the same 15 percent recovery rate.

Biochemical evidence of liver disease was found in 56 percent of SIA-positives on initial evaluation and in 69 percent of those who were followed over time. The extent of ALT elevation was modest (median 48 U/L, range 4–556). During followup, 31 percent had persistently normal ALT and only 15 percent had ALT levels that exceed two times the upper limit of normal. Elevated ALT strongly correlated with the presence of HCV RNA. Liver biopsy was performed in 77 SIA-positive participants; 6 (8 percent) had no histologic evidence of hepatitis; these 6 had normal ALT and 5 of 6 were
HCV RNA negative. Sixty-six (86 percent) had mild to moderate chronic hepatitis and 5 (6 percent) had severe lesions, including severe chronic hepatitis and/or cirrhosis. All with severe lesions were HCV RNA positive and had ALT levels greater than twice the upper limit of normal. No participants had characteristic symptoms of hepatitis and although fatigue was common, its frequency was similar in infected and uninfected subjects.

Thus, among donors with confirmed antibody to HCV, approximately 85 percent appear to be chronic carriers and 15 percent appear to have recovered from prior infection. Among the carriers, there were no distinguishing symptoms. Although the majority had both biochemical and histologic evidence of chronic viral hepatitis, the extent of liver injury was generally mild. Only 6 percent had evidence of severe hepatitis or cirrhosis, despite a duration of infection that generally exceeded 10 years and frequently exceeded 20 years. Severe histologic lesions correlated with the highest ALT levels. Standard parenteral sources of infection were identified in 75 percent of HCV-infected individuals. In addition, there was a very strong association with intranasal cocaine use and this may represent a covert form of parenteral transmission. There was no evidence for sexual or familial transmission when specific contacts of the index cases were tested.

References

1. Choo Q-L, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244:359–62.

2. Kuo G, Choo Q-L, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B viral hepatitis genome. Science 1989;244:362–4.

3. Alter HJ. New Kit on the Block: Evaluation of second-generation assays for detection of antibody to the hepatitis C virus. Hepatology 1992;15:350–3.

4. Alter HJ, Purcell RH, Shih JW, Melpolder JC, Houghton M, Choo Q-L, Kuo G. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med 1989;321:1494–500.

5. Conry-Cantilena C, VanRaden MA, Gibble J, Melpolder J, Shakil AO, Viladomiu L, Chueng L, DiBisceglie A, Hoofnagle J, Shih JW, Kaslow R, Ness P, Alter HJ. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med 1996;334:1691–6.

Hepatitis C and Hepatocellular Carcinoma

Adrian M. Di Bisceglie, M.D.

It has become apparent that hepatitis C virus (HCV) infection is a major risk factor for the development of hepatocellular carcinoma (HCC) worldwide. Evidence linking HCV with HCC includes the following: (1) A high proportion of patients with HCC have anti-HCV or HCV RNA detectable in serum. This is particularly apparent in southern Europe and Japan where 50–75 percent of patients with HCC have evidence of HCV infection.[1–3] (2) In patients with chronic HCV infection, progression can be noted from milder forms of hepatitis to cirrhosis and eventually, to HCC. This progression may take decades to occur.

The precise mechanism by which HCV causes HCC is not known. Unlike the hepatitis B virus (HBV), HCV is not a DNA virus and does not become integrated within the genome of hepatocytes. It is more likely that HCC occurs against a background of inflammation and regeneration, associated with liver injury due to chronic hepatitis. Most, but not all, cases of HCV-related HCC occur in the presence of cirrhosis, suggesting that it is the underlying liver disease *per se* that is the risk factor for HCC rather than HCV infection.[4] The prevailing hypothesis has been that some cirrhotic nodules which grow larger than others (referred to as adenomatous hyperplasia) were the precursor for HCC. Recently, however, it has been suggested that foci of transformed hepatocytes may arise in between cirrhotic nodules and grow to become adenomatous hyperplasia and, eventually, HCC.[5]

Host factors which have been implicated in increasing the risk for development of HCC include age, male gender, and severity of underlying liver disease. Viral genotype may be important, although early suggestions that infection with genotype 1b is more likely to result in the development of HCC have not been confirmed in larger studies.[6] Although viral load has been related to the severity of liver disease, no clear link has been established between serum levels of HCV RNA and progression to HCC. Some external factors that might add to the risk for HCC in patients with HCV infection include alcohol consumption, coexistent HBV infection, and porphyria cutanea tarda, although this latter condition is found only in some geographic areas.

The risk for a patient with HCV infection developing HCC cannot be calculated with any precision. It is known that approximately 20 percent of patients with chronic HCV infection develop histologic evidence of cirrhosis over a 10-year period. Furthermore, among patients with established cirrhosis due to HCV infection in screening programs, it has been found that 3–4 percent per year develop HCC, at least for the first 4–5 years of screening.[7,8] By extrapolation, after 20 years of infection, 6–8 percent of patients with chronic hepatitis C can be expected to have developed HCC, although these calculations need to be validated by more prospective studies. Studies from Japan have found that the mean interval from HCV infection to the development of HCC is approximately 25 years, but these periods have a very wide range of variation.[9] In the United States, HCC has been described as soon as 5 years from the onset of HCV infection.[4]

Typically, HCC carries a poor prognosis, with survival times from diagnosis measured in months. Screening studies have shown that small amounts of HCC can be detected at an early stage when it may be more amenable to curative therapy.[7] At present surgical resection offers the best hope for prolonged disease-free survival. This may take the form of partial or total hepatectomy. Unfortunately, partial hepatectomy for HCC is associated with a very high recurrence rate (approximating 25 percent per year) while total hepatectomy implies liver transplantation. Thus, the true cost-effectiveness of screening for HCC remains uncertain.

It has been suggested that progression to HCC can be halted or slowed down by treatment of the underlying hepatitis C. Recent studies from Japan, for example, have suggested that patients with

cirrhosis due to chronic HCV infection have a significantly lower risk of HCC if treated with alpha interferon than patients who were not treated.[8] This improvement in risk was noted both in patients who had a good response to interferon as well those who did not. Data from these studies await confirmation in Europe or the United States.

References

1. Nishioka K, Watanabe J, Furuta S, Tanaka E, Iino S, Suzuki H, Tsuji T, Yano M, Kuo G, Choo Q-L, Houghton M, Oda T. A high prevalence of antibody to the hepatitis C virus in patients with hepatocellular carcinoma in Japan. Cancer 1991;67:429–33.

2. Bruix J, Barrera JM, Calvet X, Ercilla G, Costa J, Sanchez-Tapias JM, Ventura M, Vall M, Bruguera M, Bru C, Castillo R, Rodes J. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. Lancet 1989;ii:1004–6.

3. Di Bisceglie AM, Order SE, Klein JL, Waggoner JG, Sjogren MH, Kuo G, Houghton M, Choo Q-L, Hoofnagle JH. The role of chronic viral hepatitis in hepatocellular carcinoma in the United States. Am J Gastroenterol 1991;86:335–8.

4. Di Bisceglie AM, Simpson LH, Lotze MT, Hoofnagle JH. Development of hepatocellular carcinoma among patients with chronic liver disease due to hepatitis C viral infection. J Clin Gastroenterol 1994;19:222–6.

5. Tong MJ, El-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 1995;332:1463–6.

6. Silini E, Bottelli R, Asti M, Bruno S, Candusso ME, Brambilla S, Bono F, Iamoni G, Tinelli C, Mondelli MU, Ideo G. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: A case-control study. Gastroenterology 1996;111:199–205.

7. Zoli M, Magalotti D, Bianchi G, Gueli C, Marchesini G, Pisi E. Efficacy of a surveillance program for early detection of hepatocellular carcinoma. Cancer 1996;78:977–85.

8. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, Shiomi S, Seki S, Kobayashi K, Otani S. Randomised trial of effects of interferon-a on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995;346:1051–5.

9. Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, Furuta S, Akahane Y, Nishioka K, Purcell RH, Alter HJ. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: Analysis by detection of antibody to hepatitis C virus. Hepatology 1990;12:671–5.

Hepatitis C and Alcohol

Eugene R. Schiff, M.D.

Introduction

The alcoholic patient is no less subject to the spectrum of hepatobiliary disorders that may afflict the nonalcoholic patient and, in some cases, may be predisposed to liver injury because of specific socioeconomic, epidemiologic, or metabolic risk factors.

Prevalence of Anti-HCV Markers

Multiple studies have clearly demonstrated a high prevalence of anti-HCV among alcoholic patients with liver disease.[1–5] Testing with supplemental assays (e.g., recombinant immunoblot assay [RIBA]) confirmed that 8–45 percent of alcoholic patients with liver disease have anti-HCV (RIBA+). The prevalence of anti-HCV is sevenfold higher among alcoholics than in the population at large (10 percent vs. 1.4 percent), but is even higher in those with liver disease (30 percent). Most of those with liver disease have detectable HCV RNA which may also be present in some anti-HCV(-)patients. Anti-HCV(+)(RIBA+) patients are likely to have HCV RNA detected, which is indicative of active viral infection, usually associated with some degree of necroinflammatory changes, with or without fibrosis, regardless of alanine aminotransferase (ALT) levels.

HCV Correlation With Severity of Liver Injury

The prevalence of anti-HCV(RIBA+) correlates with the severity of liver injury seen in alcoholic patients. Anti-HCV positivity (RIBA+) correlated positively and significantly with cirrhosis, cellular unrest, periportal inflammation, and piecemeal necrosis, in contrast to anti-HBc, which did not correlate with any of these histologic features, in a large Veterans Administration (VA) study.[6] In a study of 144 alcoholic patients, a prevalence of 20 percent anti-HCV positivity in alcoholic fibrosteatosis, 21.4 percent in alcoholic hepatitis, and 42.6 percent in alcoholic cirrhosis, as compared to 2.2 percent in alcoholic patients without liver disease, was noted.[7] Histologic features, with the exception of sinusoidal cellularity, were comparable in alcoholic patients with and without anti-HCV. Nishiguchi et al. performed both immunoblot and HCV RNA determinations among 80 alcoholic patients with liver disease.[8] Patients with cirrhosis and HCV RNA had higher ALT activity than comparable patients without HCV RNA. The HCV RNA(+) patients had higher histologic activity indices (Knodell) than those without detectable HCV RNA. The presence of HCV RNA conferred a more severe degree of periportal and bridging necrosis, intralobular degeneration, focal necrosis, and portal inflammation.

Effect of Abstinence on Alcoholic Patients with Histologic Evidence of Chronic Hepatitis

In HCV RNA(+) alcoholic patients with histologic evidence of chronic hepatitis, abstinence was not followed by resolution of aminotransferase elevation, which has been observed in both anti-HCV(+) HCV RNA(-) and anti-HCV(-), HBsAg(-) alcoholic patients with similar histologic features.[9] This suggests that chronic hepatitis C infection perpetuates the liver damage in these alcoholic patients who have abstained. Nevertheless, serum HCV RNA levels will decrease with abstinence.[10]

Epidemiology of Hepatitis C Among Alcoholic Patients

The epidemiology of hepatitis C among alcoholic patients with bonafide viral C infection has not been definitively characterized. Intravenous drug abuse (IVDA) is the most common risk factor. Yet

there has not been a good explanation for the disproportionately high prevalence of HCV among alcoholic patients with liver disease without a history of IVDA.[11] Caldwell et al. found the prevalence of anti-HCV similar among patients with alcoholic liver disease who had high risk factors as compared to those without identifiable modes of parenteral transmission.[12]

Effect of Alcohol on HCV Replication

A critical question is whether or not alcohol and hepatitis C infection are synergistic in a combined liver injury. In some patients, there are both histologic features of alcoholic liver injury and chronic viral hepatitis, but in most studies the predominant pattern is chronic hepatitis.[13] Alcohol may enhance the replication of hepatitis C and produce a more severe injury independent of the direct alcohol-induced toxic injury. There is a correlation between HCV RNA levels and amount of alcohol consumed.[14] Alcoholic patients with HCV infection have higher hepatic iron concentrations, which may be germane to increased HCV replication.[15] Clinical evidence of hepatic activity and viral levels is significantly greater in those consuming greater than 10g of alcohol per day.[16]

Effect of Alcohol on Progression of Chronic Viral C Hepatitis to Cirrhosis and Hepatocellular Carcinoma

There is a more rapid development of cirrhosis and hepatocellular carcinoma in the alcoholic with chronic HCV infection.[17,18] The period from transfusion to the diagnosis of cirrhosis is shorter in the heavy drinker. The risk for the development of hepatocellular carcinoma in alcoholic cirrhotics is 8.3 times higher in the HCV(+) patients than HCV(-) patients, and the prevalence of anti-HCV among alcoholics with HCC is 50–70 percent.[20,21] Therefore, alcohol may modify the replication of HCV as well as the oncogenicity of HCV in hepatocellular carcinoma.

Interferon Therapy in Alcoholic Patients with Chronic Hepatitis C

Among alcoholic patients with chronic hepatitis C who remained abstinent during therapy with interferon, there was a significantly lower rate of HCV RNA clearance in those who consumed >70g/day of ethanol as compared to <70g/day drinkers or nondrinkers.[22] A similar experience noted zero HCV RNA clearance in those consuming >70g/day up to the time of interferon therapy.[23]

Conclusion

The most common type of nonalcoholic liver disease seen in alcoholic patients is chronic viral hepatitis C. Evidence accumulated thus far supports the concept that superimposed hepatitis C infection confers a more severe liver injury in alcoholic patients, possibly by enhancing viral replication. The progression of the liver disease is more rapid and the risk for the development of hepatocellular carcinoma, once cirrhosis has developed, is high. It remains to be proven whether or not successful antiviral therapy will change the natural history and improve the prognosis in such patients who abstain. Regardless, part of the mystery of why some alcoholics develop liver disease while most do not can be explained by the presence of chronic viral C hepatitis.

References

1. Koff RS, Dienstag JL. Extrahepatic manifestations of hepatitis C and the association with alcoholic liver disease. Semin Liver Dis 1995;15(1):101-9.

2. Befrits R, Hedman M, Blomquist L, Allander T, Grillner L, Kinnman N, Rubio C, Hultcrantz R. Chronic hepatitis C in alcoholic patients: prevalence, genotypes, and correlation to liver disease. Scand J Gastroenterol 1995;30(11):1113–8.

3. Mendenhall CL, Moritz T, Rouster S, Roselle G, Polito A, Quan S, KiNelle RK, and the VA Cooperative Study Group 275. Epidemiology of hepatitis C among veterans with alcoholic liver disease. Am J Gastroenterol 1993;88(7):1022–6.

4. Coelho-Little ME, Jeffers LJ, Bernstein DE, Goodman JJ, Reddy KR, deMedina M, Li X, Hill M, LaRue S, Schiff ER. Hepatitis C virus in alcoholic patients with and without clinically apparent liver disease. Alcohol Clin Exp Res 1995;19(5):1173-6.

5. Caldwell SH, Li X, Rourk RM, Millar A, Sosnowski KM, Sue M, Barritt AS, McCallum RW, Schiff ER. Hepatitis C infection by polymerase chain reaction in alcoholics: false-positive ELISA results and the influence of infection on a clinical prognostic score. Am J Gastroenterol 1993;88(7):1016-21.

6. Mendelhall CL, Seeff L, Diehl AM, Ghosen SJ, French SW, Gartside PS, et al. Antibodies to hepatitis B virus and hepatitis C virus in alcoholic hepatitis and cirrhosis: their prevalence and clinical relevance. Hepatology 1991;14(4):581-9.

7. Pares A, Barrera JM, Caballeria J, Ercilla G, Bruguera M, Caballeria L, Castillo R, Rodes J. Hepatitis C virus antibodies in chronic alcoholic patients: association with severity of liver injury. Hepatology 1990; 12(6):1295-9.

8. Nishiguchi S, Kuroki T, Yabusako T, Seki S, Kobayashi K, Monna T, Otani S, et al. Detection of hepatitis C virus antibodies and hepatitis C virus RNA in patients with alcoholic liver disease. Hepatology 1991; 14(6):985-9.

9. Takase S, Takada N, Enomoto N, et al. Different types of chronic hepatitis in alcoholic patients: does chronic hepatitis induced by alcohol exist? Hepatology 1991;13:876-81.

10. Sata M, Fukuizumi K, Uchimura Y, Nakano H, Ishii K, Kumashiro R, Mizokami M, Lau JYN, Tanikawa K. Hepatitis C virus infection in patients with clinically diagnosed alcoholic liver diseases. J Viral Hepatitis 1996;3:143-8.

11. Rosman AS, Waraich A, Galvin K, Casiano J, Paronetto F, Liever CS. Alcoholism is associated with hepatitis C but not hepatitis B in an urban population. Am J Gastroenterol 1996;91(3):498-505.

12. Caldwell SH, Jeffers LJ, Ditomaso A, Millar A, Clark RM, Rabassa A, Reddy KR, deMedina M, Schiff ER. Antibody to hepatitis C is common among patients with alcoholic liver disease with and without risk factors. Am J Gastroenterol 1991;86(9):1219-23.

13. Uchimura Y, Sata M, Kage M, Abe H, Tanikawa K. A histopathological study of alcoholics with chronic HCV infection: comparison with chronic hepatitis C and alcoholic liver disease. Liver 1995;15(6):300-6.

14. Oshito M, Takei Y, Kawano S, Hijioka T, Masuda E, Goto M, Nishimuro Y, Nagui H, Ito S, Tsuji S, Fusamoto H, Kamada T. Endogenous nitric oxide attenuates ethanol-induced perturbation of hepatic circulation in the isolated perfused rat liver. Hepatology 1994;20:961-5.

15. Izumi N, Enomoto N, Uchihara M, Murakami T, Ono K, Noguchi O, Miyake S, Nouchi T, Fujisawa K, Marumo F, Sato C. Hepatic iron contents and response to interferon-a in patients with chronic hepatitis C. Dig Dis Sci 1996;41(5):989-94.

16. Cromie SL, Jenkins PJ, Bowden DS, Dudley FJ. Chronic hepatitis C: effect of alcohol on hepatic activity and viral titre. J Hepatol 1996;25:821-6.

17. Takase S, Tsutsumi M, Kawahara H, et al. The alcohol-altered liver membrane antibody and hepatitis C virus infection in the progression of alcoholic liver disease. Hepatology 1993;17:9–13.

18. Noda K, Yoshihara H, Suzuki K, Yamada Y, Kasahara A, Hayashi N, Fusamoto H, Kamada T. Progression of type C chronic hepatitis to liver cirrhosis and hepatocellular carcinoma—its relationship to alcohol drinking and the age of transfusion. Alcohol Clin Exp Res 1996;2(1):95A-100A.

19. Sato Y, Okabe K. Studies on the incidence of hepatocellular carcinoma in heavy drinkers with liver cirrhosis [abstract]. Alcohol Alcohol 1993;(1B Suppl):109–14.

20. Nalpas B, Feitelsol M, Brechot C, Rubin E. Alcohol, hepatotropic viruses, and hepatocellular carcinoma [editorial]. Alcohol Clin Exp Res 1995;19(5);1089–95.

21. Miyakawa H, Sato C, Izumi N, Tazawa J, Ebata A, Hattori K, Sakai H, Ikeda T, Hirata R, Sakai Y, et al. Hepatitis C virus infection in alcoholic liver cirrhosis in Japan: its contribution to the development of hepatocelluar carcinoma. Alcohol Alcohol 1993;(1A Suppl):85–90.

22. Okazaki T, Yoshihara H, Suzuki K, Yamada Y, Tsujimura T, Kawano K, Yamada Y, Abe H. Efficacy of interferon therapy in patients with chronic hepatitis C. Comparison between non-drinkers and drinkers. Scand J Gastroenterol 1994;29(11):1039–43.

23. Ohnishi K, Matsuo S, Matsutani K, Itahashi M, Kakihara K, Suzuki K, Ito S, Fujiwara K. Interferon therapy for chronic hepatitis C in habitual drinkers: comparison with chronic hepatitis C in infrequent drinkers. Am J Gastroenterol 1996;91(7):1374–9.

Diagnostic Tests for Hepatitis C

David Gretch, M.D., Ph.D.

Diagnostic tests for hepatitis C (HCV) can be divided into two general categories: (1) serologic assays which detect anti-HCV antibodies, and (2) molecular assays which detect, quantify, and/or characterize HCV RNA genomes within an infected patient. Serologic assays have been subdivided into screening tests for anti-HCV and supplemental antibody tests. Molecular assays can be divided into qualitative tests for HCV RNA, quantitative tests for assessing viral RNA levels, and HCV genotype tests.

Screening Assays for Anti-HCV

The main screening assay for detecting anti-HCV antibodies is the enzyme immunoassay (EIA). The EIA has many advantages in the diagnostic setting, including ease of use, low variability, ease of automation, and relatively low expense. The first-generation anti-HCV test (EIA-1) contained a single HCV recombinant antigen derived from the nonstructural (NS) 4 gene, designated c100-3.[1] Although development of this test represented a dramatic breakthrough in terms of diagnosing HCV infection and reducing HCV transmission via blood transfusion,[2–5] EIA-1 lacked optimal sensitivity and specificity and was subsequently replaced in 1992.[6] The EIA-2 test contains HCV antigens from the core and NS3 genes in addition to the NS4 antigen, and thus represents a multi-antigen EIA.[7] Introduction of the new antigens led to a substantial improvement in sensitivity and a slight increase in specificity relative to the EIA-1 (Table 1).[7–15] The use of core and NS3 antigens in the EIA-2 test shortened the average "window period" for HCV seroconversion by 4–10 weeks relative to the EIA-1 test.[10,16] A third-generation anti-HCV test (e1a-3), which contains reconfigured core and NS3 antigens plus an additional HCV antigen (NS5) not present in the EIA-2,[17–20] has recently been approved for screening blood products. While preliminary studies suggest an incremental improvement in sensitivity in blood donors, immunosuppressed populations, and liver clinic populations, the specificity of the EIA-3 test has not been adequately defined in the routine diagnostic setting, and utility of the NS5 antigen in this assay has been controversial.

A progressive improvement in sensitivity of detection of anti-HCV has been accomplished by the three generations of EIA screening assays (Table 1). However, testing in high-prevalence populations has indicated that not all patients with active HCV infection (e.g., HCV RNA positive) are identified with the EIA screening tests. Preliminary studies suggest the envelope 2 (E2) antigen may be a good candidate for subsequent versions of the EIA test.[21–23] Although false-positive EIA testing remains a problem in low-prevalence populations, the accuracy of the EIA-2 test is very good in high-prevalence populations, and therefore, supplemental anti-HCV tests may not be necessary in high-risk patients with a positive anti-HCV screen.

TABLE 1. Sensitivity and Accuracy of Anti-HCV Screening Tests					
Low-Prevalence (Blood Donor)			High-Prevalence (Liver Clinic)		
Test	Sensitivity	Accuracy*	Test	Sensitivity	Accuracy*
EIA-1	95–98%	30–50%	EIA-1	60–80%	70–85%
EIA-2	99.7–99.8%	50–61%	EIA-2	92–95%	88–95%
EIA-3	99.9+%	n.d.	EIA-3	97%	n.d.

* Percentage of specimens with a positive anti-HCV screen which are also positive by supplemental anti-HCV test. Modified from references cited in text, and Gretch, et al., unpublished data.

Supplemental Tests for Anti-HCV

Supplemental tests for anti-HCV were developed to help resolve false-positive EIA test results. The prototype supplemental test in the United States is the FDA-licensed second-generation recombinant immunoblot assay (RIBA-2), which contains the same HCV antigens as EIA-2 in an immunoblot format.[7] Results are either positive (two or more positive antigens), indeterminate (one positive antigen), or negative. Interpretation of HCV serology depends on the patient risk status (Table 1). For example, in the low-prevalence blood bank setting, (1) about 40–50 percent of specimens with positive EIA results are false positives (i.e., RIBA-negative), and (2) few RIBA-2 indeterminate results are HCV RNA positive.[11–13, 24–28] However, in the high-prevalence setting (e.g., the University of Washington Viral Hepatitis Reference Laboratory), approximately 90 percent of EIA-positive specimens are also positive by RIBA (Gretch, et al., unpublished data). In this setting, about 85 percent of RIBA-positive specimens and 20–50 percent of RIBA core or NS3 indeterminate specimens are positive for HCV RNA by PCR.[28–36] A third-generation supplemental test (RIBA-3) has been introduced in Europe, which appears to be more specific than the RIBA-2 test based on a better correlation with RNA PCR results and a reduced number of RIBA-indeterminate results,[31,37–39] as yet, RIBA-3 has not been approved in the United States.

Qualitative Tests for HCV RNA

Detection of HCV RNA in patient serum by highly sensitive tests such as reverse transcription polymerase chain reaction (RT-PCR) has become an increasingly important tool for confirming the diagnosis of hepatitis C and for assessing the antiviral response to interferon therapy.[40,41] The role of tests for HCV RNA in the diagnosis and management of hepatitis C is discussed in subsequent presentations.

Many variations in the RT-PCR assay have been described in the literature, and standardization of such "home-brew" assays has been difficult, as illustrated by a European survey, where only 16 percent of laboratories scored perfectly on a standardized test panel.[42] Numerous factors contribute to RT-PCR variability, including specimen handling and storage, correct design of amplification primers, variability of biochemical reactions, DNA product contamination, and efficiency of postamplification detection systems.[43–50] It is therefore important to emphasize the need for evidence of rigorous proficiency testing by qualified diagnostic laboratories before HCV RNA testing can be reliably used in patient management. Nonetheless, several excellent home-brew assays with proven clinical utility have been described,[48–56] of which the most sensitive can detect HCV RNA at a level of less than 100 copies per ml of patient serum. In this regard, HCV RNA proficiency testing of laboratories in the U.S. has only recently been initiated by the College of American Pathologists.

Roche Molecular Diagnostics has recently introduced the Amplicor test kit for qualitative HCV RNA detection by the RT-PCR technique.[57,58] The kit is reliable, and has built-in controls for assay sensitivity and specificity. The assay was originally designed to test 50 ul of serum, but was found to be 4–10 fold less sensitive than optimized RT-PCR assays in research reference laboratories.[57] However, modifications of the Amplicor test allow HCV RNA detection at less than 100 HCV RNA copies per ml of serum, with a specificity of 97–99 percent (Gretch, et al., unpublished data).

Quantitative Tests for HCV RNA

In addition to being a valuable research tool, the quantitative assessment of HCV RNA levels in patients before, during, and after therapy has tremendous potential for improving the clinical management of chronic hepatitis C.[59] In a recent study of HCV viremia, it was established that HCV RNA levels are relatively stable (without significant fluctuation) in untreated patients with chronic hepatitis C.[60] These findings are important because, although numerous studies have demonstrated that therapy may reduce HCV RNA levels, the assumption that HCV RNA levels are stable before therapy was unproven. The following paragraph briefly describes current methods for assessing HCV "viral load," while application of HCV RNA testing in monitoring of virologic response to therapy is discussed in subsequent sections.

Two different technologies have been developed to assess HCV RNA levels in patient specimens: target amplification methods such as quantitative PCR (Q-PCR), and signal amplification technologies such as branched DNA assay (bDNA).[61] Quantitative PCR tests have been described by several laboratories, and differ markedly in the reported performance characteristics.[61–71] The only standardized quantitative PCR assay available in kit format is the Roche Monitor assay. Unfortunately, experience with this assay has been limited. The main strength of Q-PCR is high analytical sensitivity, with reports as low as 1,000 RNA copies per ml; on the other hand, major problems include high assay variability, and limited linear range. By comparison, the bDNA test has been extensively evaluated, and appears to be highly standardized, although the sensitivity of bDNA assay is 2–3 logs less than PCR-based methods.[61, 72–78] Therefore, PCR testing has been recommended on bDNA-negative specimens.[61, 73] It is also important to note that a "genotype bias" is possible for all HCV molecular assays because of the extensive genetic heterogeneity of the virus. For example, the first-generation bDNA test (bDNA 1.0) apparently under-reported HCV RNA levels for a subset of HCV genotypes,[76, 77] while the second-generation test (bDNA 2.0) appears to be more accurate.[79] Unfortunately, additional refinements may be necessary before standardized tests are licensed for routine use in hepatitis C management.

HCV Genotype Testing

HCV is a remarkably heterogeneous family of viruses, with at least six distinct genotypes and numerous subtypes of HCV identified throughout the world.[80–82] Tests to determine HCV genotype fall into two categories: (1) Screening tests which detect point mutations and (2) confirmatory tests which evaluate larger segments of HCV genes. Commonly used screening tests include 5'-RFLP analysis, core-gene nested PCR, and the LIPA assay.[83–85] Confirmatory tests include nucleotide sequencing and phylogenetic analysis of the E1 gene or NS5B gene.[86–88] HCV genotype determination is an important aspect of ongoing clinical trials, since HCV genotype may be an independent predictor of response to therapy, as will be discussed later. However, there is as yet little role for HCV genotyping in the routine clinical setting, since optimal treatment regimens have not been defined for different HCV genotype infections.

References

1. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, Miyamura T, Dienstag JL, Alter MJ, Stevens CE, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science 1989;244:362–4.

2. Alter HJ, Purcell RH, Shih JW, Melpolder JC, Houghton M, Choo QL, Kuo G. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. N Engl J Med 1989;321:1494–500.

3. Esteban JI, Esteban R, Viladomiu L, L'Opez Talavera JC, Gonzalez A, Hernandez JM, Roget M, Vargas V, Genesca J, Buti M, et al. Hepatitis C virus antibodies among risk groups in Spain. Lancet 1989;2:294–7.

4. Esteban J, Gonzalez A, Hernandez J, Viladomiu L, Sanchez C, Lopez-Talavera J, Lucea D, Martin-Vega C, Vidal X, Esteban R, Guardia J. Evaluation of antibodies to hepatitis C virus in a study of transfusion associated hepatitis. N Engl J Med 1990;323:1107–12.

5. Alter MJ, Hadler SC, Judson FN, Mares A, Alexander WJ, Hu PY, Miller JK, Moyer LA, Fields HA, Bradley DW, et al. Risk factors for acute non-A, non-B hepatitis in the United States and association with hepatitis C virus infection. JAMA 1990;264:2231–5.

6. Alter H. New kit on the block: evaluation of second-generation assays for detection of antibody to the hepatitis C virus. Hepatology 1992;15:350–3.

7. Younossi Z, McHutchison J. Serological tests for HCV infection. Viral hepatitis reviews 1996;2:161–73.

8. Takano S, Nakamuar K, Kawai S, Yokosuka O, Satomura Y, Omata M. Prospective assessment of donor blood screening for antibody to hepatitis C virus by first-and second-generation assays as a means of preventing posttransfusion hepatitis. Hepatology 1996;23:708–12.

9. Nakatsuji Y, Matsumoto A, Tanaka E, Ogata H, Kiyosawa K. Detection of chronic hepatitis C virus infection by four diagnostic systems: first-generation and second-generation enzyme-linked immunosorbent assay, second-generation recombinant immunoblot assay and nested polymerase chain reaction analysis. Hepatology 1992;16:300–5.

10. Hosein B, Fang C, Popovsky M, Ye J, Zhang M, Wang C. Improved serodiagnosis of hepatitis C virus infection with synthetic peptide antigen from capsid protein. Proc Natl Acad Sci U S A 1991;88:3647–51.

11. Kleinman S, Alter H, Busch M, Holland P, Tegtmeier G, Nelles M, Lee S, Page E, Wilbur J, Polito A. Increased detection of hepatitis C virus (HCV)-infected blood donors by a multiple-antigen HCV enzyme immunoassay. Transfusion 1992;32:805–13.

12. Aach R, Stevens C, Hollinger F, Mosley J, Peterson D, Taylor P, Johnson R, Barbosa L, Nemo G. Hepatitis C virus infection in post-transfusion hepatitis. An analysis with first- and second-generation assays. N Engl J Med 1991;325:1325–9.

13. McHutchison J, Person J, Govindarajan S, Valinluck B, Gore T, Lee S, Nelles M, Polito A, Chien D, DiNello R, et al. Improved detection of hepatitis C virus antibodies in high-risk populations. Hepatology 1992;15:19–25.

14. Marcellin P, Martinot-Peignoux M, Boyer N, Pouteau M, Aumont P, Erlinger S, Benhamou J. Second-generation (RIBA) test in diagnosis of chronic hepatitis C. Lancet 1991;337:551–2.

15. Lelie P, Cuypers H, Reesink H, van der Poel C, Winkel I, Bakker E, van Exel-Oehlers P, Vallari D, Allain J, Mimms L. Patterns of serological markers in transfusion-transmitted hepatitis C virus infection using second-generation HCV assays. J Med Virol 1992;37:203–9.

16. Okamoto H, Tsuda F, Machida A, Munekata E, Akahane Y, Sugai Y, Mashiko K, Mitsui T, Tanaka T, Miyakawa Y, et al. Antibodies against synthetic oligopeptides deduced from the putative core gene for the diagnosis of hepatitis virus infection. Hepatology 1992;15:180–6.

17. Kao J-H, Lai M-Y, Hwang Y-T, Yang P-M, Chen P-J, Sheu J-C, Wang T-H, Hsu H-C, Chen D-S. Chronic hepatitis C without anti-hepatitis C antibodies by second-generation assay: a clinicopathologic study and demonstration of the usefulness of a third-generation assay. Dig Dis Sci 1996;41:161–5.

18. Uyttendaele S, Claeys H, Mertens W, Verhaert H, Vermylen C. Evaluation of third-generation screening and confirmatory assays for HCV antibodies. Vox Sanguinis 1994;66:122–9.

19. Barrera J, Prancis B, Ercilla G, Nelles M, Achord D, Darner J, Lee S. Improved detection of anti-HCV in post-transfusion hepatitis by a third-generation ELISA. Vox Sanguinis 1995;68:15–8.

20. Atrah H, Ahmed M. Hepatitis C virus seroconversion by a third-generation ELISA screening test in blood donors. J Clin Pathol 1996;49:254–5.

21. Yuki N, Hayashi N, Kashahara A, Hagiwara H, Mita E, Ohkawa K, Katayama K, Fusamoto H, Kamada T. Quantitative analysis of antibody to hepatitis C virus envelope 2 glycoprotein in patients with chronic hepatitis C virus infection. Hepatology 1996;23:947–52.

22. Lesniewski R, Okasinkski G, Carrick R, Van Sant C, Desai S, Johnson R, Scheffel J, Moore B, Mushahwar I. Antibody to hepatitis C virus second envelope (HCV-E2) glycoprotein: a new marker of HCV infection closely associated with viremia. J Med Virol 1995;45:415–22.

23. Zaaijer HL, Vallari DS, Cunningham M, Lesniewski R, Reesink HW, van der Poel CL, Lelie PN. E2 and NS5: new antigens for detection of hepatitis C virus antibodies. J Med Virol 1994;44:395–7.

24. van der Poel C, Cuypers H, Reesink H, Weiner A, Quan S, Di Nello R, van Boven J, Winkel I, Mulder-Folkerts D, Exel-Oehlers P, et al. Confirmation of hepatitis C virus infection by new four-antigen recombinant immunoblot assay. Lancet 1991;337:317–9.

25. Evans C, Tobler L, Polito A, Stewart J, Chien D, Wilber J, Quan S, Delaney S, Kuo G, Busch M. Comparative evaluations of supplemental hepatitis C virus antibody test systems. Transfusion 1992;32:408–14.

26. Craxi A, Fiorentino G, Di Marco V, Marino L, Magrin S, Fabriano C, Pagliaro L. Second-generation tests in diagnosis of chronic hepatitis C. Lancet 1991;337:1354.

27. Alter H, Tegtmeier G, Jett B, Quan S, Shih J, Bayer W, Polito A. The use of a recombinant immunoblot assay in the interpretation of anti-hepatitis C virus reactivity among prospectively followed patients, implicated donors, and random donors. Transfusion 1991;31:771–6.

28. Busch M, Tobler L, Quan S, Wilber J, Johnson P, Polito A, Steane E, Zola A, Bahl C, Nelles M, et al. A pattern of 5–1–1 and c100–3 only on hepatitis C virus (HCV) recombinant immunoblot assay does not reflect HCV infection in blood donors. Transfusion 1993;33:84–8.

29. Gretch DR, Lee W, Corey L. Use of aminotransferase, hepatitis C antibody, and hepatitis C polymerase chain reaction RNA assays to establish the diagnosis of hepatitis C virus infection in a diagnostic virology laboratory. J Clin Microbiol 1992;30:2145–9.

30. Lok A, Chien D, Choo Q, Chan T, Chiu E, Cheng I, Houghton M, Kuo G. Antibody response to core, envelope and nonstructural hepatitis C virus antigens: comparison of immunocompetent and immunosuppressed patients. Hepatology 1993;18:497–502.

31. Pawlotsky J, Bastie A, Pellet C, Remire J, Darthuy F, Wolfe L, Sayada C, Duval J, Dhumeaux D. Significance of indeterminate third-generation hepatitis C virus recombinant immunoblot assay. J Clin Microbiol 1996;34:80–3.

32. Feucht H, Zollner B, Polywka S, Laufs R. Study on reliability of commercially available hepatitis C virus antibody tests. J Clin Microbiol 1995;33:620–4.

33. Bresters D, Zaaijer H, Cuypers H, Reesink H, Winkel I, van Exel-Oehlers P, van Drimmelen A, Jansen P, van der Poel C, Lelie P. Recombinant immunoblot assay reaction patterns and hepatitis C virus RNA in blood donors and non-A, non-B hepatitis patients. Transfusion 1993;33:634–8.

34. Lazizi Y, Elfassi E, Pillot J. Detection of hepatitis C virus sequences in sera with controversial serology by nested polymerase chain reaction. J Clin Microbiol 1992;30:931–4.

35. Martinot-Peignoux M, Marcellin P, Xu L, Bernuau J, Erlinger S, Benhamou J, Larzul D. Reactivity to c33c antigen as a marker of hepatitis C virus multiplication. J Infect Disease 1992;165:595–6.

36. Weiner A, Truett M, Rosenblatt J, Han J, Quan S, Polito A, Juo G, Choo Q, Houghton M, Agius C, et al. HCV testing in low-risk population. Lancet 1990;336:695.

37. Damen M, Zaaijer HL, Cuypers HTM, Vrielink H, van der Poel CL, Reesink HW, Lelie PN. Reliability of the third-generation recombinant immunoblot assay for hepatitis C virus. Transfusion 1995;35:745–9.

38. Soffredini R, Rumi M-G, Lampertico P, Aroldi A, Tarantino A, Ponticelli C, Colombo M. Increased Detection of Antibody to Hepatitis C Virus in Renal Transplant Patients by Third-Generation Assay. Am J Kidney Dis 1996;28:437–40.

39. Dow BC, Munro H, Buchanan I, Follett EAC, Davidson F, Yap PL, Simmonds P. Third-generation recombinant immunoblot assay: comparison of reactivities according to hepatitis C virus genotype. Transfusion 1996;36:547–51.

40. Alter H. To C or not to C: these are the questions. Blood 1995;85:1681–95.

41. Houghton M, Weiner A, Han J, Kuo G, Choo Q. Molecular biology of the hepatitis C viruses: implications for diagnosis, development and control of viral disease. Hepatology 1991;14:381–8.

42. Zaaijer HL, Cuypers HT, Reesink HW, Winkel IN, Gerken G, Lelie PN. Reliability of polymerase chain reaction for detection of hepatitis C virus. Lancet 1993;341:722–4.

43. Busch M, Wilber J, Johnson P, Tobler L, Evans C. Impact of specimen handling and storage on detection of hepatitis C virus RNA. Transfusion 1992;32:420–5.

44. Davis GL, Lau JY, Urdea MS, Neuwald PD, Wilber JC, Lindsay K, Perrillo RP, Albrecht J. Quantitative detection of hepatitis C virus RNA with a solid-phase signal amplification method: definition of optimal conditions for specimen collection and clinical application in interferon-treated patients. Hepatology 1994;19:1337–41.

45. Kwok S, Higuchi R. Avoiding false positives with PCR. Nature 1989;339:237–8.

46. Wang J, Wang T, Sheu J, Lin S, Lin J, Chen D. Effects of anticoagulants and storage of blood samples on efficacy of the polymerase chain reaction assay for hepatitis C virus. J Clin Microbiol 1992;30:750–3.

47. Bukh J, Purcell R, Miller R. Importance of primer selection for the detection of hepatitis C virus RNA with the polymerase chain reaction assay. Proc Natl Acad Sci U S A 1992;89:187–91.

48. Fong T, Charboneau F, Valinluck B, Govindarajan S. The stability of serum hepatitis C viral RNA in various handling and storage conditions. Arch Pathol Lab Med 1993;117:150–1.

49. Cristiano K, Di Bisceglie A, Hoofnagle J, Feinstone S. Hepatitis C viral RNA in serum of patients with chronic non-A, non-B hepatitis: detection by the polymerase chain reaction using multiple primer sets. Hepatology 1991;14:51–63.

50. Castillo I, Bartolome J, Quiroga JA, Carreno V. Comparison of several PCR procedures for detection of serum HCV-RNA using different regions of the HCV genome. J Virol Methods 1992;38:71–9.

51. Ulrich P, Romeo J, Lane P, Kelly I, Daniel L, Vyas G. Detection, semiquantification, and genetic variation in hepatitis C virus sequences amplified from the plasma of blood donors with elevated alanine aminotransferase. J Clin Invest 1990;86:1609–14.

52. Lin HJ, Shi N, Mizokami M, Hollinger FB. Polymerase chain reaction assay for hepatitis C virus RNA using a single tube for reverse transcription and serial rounds of amplification with nested primer pairs. J Med Virol 1992;38:220–5.

53. Gretch D, Wilson J, Carithers Jr R, dela Rosa C, Han J, Corey L. Detection of hepatitis C virus RNA: comparison of one-stage polymerase chain reaction (PCR) with nested-set PCR. J Clin Microbiol 1993;31:289–91.

54. Hu KQ, Yu CH, Vierling JM. One-step RNA polymerase chain reaction for detection of hepatitis C virus RNA. Hepatology 1993;18:270–4.

55. Cheung R, Matsui S, Greenberg H. Rapid and sensitive method for detection of hepatitis C virus RNA by using silica particles. J Clin Microbiol 1994;32:2593–7.

56. Schmidt W, Klinzman D, LaBrecque D, Macfarlane D, Stapleton J. Direct detection of hepatitis C virus (HCV) RNA from whole blood, and comparison with HCV-RNA in plasma and peripheral blood mononuclear cells. J Med Virol 1995;47:153–60.

57. Nolte FS, Thurmond, C, Fried MW. Pre-clinical evaluation of amplicor hepatitis C virus test for detection of hepatitis C virus RNA. J Clin Microbiol 1995;33:1775–8.

58. Young K, Archer J, Yokosuka O, Omata M, Resnick R. Detection of hepatitis C virus RNA by a combined reverse transcription PCR assay: comparison with nested amplification and antibody testing. J Clin Microbiol 1995;33:654–7.

59. Gretch D, dela Rosa D, Corey L, Carithers R. Assessment of hepatitis C viremia using molecular amplification technologies. Viral Hepatitis Reviews 1996;2:85–96.

60. Nguyen T, Sedghi-Vaziri A, Wilkes L, Mondala T, Pockros P, Lindsay K, McHutchison J. Fluctuations in viral load (HCV-RNA) are relatively insignificant in untreated patients with chronic HCV infection. J Viral Hepatitis 1996;3:75–8.

61. Gretch D, dela Rosa C, Carithers R, Willson R, Williams B, Corey L. Assessment of hepatitis C viremia using molecular amplification technologies: Correlations and clinical implications. Ann Intern Med 1995;123:321–9.

62. Besnard NC, Andre PM. Automated quantitative determination of hepatitis C virus viremia by reverse transcription-PCR. J Clin Microbiol 1994;32:1887–93.

63. Shindo M, Di BAM, Silver J, Limjoco T, Hoofnagle JH, Feinstone SM. Detection and quantitation of hepatitis C virus RNA in serum using the polymerase chain reaction and a colorimetric enzymatic detection system. J Virol Methods 1994;48:65–72.

64. Kato N, Yokosuka O, Hosoda K, Ito Y, Ohto M, Om M. Quantification of hepatitis C virus by competitive reverse transcription-polymerase chain reaction: increase of virus in advanced liver disease. Hepatology 1993;18:16.

65. Hagiwara H, Hayashi N, Mita E, Naito M, Kasahara A, Fusamoto H, Kamada T. Quantitation of hepatitis C virus RNA in serum of asymptomatic blood donors and patients with type C chronic liver disease. Hepatology 1993;17:545–50.

66. Kobayashi Y, Watanabe S, Konishi M, Yokoi M, Kakehashi R, Kaito M, Kondo M, Hayashi Y, Jomori T, Suzuki S. Quantitation and typing of serum hepatitis C virus RNA in patients with chronic hepatitis C treated with interferon-b. Hepatology 1993;18:1319–25.

67. Goergen B, Jakobs S, Symmons P, Hornes E, Meyer zBKH, Gerken G. Quantitation of HCV-replication using one-step competitive reverse transcription-polymerase chain reaction and a solid phase, colorimetric detection method. J Hepatol 1994;21:678–82.

68. Kaneko S, Murakami S, Unoura M, Kobayashi K. Quantitation of hepatitis C virus RNA by competitive polymerase chain reaction. J Med Virol 1992;37:278–82.

69. Yun Z, Lundeberg J, Johansson B, Hedrum A, Weiland O, Uhl'en M, Sonnerborg A. Colorimetric detection of competitive PCR products for quantification of hepatitis C viremia. J Virol Methods 1994;47:1–13.

70. Gretch D, Corey L, Wilson J, dela Rosa C, Willson R, Carithers R, Jr., Busch M, Hart J, Sayers M, Han J. Assessment of hepatitis C virus RNA levels by quantitative competitive RNA polymerase chain reaction: high-titer viremia correlates with advanced stage of disease. J Infect Dis 1994;169:1219–25.

71. Simmonds P, Zhang L, Watson H, Rebus S, Ferguson E, Balfe P, Leadbetter G, Yap P, Peutherer J, Ludlam C. Hepatitis C quantification and sequencing in blood products, haemophiliacs and drug users. Lancet 1990;336:1469–72.

72. Chan CY, Lee SD, Hwang SJ, Lu RH, Lu CL, Lo KJ. Quantitative branched DNA assay and genotyping for hepatitis C virus RNA in Chinese patients with acute and chronic hepatitis C. J Infect Dis 1995;171:443–6.

73. Bresters D, Cuypers H, Reesink H, Mauser-Bunschoten E, van den Berg H, Schaasberg W, Wilber J, Urdea M, Neuwald P, Lelie P. Comparison of quantitative cDNA-PCR with the branched DNA hybridization assay for monitoring plasma hepatitis C virus RNA levels in haemophiliac patients participating in a controlled interferon trial. J Med Virol 1994;43:262–8.

74. Lau JY, Davis GL, Kniffen J, Qian KP, Urdea MS, Chan CS, Mizokami M, Neuwald PD, Wilber JC. Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. Lancet 1993;341:1501–4.

75. Martinot-Peignoux M, Marcellin P, Gournay J, Gabriel F, Courtois F, Branger M, Wild A, Erlinger S, Benhamou J. Detection and quantitation of serum HCV-RNA by branched DNA amplification in anti-HCV positive blood donors. J Hepatol 1994;20:676–8.

76. Toyoda H, Nakano S, Kumada T, Takeda I, Sugiyama K, Osada T, Kiriyama S, Orito E, Mizokami M. Comparison of serum hepatitis C virus RNA concentration by branched DNA probe assay with competitive reverse

transcription polymerase chain reaction as a predictor of response to interferon-a therapy in chronic hepatitis C patients. J Med Virol 1996;48:354–9.

77. Hayashi J, Yoshimura E, Kishihara Y, Yamaji K, Etoh Y, Ikematsu H, Kashiwagi S. Hepatitis C virus RNA levels determined by branched DNA probe assay correlated wtih levels assessed using competitive PCR. Am J Gastroenterol 1996;91:314–8.

78. Eyster M, Fried M, Di Bisceglie A, Goedert J. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Blood 1994;84:1020–3.

79. Lau J, Simmonds P, Urdea M. Implications of variations of "conserved" regions of hepatitis C virus genome. Lancet 1995;346:425–6.

80. Simmonds P. Variability of hepatitis C virus. Hepatology 1995;21:570–82.

81. Marrone A, Sallie R. Genetic heterogeneity of hepatitis C virus: The clinical significance of genotypes and quasispecies behavior. In: Feitelson M, Zern M, eds. Clinics in laboratory medicine. Vol 16(2). Philadelphia: WB Saunders 1996:429–49.

82. Bukh J, Miller R, Purcell R. Genetic heterogeneity of hepatitis C virus: quasispecies and genotypes. Semin Liver Dis 1995;15:41–63.

83. Simmonds P, McOmish F, Yap PL, Chan SW, Lin CK, Dusheiko G, Saeed AA, Holmes EC. Sequence variability in the 5' non-coding region of hepatitis C virus: identification of a new virus type and restrictions on sequence diversity. J Gen Virol 1993;74:661–8.

84. Okamoto H, Sugiyama Y, Okada S, Kurai K, Akahane Y, Sugai Y, Tanaka T, Sato K, Tsuda F, Miyakawa Y, et al. Typing hepatitis C virus by polymerase chain reaction with type-specific primers: application to clinical surveys and tracing infectious sources. J Gen Virol 1992;73:673–9.

85. Stuyver L, Rossau R, Wyseur A, Duhamel M, Vanderborght B, Van HH, Maertens G. Typing of hepatitis C virus isolates and characterization of new subtypes using a line probe assay. J Gen Virol 1993;74:1093–102.

86. Stuyver L, Van Arnhem W, Wyseur A, Hernandez F, Delaporte E, Maertens G. Classification of hepatitis C viruses based on phylogenetic analysis of the envelope 1 and nonstructural 5B regions and identification of five additional subtypes. Proc Natl Acad Sci U S A 1994;91:10134–8.

87. Simmonds P, Holmes E, Cha T, Chan S, McOmish F, Irvine B, Beall E, et al. Classification of hepatitis C virus into six major genotypes and a series of subtypes by phylogenetic analysis of the NS-5 region. J Gen Virol 1993;74:2391–9.

88. Bukh J, Purcell R, Miller R. At least 12 genotypes of hepatitis C virus predicted by sequence analysis of the putative E1 gene of isolates collected worldwide. Proc Natl Acad Sci U S A 1993;90:8234–8.

Diagnosis of Hepatitis C

Anna Lok, M.D., and Naresh T. Gunaratnam, M.D.

Diagnosis of hepatitis C involves confirmation of the diagnosis of hepatitis C virus (HCV) infection and assessment of the severity of liver disease. In addition, evaluation of patients with hepatitis C should include determination of the patients' suitability for treatment.

Currently, the second-generation enzyme immunoassay (EIA-2) for antibodies to HCV (anti-HCV) is the most practical screening test for HCV infection. The diagnosis of HCV infection can be supported or confirmed by the recombinant immunoblot assay (RIBA) or tests for HCV RNA. RIBA detects antibodies to individual HCV antigens and confers increased specificity compared to EIA-2. Qualitative reverse transcription-polymerase chain reaction (RT-PCR) assays for HCV RNA are simpler than quantitative tests and sufficient for confirmation of the diagnosis of HCV infection.

While the vast majority of anti-HCV-positive patients who present with chronic liver disease have ongoing HCV infection as confirmed by the presence of HCV RNA in serum, only 35 percent and 25 percent of anti-HCV-positive blood donors are RIBA- and HCV RNA-positive, respectively.[1–5] The proportion of anti-HCV-positive blood donors who are confirmed to be HCV RNA-positive varies from 70 percent for those who are RIBA-positive to 2–25 percent for those who are RIBA-indeterminate and none for those who are RIBA-negative. Thus, supplementary and confirmatory tests for HCV infection should always be performed in asymptomatic low-risk subjects who are found to be anti-HCV-positive, particularly if they have normal aminotransferase (ALT) levels; but these tests may not be necessary in all anti-HCV-positive patients who present with chronic liver disease.

Severity of liver disease is best assessed by liver biopsy. There is in general a poor correlation between serum ALT level and activity of liver disease. More importantly, several recent studies found that significant liver disease can be found in anti-HCV-positive patients despite normal ALT levels.[1–3, 5–8] These studies reported that 70 percent of RIBA-positive blood donors who had persistently normal ALT levels have chronic hepatitis or cirrhosis on biopsy. Although most donors (77 percent) who had abnormal liver histology were HCV RNA-positive, significant liver disease was also found in 30 percent of RIBA-positive donors who were HCV RNA-negative and had normal ALT levels on three separate occasions. This may be related to the fluctuating course of chronic HCV infection with intermittently normal ALT levels and undetectable levels of viremia. It may also reflect variations in sensitivities of "home-made" RT-PCR assays for HCV RNA.[9] Several studies reported that patients with more advanced liver disease had higher serum HCV RNA levels.[10–13] However, these findings were not confirmed by other studies.[14,15] It is unlikely that quantitative tests for HCV RNA will replace liver biopsy in the determination of activity or stage of liver disease. HCV genotype 1b has been shown to be associated with more advanced liver disease.[16–18] Nevertheless, there is a wide spread in severity of liver disease associated with each genotype. Thus, genotyping cannot be used to determine severity of liver disease.

The most important factors associated with favorable response to interferon therapy are low pretreatment serum HCV RNA level, HCV genotypes 2 and 3, and absence of cirrhosis or significant fibrosis.[19–24] More recently, some studies have also reported that responders have a more rapid fall in serum HCV RNA level during the first few weeks of treatment.[25,26] The predictive factors of response will be discussed in more detail by Dr. Davis. Qualitative tests for HCV RNA are increasingly used to assess virological response during treatment. However, it is uncertain whether results of diagnostic evaluation should be used to exclude patients who have low probability of response from receiving treatment.

In summary, the diagnostic algorithm of hepatitis C depends on the clinical context. In asymptomatic, low-risk subjects, who are found to be anti-HCV-positive by EIA-2, the diagnosis of

HCV infection needs to be confirmed, especially if the initial biochemical tests reveal normal ALT levels. This may be achieved by retesting for anti-HCV by RIBA. Those who are RIBA-positive or indeterminate will then be tested for HCV RNA using qualitative RT-PCR assays. It can be argued that confirmation of the diagnosis of HCV infection can be accomplished in a single step by testing for HCV RNA directly, since this test will eventually be performed on 70 percent of these subjects. Nevertheless, 30 percent of RIBA-positive blood donors are HCV RNA negative when tested on a single occasion,[1,3,4] and significant liver disease had been detected in 30 percent of RIBA-positive blood donors who are HCV RNA- negative.[1] In addition, new versions of RIBA may reduce the proportion of those with indeterminate results, thus decreasing the need for HCV RNA testing. In view of the fluctuating nature of chronic HCV infection, repeat tests for ALT levels are needed to differentiate subjects with persistently normal ALT levels from those with intermittently elevated ALT levels, since the prognosis and plan of treatment may be different in these two groups of patients. Several studies reported that the proportion of anti-HCV blood donors with elevated ALT levels increased by 10 percent to 20 percent during a 6-month followup period.[5,6] While it is clear that liver biopsy is the most reliable way to assess the activity and stage of liver disease and should be recommended in anti-HCV-positive subjects who are HCV RNA-positive and have elevated ALT levels, it is less clear whether liver biopsy should be routinely recommended in those who are HCV RNA-positive and have persistently normal ALT levels, until the natural history of this subset of patients is better defined and when an effective treatment becomes available.

The vast majority of patients who present with chronic liver disease and are found to be anti-HCV-positive by EIA-2 have HCV infection, especially if risk factors are present. Confirmatory tests may not be necessary in all patients. When performed, tests for HCV RNA are more appropriate than RIBA. While qualitative test for HCV RNA will suffice to confirm the diagnosis, quantitative RT-PCR or branched DNA assay to determine HCV RNA level may be performed if treatment is contemplated. Liver biopsy should be recommended except in elderly patients, patients with severe concomitant medical problems, and those with coagulopathy, since neither serum HCV RNA nor ALT level can reliably predict activity or degree of fibrosis.

At the moment, HCV genotyping should be considered a research tool and not a part of the diagnostic algorithm in clinical practice.

References

1. Prieto M, Olaso V, Verdu C, et al. Does the healthy hepatitis C virus carrier state really exist? An analysis using polymerase chain reaction. Hepatology 1995;22:413–7.

2. Zanella A, Conte D, Prati D, et al. Hepatitis C virus RNA and liver histology in blood donors reactive to a single antigen by second-generation recombinant immunoblot assay. Hepatology 1995;21:913–7.

3. McGuinness P, Bishop GA, Lien A, et al. Detection of serum hepatitis C virus RNA in HCV antibody-seropositive volunteer blood donors. Hepatology 1993;18:485–90.

4. Bresters D, Zaauer HL, Cuypers HTM, et al. Recombinant immunoblot assay reaction patterns and hepatitis C virus RNA in blood donors and non-A, non-B hepatitis patients. Transfusion 1993;33:634–8.

5. Esteban JI, Lopez-Talavera JC, Genesca J, et al. High rate of infectivity and liver disease in blood donors with antibodies to hepatitis C virus. Ann Intern Med 1991;115:443–9.

6. Serfaty L, Nousbaum JB, Elghouzzi MH, et al. Prevalence, severity, and risk factors of liver disease in blood donors positive in a second-generation anti-hepatitis C virus screening test. Hepatology 1995;21:725–9.

7. Alberti A, Chemello L, Cavalletto D, et al. Antibody to hepatitis C virus and liver disease in volunteer blood donors. Ann Intern Med 1991;114:1010–2.

8. Shakil AO, Conry-Cantilena C, Alter HJ, et al. Volunteer blood donors with antibody to hepatitis C virus: clinical, biochemical, virologic, and histologic features. Ann Intern Med 1995;123:330–7.

9. Zaauer HL, Cuypers HTM, Reesink HW, et al. Reliability of polymerase chain reaction for detection of hepatitis C virus. Lancet 1993;341:722–4.

10. Gretch D, Corey L, Wilson J, et al. Assessment of hepatitis C virus RNA levels by quantitative competitive RNA polymerase chain reaction: high-titer viremia correlates with advanced stage of disease. J Infect Dis 1994;169:1219–25.

11. Kato N, Yokosuka O, Hosoda K, et al. Quantification of hepatitis C virus by competitive reverse transcription-polymerase chain reaction: increase of the virus in advanced liver disease. Hepatology 1993;18:16–20.

12. Gordon SC, Kodali VP, Silverman AL, et al. Levels of hepatitis C virus RNA and liver histology in chronic type C hepatitis. Am J Gastroenterol 1994;89:1458–61.

13. Hagiwara H, Hayashi N, Mita E, et al. Quantitation of hepatitis C virus RNA in serum of asymptomatic blood donors and patients with type C chronic liver disease. Hepatology 1993;17:545–50.

14. Magrin S, Craxi A, Fabiano C, et al. Hepatitis C. Viremia in chronic liver disease relationship to interferon or corticosteroid treatment. Hepatology 1994;19:273–9.

15. Shindo M, Arai K, Sokawa Y, et al. The virological and histological states of anti-hepatitis C virus-positive subjects with normal liver biochemical values. Hepatology 1995;22:418–25.

16. Dusheiko G, Schmilovitz-Weiss H, Brown D, et al. Hepatitis C virus genotypes: an investigation of type-specific differences in geographic origin and disease. Hepatology 1994;19:13–8.

17. Silini E, Bono F, Cividini A, et al. Differential distribution of hepatitis C virus genotypes in patients with and without liver function abnormalities. Hepatology 1995;21:285–90.

18. Qu D, Li JS, Vitvitski L, et al. Hepatitis C virus genotypes in France: comparison of clinical features of patients infected with HCV type 1 and type II. J Hepatol 1994;21:70–5.

19. Martinot-Peignoux M, Marcellin P, Pouteau M, et al. Pretreatment serum hepatitis C virus RNA levels and hepatitis C virus genotype are the main and independent prognostic factors of sustained response to interferon alfa therapy in chronic hepatitis C. Hepatology 1995;22:1050–6.

20. Hagiwara H, Hayashi N, Mita E, et al. Quantitative analysis of hepatitis C virus RNA in serum during interferon alfa therapy. Gastroenterology 1993;104:877–83.

21. Yamada G, Takatani M, Kishi F, et al. Efficacy of interferon alfa therapy in chronic hepatitis C patients depends primarily on hepatitis C virus RNA level. Hepatology 1995;22:1351–4.

22. Hayashi J, Ohmiya M, Kishihara Y, et al. A statistical analysis of predictive factors of response to human lymphoblastoid interferon in patients with chronic hepatitis C. Am J Gastroenterol 1994;89:2151–6.

23. Conjeevaram HS, Everhart JE, Hoofnagle JH. Predictors of a sustained beneficial response to interferon alfa therapy in chronic hepatitis C. Hepatology 1995;22:1326–9.

24. Chemello L, Bonetti P, Cavalletto L, et al. Randomized trial comparing three different regimens of alpha-2a-interferon in chronic hepatitis C. Hepatology 1995;22:700–6.

25. Chayama K, Tsubota A, Arase Y, et al. Genotype, slow decrease in virus titer during interferon treatment and high degree of sequence variability of hypervariable region are indicative of poor response to interferon treatment in patients with chronic hepatitis type C. J Hepatol 1995;23:648–53.

26. Kohara M, Tanaka T, Tsukiyama-Kohara K, et al. Hepatitis C virus genotypes 1 and 2 respond to interferon-a with different virologic kinetics. J Infect Dis 1995:172:934–8.

Role of Liver Biopsy

Robert P. Perrillo, M.D.

Liver biopsy has traditionally been the gold standard for assessing the extent of injury and determining prognosis in chronic viral hepatitis. With the growth in our knowledge about the natural history of hepatitis C and the recent development of newer therapeutic modalities, including alpha interferon and transplantation, the number of biopsies for this condition has increased. Indirect support for this may be seen in a survey of 1,400 American Gastroenterological Association (AGA) physician members (unpublished data courtesy of J. Everhart), which revealed that most (89 percent) would recommend biopsy for symptomatic cases with a moderately elevated ALT, but a substantial number
(42 percent) would also recommend biopsy in an asymptomatic patient with normal ALT. At the current time, however, uniform guidelines for the use of liver biopsy in hepatitis C are lacking, and a number of questions remain for which the literature provides no direct answer. Physicians may question, for example, the need for biopsy if all grades of histologic severity are viewed as an indication for treatment. Furthermore, the small but definite risk to the patient, the cost of biopsy, and a reliance on ALT testing may lead to questions about the relative importance of periodic histologic assessments to follow the patient's disease. Even physicians who acknowledge that biopsy provides the most useful information on disease progression may have different opinions on how long an interval should lapse before repeat histologic assessment. Thus, a consensus statement on when and how liver biopsy is useful in the diagnosis, management, and therapy of hepatitis C is needed.

Safety and Selection

A number of studies published in the past 30 years have indicated that liver biopsy can be safely performed as an outpatient procedure.[1,2] Complication rates have generally not exceeded 5 percent, and mortality from this procedure is very low (ranging from 0 to 0.12 percent). The procedure can be done safely on an outpatient basis. Nonetheless, since it is often done in a blind fashion, it is reasonable to conclude that liver biopsies should be done only by or with the assistance of gastroenterologists, hepatologists, transplant surgeons or other physicians (e.g., radiologists) who perform this procedure regularly.

In some instances, it may be appropriate to forgo biopsy before initiating antiviral therapy. Consideration should be given to omitting biopsy whenever this is associated with excessive risk to the patient such as in hemophilia and severely decompensated cirrhosis. Also, some experts question the need for biopsy in individuals with persistently normal ALT levels unless they are part of a research protocol.

Unique Information Provided by Liver Biopsy

There are several types of information that can only be provided by liver biopsy. A number of studies have shown that both in the acute and chronic forms of hepatitis, characteristic although not pathognomonic abnormalities are present: steatosis, portal lymphoid aggregates, and bile duct injury.[3,4] This may have particular value when more than one source of liver injury is possible (e.g., hepatitis B and C and, alcoholic liver disease). The Histologic Activity Index (HAI) or “Knodell score” is a semiquantitative method proposed to standardize interpretation of the biopsy, allowing comparison between subsequent biopsies in the same patient and between different patients in large studies.[5] While the observations inherent to the score are still subjective, the grading system has the advantage of being simple and the numerical results can be statistically computed. Moreover, this scoring system has been shown to have relatively little intraobserver variation, and it provides a systematic means of comparing pre- and post-therapy biopsies. Liver cell dysplasia is not an uncommon abnormality in the biopsies of patients with cirrhosis due to hepatitis C, being found in as many as 16 percent.[3]

Longitudinal observations are necessary to define whether the presence of dysplasia could conceivably be useful in targeted screening for hepatoma. New immunochemical and molecular techniques for localizing the virus in liver tissue may lead to greater understanding of the pathogenesis of chronic hepatitis C and can be useful in monitoring a response to therapy.[6] Rarely, the finding of talc crystals in liver tissue may lead to more accurate assessment of past intravenous drug abuse.[7]

Serum Aminotransferase Versus Liver Biopsy in Chronic Hepatitis C

Several studies have shown that serum aminotransferase levels do not accurately reflect the level of inflammatory changes and/or the presence of fibrosis in chronic hepatitis C. For example, in 1990 Schoeman et al. from Australia found that a correlation was lacking between the degree of liver function test abnormality and histologic severity in 42 patients with parenterally acquired non-A, non-B hepatitis.[8] With the advent of specific tests for hepatitis C, several other groups (see Table 1) demonstrated histological evidence for chronic hepatitis and even cirrhosis despite normal ALT values.[9–12] In several of these studies, a better correlation was seen between abnormal histology and the presence of HCV RNA in serum, casting doubt on the validity of the "healthy" carrier state.

Another way of examining the relationship between ALT level and liver histology has been to assess the relationship of the HAI score to the height of the ALT. There are no definitive studies in this area. However, in a recent study by McCormick et al. involving 59 biopsies taken from 44 patients with chronic hepatitis C, only a weak association was seen between the level of ALT and the degree of inflammatory changes, and it was deemed to be of no clinical use.[13] In another study from Scandinavia, it was observed that logarithmic values of ALT were correlated with periportal inflammation and lymphocytic follicles but not with lobular inflammation, ballooning change, or the presence or absence of acidophilic bodies.[14]

One can conclude from the above studies that when attempting to evaluate the extent of liver injury in patients with chronic hepatitis C, liver biopsy is inherently more sensitive and accurate and provides information that can not be derived from determination of serum ALT alone.

TABLE 1. Relationship Between Serum Alanine Aminotransferase Levels, HCV RNA, and Liver Histology in Chronic Hepatitis C Virus Infection

Author/Year (Ref. #)	No.	Histologic Diagnosis (Percent of Total)	Percent with Abnormal ALT	Percent with Positive HCV RNA
Esteban, 1991[9]	54	CAH, AC	89*	NA
	22	CPH	55	–
	12	Minimal change	25	–
	17	Normal	0	
Alberti, 1992[10]	6	CAH, C	50	100
	10	CPH	40	100
	7	Normal	0	0
Naito, 1994[11]	19	CPH	0	100
	3	Normal	0	100
Shakil, 1995[12]	20		0	65
	8	Mild hepatitis		NA
	6	Moderate hepatitis		NA
	3	Nonspecific changes		33
	3	Normal		0

* Defined as intermittently abnormal or persistently abnormal
Abbreviations: CAH = chronic active hepatitis; CPH = chronic persistent hepatitis; C = cirrhosis; AC = active cirrhosis.

Role of Liver Biopsy in Defining Natural History of Hepatitis C

Serial liver biopsy remains the best way of monitoring the progression of chronic hepatitis C. Cirrhosis may frequently develop in chronic hepatitis C, often with an asymptomatic course, and progression is generally slow. Early observations indicated that cirrhosis develops in 20–25 percent of patients with chronic hepatitis C after 10 years.[15,16] In one study, the mean intervals between the date of transfusion and the date of diagnosis of chronic hepatitis, cirrhosis, and hepatocellular carcinoma were 10, 21.2, and 29 years, respectively.[17] Studies from Asia have shown that on average, it takes about 30 years for chronic hepatitis C to progress from initial infection to cirrhosis and cancer, and the disease progresses much more rapidly in elderly patients.[18] Disturbingly, even mild hepatitis has been shown to progress to more advanced disease with prolonged followup.[19] Therefore, the initial biopsy may be of less prognostic value than with many other chronic liver disorders.

Liver Histology and Antiviral Therapy

A number of studies have demonstrated that patients with severe fibrosis and/or cirrhosis respond less frequently to interferon therapy.[20] It is also known that inflammatory changes, particularly periportal necrosis, subside when a response is achieved.[21] Preliminary studies suggest that a sustained biochemical and virologic response is associated with lasting improvement in histology.[22] Further studies are necessary to assess the durability of response and determine the appropriate interval which should transpire before consideration is given to repeat histological assessment.

References

1. Garcia-Tsao G. Outpatient liver biopsy: How safe is it? Ann Intern Med 1993;118:150–3.

2. McGill DB, Rakela J, Sinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. Gastroenterology 1990;99:1392–400.

3. Lefkowitch JH, Schiff ER, Davis GL, Perrillo RP, Lindsay K, Bodenheimer HC, Balart LA, Ortego TJ, Payne J, Dienstag JL, Gibas A, Jacobson IM, Tamburro CH, Carey W, O'Brien C, Sampliner R, Van Thiel DH, Feit D, Albrecht J, Meschievitz C, Sanghvi B, Vaughan RD. Pathological diagnosis of chronic hepatitis C: A multicenter comparative study with chronic hepatitis B. Gastroenterology 1993;104:595–603.

4. Goodman ZD, Ishak KG. Histopathology of hepatitis C virus infection. Semin Liver Dis 1995;15:70–81.

5. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, Wollman J. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1:431–5.

6. Krawczynski K, Beach MJ, Bradley DW, Kuo G, DiBisceglie AM, Houghton M, Reyes GR, Kim JP, Choo QL, Alter MJ. Hepatitis C antigens in hepatocytes. Immuno-morphologic detection and identification. Gastroenterology 1992;103:622–9.

7. Sherman KE, Lewey SM, Goodman ZD. Talc in the liver of patients with chronic hepatitis C infection. Am J Gastroenterol 1995;90:2164–6.

8. Schoeman M, Liddle C, Bilous M, Grierson J, Craig PI, Batey RG, Farrell GC. Chronic non-A, non-B hepatitis: lack of correlation between biochemical and morphological activity, and effects of immunosuppressive therapy on disease progression. Aust N Z J Med 1990;20:56–62.

9. Esteban JI, Lopez-Talavera JC, Genesca J, Madoz P, Viladomiu L, Muniz E, Martin-Vega C, Rosell M, Allende H, Vidal X, Gonzalez A, Hernandez JM, Esteban R, Guardia J. High rate of infectivity and liver disease in blood donors with antibodies to hepatitis C virus. Ann Intern Med 1991;115:443–9.

10. Alberti A, Chemello L, Noventa F, Morsica G, Cavalletto D, Pontisso P, Ruol A. Hepatitis C viremia and liver disease in symptom-free individuals with anti-HCV. Lancet 1992;340:697–8.

11. Naito M, Hayashi N, Hagiwara H, Hiramatsu N, Kasahara A, Fusamoto H, Kamada T. Serum hepatitis C virus RNA quantity and histological features of hepatitis C virus carriers with persistently normal ALT levels. Hepatology 1994;19:871–5.

12. Shakil AO, Conry-Cantilena C, Alter HJ, Hayashi P, Kleiner DE, Tedeschi V, Krawczynski K, Conjeevaram HS, Sallie R, Di Bisceglie AM. Volunteer blood donors with antibody to hepatitis C virus: clinical, biochemical, virologic, and histologic features. Ann Intern Med 1995;123:330–7.

13. McCormick S, Goodman ZD, Maydonovitch CL, Sjogren MH. Evaluation of liver histology, ALT elevation, and HCV-RNA titer in patients with chronic hepatitis C. Am J Gastroenterol 1996;91:1516–22.

14. Cahen DL, van Leeuwen DJ, ten Kate FJW, Blok APR, Oosting J, Chamuleau RAFM. Do serum ALT values reflect the inflammatory activity in the liver of patients with chronic viral hepatitis? Liver 1996;16:105–9.

15. Genesca J, Esteban JI, Alter HJ. Blood-borne non-A, non-B hepatitis: hepatitis C. Semin Liver Dis 1991;11: 147–64.

16. DiBisceglie A, Goodman ZD, Ishak KG, Hoofnagle JH, Melpolder JJ, Alter HJ. Long-term clinical and histopathological follow-up of chronic post-transfusion hepatitis. Hepatology 1991;14:969–74.

17. Kiyosawa K, Sodeyama T, Tanaka E, Gibo Y, Yoshizawa K, Nakano Y, Furuta S, Akahane Y, Nishioka K, Purcell RH, Alter HJ. Interrelationship of blood transfusion, non-A, non-B hepatitis and hepatocellular carcinoma: analysis by detection of antibody to hepatitis C virus. Hepatology 1990;12:671–5.

18. Yano M, Yatshuhashi H, Inoue O, Inokuchi K, Koga M. Epidemiology and long term prognosis of hepatitis C virus infection in Japan. Gut 1993;(Suppl)1:S13–16.

19. Takahashi M, Yomada G, Miyamoto R, Doi T, Endo H, Tsuji T. Natural course of chronic hepatitis C. Am J Gastroenterol 88:240–3.

20. Davis GL. Prediction of response to interferon treatment of chronic hepatitis C. J Hepatol 1994; 21:1–3.

21. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC, Perrillo RP, Carey W, Jacobson IM, Payne J, Dienstag JL, Van Thiel D, Tamburro C, Lefkowitch J, Albrecht J, Meschievitz C, Ortego TJ, Gibas A. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter, randomized controlled trial. N Engl J Med 1989;321:1501–6.

22. Rizzetto M, Goldin R, Marcellin P, Farrell G, Bacon B, Mostelleer M, Howe I, et al. Correlations between virologic and histologic responses in chronic hepatitis C patients: Analyses from a large international comparative study of alph-interferon therapy [Abstract]. J Hepatol 1996;24:57.

Epidemiology of Hepatitis C

Miriam J. Alter, M.D., Ph.D.

In the United States, the annual number of acute hepatitis C virus (HCV) infections has declined during the past decade from 180,000 to 35,000, but an estimated 3.9 million Americans are currently infected with HCV, and an estimated 8,000–10,000 deaths each year result from HCV-associated chronic liver disease. HCV infection affects persons of all ages, but most acute cases of hepatitis C and the highest seroprevalence of HCV infection are found among young adults. The highest proportion both of incident cases and of prevalent infections is among whites, but the highest incidence and prevalence rates are among nonwhite racial/ethnic groups. Although the incidence of acute hepatitis C has declined, there is a large reservoir of chronically infected Americans who can serve as a source of transmission to others and who are at risk of the severe consequences of chronic liver disease.

Case-control studies of patients with symptomatic acute non-A, non-B hepatitis, conducted prior to the discovery of HCV, found a significant association between acquiring disease and a history in the 6 months prior to illness of blood transfusion, injection drug use, health care employment (specifically patient care or laboratory work), sexual or household exposure to a contact who had hepatitis, multiple sexual partners, and low socioeconomic level. Direct percutaneous exposures, such as transfusion of blood or blood products or transplantation of organs or tissues from infectious donors and sharing of contaminated needles among injection drug users, are associated with the most efficient transmission of HCV. Hemophilia patients who have been heavily transfused with nontreated factor concentrates and injection drug users have prevalence rates of antibody to HCV (anti-HCV) exceeding 90 percent, higher than for any other group studied. HCV is now infrequently transmitted by transfusion because of screening tests that exclude infectious donors, and the current risk for transfusion-associated HCV infection is estimated at .01–.001 percent per unit transfused. In addition, the viral inactivation of clotting factor concentrates has virtually eliminated these blood products as the source of HCV infection. Although there has been a dramatic decline in the number of acute cases of hepatitis C among injection drug users, this group continues to account for half of the new infections acquired annually, and probably half or more of all chronic infections. Furthermore, HCV infection is acquired rapidly after initiation of injection with 50–80 percent of new injectors testing positive for anti-HCV within 6–12 months after beginning injection.

Other persons at risk as a result of exposure to infectious blood are health care workers and hemodialysis patients, accounting for less than 5 percent of acute cases. Seroprevalence studies have reported average anti-HCV rates of 1 percent among hospital-based health care workers, and in one study, a history of accidental needle sticks was independently associated with anti-HCV positivity. In follow up studies of health care workers who sustained percutaneous exposures to blood from anti-HCV–positive patients, the incidence of anti-HCV seroconversion (based on second-generation testing) averaged 3.5 percent (range, 0–7 percent), but in one study the reported incidence was 10 percent based on detection of HCV RNA. There has been one case report of the transmission of HCV from a blood splash to the conjunctiva.

Because of both underreporting and high rates of subclinical infection, hemodialysis patients are underrepresented among cases of acute disease, but the prevalence of anti-HCV in this group averages 10–20 percent. Studies have demonstrated an association between anti-HCV positivity and increasing years on dialysis that was independent of blood transfusion. These studies, as well as investigations of dialysis-associated outbreaks of hepatitis C, suggest that HCV may be transmitted between patients in the dialysis center because of poor infection control practices, particularly those involving sharing medication vials and supplies among patients. Nosocomial transmission of HCV is possible in other health care settings if breaks in technique occur or disinfection procedures are inadequate and contaminated equipment is shared among patients. Case-control studies have not found an association between standard medical care procedures and transmission of HCV in the United States, although such

transmission has been reported from other countries. There has been one report from Spain of HCV transmission from a health care worker (cardiovascular surgeon) to patients, but the factors responsible for transmission were not identified.

HCV also may be transmitted by sexual and household exposure to an infected contact, exposure to multiple partners, and perinatal exposure, but the efficiency of transmission in these settings appears to be low. These exposures account for 10–15 percent of cases, and their importance is discussed in a separate abstract. Of persons with acute hepatitis C, 30–40 percent deny a specific exposure associated with acquiring infection in the 6 months preceding onset of their illness, and 10–20 percent of persons with chronic HCV infection deny a specific exposure associated with acquiring infection in their lifetime. However, among such persons with acute hepatitis C, about 65 percent have a lifetime history of some high-risk drug or sexual behavior (injection of illegal drugs in the past but not in the 6 months prior to onset of illness, use of noninjection illegal drugs, history of sexually transmitted diseases), and 9 percent have characteristics associated with low socioeconomic level. Low socioeconomic level and the other high-risk attributes identified among these patients have been associated with the transmission of a number of infectious diseases and may indicate that these persons acquired their HCV infection through unacknowledged recent high-risk drug or sexual behavior or unrecognized contact with an infected person. Use of noninjection illegal drugs (intranasal cocaine) and low socioeconomic level (in addition to traditional percutaneous and high-risk sexual exposures) also were associated with HCV infection among healthy blood donors accepted for donation by history but later found to have HCV infection. Thus, high-risk drug and sexual behaviors appear to account for most of the HCV infections transmitted in the United States. Unfortunately, persons with these behaviors are the most difficult to reach with prevention efforts, and currently no programs are aimed at prevention of hepatitis C in these high-risk populations.

No vaccine is available for hepatitis C. Postexposure prophylaxis with immune globulin does not appear to be effective in preventing HCV infection, and is not recommended by the Advisory Committee on Immunization Practices. There is no information regarding the use of antiviral agents (e.g., alpha interferon) for postexposure prophylaxis, and such treatment is not recommended. Employers of persons at occupational risk of exposure should consider implementing policies and procedures for followup of workers after percutaneous or permucosal exposure to anti-HCV-positive blood to address individual workers' concerns about their risk and outcome. T***here are currently no recommendations regarding restriction of health care workers with hepatitis C.***

Physicians and other health care providers need to be educated not only about the appropriate medical management of HCV-infected patients but also about the known and potential risks for HCV infection and transmission, the need to ascertain complete risk behavior histories from their patients, and appropriate evaluation of high-risk patients for evidence of infection. Although all anti-HCV-positive patients should be considered infectious and informed of the possibility of transmission to others, no reliable tests are available that can determine infectivity. Counseling recommendations to prevent transmission of HCV to others were published by the U.S. Public Health Service in 1991. These guidelines state that persons who are anti-HCV-positive should refrain from donating blood, organs, tissues, or semen. Among household contacts, toothbrushes and razors should not be shared. There are no recommendations for changes in sexual practices among HCV-infected persons with a steady partner; although HCV is sometimes transmitted from persons with chronic disease to their steady sex partners, the transmission rate is low despite long-term, ongoing sexual activity. This area is perhaps the most controversial, and infected persons should be informed of the potential risk of sexual transmission so they can decide if they wish to take precautions. In practice, the type of information provided to the patient is highly variable and may range from advising the patient that there is no risk of transmitting HCV through sexual intercourse to advising the patient to always use barrier precautions (e.g., condoms). Persons with multiple sex partners should follow safer sex practices, including reducing the number of sex partners and using barriers (e.g., latex condoms) to prevent contact with body fluids. There is still no evidence to support advising against pregnancy or breast-feeding.

Because of limited data, recommendations in some areas are limited in scope. More specific recommendations will depend not only on determining the specific factors responsible for transmission in different epidemiologic settings but also on the ability to measure them.

Bibliography

1. Alter MJ. Epidemiology of hepatitis C in the West. Sem Liver Dis 1995;15:5–14.

2. Alter MJ, Gerety RJ, Smallwood L, et al. Sporadic non-A, non-B hepatitis: frequency and epidemiology in an urban United States population. J Infect Dis 1982;145:886–93.

3. Alter MJ, Coleman PJ, Alexander WJ, et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. JAMA 1989;262:1201–5.

4. Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. N Engl J Med 1996;334:1685–90.

5. Garfein RS, Vlahov D, Galai N, Doherty MC, Nelson KE. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. Am J Public Health 1996;86:655–61.

6. Polish LB, Tong MJ, Co RL, et al. Risk factors for hepatitis C virus infection among health care personnel in a community hospital. Am J Infect Control 1993;21:196–200.

7. Sartori M, La Terra G, Aglietta M, et al. Transmission of hepatitis C via blood splash into conjunctiva. Scand J Infect Dis 1993;25:270–1.

8. Centers for Disease Control and Prevention. Risk of acquiring hepatitis C for health care workers and recommendations for prophylaxis and follow-up after occupational exposure. Hepatitis Surveillance Report No. 56. Atlanta, 1995, p. 3–6.

9. Moyer LA, Alter MJ. Hepatitis C virus in the hemodialysis setting: a review with recommendations for control. Sem Dial 1994;7:124–7.

10. Esteban JI, Gomez J, Martell M, et al. Transmission of hepatitis C virus by a cardiac surgeon. N Engl J Med 1995;334:555–60.

11. Mast EE, Alter MJ. Hepatitis C. Sem Ped Infect Dis 1997;8:1–7.

12. Conry-Cantilena C, Vanraden M, Gibble J, et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med 1996;334:1691–6.

13. Centers for Disease Control. Public Health Service inter-agency guidelines for screening donors of blood, plasma, organs, tissues, and semen for evidence of hepatitis B and hepatitis C. Morb Mortal Wkly Rep 1991:40(RR-4):1–17.

Sexual and Perinatal Spread of Hepatitis C Virus Infection

Jules L. Dienstag, M.D.

Compared with the level of viremia in patients with chronic hepatitis B, the level of viremia in patients with hepatitis C virus (HCV) infection is relatively low. This difference, by many orders of magnitude, between the concentrations of circulating virus, translates to less efficient transmission of hepatitis C from person to person. Whereas direct, percutaneous inoculation—e.g., via transfusion or intravenous self-injection of addictive drugs—is very efficient in transmitting HCV infection, less direct, so-called nonpercutaneous routes of infection are inefficient in the spread of hepatitis C.

Sexual Transmission

Among patients with reported cases of acute hepatitis C in the United States, a history of sexual contact with a person at risk for HCV infection—that is, *potential* sexual exposure—can be elicited in approximately 10 percent of cases.[1,2] In addition, certain subpopulations with recognized frequent multipartner sexual activity, such as professional sex workers (prostitutes), promiscuous homosexual men, and persons of both sexes attending clinics for sexually transmitted diseases (STDs), have serologic markers of HCV infection that are many fold more frequent than in the general population and may reach prevalences as high as 20 percent. In some of these populations, concomitant percutaneous exposures, such as intravenous drug use, tattoos, and so on, contribute to HCV exposure, but, in some studies, the rate of HCV infection is higher in such persons with frequent, multiple sexual partners, independent of other potential risk factors. In a survey of patients presenting to a Baltimore emergency room, the frequency of anti-HCV was high, at 18 percent.[3] The frequency in homosexual men was 21 percent, not substantially different from the figure in the entire group, and the frequency was much lower, 6 percent, for those with heterosexual exposure to a partner with high-risk behavior for blood-borne infection. These findings did not point toward substantial sexual exposure to HCV, but the frequency of anti-HCV in a subset of black men between the ages of 35 and 44 was 51 percent. Although intravenous drug use is common in this decade of life in this population, sexual exposure was another hypothetical mode of exposure likely to be operative in this group. In a subsequent study of patients attending STD clinics in the same city, among 309 sexual partners of 1039 non–drug-using patients, anti-HCV was found in 7 percent of men and 4 percent of women; the risk was substantially higher primarily for female partners of men with anti-HCV, but not for male partners of women with anti-HCV, suggesting that male-to-female transmission is more efficient.[4] Other risk factors in the index case that were associated with transmission to the sexual partner included HIV infection, age more than 28 years, more than 24 life-time sexual partners, other STDs and cigarette smoking.[4]

Although frequent sexual activity with multiple partners may be associated with sexual transmission of HCV infection, studies to define sexual transmission between monogamous, stable sexual partners usually fail to provide convincing evidence for efficient transmission.[5] Although several studies do show increases in serologic and virologic evidence for HCV infection in sexual partners of persons with chronic hepatitis C, several of the most definitive failed, with very rare exceptions, to detect HCV infection in sexual partners unless the partners had independent, nonsexual risk factors for acquisition of hepatitis C.[6,7] In a widely cited point-prevalence study from Japan, 18 percent of the spouses of 154 index patients with chronic hepatitis C had evidence of HCV infection, and the frequency of HCV markers increased for each decade of marriage—50 percent increase in antibody to HCV per decade and 90 percent increase in HCV RNA per decade of marriage.[8] At face value, these data suggest that sexual exposure to HCV increases continuously over time during marriage; however, the lowest frequencies of HCV infection were documented during the early years of marriage, when sexual activity is at a peak, and the highest frequencies of HCV infection were documented during very late decades of marriage, when sexual activity is substantially lower. Therefore, rather than demonstrating an increase in HCV exposure with successive decades of

marriage, this point-prevalence survey appears to be detecting a cohort effect, in which older spouses were infected early in life and not necessarily via sexual contact.

A consensus is difficult to draw among the many studies reported to date of sexual transmission of hepatitis C. Given documentation of genetic homogeneity in circulating HCV between spouse pairs in some studies, given the higher frequency of HCV markers in some groups with potential sexual exposure, we cannot ignore the reality that, under certain circumstances, HCV infection can be transmitted sexually. A distinction does appear to exist, however, between promiscuous, frequent sexual activity—associated with transmission—and stable, monogamous sexual activity—rarely associated with transmission. An estimate of the likelihood of sexual transmission is on the order of 5 percent, supporting a relatively low risk of infection.

Accordingly, based on such a low risk, the U.S. Public Health Service has not recommended barrier precautions between stable, monogamous sexual partners.

Perinatal Transmission

Passive acquisition of anti-HCV from mother to baby occurs at the time of birth, but infection of the neonate is much less likely. The occasional, documented case of perinatal transmission of HCV infection notwithstanding, perinatal spread of HCV infection is uncommon. Both serologic surveys and studies in which sensitive assays are applied to detect HCV RNA in the neonate fail to document efficient transmission of sustained infection; thus, although anti-HCV and even HCV RNA can be documented after birth in babies born to mothers with HCV infection, these infections are rarely associated with chronic infection.[9] A much-cited study from Japan demonstrated HCV transmission from mother to infant in 6 percent of babies born to mothers with anti-HCV and in 10 percent in babies born to mothers with HCV RNA. An important observation linked transmission to the level of viremia. Among babies born to mothers whose HCV RNA levels were $<10^6$ copies per ml, no maternal–fetal transmission of HCV infection occurred; in contrast, among babies born to mothers with circulating levels of HCV RNA, 310^6 copies per ml, the efficiency of transmission was as high as 36 percent.[10] Although long-term followup monitoring of these babies was not reported, data such as these suggest that transmission can occur between mother and baby at the time of birth; however, the rarity of documented perinatal transmission of HCV infection in the United States, except perhaps in babies born to mothers who are infected with both HCV and HIV, is consistent with the observation that high-level viremia is uncommon.

Weighing the many, often-conflicting reports concerning perinatal transmission, the Centers for Disease Control of the U.S. Public Health Service has estimated that the likelihood of perinatal transmission is low, on the order of 5–6 percent. Data collected to date show no increase in HCV infection among breast-fed babies;[11] therefore, breast feeding is not discouraged for mothers with chronic hepatitis C.

Household/Intrafamilial Transmission

Although increased frequencies of anti-HCV have been reported in household members of persons with chronic HCV infection, most studies, especially in the United States, have failed to demonstrate any serologic or virologic evidence of HCV transmission to nonsexual partners within households.[5] Current data, therefore, do not support household exposure as a risk for HCV infection.

Conclusion

Although sexual and perinatal routes may play a small role in the transmission of HCV infection, neither is considered an efficient mode of exposure to HCV; the likelihood of such exposures is approximately 5 percent. Household/familial contact is not considered a risk factor for the transmission of hepatitis C. Common-sense precautions between sexual partners include avoidance of the interchange of body fluids and shared percutaneous exposures, but barrier precautions are not recommended routinely for monogamous, stable partners. For persons with multiple sexual partners, "safe-sex" precautions, including the use of latex condoms, should be recommended. Because of the low risk of perinatal transmission, data are insufficient to support the interdiction of pregnancy in women with chronic hepatitis C, screening of pregnant women for HCV infection is not recommended, andbreast feeding is permitted. There is no known prophylaxis with globulin against sexual or perinatal HCV infection.

References

1. Alter MJ, Coleman PJ, Alexander WJ, et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. JAMA 1989;262:1201–5.

2. Alter MJ, Hadler SC, Judson FN, et al. Risk factors for acute non-A, non-B hepatitis in the United States and association with hepatitis C virus infection. JAMA 1990;264:2231–5.

3. Kelen GD, Green GB, Purcell RH, et al. Hepatitis B and hepatitis C in emergency department patients. N Engl J Med 1992;326:1399–1404.

4. Thomas DL, Zenilman JM, Alter HJ, et al. Sexual transmission of hepatitis C virus among patients attending sexually transmitted disease clinics in Baltimore—An analysis of 309 sex partnerships. J Infect Dis 1994;171:768–75.

5. Everhart JE, Di Bisceglie AM, Murray LM, et al. Risk for non-A, non-B (type C) hepatitis through sexual or household contact with chronic carriers. Ann Intern Med 1990;112:544–5.

6. Weinstock HS, Bolan G, Reingold AL, Polish LB. Hepatitis C virus infection among patients attending a clinic for sexually transmitted diseases. JAMA 1993;269:392–4.

7. Osmond DH, Padian NS, Sheppard HW, Glass S, Shiboski SC, Reingold A. Risk factors for hepatitis C virus seropositivity in heterosexual couples. JAMA 1993;269:361–5.

8. Akahane Y, Kojima M, Sugai Y, et al. Hepatitis C virus infection in spouses of patients with type C chronic liver disease. Ann Intern Med 1994;120:748–52.

9. Reinus JF, Leikin EL, Later HJ, et al. Failure to detect vertical transmission of hepatitis C virus. Ann Intern Med 1992;117:881–6.

10. Ohto H, Terazawa S, Sasaki N, et al. Transmission of hepatitis C virus from mothers to infants. N Engl J Med 1994;330:744–50.

11. Zanetti AR, Tanzi E, Paccagnini S, et al. Mother-to-infant transmission of hepatitis C virus. Lancet 1995;345:289–91.

Therapy of Hepatitis C: Overview

Karen L. Lindsay, M.D.

A great deal has been learned about the treatment of hepatitis C since the original report describing the use of interferon alfa-2b in 1986.[1] Most of the studies have been done in patients with chronic hepatitis C infection, elevated aminotransferases, and clinically compensated liver disease without other significant medical or psychiatric problems. Interferons remain the only agents shown to be effective. To date, the majority of studies have evaluated initial therapy using fixed-dose, fixed-duration regimens rather than regimens tailored to treatment response.

In early studies, serum alanine aminotransferase (ALT) was used as a surrogate marker of treatment effectiveness, and optimal response was defined as the normalization of ALT at the end (complete response [CR]) and for 6 months after (sustained response [SR]) therapy.[2] With the application of recently available virological assays to serum stored during early studies, it has become clear that not all patients treated for 6 months who develop persistent normalization of serum aminotransferases will clear HCV RNA from the serum. Instead, HCV RNA remains detectable in 20–25 percent[3] of such patients, and biochemical relapse occurs in the majority during followup.[4] Studies are now in progress using virological endpoints during treatment, and response definitions are now being refined to include biochemical and virological endpoints.

Two recombinant alpha interferons are currently FDA-approved as initial therapy for chronic hepatitis C. Three million units (MU) of interferon alfa-2b given subcutaneously three times weekly (tiw) for 6 months was approved in 1991, and 3 MU of interferon alfa-2a given subcutaneously tiw for 12 months was approved in 1996. Other products studied for use in hepatitis C include interferon alfa-n1, consensus interferon, leukocyte-derived interferon, and several beta interferon products. Standardization of the various interferon products and means by which biological potency can be best compared among the products is not yet established. This problem is currently being addressed by a WHO international collaborative study.

Hundreds of studies have been performed to evaluate various dosing regimens of the different interferon products. In many of these trials, problems in study design and data analysis make interpretation of the results and comparison with other studies difficult. A recent meta-analysis of randomized trials concluded that the best efficacy/risk ratio favored the use of 3 MU three times per week for at least 12 months in patients with chronic hepatitis C who had never been treated with interferon.[5]

In order to better understand which factors influence the response to interferon, many investigators have retrospectively analyzed baseline features of the patients and their disease characteristics in relationship to eventual end-of-treatment response (ETR) or sustained response. Using multivariate analyses, HCV genotype and the presence of cirrhosis or fibrosis on the pretreatment biopsy have been identified as factors that influence response to a 6-month course of treatment.[6,7] Baseline level of HCV RNA has been shown to be important in some studies,[6] but not in others.[7] The degree to which these factors influence response to interferon during the first 12 weeks of treatment, and whether the negative effect of these baseline factors can be overcome by treating patients longer than 6 months are not yet established. In view of the flaws inherent in the multivariate analyses that have been performed to date and the lack of data on longer treatment courses, as well as the side effects and cost of treatment, controversy exists as to whether some patients should be excluded from treatment[8] or all patients should be given a therapeutic trial[7] of interferon. Data generated through analysis of variables which influence response have been extremely important, however, in understanding which variables need to be controlled by study design and reported in treatment trial response analyses.

Response to treatment is evaluated during three phases of therapy—at the end of treatment (ETR), during followup after treatment (SR; at followup week 24, e.g., SR-WK24), and during treatment. Conventionally, end-treatment response is defined as normal serum ALT at the end of treatment and 4 weeks earlier. SR is an end-treatment response followed by normal ALT during the period of followup. In addition to ALT as a primary endpoint of therapy, response is also evaluated virologically. End-treatment virological response is conventionally defined as the nondetectability of serum HCV RNA by reverse transcriptase polymerase chain reaction (RT-PCR) at the end of treatment. Sustained virologic response is defined as an end-treatment virologic response followed by nondetectability of HCV RNA at defined timepoints during followup.

During therapy, the ALT values follow one of three general patterns: ALT normalizes and remains normal to the ETR, ALT remains abnormal throughout therapy, or ALT becomes temporarily normal and then abnormal again during treatment, a pattern which has been called *breakthrough*. Both of the latter two ALT response patterns have conventionally been considered *nonresponders* at the end of treatment. There is evidence that breakthrough may be related to the development of viral quasispecies[9] or neutralizing antibodies to interferon.[10] In order to best understand the effects of interferons on hepatitis C, and to be able to compare the potential differences between various interferon products, the reporting of on-treatment response rates and rates of breakthrough is extremely important.

In patients who have demonstrated an end-treatment response, ALT may remain normal after treatment is complete (SR), or may become elevated, which is defined as *relapse*. In studies that evaluate retreatment regimens, it is extremely important to define whether the population being re-treated has demonstrated previous nonresponse, breakthrough, or response and relapse patterns during initial interferon therapy.

In most studies, histological evaluation has been a secondary endpoint of treatment. Liver biopsies are performed within the 12 months prior to treatment, and at the end of treatment and/or during followup. Blinded objective scoring and subjective comparisons are performed and reported. In the majority of studies reported to date, the Knodell histological activity index (HAI)[11] has been used.

At this time, the optimal goal of therapy is the achievement of a sustained ALT and virological response with histological improvement. Long-term followup of patients who experienced a sustained response to interferon therapy indicates that more than 90 percent will maintain normal ALT values and non-detectability of HCV RNA over 1–6 years of followup. In such patients, histologic activity markedly improves.[12] Whether this represents a "cure" of hepatitis C viral infection with permanent eradication of virus remains uncertain, but, in view of the marked improvement in hepatic histology, it is anticipated that future hepatic function in such patients will be better than that in untreated patients or those whose disease does not respond to interferon.

Because of incomplete data, a number of issues remain unresolved, including the utility of dose escalation or adjunctive therapy in patients whose disease does not initially respond to interferon therapy, or in those who experience "breakthrough" on treatment. In addition, the optimal treatment and management of chronic hepatitis C in several special patient populations has yet to be determined, including children, patients with other significant medical diseases, such as renal insufficiency or end-stage renal disease, immune disorders including HIV co-infection, organ transplants, or severe psychiatric disorders. Finally, optimal treatment for acute hepatitis C infection remains unclear.

At this time, it remains uncertain whether long-term suppression of virus (rather than eradication) is a meaningful therapeutic endpoint. Finally, several studies have noted an improvement in hepatic histology in patients who did not normalize aminotransferases on therapy.[2,7,13] Whether this is due to viral suppression or an effect of interferon independent of viral suppression needs further investigation.

With the data currently available, however, we need to determine which patients with chronic hepatitis C should receive initial therapy, and whether there are patient groups in whom the likelihood of effectiveness of treatment is so low that a therapeutic trial should not be given. Among patients who begin initial therapy with interferon, we need to determine whether there are parameters of treatment effectiveness that indicate such a low likelihood of ultimate response to treatment that interferon should be discontinued. We need to decide what is the optimal duration of treatment in patients whose disease is responding to interferon. And, finally, we should determine whether retreatment with interferon should be given to patients whose disease responds to initial treatment, but relapses when interferon is stopped, or those in whom response to an initial course of treatment does not occur.

References

1. Hoofnagle JH, Mullen KD, Jones DB, et al. Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon: a preliminary report. N Engl J Med 1986;315:1575–8.

2. Davis GL, Balart LA, Schiff ER, Lindsay KL, Bodenheimer HC, Perrillo RP, Carey W, Jacobson IM, Payne J, Dienstag, JL, Van Thiel DH, Tamburro C, Lefkowitch J, Albrecht J, Meschievitz C, Ortego TJ, Gibas A, Hepatitis Interventional Therapy Group. N Engl J Med 1990;22:1501–6.

3. Lau JYN, Mizokami M, Ohno T, Diamond DA, Kniffen J, Davis GL. Discrepancy between biochemical and virological responses to interferon-a in chronic hepatitis C. Lancet 1993;342:1208–9.

4. Colloredo G, Bellati G, Ricci A, Scalori A, Redaeli A, Bellobuono A, Bissoli F, Civardi E, Santambrogio C, Roffi L, Ideo G. HCV RNA as a predictor of relapse after interferon therapy for chronic hepatitis C. Hepatology 1996; 24:156A.

5. Poynard T, Leroy V, Cohard M, Thevenot T, Mathurin P, Opolon P and Zarski JP. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996;24:778–89.

6. Martinot-Peignoux M, Marcellin P, Pouteau M, Castelnau C, Boyer N, Pouliquin M, Degott C, et al. Pretreatment serum hepatitis C virus RNA levels and hepatitis C virus genotypes are the main and independent prognostic factors of sustained response to interferon alfa therapy in chronic hepatitis C. Hepatology 1995;22:1050–6.

7. Lindsay KL, Davis GL, Schiff, ER, Bodenheimer HC, Balart LA, Dienstag JL, Perrillo RP, Tamburro CH, Goff JS, Everson GT, Silva M, Katkov WN, Goodman Z, Lau JYN, Maertens G, Gogate J, Sanghvi B, Albrecht J, Hepatitis Interventional Therapy Group. Hepatology 1996;24:1034–40.

8. Conjeevaram HS, Everhart JE, Hoofnagle JH. Predictors of a sustained beneficial response to alpha interferon therapy in chronic hepatitis C (editorial). Hepatology 1995;22:1326–9.

9. Okada SI, Akahane Y, Suzuki H, Okamoto H, Mishiro S. The degree of variability in the amino terminal region of the E2/NS1 protein of hepatitis C virus correlates with responsiveness to interferon therapy in viremic patients. Hepatology 1992;16:619–24.

10. Roffi L, Colloredo M, Antonelli G, Bellati G, Panizzuti F, Piperno A, Pozzi M, Ravizza D, Angeli G, Dianzani F, Mancia G. Breakthrough during recombinant interferon alfa therapy in patients with chronic hepatitis C virus infection: prevalence, etiology and management. Hepatology 1995;21:645–9.

11. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1981;1:431–5.

12. Boyer N, Marcellin P, Duchatelle V, Martinot M, Kilani A, Pouteau M, Descombes I, Benhamou JP, Degott C, Erlinger S. Sustained response after a interferon therapy in patients with chronic hepatitis C. Hepatology 1995; 22:291A.

13. Poynard T, Bedossa P, Chevallier M, Mathurin P, Lemonnier C, Trepo C, Couzigou P, et al. A comparison of three interferon alfa-2b regimens for the long-term treatment of chronic non-A non-B hepatitis. N Engl J Med 1995;332:1457–62.

Management of Hepatitis C: A National Survey of Gastroenterologists and Hepatologists

James Everhart, M.D., M.P.H.

Knowledge about hepatitis C virus (HCV) infection has expanded rapidly since isolation of the virus only a few years ago. New tests and treatments have rapidly appeared, but without a firm knowledge base for using them. In making recommendations for management of patients with HCV infection, it would be useful to know how physicians are currently managing patients. With this goal in mind, the American Digestive Health Foundation conducted a national survey of members of the American Gastroenterological Association (AGA) and American Association for the Study of Liver Diseases (AASLD) for presentation at this consensus conference. No Federal funds were expended in conducting the survey.

HCV infection is a very common condition, and the majority of patients are probably managed not by liver disease specialists but by internists and other generalists. The target of this survey, however, was not the general population of physicians who see patients with HCV, but rather practitioners who are most familiar with management of HCV infection. These specialists can be considered "opinion leaders" whose approach and recommendations most influence the management of patients with HCV in their communities.

The two-page survey was sent to a random sample of 2,500 AGA and AASLD members chosen from a combined membership list. The questionnaire was initially mailed on October 7, 1996, followed by a reminder postcard and a third mailing to nonresponders during the following month. Questionnaires were accepted until November 21, 1996, at which time a total of 1,416 forms had been returned. One hundred and sixty-seven questionnaires were returned in which the respondent did not meet the screening criterion of spending at least 1 day a week in patient care, leaving 1,249 usable responses. The overall response rate was 56.6 percent. Sampling error for responses was approximately 3 percent. Questions covered three areas: practice characteristics, general management of patients with HCV infection, and two case studies of patients with typical presentations of HCV infection. Some questions were not answered by all respondents. Therefore, total percentage response for each question may be less than 100 percent.

Practice Characteristics

Most physicians managed some patients with liver disease; approximately 15 percent of the respondents said that more than 25 percent of their patients have liver disease (Table 1). Ninety percent of respondents had diagnosed or provided treatment to a patient with HCV during the last 6 months. Nearly three quarters of the respondents had also treated HCV-infected patients with interferon during that time. In addition, one-third of respondents were more likely to treat patients with HCV with interferon than a year previously and only 15 percent were less likely (data not shown). Respondents were evenly split on whether they had restrictions placed on the care they provided for HCV patients by the patient's health care plan or managed care company.

TABLE 1. Practice Characteristics of Physicians		
Yes	No	Question
88.2%	10.4%	Do you spend at least 1 day per week taking care of patients? If NO, stop here and return form in the envelope provided. (N=1416)
90.3%	6.6%	In the past 6 months, have you diagnosed or provided treatment to any patient with hepatitis C? (N=1249)
16.4%	79.7%	Do you generally refer patients with suspected or diagnosed hepatitis C to other physicians for further evaluation and treatment?
73.6%	26.1%	In the past 6 months, have you treated any patient with hepatitis C with interferon?
47.3%	46.0%	For any of your hepatitis C patients, are there restrictions placed on the care you provide by the patient's health care plan or managed care company? For example, must you obtain prior approval before certain diagnostic tests can be ordered or before prescribing interferon?

General Management

Questions were asked about the general management of patients with HCV infection that would apply to most patients regardless of clinical state. The greatest range of opinions were for the following recommendations: use condoms to prevent transmission in a monogamous sexual relationship, do not drink at all, and vaccination against hepatitis B infection (Table 2). Advice regarding sexual practices and drinking touches on critical issues related to spread of infection and the factors that influence natural history of the disease.

TABLE 2. General Management of Patients with HCV Infection			
Close to 100% of the time	Some-times	Almost never	What do you recommend to patients with hepatitis C?
78.4%	9.2%	9.0%	Do not share toothbrushes or razors
13.8%	12.6%	70.0%	Do not share drinking glasses or dishes
1.8%	4.0%	90.8%	Do not hug or kiss children
28.3%	31.5%	36.3%	Use condoms to prevent transmission in a monogamous sexual relationship
71.0%	18.3%	6.8%	Minimize alcohol consumption
31.2%	35.9%	28.0%	Do not drink at all
52.4%	33.5%	10.7%	Have sexual partners checked for HCV
17.3%	24.7%	53.3%	Vaccination against hepatitis A
30.8%	36.8%	29.5%	Vaccination against hepatitis B

Case Studies

The two brief case studies concerned patients with common presentations of HCV infection. The first patient was a 36-year-old woman positive for antibody to HCV (anti-HCV) who was asymptomatic and had normal aminotransferase activities as well as other tests. Such patients are often identified following attempted blood donation and have not been shown to benefit from therapeutic intervention. The survey indicated that a high proportion of physicians would perform subsequent tests, but only 13 percent would treat with interferon (Table 3).

TABLE 3. Asymptomatic Patient With Normal Serum Aminotransferase Activities			
Yes	No	Maybe	Would you order any of the following tests?
55.4%	23.1%	12.6%	Anti-HCV by recombinant immunoblot assay (RIBA)
46.3%	22.2%	25.4%	Hepatitis C virus RNA by polymerase chain reaction (PCR)
4.4%	70.9%	11.9%	Hepatitis C virus genotyping
14.7%	53.5%	20.3%	Branched DNA or other quantitative test for HCV RNA
Yes	No	Maybe	If HCV infection is confirmed, which of the following would you recommend?
41.8%	27.9%	23.4%	Liver biopsy
27.9%	39.9%	20.3%	Ultrasound of the abdomen
13.2%	39.1%	37.3%	Treatment with alpha interferon
72.7%	7.0%	13.3%	Monitoring with repeat aminotransferases every 6–12 months
1.4%	79.3%	5.5%	Encouragement and no further followup or evaluation

The second patient was a 54-year-old man who also had anti-HCV, but with more severe disease: he was symptomatic and had markedly elevated serum aminotransferase activities. There is wide experience with use of alpha interferon in such symptomatic patients with enzyme abnormalities suggestive of liver injury. In the survey, further characterization of the infection was recommended for this patient no more often than for the first patient (Table 4). However, a liver biopsy was recommended more often, and over half of the respondents said they would have treated the patient with alpha interferon. Importantly, for both patients, more than one-third of physicians were uncertain whether to treat with interferon.

TABLE 4. Symptomatic Patient With Elevated Serum Aminotransferase Activities			
Yes	No	Maybe	Would you order any of the following tests?
40.0%	39.0%	10.7%	Anti-HCV by recombinant immunoblot assay (RIBA)
48.0%	25.2%	18.7%	Hepatitis C virus RNA by polymerase chain reaction (PCR)
12.1%	56.4%	19.8%	Hepatitis C virus genotyping
29.1%	41.4%	18.4%	Branched DNA or other quantitative test for HCV RNA
Yes	No	Maybe	If HCV infection is confirmed, which of the following would you recommend?
89.0%	0.8%	7.5%	Liver biopsy
57.3%	16.3%	16.5%	Ultrasound of the abdomen
56.1%	2.6%	35.5%	Treatment with alpha interferon
49.8%	24.5%	12.8%	Monitoring with repeat aminotransferases every 6–12 months

Therapy of Hepatitis C: Interferon Alfa-2b

Robert L. Carithers, Jr., M.D.

Preliminary studies performed at the NIH in the 1980s suggested the potential benefit of interferon alfa-2b in patients with chronic non-A, non-B hepatitis.[1,2] A series of randomized, double-blind, placebo-controlled trials confirmed the efficacy of this agent in normalizing alanine aminotransferase (ALT) values and improving histological features of disease activity.[3–6] In each of these trials, superior efficacy was seen with 3 million units (3 MU), compared with 1 million units of drug administered three times weekly (tiw) for 6 months.

Based on these studies, in 1991 the Food and Drug Administration approved interferon alfa-2b for treatment of patients with chronic non-A, non-B hepatitis (hepatitis C [HCV]) at a dosage and duration of 3 MU tiw for 6 months. This dosage and duration of interferon alfa-2b therapy has been the standard of care for treatment of patients with chronic hepatitis C in the United States until recently.

The discovery of the hepatitis C virus in 1989 and extensive clinical use of the drug have expanded our understanding of both the benefits and limitations of interferon alfa-2b treatment. Complete normalization of ALT values at the end of therapy is seen in 35–45 percent of patients treated with 3 MU interferon alfa-2b tiw for 6 months.[3–7] ALT values return to normal twice as frequently in patients without histological evidence of cirrhosis as in those with cirrhosis on pretreatment biopsy.[7] Biochemical improvement in disease activity is accompanied by disappearance of circulating HCV RNA in 75–85 percent of cases.[8–10] Histologic improvement, which is seen in 50–70 percent of treated patients, is not confined to those with biochemical and virological response.[3,5,6]

Patients receiving interferon alfa-2b can experience a number of side effects. The most common of these are nausea, headache, fever, myalgias, fatigue, leukopenia, thrombocypenia, alopecia, irritability, and depression. Thyroid abnormalities are seen less frequently. Rarely, patients experience retinal or pulmonary abnormalities. Temporary dosage reduction is required in some patients, usually for transient leukopenia and thrombocytopenia. However, most patients are able to complete a full course of therapy.

A major limitation of interferon alfa-2b therapy has been the high relapse rate when patients discontinue treatment. Among patients who achieve a complete biochemical response to 3 MU interferon alfa-2b tiw for 6 months, 30–70 percent relapse within the first few months after completion of therapy.[3–7] Sustained biochemical and virological response, defined as persistently normal ALT values and absence of circulating virus for at least 6 months after discontinuing treatment, is seen in only 10–15 percent of patients. However, most patients who achieve this important endpoint remain free of detectable circulating virus without biochemical or histological evidence of disease progression.[11–13]

Because of the low sustained virological and biochemical response rates in patients treated with 3 MU interferon alfa-2b tiw for 6 months, a number of investigations have been initiated to explore different dosages and durations of treatment. Most studies suggest that the most effective means of improving long-term efficacy of interferon alfa-2b therapy for chronic hepatitis C are to extend the duration of treatment from 6 months to 12–18 months or to add additional antiviral agents such as ribavirin.[14–16]

References

1. Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, et al. Treatment of chronic non-A, non-B hepatitis with recombinant human alpha-interferon. N Engl J Med 1986;315:1575–8.

2. Di Bisceglie AM, Martin P, Kassianides C, Lisker-Melman M, Murray L, Waggoner J, et al. Recombinant interferon alfa therapy for chronic hepatitis C: a randomized, double-blind, placebo-controlled trial. N Engl J Med 1989;321:1506–10.

3. Davis GL, Balart LA, Schiff ER, Lindsay K, Bodenheimer HC, Jr., Perrillo RP, et al. Treatment of chronic hepatitis C with recombinant interferon alfa: a multicenter randomized, controlled trial. N Engl J Med 1989;321:1501–6.

4. Marcellin P, Boyer N, Giostra E, Degott C, Courouce AM, Degos F, et al. Recombinant human alpha-interferon in patients with chronic non-A, non-B hepatitis: a multicenter randomized controlled trial from France. Hepatology 1991;13:601–3.

5. Saracco G, Rosina F, Torrani-Cerenzia MR, Lattore V, Chiandussi L, Gallo V, et al. A randomized controlled trial of interferon alfa-2b as therapy for chronic non-A, non-B hepatitis. J Hepatol 1990;11(suppl 1):S43–9.

6. Causse X, Godinot H, Chevallier M, Chossegros P, Zoulim F, Ouzan D, et al. Comparison of 1 or 3 MU of interferon alfa-2b and placebo in patients with chronic non-A, non-B hepatitis. Gastroenterology 1991;101:497–502.

7. Jouët P, Roudot-Thoraval F, Dhumeaux D, Métreau J, et al. Comparative efficacy of interferon alpha in cirrhotic and noncirrhotic patients with non-A, non-B hepatitis. Gastroenterology 1994;106:686–90.

8. Shindo M, Di Bisceglie AM, Cheung L, Shih W, Cristiano K, Feinstone SM, et al. Decrease in serum hepatitis C viral RNA during alpha-interferon therapy for chronic hepatitis C. Ann Intern Med 1991;115:700–4.

9. Kleter GEM, Brouwer JT, Heijtink RA, Schalm SW, Quint WGV. Detection of hepatitis C virus RNA in patients with chronic hepatitis C virus infections during and after therapy with alpha interferon. Antimicrob Agents Chemother 1993;37:595–7.

10. Gerweck KK, Cheung AM, Wong DKH. Comparison of biochemical and virological responses to interferon therapy in chronic hepatitis C: a meta-analysis [abstract]. Hepatology 1995;22:420A.

11. Shindo M, Di Bisceglie AMD, Hoofnagle JM. Long-term follow-up of patients with chronic hepatitis C treated with a-interferon. Hepatology 1992;15:1013–6.

12. Saracco G, Rosina F, Abate ML, Chiandussi L, Gallo V, Cerutti E, et al. Long-term follow-up of patients with chronic hepatitis C treated with different doses of interferon-a2b. Hepatology 1993;18:1300–5.

13. Reichard O, Glaumann H, Fryden A, Norkrans G, Schvarcz R, Sonnerborg A, et al. Two-year biochemical, virological, and histological follow-up in patients with chronic hepatitis C responding in a sustained fashion to interferon alfa-2b treatment. Hepatology 1995;21:918–22.

14. Poynard R, Bedossa P, Chevallier M, Mathurin P, Lemonnier C, Trepo C, et al. A comparison of three interferon alfa-2b regimens for the long-term treatment of chronic non-A, non-B hepatitis. N Engl J Med 1995;332:1457–62.

15. Poynard T, Leroy V, Cohard M, Thevenot T, Mathurin P, Opolon P, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996;24:778–89.

16. Hoofnagle JH, Lau D. Chronic viral hepatitis—benefits of current therapies. N Engl J Med 1996;334:1470–1.

Therapy of Hepatitis C With Interferon Alfa-2a

William M. Lee, M.D.

Interferon alfa-2a (IFN alfa-2a, Roferon®-A) is an alfa interferon that differs in peptide sequence by one amino acid from interferon alfa-2b. Studies have been performed worldwide over the last 7 years, documenting its safety and efficacy in more than 2,000 patients. Roferon®-A is licensed in Europe and was cleared by the U.S. Food and Drug Administration for use in chronic hepatitis C in November 1996. This report will present results of previous clinical trials with Roferon®-A, focusing on end-treatment and end-followup responses and on experience with more prolonged treatment, escalating dosages, and retreatment. Integrated results of the Roche worldwide clinical program in chronic hepatitis C will be reviewed. An additional study of 422 patients was just completed and data analysis is in progress.

Study Population

In the 10 trials reported, 1,701 patients were treated in one of three regimens: fixed dosages (n = 1,300), escalating dosage in 117 patients, and de-escalating dosage in 284 patients. Administered doses of Roferon®-A varied between 1 and 9 million units (MU) thrice weekly (tiw). Variation in dosage was determined (up or down) by alanine aminotransferase (ALT) response. A normal ALT response during treatment led to diminution in dosage (6 to 3) in certain protocols, and an abnormal ALT response led to escalation in others (3 to 6 to 9 at 2-month intervals if ALT response was abnormal). One hundred thirty untreated or placebo controls were considered in the analysis. Sites in Europe, the United States, Australia, Canada, Brazil, and Israel were included. The mean age was 45 (range 18–81) and the proportion of men to women was 2:1. Most patients (83 percent) had ALT levels between 1.5 and 7 times normal values. Histologic diagnoses included chronic active hepatitis (CAH) (58 percent) or CAH with cirrhosis (27 percent). Caucasians made up 97 percent of the study population, and the mean body surface area for all groups was 1.8 m^2.

Definition of Response

Responses to treatment were considered to be biochemical or virological and correlated with histological measures. The primary parameter of efficacy in the early studies was a biochemical response based on serum ALT measurement. In these studies, a complete end-treatment or followup response required two consecutive normal ALT values 321 days apart. A sustained response (SR) is defined as a complete response maintained for 36 months after end of treatment. Virological responses were defined as follows:

- Complete response: HCV RNA undetectable by Amplicor®-HCV MONITOR™ quantitative reverse transcription polymerase chain reaction (RT-PCR) at a timepoint specified.

- Nonresponse: HCV RNA measurable by the same technique at a timepoint specified.

Results

The results in three fixed-dose studies demonstrated a dose-response curve for induction of complete biochemical response with values of 23, 38, and 56 percent, respectively, for 1, 3, and 4.5 MU. This was paralleled by the data for induction of virological response: the percentages of patients with a virologic response at 3 months of treatment were 5, 11, 35, and 39 percent, respectively, for placebo, 1 MU, 3 MU, and 4.5 MU doses. End-treatment results were similar. A marginal improvement in virological end-treatment responses was observed in the escalating dose protocol when compared with the fixed-dose protocol: 38 percent vs. 27 percent. End-treatment and followup responses (6 months) for six regimens—three with fixed and three with de-escalating doses—showed SRs at followup of 8–25 percent with 6 months of treatment and 24–39 percent with 12 months of treatment. It should be noted that the studies employing 12 months of treatment all used de-escalating (6 to 3) regimens. SRs at 6-month followup varied from 8 to 39 percent, depending on the regimen and, presumably, other factors. These studies varied, for example, in the severity of histologic lesions (i.e., the percentage of patients with established cirrhosis). Twelve months of treatment appeared to be associated with increased SRs. Histological improvement in terms of reduction of histologic activity index (HAI) paralleled the biochemical responses and showed a similar dose-response curve. No improvement in HAI was observed in nonresponders (biopsy at end of treatment).

Analysis of a cohort of sustained responders (n = 40) for whom PCR data were available from a total of 317 patients (including untreated/placebo, 1, 3, or 4.5 MU) were compared for demographic features, baseline biochemistry, pretreatment liver histology, viral titers, and genotypes. The cohort of sustained responders showed no difference when compared with nonresponding or relapsing patients in demographic features or baseline biochemistries but did demonstrate fewer patients with cirrhosis, a lower mean viral titer, and fewer patients with the 1B genotype.

Additional Studies

Additional data are available on longer treatment regimens. A study employing 6 MU for 4 months followed by 3 MU for 8 months demonstrated 42 percent sustained ALT and virological response at 6-month followup, compared with 25 percent for those treated with 3 MU for 12 months. Retreatment regimens for patients who demonstrated biochemical relapse have been employed. In a study employing dose escalation for a group of patients initially treated with 3 or 6 MU, those who relapsed were treated within 6 months of previous therapy with either the same dose or an escalating dose (3 to 6, 6 to 9 MU). The complete responses were 79 and 85 percent for those retreated with the same dose or an escalating dose, respectively, and the SRs (at 3 months) were 21 percent and 41 percent, respectively, for retreatment with the same or the escalated dose, suggesting a role for escalating dose to obtain greater SRs in those considered for retreatment. Long-term followup is available on a group of sustained responders followed to 4.5 years. For patients found to have biochemical and virological complete responses at 3 or 6 months, continued biochemical and virological responses were maintained in more than 90 percent of these patients at the 4.5-year followup.

Conclusions

Interferon alfa-2a demonstrates a safety and efficacy profile similar to those of other alpha interferons. Additional experience with this agent is available for prolonged-duration regimens (12 months), for higher dose induction with subsequent de-escalation, and for retreatment. Taken together, these studies demonstrate a dose-response curve for IFN alfa-2a in chronic hepatitis C patients, in terms of biochemical, virological, and histological responses, and suggest that use of higher doses for induction, more prolonged treatment, and retreatment may all be valid strategies to improve overall the number of sustained responders.

Bibliography

1. Haria M, Benfield P. Interferon alfa 2a. A review of its pharmacological properties and therapeutic use in the management of viral hepatitis. Drugs 1995;50:873–96.

2. Ryff J-C. Usefulness of interferon for treatment of chronic hepatitis C. J Hepatol 1995:22(Suppl 1):101–9.

3. Chemello L, Bonetti P, Cavalletto Talato F, Donadon W, Casarin P, et al. Randomized trial comparing three different regimens of alpha 2a interferon in chronic hepatitis C. Hepatology 1995;22:700–6.

4. Douglass DD, Rakela J, Lin HJ, et al. Randomized controlled trial of recombinant alpha 2a-interferon for chronic hepatitis C. Dig Dis Sci 1993;38:601–7.

Interferon Alfa-n1 Trials

Geoffrey C. Farrell, M.D., F.R.A.C.P.

Background

Lymphoblastoid interferon (IFN-an1) is produced from a human lymphoid cell line and consists of multiple IFN-a subtypes of which at least two are glycosylated.[1] This differs from the recombinant IFNs, which are single unglycosylated proteins produced from individual IFN-a genes (usually subtype 2) expressed in *E. coli*. The differences between IFN-a preparations provide a potential basis for varying clinical effects. A meta-analysis of earlier published trials indicated that IFN-an1 was at least as efficacious against hepatitis C as recombinant products (IFN-a2b, IFN-a2a).[2] One apparent difference, however, was a lower rate of posttreatment relapse after IFN-an1. Thus, sustained response (SR) was
25 percent with IFN-an1 compared with 16 percent for recombinant products. In order to provide sufficient power to detect a 10 percent difference in response rate between lymphoblastoid and recombinant IFN-a, a randomized, clinical trial (the 096 study) was conducted at 63 centers in 13 countries.

Methods

Patients had previously untreated, chronic hepatitis C virus (HCV) infection, defined by positive anti-HCV, consistently raised alanine aminotransferases (ALT), appropriate liver histology, and exclusion of other disease. Patients (n=1071) were randomized to receive lymphoblastoid interferon (IFN-an1) or recombinant interferon-alfa2b (IFN-a2b), both 3 million units (MU) tiw subcutaneously for 24 weeks. HCV genotype (by line probe assay) and serum HCV RNA titer (by quantitative polymerase chain reaction [PCR]) were determined at baseline. Primary endpoints were: end-treatment response (ETR)—two or more successively normal serum ALT levels including the week 24 value; sustained response (SR)—continued normal ALT after an ETR, with normal values at weeks 48 (week 48 SR) and 72 (week 72 SR). Secondary endpoints were serum HCV RNA at weeks 24, 48, and 72, and quantitative histology (by Knodell's histologic activity index [HAI] score) at weeks 24 and 72. Primary endpoints were analyzed by intent to treat, and secondary endpoints were according to treatment received.

Results

Groups were well matched for demographic, viral, clinical, and histologic variables; about 10 percent had cirrhosis. Predominant genotypes were 1a and 1b in the United States, and types 1b, 2a, and 3a in Europe and Australia. At end of treatment, ALT response was 35.3 percent for IFN-an1 and 37.9 percent for IFN-a2b (NS). The type and frequency of reported adverse experiences were similar; 26 patients (5 percent) receiving IFN-an1 and 19 (4 percent) receiving IFN-a2b withdrew because of adverse experiences. Viral and histologic responses were determined in the 970 evaluable patients. At 24 weeks, there was no difference between the groups in the proportion who were HCV RNA negative (IFN-an1, 37.9 percent vs. IFN-a2b, 42.0 percent, NS). More than 70 percent of ALT responders had cleared serum HCV RNA. Among patients who had an ETR, liver histology at 24 weeks was improved (2-point or greater reduction in HAI activity score) in 61 percent; there were no differences between treatment groups. Among responders (ETR), posttreatment relapse was less frequent with IFN-an1 than with IFN-a2b. Thus sustained ALT responses (SR) to IFN-an1 were more frequent than to IFN-a2b (12.0 percent vs 7.6 percent at 48 weeks, P=0.01; 10.3 percent vs 6.7 percent at 72 weeks, P=0.02).

Relapse was more likely if HCV RNA was present at end treatment. SR was associated with viral loss, and more patients treated with IFN-an1 were HCV RNA negative at week 72 compared with

IFN-a2b (9.9 percent vs. 5.7 percent, $p<0.05$). By weeks 48 and 72, approximately 80 percent and 90 percent, respectively, of sustained responders had cleared HCV RNA. At week 72, liver biopsy for patients with SR was almost invariably improved compared with baseline; there were no significant differences between those treated with IFN-an1 and those who received IFN-a2b.

Sixteen candidate variables were examined by multivariate regression analysis in relation to treatment response. Heavier weight, cirrhosis at screen, and genotypes 1 were associated with lack of ETR, whereas larger body surface area and white race were positively associated with ETR. Viral titer was not associated with ETR, but was independently associated with SR. SR varied from 3 percent with genotype 1, to 20 percent for genotypes 2, 3, and mixed infections. SR (72 weeks) after treatment with IFN-an1 was superior across all genotypes compared with IFN-a2b.

Discussion

The finding that IFN-an1 conferred an efficacy advantage compared with a recombinant alpha-interferon when given at 3 MU, tiw for 24 weeks was not due to a greater number of patients having an ETR. Rather, it was attributable to the lower proportion of patients who subsequently relapsed. This reduction in relapse rate produced a higher SR for IFN-an1, and more patients treated with IFN-an1 had sustained clearance of serum HCV RNA. The findings of this prospective study are consistent with the earlier meta-analysis of interferon trials for hepatitis C; i.e., there is no difference between lymphoblastoid and recombinant alpha-interferon products in ETR, but 50 percent improvement in SR with the lymphoblastoid interferon due to a lower relapse rate.[2] It appears likely that the clinical difference in efficacy results from IFN-an1 exerting more potent anti-HCV activity across all HCV genotypes. The greater diversity of alpha-interferon subtypes present in the lymphoblastoid product might be responsible for this.

The present results provide more extensive data concerning the posttreatment course following 24 weeks of treatment with IFN-a than have been previously available. The proportion of patients with normalization of ALT who were negative with regard to HCV RNA in serum increased from 70 percent at end treatment, to 80 percent at 48 weeks and 90 percent at 72 weeks. This indicates a relationship between sustained ALT normalization and clearance of HCV RNA. The minority of ALT responders who remain HCV RNA positive are likely to undergo clinical relapse in the year following treatment. The present data also confirm that sustained ALT and viral response are associated with histologic improvement of liver inflammation and necrosis, but not of fibrosis.

Several studies with recombinant IFN-a have shown that treatment courses of 12 months (or longer) reduce the relapse rate by around 50 percent, thereby effectively doubling SR.[3] Data regarding the comparative efficacy of higher interferon doses have been conflicting, and improvement in efficacy may be compromised by a higher rate of intolerable adverse experiences.[3,4] The issue therefore arises as to whether lymphoblastoid interferons also exhibit greater potency when administered in higher doses or for longer. This was addressed in a large European multicenter trial (091) of IFN-an1.[5] Entry and response criteria were similar to the 096 study; SR was at 48 week followup. Patients (n=440) were randomly assigned to receive one of the following four regimens (all tiw): 3 MU for 24 weeks, 3 MU for 48 weeks, 5 MU for 24 weeks, and 5 MU for 48 weeks. ETR ranged from 38 percent to 50 percent (NS). There was no difference in SR between the 24 weeks 3 MU and 5 MU arms [6 percent vs. 14 percent, NS] or between the corresponding two 48-week arms (19 percent vs. 20 percent, NS). However, at both dose increments, prolongation of therapy to 12 months effectively doubled the SR ($P=0.001$) by halving the relapse rate. Histological improvement, as seen by reduction in the necroinflammatory activity of the HAI score, was most effectively maintained in the group receiving 5 MU for 48 weeks ($P<0.05$). Any apparent benefit in the group receiving 5 MU for 48 weeks compared with the groups receiving 3 MU in terms of histology as the efficacy endpoint needs to be considered in relation to the higher rate of adverse experiences, dose reductions, and terminations at the higher dose.

Conclusions

IFN-an1 and IFN-a2b have similar ETR rates and safety profiles, but the SR rate is higher with IFN-an1. Sustained response was associated with loss of HCV viremia and with histologic improvement, the latter being maximal in those who exhibited clearance of HCV RNA. HCV genotype was the most powerful determinant of SR, and the greater efficacy of lymphoblastoid interferon appeared to extend to all major genotypes. There is definite evidence that 12 months of treatment is superior to 6 months in terms of ALT and HCV RNA as efficacy endpoints, and whether there is truly benefit for histologic response at the higher dose of IFN-an1 (5 MU vs. 3 MU tiw) needs to be considered in relation to adverse experiences. Finally, the possibility that lymphoblastoid interferons could produce a better SR than recombinant alpha-interferons when given for a 12-month (or longer) treatment course is an important issue that requires further study.

References

1. Zoon K, et al. Purification and characterization of multiple components of human lymphoblastoid interferon-alpha. J Biol Chem 1992;1267:15210–6.

2. Bardelli F, Messori A, Rampazzo R, Alberti A, Martini N. Effect of recombinant or lymphoblastoid interferon-a on alanine aminotransferase in patients with chronic hepatitis C or chronic non-A non-B hepatitis. A meta-analysis. Clin Drug Invest 1995;9:239–54.

3. Poynard T, Leroy V, Cohard M, Thevenot T, Mathurin P, Opolon P, Zarski JP. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996;24:778–9.

4. Lindsay KL, Davis GL, Schiff ER, et al. Response to higher doses of interferon alfa-2b in patients with chronic hepatitis C: a randomized multicenter trial. Hepatology 1996;24:1034–40.

5. Marcellin P, Hopf U, Trepo C, et al. A randomized, double-blind, controlled, multicentre study of lymphoblastoid interferon alpha n1 in the treatment of adults with chronic hepatitis C. J Hepatol. In press.

Consensus Interferon Trials

**Emmet B. Keeffe, M.D., F. Blaine Hollinger, M.D.,
and Consensus Interferon Study Group**

Introduction

Interferons are a family of naturally occurring small proteins that are produced and secreted by cells in response to viral infections. Alpha and beta interferons are classified as type 1 interferons and include more than 25 different molecules. Consensus interferon (CIFN) is a novel, recombinant type 1 interferon containing 166 amino acids. CIFN was derived by scanning the sequences of several natural alpha interferons and assigning the most frequently observed amino acid in each corresponding position. CIFN, when compared on an equal mass basis with interferon (IFN) alfa-2a and alfa-2b in *in vitro* assays, typically displays 5–10 times higher biological activity.[1]

Studies

Three studies were conducted to evaluate the safety and efficacy of CIFN for the treatment of chronic hepatitis C virus (HCV) infection. An initial phase 2 study was performed to determine the safety and efficacy of CIFN in doses ranging from 3 mg to 15 mg three times a week (tiw) in 55 patients with chronic HCV infection.[2] The promising results of this early study led to a large, randomized, double-blind, controlled, phase 3 study of 704 patients with chronic HCV infection, comparing 3 mg or 9 mg of CIFN with 3 million units (MU) (15 mg) of IFN alfa-2b tiw over 24 weeks of treatment.[3] A third, randomized, open-label study was conducted to evaluate the safety and efficacy of CIFN retreatment at a higher dose (15 mg) tiw for either 24 or 48 weeks in patients with chronic HCV infection who did not respond or who relapsed after treatment with either CIFN or IFN alfa-2b in the earlier study.[4]

Phase 2 Dose-Finding Study

Five doses of CIFN, ranging from 3 mg to 15 mg, were administered tiw for 24 weeks to 55 patients with chronic HCV infection.[2] Responses at the end of treatment using alanine aminotransferase (ALT) ranged from 18 percent to 42 percent, and treatment responses using serum HCV RNA ranged from
27 percent to 75 percent. After 24 weeks of posttreatment observation, approximately 50 percent of patients relapsed, except for patients receiving 15 mg who had a 100 percent sustained response by ALT and 50 percent sustained virologic response. Dose limiting toxicity was not found in patients receiving
3 mg, 6 mg, and 9 mg, but was noted in 18 percent of patients in the 12-mg cohort and 36 percent of patients in the 15-mg cohort. This preliminary study suggested that CIFN was a safe and effective treatment of chronic hepatitis C and that there may be a dose effect for sustained responses.

Phase 3 CIFN Study

A large, randomized, double-blind, controlled study was conducted in 704 North American patients with chronic HCV infection who had not previously been treated with interferon.[3] Patients received CIFN at doses of 3 mg (n=232) or 9 mg (n=232) or IFN alfa-2b at a dose of 3 MU (15 mg) (n=240) tiw for 24 weeks followed by 24 weeks of observation. Biochemical and virological responses were assessed at the end of treatment and end of posttreatment observation by measuring changes in serum ALT and serum HCV RNA (quantitative multicycle reverse transcription-polymerase chain reaction [RT-PCR] method with a lower limit of sensitivity of 100 copies/mL [National Genetics Institute, Culver City, CA]). Histological responses were assessed by comparing liver biopsies at baseline with

biopsies at the end of posttreatment observation using the histological activity index (HAI, or Knodell score). Among the three treatment groups, there were no differences in demographics; mode of acquisition of HCV infection; or baseline liver biochemical tests, serum HCV RNA concentrations, genotypes, or histology (cirrhosis was present in 20.3 percent of the 3 mg CIFN cohort, 17.6 percent of the 9 mg CIFN cohort, and 11.9 percent of the IFN alfa-2b cohort). Results using the endpoints of ALT levels below normal limits and serum HCV RNA below detection are shown in Table 1.

TABLE 1. Serum HCV RNA and ALT Response Rates in Three Treatment Groups

Treatment	No.	Serum HCV RNA Response		ALT Response	
		End of Treatment	End of Observation	End of Treatment	End of Observation
3 µg CIFN	232	7%	3%	16%	6%
9 µg CIFN	232	35%	12%	42%	21%
3 MU (15 µg) IFN a2b	240	27%	11%	37%	20%

Patients treated with 9 mg of CIFN had a significantly greater mean reduction in HCV RNA levels at the end of treatment ($p=0.037$) and over the course of the study ($p<0.01$) than the IFN alfa-2b group. The mean change in HAI score was -1.73, -2.01, and -2.03 for the 3 mg CIFN, 9 mg CIFN, and 3 MU
(15 mg) IFN alfa-2b groups, respectively.

The serum HCV RNA responses among subjects infected with genotype 1a and 1b are shown in Table 2 and suggest that CIFN 9 mg is more effective therapy for patients infected with genotype 1 than 3 MU (15 mg) of IFN alfa-2b.[5] The serum HCV RNA response at the end of treatment for all genotype 1 patients (1a and 1b) was better after CIFN treatment compared to IFN alfa-2b treatment ($p=0.013$).

TABLE 2. Serum HCV RNA Response to 9 mg CIFN vs. 3 MU (15 mg) IFN alfa-2b

Genotype	End of Treatment		End of Observation	
	9 µg CIFN	3 MU(15 µg) IFN a2b	9 µg CIFN	3 MU(15 µg) IFN a2b
1a (n=153)	24%	11%	8%	3%
2b (n=115)	26%	15%	11%	6%

The median baseline concentration of serum HCV RNA was 3.0×10^6 copies/mL. The upper 25 percent of HCV RNA values ($>4.8 \times 10^6$ copies/mL) were analyzed for response rates to treatment. At the end of observation, 7 percent of CIFN-treated patients had undetectable serum HCV RNA ($p<0.01$), compared with none of the IFN alfa-2b-treated patients.

The adverse event and laboratory profiles observed for 9 mg CIFN were similar to those observed for 3 MU (15 mg) IFN alfa-2b and to those reported for other type 1 interferons.

Retreatment Study

The primary objective of this study was to determine the safety and efficacy of CIFN retreatment at a higher dose (15 mg) in patients with chronic HCV infection who had completed the phase 3 study and who either did not respond or relapsed after treatment with either CIFN or IFN alfa-2b.[4] Eligible patients had at least two consecutive serum ALT levels above the upper limits of normal either at the end of treatment or end of observation. Patients were randomized to receive 24 or 48 weeks of retreatment. A total of 167 patients received CIFN 15 mg tiw for 24 weeks followed by 24 weeks of observation. The ALT and HCV RNA response rates are shown in Table 3.

TABLE 3. Serum ALT and HCV RNA Responses to CIFN Retreatment for 24 Weeks

	All Patients	Nonresponders	Relapsers
ALT responses	(n=166)	(n=122)	(n=44)
End of retreatment	45%	30%	84%
End of observation	21%	12%	46%
HCV RNA responses	(n=166)	(n=128)	(n=38)
End of retreatment	35%	24%	71%
End of observation	13%	8%	32%

The retreatment response rates were the same regardless of whether patients had received CIFN or IFN alfa-2b as initial therapy. The adverse events observed with 15 mg CIFN were no greater than those observed with 9 mg CIFN. However, the protocol allowed for dose reduction based on side effects;
37 patients (22 percent) had one dose reduction to 12 mg, and 18 patients (11 percent) had more than one dose reduction. Data from patients retreated for 48 weeks with 15 mg CIFN is pending and will provide information on the efficacy of retreatment for a longer duration.

Conclusions

1. CIFN at a dose of 9 mg administered tiw for 24 weeks is safe and effective for the treatment of chronic HCV infection in interferon-naive patients and results in a sustained HCV RNA response rate of 12 percent.

2. When compared to with MU (15 mg) IFN alfa-2b, 9 mg CIFN may result in higher sustained HCV RNA response rates in patients with genotype 1 and in patients with high pretreatment viral loads.

3. In patients failing prior CIFN or IFN alfa-2b therapy, retreatment with a higher dose of CIFN (15 mg) for 24 weeks results in sustained HCV RNA response rates in 8 percent of nonresponders and 32 percent of relapsers and is well tolerated.

References

1. Blatt LM, Davis JM, Klein SB, Taylor MW. The biologic activity and molecular characterization of a novel synthetic interferon-alpha species, consensus interferon. J Interferon Cytokine Res 1996;16:489–99.

2. Tong MJ, Blatt LM, Resser K, Klein M, Figueroa TA. Treatment of patients with chronic HCV infection with a novel type-1 interferon, consensus interferon [abstract]. Hepatology 1993;18:150A.

3. Blatt LM, Hollinger FB, Tong MJ, Reddy KR, Lee WM, Pockros PJ, Hoefs JC, Keeffe E, Heathcote JL, White H, Foust RT, Jensen DM, Krawitt EL, Fromm H, Black M, Klein M, Lubina J, Manyak C, CIFN Study Group. A phase 3 study for the treatment of patients with chronic hepatitis C (HCV) infection with consensus interferon (CIFN) [abstract]. Abstract Volume of the IX Trienniel International Symposium on Viral Hepatitis and Liver Disease, 1996, p 26.

4. Heathcote J, Keeffe E, Lee S, Feinman S, Tong M, Consensus Inteferon Study Group. Retreatment of chronic HCV infection with a higher dose (15 mg) of consensus interferon (CIFN) produces sustained responses in nonresponders and relapsers [abstract]. Gastroenterology. In press.

5. Hollinger FB, Blatt LM, Tong MJ, Conrad A, Balart L, Pockros P, Bonkovsky HL, Ehrinpreis MN, Lubina J, Consensus Interferon Study Group. Differential response to treatment with consensus interferon (CIFN) and IFN-a 2b in chronic HCV patients infected with genotype 1a and 1b [abstract]. Gastroenterology 1996;110:A1213.

6. Jensen DM, Blatt LM, Tong MJ, Lee WM, Mullen K, Hoefs JC, Keeffe E, Hollinger FB, Heathcote EJL, White H, Foust RT, Krawitt EL, Fromm H, Black M, Albert D, Gerrard T, and the Consensus Interferon Study Group. Treatment of high viral titer chronic HCV patients with consensus interferon (CIFN) results in a significantly greater number of sustained HCV-RNA responders as compared to treatment with interferon a-2b [abstract]. Hepatology 1996;24:275A.

Ribavirin Treatment Alone or in Combination With Interferon

Olle Reichard, M.D., Ph.D., and Ola Weiland, M.D., Ph.D.

Background

Only a small fraction of chronic hepatitis C virus (HCV) infected patients will achieve long-term benefit with viral eradication from standard interferon treatment.[1–3] Furthermore, patients with autoimmune disorders, thyroid dysfunctions, decompensated cirrhosis, thrombocytopenia, and posttransplant patients, usually are withheld from interferon therapy due to the risk of serious adverse reactions. Thus, the need for alternative treatments for chronic HCV infection is evident. Presently, ribavirin (1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide), a guanosine analogue with a broad spectrum of activity against several RNA and DNA viruses including the flavivirus family, is the most extensively evaluated and promising alternative.[4] Ribavirin is usually well tolerated and has the advantage of oral administration. The exact mode of action is poorly understood. Possible mechanisms include depletion of the intracellular triphosphate pools through the direct inhibition of inosine monophosphate dehydrogenase, inhibition of the 5'-cap structure of viral mRNA, and inhibition of the viral dependent RNA polymerases. Moreover, it has recently been proposed that ribavirin does not act as an antiviral drug, but rather as an inhibitor of macrophage pro-inflammatory cytokines and as an immune modulator preserving the Th1 and reducing the Th2 cytokine production.[5] Unfortunately, it is not possible to test drugs including ribavirin for antiviral effect against HCV in vitro, since no tissue culture system is readily available for HCV replication.

Ribavirin Monotherapy Studies

Ribavirin as therapy for chronic HCV infection was first suggested 1991 in a pilot study from Sweden.[6] Ten HCV patients were treated with oral ribavirin at a dose of 1000–1200 mg/day for 12 weeks. A significant reduction of mean serum transaminase levels during treatment, with a subsequent relapse when treatment was withdrawn, was seen. The effect on HCV replication, as measured by polymerase chain reaction (PCR) in serum, was disappointing. No patient cleared viremia during treatment in spite of normalization of transaminases.[7] Several uncontrolled studies later confirmed these initial results.[8,9]

Recently, two randomized, double-blind, placebo-controlled ribavirin trials were reported.[10,11] The results were consistent with previous uncontrolled studies. Thus, a biochemical response with reduction of transaminase levels during treatment was seen in ribavirin treated patients, whereas no virological eradication was achieved (Table 1). However, a slight but significant decline of serum HCV RNA levels during treatment as measured by branched DNA assay was seen in the ribavirin group.[11] After treatment, rebound to pretreatment levels was noted. The necro-inflammatory activity, particularly periportal and intralobular inflammation, was significantly reduced for patients treated with ribavirin when liver biopsies from before and at the end of treatment were compared. The predominant adverse events noted

TABLE 1. Treatment Results of Two Randomized Placebo-Controlled Ribavirin Studies in Patients with Chronic Hepatitis C

	Normalization of Transaminases*		Clearance of Viremia*	
	Ribavirin	Placebo	Ribavirin	Placebo
Di Bisceglie et al. (48 weeks)	10/29 (35%)	0/29 (0%)	0/29 (0%)	0/29 (0%)
Dusheiko et al. (24 weeks)	42/76 (55%)	2/38 (5%)	2/67 (3%)	1/36 (3%)

* During treatment.

were hemolysis (necessitating a dose reduction in 13 percent of patients), nervous system disorders (fatigue, depression, insomnia, and vertigo), gastrointestinal disorders (anorexia and nausea), and skin disorders (pruritus, rash, and eczema).

Interferon/Ribavirin Combination Studies

In order to improve response rates and to minimize drug resistance, combination therapy is of value in many infectious diseases. The combination of interferon and ribavirin as therapy for chronic HCV infection thus seemed reasonable. Pilot studies have shown that approximately 80 percent of relapsers and 10–25 percent of nonresponders to previous interferon therapy will have a sustained virological and biochemical response when ribavirin is combined with interferon during a 24-week treatment course.[12–14] In an Italian study, 45 interferon-naive chronic HCV patients were randomized in three groups (1:1:1) to receive either alpha interferon alone, ribavirin alone, or alpha interferon in combination with ribavirin. Standard doses of interferon (3 million units [MU] thrice weekly) and ribavirin (1,000–1,200 mg/day) were used. The sustained virological response rate was 0 percent in the ribavirin group, 13 percent in the interferon group, and 47 percent in the combination group.[15] Similar results were obtained in an open study from Sweden where 7/14 (50 percent) of interferon-naive patients had a sustained response to combination treatment.[16] Furthermore, a recent long-term followup study from Taiwan reported sustained virological response 2 years after stopping treatment in 9/21 (43 percent) of patients treated with interferon/ribavirin vs. only 1/19 (6 percent) of patients treated with interferon alone ($p=0.017$).[17]

A randomized double-blind placebo-controlled study comprising 100 interferon-naive chronic HCV patients has been performed by our group in Sweden.[18] All patients were treated with interferon alfa-2b 3 MU thrice weekly, in combination with either ribavirin 1,000–2,000 mg/day (n=50) or placebo (n=50) for 24 weeks. The followup period after treatment was 24 weeks. The study groups were comparable with regard to age, gender, mode of transmission, liver histology, pretreatment ALT level, pretreatment HCV RNA level, and genotype. Preliminary results confirmed those of previous pilot studies. Thus the sustained virological response rate was 45 percent in the combination group vs. 23 percent in the interferon group ($p<0.05$). In the combination group, significantly more patients either required reduction in dose or withdrew from treatment due to adverse events, primarily anemia, fatigue, and depression.

Moreover, in order to prevent recurrent HCV in the posttransplant setting, ribavirin alone or in combination with alpha interferon seems to offer promising results.[19,20]

Discussion

Ribavirin alone is apparently not the answer to antiviral therapy for chronic HCV infection, since it does not achieve eradication of the viremia. Nevertheless, ALT levels frequently normalize, and more importantly, histological activity improves during therapy. Ribavirin is also generally well tolerated, with a mild, dose-dependent, and reversible hemolysis being the predominant adverse reaction. For nonresponders to interferon therapy, and for patients where interferon cannot be used, maintenance therapy with ribavirin could be an option. However, the long-term consequences of continuous hemolysis have not been fully elucidated. Hemolyzed red blood cells release iron, and significantly increased hepatic iron stores have been noted after prolonged ribavirin therapy.[21]

Combination treatment with interferon and ribavirin for 24 weeks is clearly associated with higher sustained response rates than interferon alone. However, many questions remain to be solved. Should all HCV patients receive combination treatment as a first choice, regardless of genotype, pretreatment viral load, liver histology, or other factors shown to be predictive of sustained response to interferon monotherapy? What are the optimal dose and duration of combination therapy? Should relapsers of 24 weeks of combination therapy receive prolonged combination treatment courses? Do patients tolerate prolonged combination therapy? What is the optimal treatment for nonresponders to combination therapy? Should patients with unfavorable prognostic pretreatment factors like cirrhosis, genotype 1b, and/or high pretreatment viral loads receive more aggressive and prolonged combination treatment courses? Is the risk for drug resistance diminished by combination treatment?

Ongoing international, randomized, multicenter, placebo-controlled studies comparing 24- and 48-week treatment with interferon alone vs. combination treatment, in naive, chronic HCV patients, will answer some of these questions in the forthcoming years. Controlled combination studies in relapsers after prior interferon treatment, and ribavirin dose-finding studies, are also in progress.

References

1. Davis G, Balart L, Schiff E, et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized controlled trial. N Engl J Med 1989;321:1501–6.

2. Di Bisceglie A, Martin P, Kassianides C, et al. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. N Engl J Med 1989;321:1506–10.

3. Tine F, Magrin S, Craxi A, Pagliaro L. Interferon for non-A, non-B chronic hepatitis. A meta-analysis of randomized clinical trials. J Hepatol 1991;13:192–9.

4. Patterson J, Fernandez-Larson R. Molecular action of ribavirin. Rev Infect Dis 1990;12:1132–46.

5. Ning Q, Brown D, Parodo J, et al. Ribavirin inhibits viral induced macrophages production of tumor necrosis factor, interleukin 1 and procoagulant activity and preserves Th1 cytokine production, but inhibits Th2 cytokine response. Hepatology 1996;24:355A.

6. Reichard O, Andersson J, Schvarez R, Weiland O. Ribavirin treatment for chronic hepatitis C. Lancet 1991;337:1058–61.

7. Reichard O, Yun Z-B, Sönnerborg A, Weiland O. Hepatitis C viral RNA titers in serum prior to, during, and after oral treatment with ribavirin for chronic hepatitis C. J Med Virol 1993;41:99–102.

8. Di Bisceglie A, Shindo M, Fong T-L, et al. Pilot study of ribavirin therapy for chronic hepatitis C. Hepatology 1992;16:649–54.

9. Camps J, Garcia N, Rieza-Boj J, Civiera M, Prieto J. Ribavirin in the treatment of chronic hepatitis C unresponsive to alfa interferon. J Hepatol 1993;19:408–12.

10. Di Bisceglie A, Conjeevaram H, Fried M, et al. Ribavirin as therapy for chronic hepatitis C: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:897–903.

11. Dusheiko G, Main J, Thomas HR, et al. Ribavirin treatment for patients with chronic hepatitis C: results of a placebo-controlled study. J Hepatol 1996;25:591–8.

12. Brillianti S, Garson J, Foli M, et al. A pilot study of combination therapy with ribavirin plus interferon alfa for interferon alfa-resistant chronic hepatitis C. Gastroenterology 1994;107:812–7.

13. Kakumu S, Yoshioko K, Wakita T, Ishikawa T, Takayanagi M, Higashi Y. A pilot study of ribavirin and interferon beta for the treatment of chronic hepatitis C. Gastroenterology 1993;105:507–12.

14. Schvarez R, Ando Y, Sönnerborg A, Weiland O. Combination treatment with interferon alfa-2b and ribavirin for chronic hepatitis C in patients who have failed to achieve sustained response to interferon alone: Swedish experience. J Hepatol 1995;23(suppl 2):17–21.

15. Chemello L, Cavaletto L, Bernardinello E, Guido M, Pontisso P, Alberti A. The effect of interferon alfa and ribavirin combination therapy in naive patients with chronic hepatitis C. J Hepatol 1995;23(suppl 2):8–12.

16. Braconier J, Paulsen O, Engman K, Widell A. Combined alpha-interferon and ribavirin treatment for chronic hepatitis C virus infection. Scand J Infect Dis 1995;27:325–9.

17. Lai M-Y, Kao J-H, Yang P-M, et al. Long-term efficacy of ribavirin plus interferon alfa in the treatment of chronic hepatitis C. Gastroenterology 1996;111:1307–12.

18. Reichard O, Norkrans G, Fryden A, et al. Alfa-interferon and ribavirin versus alfa-interferon alone as therapy for chronic hepatitis C: a randomized, double-blind, placebo-controlled study. Hepatology 1996;24:356A.

19. Gane E, Lo S, Portman B, Lau J, Naoumov N, Williams R. A randomized study of the safety and efficacy of ribavirin vs. interferon monotherapy for recurrent HCV infection in liver transplant recipients. Hepatology 1996;24:293A.

20. Bizzolon T, Palazzo U, Chevallier M, Dicerf C, Trepo C. HCV recurrence after OLT: a pilot study of ribavirin therapy following initial combination with IFN. Hepatology 1996;24:293A.

21. Di Bisceglie A, Bacon B, Kleiner D, Hoofnagle J. Increase in hepatic iron stores following prolonged therapy with ribavirin in patients with chronic hepatitis C. J Hepatol 1994;21:1109–12.

Side Effects of Interferon Alpha in Viral Hepatitis

Geoffrey Dusheiko, M.D., F.R.C.P.

Interferon alphas have been widely used to treat chronic hepatitis C virus infection. These include recombinant interferons, or purified natural leucocyte or lymphoblastoid interferon. Interferon alpha is usually administered by subcutaneous or intramuscular injection. The terminal half-life of interferon alpha is 4–5 hours. Renal excretion is the predominant route of elimination.

A wide array of side effects have been encountered in several large trials of treatment of hepatitis C. Side effects are common; they are usually minor but are problematic for a significant proportion of patients. Major adverse events can occur, but life-threatening adverse events have been rare in large surveys.[1] Tolerance in elderly patients and children is usually similar.[2–4]

Early flu-like side effects are predictable and are encountered in the majority of patients. These tend to occur within 6–8 hours after starting treatment and are worst with the first injections. These side effects include fever, malaise, tachycardia, chills, headache, arthralgias, and myalgias. However, they are usually acceptable at doses of 3–6 million units (MU) of interferon alpha, and tachyphylaxis generally develops after the first few injections. These side effects are ameliorated by paracetamol (acetaminophen).

Later side effects develop after some days. These include fatigue, malaise, apathy, and cognitive changes. Between 10 and 15 percent of patients find the chronic side effects intolerable and discontinue treatment. Higher doses (above 5–6 MU three times weekly) tend to give higher rates of adverse events.[5–7]

Neuropsychiatric Side Effects

Neuropsychiatric side effects can be the most troublesome and unpredictable, but their mechanisms are poorly understood. Interferon is not thought to readily cross the blood-brain barrier. These effects include fatigue, asthenia, drowsiness, lack of initiative, irritability, confusion, and apathy; behavioral, mood, and cognitive changes are a relatively frequent dose-limiting toxicity. Severe depression may occur and suicidal ideation is well described. This can be more marked in patients with a history of depression, but suicide has been reported in patients without a previous psychiatric history.[8]

Administration at night may reduce the frequency of these side effects. They usually regress after discontinuing therapy, albeit after some weeks. Severe depression is a medical emergency. The overall incidence of neurotoxicity is 25–33 percent. Seizures have been recorded in 1.3 percent of patients.[9] There are isolated reports of extrapyramidal syndromes with ataxia and akathisia. Paraesthesias have been recorded. Table 1 lists common adverse events associated with interferon alpha in a recent trial, and Table 2 lists a range of laboratory variables.

TABLE 1. Most Common Adverse Events in a Recent Large Trial of Patients Treated With Consensus Interferon (CIFN) or Interferon Alfa 2b (3 MU=15 mg) (percentage)

Preferred Term	CIFN 3mg	CIFN 9mg	IFN a-2b 15mg
Headache	75	82	82
Fatigue	58	69	67
Fever	30	60	45
Rigors	22	57	44
Myalgia	46	57	55
Pain	39	54	44
Arthralgia	43	50	44
Back pain	33	41	36
Abdominal pain	37	40	39
Nausea	41	40	35
Insomnia	26	38	30
Pharyngitis	28	33	31
Nervousness	26	31	28
Infection upper	32	31	33
Diarrhea	25	28	24
Pain limb	20	26	25
Depression	21	26	25
Anorexia	17	23	17
Granulocytopenia	9	23	25
Erythema	22.2	22.5	15.3
Dizziness	25	22	24
Cough	14	22	17
Dyspepsia	22	20	18
Anxiety	15	19	18
Thrombocytopenia	11	18	16
Sinusitis	15	17	22
Influenza like	22.6	15	11
Leukopenia	7	14	12
Pain neck	10	14	12
Pain skeletal	13	14	14
Alopecia	6	14	25
Paraesthesia	10	13	9
Pruritus	13	13	13
Rash	12	13	14
Chest pain	15	12	14
Hot flushes	6	12	7.2
Emotional lability	8	12	11
Rhinitis	12	12	15
Increased sweating	5	12	11
Vomiting	12	11	10
Resp tract congestion	11	10	14
Dysmenorrhea	7.8	9.4	9.4

TABLE 1 (continued)			
Preferred Term	CIFN 3mg	CIFN 9mg	IFN a-2b 15mg
Thyroid test abnormal	3	9	4
Conjunctivitis	6.1	8.2	8.1
Constipation	10	8	5
Thinking abnormal	10	7.8	12
Hypertriglyceridemia	6	6	6
Tinnitus	3	5	4
Pain eye	2.6	4.8	5.5
Earache	10	4	6

TABLE 2. Laboratory Variables

Value	Phase	Observation	3mg CIFN	9 mg CIFN	15 mg IFN a-2b
Hemoglobin	End Rx	Median change (%)	-2.6	-4.8	-4.5
White blood cells	End Rx	Median change (%)	-9.7	-18.5	-22.8
	Treatment period	Incid low WBC (%)	19.20%	35.20%	35.20%
Neutrophil count	End Rx	Median change (%)	-13.7	-22.9	-33.4
	Treatment period	Incid low neutrophils (%)	20.10%	42.60%	40.10%
Segmented neutrophil count	End Rx	Median change (%)	-13.6	-22.8	-33.2
Basophil count	End Rx	Median change (%)	-7.7	-13	-29
Eosinophil count	End Rx	Median change (%)	14	-3.2	-19
Lymphocyte count	End Rx	Median change (%)	-0.3	-9.4	-42
Monocyte counts	End Rx	Median change (%)	9.7	10.1	13.4
Platelet counts	End Rx	Median change (%)	-7.5	-15.6	-18.9
	Treatment period	Incid low platelets (%)	38	46.1	45.3
Serum calcium	End observation	Median change (%)	-1.03	-0.3	0.07
	Treatment period	Incid low calcium (%)	7.4	8.7	9.5
Serum triglyceride	End Rx	Median change (%)	11.6	40.8	27.4

Source: Amgen Inc. Phase 3: (9210). With acknowledgment.

Immune Disorders

Interferon has important immunomodulatory properties. Non–organ-specific antibody titers may increase, and indeed may be associated with autoimmune thyroiditis, hypothyroidism, and hyperthyroidism.[10–15] Other autoimmune endocrine diseases have been induced, but thyroid disease is particularly important.[16] Thyroid disorders have been reported in 2.5–20 percent of patients. This may not be reversible after stopping therapy, unless therapy is stopped early, and long-term thyroid replacement may be required.[17–19] It is possible that underlying thyroid disease is more common in chronic hepatitis C infection.

An aggravation of the chronic hepatitis may occur. Patients may be genetically predisposed to this complication and can be recognized by prior autoantibody measurement and HLA haplotyping. An exacerbation of psoriasis may be part of this syndrome. Discontinuation may be required, particularly for hyperthyroidism, unless transient hyperthyroidism followed by hypothyroidism is recognizable. Autoimmune hepatitis usually necessitates discontinuation of therapy. Interferon may promote the development of systemic lupus erythematosus.

Cardiovascular Side Effects

Both benign and severe cardiac manifestations have been reported. Cardiac arrhythmias, including supraventricular tachycardia but also sudden death and ventricular arrhythmias, have been reported. There are single case reports of dilated cardiomyopathy. Hypotension has been reported in large trials.

Renal Side Effects

Proteinuria is relatively common, but is usually benign and not nephrotic. Interstitial nephritis and acute renal failure have been reported. Interferon alpha is, however, reasonably tolerated in hemodialyzed patients.[20] Renal impairment occurs in kidney transplant patients.[21]

Hepatic Side Effects

Serum aminotransferases may increase during interferon alpha treatment. These are generally mild and resolve with continued treatment in responsive patients. Exacerbations occur in hepatitis B infection; these severe cytolytic episodes may presage a response, but are poorly tolerated in patients with cirrhosis. Hepatic decompensation may occur in patients with cirrhosis, and these patients are more susceptible to infections.[22,23] Autoimmune hepatitis should not be misdiagnosed as hepatitis C infection, as severe exacerbation of the disease with cholestasis and severe liver injury can occur. Patients with documented hepatitis C infection may deteriorate after interferon alpha treatment if an underlying autoimmune diasthesis is present. This has been observed in LKM antibody-positive individuals. These patients require careful monitoring if interferon is considered the first line of treatment.[24] Rejection may occur if interferon is used after liver transplantation.[25]

Gastrointestinal Side Effects

Nausea, vomiting, dyspepsia, diarrhea, and abdominal pain are relatively frequent.

Dermatologic Side Effects

A variety of rashes including erythema multiforme have been noted. Pruritus can be troublesome. Mild hair loss is relatively common but is reversible. Local erythema is common. Psoriasis can develop de novo, or be aggravated, and is usually difficult to treat. Vitiligo has been reported.[26]

Myelosuppression

Granulocytes, thrombocytes, and red blood cell counts are commonly decreased during treatment. These are usually mild if normal counts are present initially, but can be dose limiting in the presence of low counts, for example in patients with hypersplenism. Patients may be predisposed to infections. The mechanism of granulocytopenia is unknown, but inhibition of cell release from the bone marrow has been suggested.

Hormonal and Metabolic Side Effects

A sustained increase in serum triglyceride levels has been reported. Diabetes mellitus may worsen or develop.

Rare Adverse Events

Ocular: Retinopathy has been reported in Japanese patients.[27] Lung: interstitial fibrosis of the lung and hearing impairment have been found.[7] The cases of pneumonitis may also be due to the use of Sho-Saiko and interferon.[28]

Conclusion

This array of side effects indicates the importance of selecting patients for therapy and optimizing response. Careful assessment is required before treatment, and monitoring is required during treatment. Relatively little is known about the mechanisms of many of the side effects of interferon alpha.[29]

Combination antiviral therapy, particularly ribavirin and interferon, is likely to be given to many patients with chronic hepatitis C. Interactive pharmacokinetic studies examining the distribution and metabolism of these two drugs are in progress.

References

1. Fattovich G, Giustina G, Favarato S, Ruol A, Macarri G, Orlandi F, Iaquinto G, Ambrosone L, Francavilla A, Pastore G, Santantonio MT, Romagno D, Bolondi L, Sofia S, Marchesini A, Pisi E, Mazzella G, Roda E, Attaro L, Chiodo F, Mori F, Verucchi G, Lanzini A, Salmi A. A survey of adverse events in 11241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 1996;24:38–47.

2. Russello M, Vasquez E, Fraggetta F, Zammataro M. Recombinant interferon alpha therapy in elderly patients with chronic hepatitis C without cirrhosis. Arch Gerontol Geriatr 1996;321–5.

3. Bresci G, Del Corso L, Romanelli AM, Giuliano G, Pentimone F. The use of recombinant interferon alfa-2b in elderly patients with anti-HCV-positive chronic active hepatitis. J Am Geriatr Soc 1993;41:857–62.

4. Bortolotti F, Giacchino R, Vajro P, Barbera C, Crivellaro C, Alberti A, Nebbia G, Zancan L, De Moliner L, Bertolini A, Balli F, Callea F. Recombinant interferon-alfa therapy in children with chronic hepatitis C. Hepatology 1995;22:1623–7.

5. Bonkovsky HL, Clifford BD, Smith LJ, Allan C, Banner B. High-dose interferon-a2b for re-treatment of nonresponders or relapsing patients with chronic hepatitis C—a controlled randomized trial. Dig Dis Sci 1996;41:149-154.

6. Iino S. High dose interferon treatment in chronic hepatitis C. Gut 1993;34 (Suppl):S114–8.

7. Okanoue T, Sakamoto S, Itoh Y, Minami M, Yasui K, Sakamoto M, Nishioji K, Katagishi T, Nakagawa Y, Tada H, Sawa Y, Mizuno M, Kagawa K, Kashima K. Side effects of high-dose interferon therapy for chronic hepatitis C. J Hepatol 1996;25:283–91.

8. Janssen HLA, Brouwer JT, Van der Mast RC, Schalm SW. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. J Hepatol 1994;21:241–3.

9. Shakil AO, Di Bisceglie AM, Hoofnagle JH. Seizures during alpha interferon therapy. J Hepatol 1996;24:48–51.

10. Mayet WJ, Hess G, Gerken G, Rossol S, Voth R, Manns M, Meyer-zum-Buschenfelde KH. Treatment of chronic type B hepatitis with recombinant alpha-interferon induces autoantibodies not specific for autoimmune chronic hepatitis. Hepatology 1989;10:24–8.

11. Preziati D, La Rosa L, Covini G, Marcelli R, Rescalli S, Persani L, Del Ninno E, Meroni PL, Colombo M, Beck-Peccoz P. Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. Eur J Endocrinol 1995;132:587–93.

12. Carella C, Amato G, Biondi B, Rotondi M, Morisco F, Tuccillo C, Chiuchiolo N, Signoriello G, Caporaso N, Lombardi G. Longitudinal study of antibodies against thyroid in patients undergoing interferon-a therapy for HCV chronic hepatitis. Horm Res 1995;44:110–4.

13. Marcellin P, Pouteau M, Renard P, Grynblat J-M, Colas Linhart N, Bardet P, Bok B, Benhamou J-P. Sustained hypothyroidism induced by recombinant a interferon in patients with chronic hepatitis C. Gut 1992;33:855–6.

14. Noda K, Enomoto N, Arai K, Masuda E, Yamada Y, Suzuki K, Tanaka M, Yoshihara H. Induction of antinuclear antibody after interferon therapy in patients with type-C chronic hepatitis: its relation to the efficacy of therapy. Scand J Gastroenterol 1996;31:716–22.

15. Nagayama Y, Ohta K, Tsuruta M, Takeshita A, Kimura H, Hamasaki K, Ashizawa K, Nakata K, Yokoyama N, Nagataki S. Exacerbation of thyroid autoimmunity by interferon alpha treatment in patients with chronic viral hepatitis: our studies and review of the literature. Endocr J 1994;41:565–72.

16. Imagawa A, Itoh N, Hanafusa T, Oda Y, Waguri M, Miyagawa J-I, Kono N, Kuwajima M, Matsuzawa Y. Autoimmune endocrine disease induced by recombinant interferon-a therapy for chronic active type C hepatitis. J Clin Endocrinol Metab 1995;80:922–6.

17. Lisker-Melman M, Di Bisceglie AM, Usala SJ, Weintraub B, Murray LM, Hoofnagle JH. Development of thyroid disease during therapy of chronic viral hepatitis with interferon alfa. Gastroenterology 1992;102:2155–60.

18. Marazuela M, García-Buey L, González-Fernández B, García-Monzón C, Arranz A, Borque MJ, Moreno-Otero R. Thyroid autoimmune disorders in patients with chronic hepatitis C before and during interferon-a therapy. Clin Endocrinol (Oxf) 1996;44:635–42.

19. Baudin E, Marcellin P, Pouteau M, Colas-Linhart N, Le Floch J-P, Lemmonier C, Benhamou J-P, Bok B. Reversibility of thyroid dysfunction induced by recombinant alpha interferon in chronic hepatitis C. Clin Endocrinol (Oxf) 1993;39:657–61.

20. Pol S, Thiers V, Carnot F, Zins B, Romeo R, Berthelot P, Bréchot C. Efficacy and tolerance of a-2b interferon therapy on HCV infection of hemodialyzed patients. Kidney Int 1995;47:1412–8.

21. Rostaing L, Izopet J, Baron E, Duffaut M, Puel J, Durand D. Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. Transplantation 1995;59:1426–31.

22. Perrillo R, Tamburro C, Regenstein F, Balart L, Bodenheimer H, Silva M, Schiff E, Bodicky C, Miller B, Denham C, Brodeur C, Roach K, Albrecht J. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus. Gastroenterology 1995;109:908–16.

23. Hoofnagle JH, Di Bisceglie AM, Waggoner JG, Park Y. Interferon alfa for patients with clinically apparent cirrhosis due to chronic hepatitis B. Gastroenterology 1993;104:1116–21.

24. Todros L, Saracco G, Durazzo M, Abate ML, Touscoz G, Scaglione L, Verme G, Rizzetto M. Efficacy and safety of interferon alfa therapy in chronic hepatitis C with autoantibodies to liver kidney microsomes. Hepatology 1995;22:1374–8.

25. Feray C, Samuel D, Gigou M, Paradis V, David MF, Lemonnier C, Reynes M, Bismuth H. An open trial of interferon alfa recombinant for hepatitis C after liver transplantation: antiviral effects and risk of rejection. Hepatology 1995;22:1084–9.

26. Simsek H, Savas C, Akkiz H, Telatar H. Interferon-induced vitiligo in a patient with chronic viral hepatitis C infection. Dermatology 1996;193:65–6.

27. Kawano T, Shigehira M, Uto H, Nakama T, Kato J, Hayashi K, Maruyama T, Kuribayashi T, Chuman T, Futami T, Tsubouchi H. Retinal complications during interferon therapy for chronic hepatitis C. Am J Gastroenterol 1996;91:309–13.

28. Nakagawa A, Yamaguchi T, Takao T, Amano H. [Five cases of drug-induced pneumonitis due to Sho-saiko-to or interferon-alpha or both]. Nippon Kyobu Shikkan Gakkai Zasshi 1995;33:1361–6.

29. Nakamuta M, Ohashi M, Fukutomi T, Tanabe Y, Hiroshige K, Nawata H. Rise of plasma myeloperoxidase during interferon therapy. J Gastroenterol Hepatol 1995;10:277–80.

Predictive Factors for a Beneficial Response

Gary L. Davis, M.D., F.R.C.P.

Interferon is the only drug proven effective in the treatment of chronic hepatitis C. Unfortunately, only a minority of patients respond, either transiently or permanently, to this agent. More than 100 randomized clinical trials of interferon treatment have been performed in patients with this disease.[1] Many of these studies have identified pretreatment patient characteristics associated with a greater or lesser likelihood of response to interferon.[2,3] Numerous pretreatment characteristics including younger age, female gender, low body mass, low pretreatment HCV RNA level, loss of detectable HCV RNA during the initial month of treatment, non-type 1 viral genotype, absence of fibrosis or cirrhosis, higher or longer doses of interferon (IFN), and low serum ferritin or hepatic iron levels have been associated with a greater likelihood of response to IFN. Yet none of these has been able to accurately and consistently predict the patients who respond to IFN. The most consistently identified factors associated with a higher response rate are liver histology, pretreatment viral levels (HCV RNA), and viral genotype.[2,3] Indeed, each of these factors is independently associated with response by the end of treatment, known as end-of-treatment response (ETR) or complete response, and a long-term response (persisting for at least 6 months after the discontinuation of treatment), known as sustained response (SR) (see Table 1, combined results from references 3–23).

Low pretreatment HCV RNA levels are associated with a lower relapse rate, but the initial response to IFN does not appear to be markedly influenced by the level of viremia.[3–14] Initial response to IFN ranges from 30–40 percent in genotype 1 to as high as 60–70 percent in genotypes 2 and 3.[3–12, 15–19] SR also varies considerably, with an 8–20 percent rate in genotype 1 and more than 30 percent in genotypes 2 and 3. There have also been reports that minor genomic variability, known as quasispecies, influences IFN responsiveness.[20] Patients with more than two predominant quasispecies tend to respond poorly
to IFN.

Liver biopsy provides an estimation of prognosis as well as an indicator of the likelihood of response to treatment. Many clinicians have excluded cirrhotic patients from treatment, because the initial response to a short course of treatment is only about 30 percent and most of these responders relapse when the drug is stopped.[21–24] However, the high risk of progression to hepatic failure in cirrhotic patients, estimated to be 25 percent, makes an attempt at treatment imperative in these patients. Whereas response is low in cirrhotic patients, recent observations and a decision analysis model suggest that patients with histologically mild liver injury, for example, mild hepatitis or portal hepatitis (CPH), respond better to IFN (60–70 percent initial response rate; >30 percent SR) and that treatment extends life expectancy at minimal cost, at least in patients less than 60 years of age.[24]

Several points are important in considering utilization of these factors in the selection of patients for interferon treatment. First, none is sufficiently predictive to allow accurate identification of patients who will or will not respond to interferon (Table 1). A review of the studies that report the relationship of these markers to response shows that the accuracy of the tests (how often the presence or absence of the

TABLE 1. Association of Pretreatment Factors With Response to a Short Course of Interferon							
		Response during IFN	Sensitivity	Specificity	Sustained Response	Sensitivity	Specificity
HCV RNA	High	51.1%			17.3%		
	Low	68.4%	0.48	0.69	50.5%	0.71	0.66
Genotype 1	Yes	41.2%			18.1%		
	No	57.8%	0.44	0.71	54.9%	0.62	0.77
Cirrhosis	Yes	30.2%			10.4%		
	No	57.8%	0.85	0.36	29.8%	0.72	0.27

Low HCV RNA connotes an HCV RNA level $<1 \times 10^6$ copies per milliliter.
IFN = interferon
Source: Davis GL, Lau JYN, Seeff LB. Modeling treatment algorithms for chronic hepatitis c: appropriate application of factors associated with response to interferon. Unpublished manuscript.

finding correctly identifies response or nonresponse) for response during treatment is only 57 percent, 58 percent, and 61 percent for HCV RNA, viral genotype, and cirrhosis, respectively.[25] Similarly, accuracy for sustained response is only 68 percent, 72 percent, and 40 percent, respectively.[25] In other words, response to interferon cannot be predicted by these factors in a significant proportion of patients. Many responders will be missed by these selection strategies. The second point to consider is that these factors have been identified in trials investigating the response to short courses (typically 6 months) of interferon. It is now clear that a longer duration of treatment or combination of interferon with ribavirin increases the SR rate.[26,27] Because there is little effect of longer treatment or combination treatment on response during treatment, it is likely that the accuracy of the above-mentioned pretreatment factors in identifying response is even less when these new treatment regimens are used. Indeed, a recent controlled trial of a 6-month course of interferon in combination with ribavirin failed to show any influence of viral levels or cirrhosis on response rates.[28] Finally, it should be noted that the most helpful clinical predictor of response to interferon is a decrease in the serum ALT level to normal and/or the serum HCV RNA below the limit of detection during the first 12 weeks of therapy.[29,30] Although not all patients identified in this way will sustain this early response, it is extremely unusual for patients who do not achieve these early endpoints to later achieve a response. In other words, in contrast to using genotype, histology, or pretreatment HCV RNA levels, no responders are discarded by this selection method.

In summary, several factors are associated with a higher likelihood of a response to short courses of interferon treatment. However, the accuracy of these factors in predicting response is poor and precludes their use in clinical selection strategies. There are insufficient data about the use of these or other factors in identifying response to longer interferon courses or combination treatment regimens. Currently, early response to treatment is the best method to identify nonresponders to interferon. Investigators will need to identify factors associated with response to newer treatment regimens and test whether algorithms that include multiple factors can be developed to more accurately identify those who would benefit from treatment.

References

1. Poynard T, Leroy V, Cohard M, Mathurin P, Opolon P, Zarski JP. Meta-analysis of interferon randomized trial in the treatment of viral hepatitis C. Effects of dose and duration. Hepatology 1996;24:778–89.

2. Davis GL. Prediction of response to interferon treatment of chronic hepatitis C. J Hepatol 1994;20:1–3.

3. Martinot-Peignoux M, Marcellin P, Pouteau M, et al. Pretreatment serum hepatitis C virus RNA levels and hepatitis C virus genotype are the main and independent prognostic factors of sustained response to interferon alfa therapy in chronic hepatitis C. Hepatology 1995;22:1050–6.

4. Yuki N, Hayahi N, Kasahara A, et al. Pretreatment viral load and response to prolonged interferon alpha course for chronic hepatitis C. J Hepatol 1995;22:457–63.

5. Orito E, Mizokami M, Suzuki K, et al. Loss of serum HCV-RNA at week 4 of interferon alpha therapy is associated with more favorable long-term response in patients with chronic hepatitis. J Med Virol 1995;46:109–15.

6. Garson JA, Brillanti S, Whitby K, Foli M, Deaville R, Masci C, Miglioli M, Barbara L. Analysis of clinical and virological factors associated with response to alpha interferon therapy in chronic hepatitis C. J Med Virol 1995;45:348–53.

7. Orito E, Mizokami M, Nakano T, et al. Serum hepatitis C virus RNA level as a predictor of subsequent response to interferon alpha therapy in Japanese patients with chronic hepatitis C. J Med Virol 1994;44:410–4.

8. Yun ZB, Reichard O, Chen M, et al. Serum hepatitis C virus RNA levels in chronic hepatitis C—importance for outcome of interferon alfa-2b treatment. Scand J Infect Dis 1994;26:263–70.

9. Mita E, Hayahi N, Hagiwara H, et al. Predicting interferon therapy efficacy from hepatitis C virus genotype and RNA titer. Dig Dis Sci 1994;39:977–82.

10. Matsumoto A, Tanaka E, Suzuki T, Ogata H, Kiyosawa K. Viral and host factors that contribute to efficacy of interferon alpha 2a therapy in patients with chronic hepatitis C. Dig Dis Sci 1994;39:1273–80.

11. Yoshioka K, Kakumu S, Wakita T, et al. Detection of hepatitis C virus by polymerase chain reaction and response to interferon alpha therapy: relationship to genotypes of hepatitis C virus. Hepatology 1992;16:293–9.

12. Lindsay KL, Davis GL, Schiff ER, et al., and the Hepatitis Interventional Therapy Group. Response to higher doses of interferon alfa-2b in patients with chronic hepatitis C: a randomized multicenter trial. Hepatology. In press.

13. Suzuki T, Tanaka E, Matsumoto A, Urushihara A, Sodeyama T. Usefulness of simple assays for serum concentration of hepatitis C virus RNA and HCV genotype in predicting the response of patients with chronic hepatitis C to interferon alpha 2a therapy. J Med Virol 1995;46:162–8.

14. Lau JYN, Davis GL, Kniffen J, et al. Significance of serum hepatitis C virus RNA levels in chronic hepatitis C. Lancet 1993;341:1501–4.

15. Pozzato G, Moretti M, Croce LS, et al. Interferon therapy in chronic hepatitis C virus: evidence of different outcome with respect to different viral strains. J Med Virol 1995;45:445–50.

16. Chemello L, Bonetti P, Cavalletto L, et al., and the TriVeneto Viral Hepatitis Group. Randomized trial comparing three different regimens of alpha 2a interferon in chronic hepatitis C. The TriVeneto Viral Hepatitis Group. Hepatology 1995;22:700–6.

17. Booth JC, Foster GR, Kumar U, Galassini R, Goldin RD, Brown JL, Thomas HC. Chronic hepatitis C virus infection: predictive value of genotype and level of viraemia on disease progression and response to interferon alpha. Gut 1995;36:427–32.

18. Mahaney K, Tedeschi V, Maertens F, Di Bisceglie AM, Vergalla J, Hoofnagle JH, Sallie R. Genotypic analysis of hepatitis C virus in American patients. Hepatology 1994;20:1405–11.

19. Tsubota A, Chayama K, Ikeda K, et al. Factors predictive of response to interferon alpha therapy in hepatitis C virus infection. Hepatology 1994;19:1088–94.

20. Enomoto N, Sakuma I, Asahina Y, et al. Comparison of full-length sequences of interferon-sensitive and resistant hepatitis C virus 1b. J Clin Invest 1995;96:224–30.

21. Yamada G, Takahashi M, Endo H, et al. Quantitative hepatitis C virus RNA and liver histology in chronic hepatitis C patients treated with interferon alfa. Gut 1993;34(suppl 2):S133–4.

22. Camps J, Garcia-Granero M, Riezo-Boj JI, et al. Prediction of sustained remission of chronic hepatitis C after a 12-month course of alfa interferon. J Hepatol 1994;21:4–11.

23. Magrin S, Craxi A, Fabiano C, et al. Serum hepatitis C virus (HCV)-RNA and response to alpha-interferon in anti-HCV positive chronic hepatitis. J Med Virol 1992;38:200–6.

24. Bennett WG, Inoue Y, Beck JR, Pauker SG, Davis GL. Justification of a single 6 month course of interferon (IFN) for histologically mild chronic active hepatitis C. Hepatology 1995;22:290A.

25. Davis GL, Lan JTN, Seeff LB. Unpublished results.

26. Poynard T, Bedossa P, Chevallier M, et al., and the Multicenter Study Group. A comparison of 3 interferon alfa-2b regimens for the long-term treatment of chronic non-A, non-B hepatitis. N Engl J Med 1995;332:1457–62.

27. Brillanti S, Garson J, Foli M, et al. A pilot study of combination therapy with ribavirin plus interferon alfa for interferon alfa-resistant chronic hepatitis C. Gastroenterology 1994;107:812–7.

28. Reichard O, Norkrans F, Fryden A, et al. Interferon-alpha and ribavirin versus interferon-alpha alone as therapy for chronic hepatitis C—a randomized double-blind placebo-controlled study. Hepatology 1996;24:3566A.

29. Davis GL, Balart LA, Schiff ER, et al. Treatment of chronic hepatitis C with recombinant interferon alfa: a multicenter randomized controlled trial. N Engl J Med 1989;321:1501–6.

30. McHutchison JG, Sedghi-Vaziri A, Russell J, Schmid P, Conrad A. Is there an optimal time to measure quantitative HCV-RNA to predict outcome following interferon treatment for chronic HCV infection? Hepatology 1996;24:356A.

Treatment of Patients With Cirrhosis

Solko W. Schalm, M.D.

The management of both compensated and decompensated cirrhosis should be viewed against the background of the natural history of the disease.

Compensated Cirrhosis

The prognosis of compensated cirrhosis type C (biopsy documented cirrhosis, anti-HCV positive, exclusion of hepatitis B, metabolic, toxic or autoimmune diseases, abnormal serum aminotransferases, and absence of complications of cirrhosis) has been assessed in 384 patients, followed for a mean period of 5 years at seven European university hospitals.[1] Five-year survival was 91 percent; hepatic decompensation or development of hepatocellular carcinoma (HCC) was observed in 18 percent and 7 percent, respectively, at 5 years.

The efficacy of alpha interferon monotherapy (3–6 million units [MU] three times per week (tiw) for 6–12 months) to induce biochemical and/or virological remission has been evaluated in four randomized controlled trials that allowed separate assessment of patients with cirrhosis; these studies comprised 212 patients with cirrhosis type C.[2–5] A sustained response (alanine aminotransferase [ALT] normal 6 months after the end of therapy) was observed in 9–16 percent; the sustained response rate for patients without cirrhosis in those trials varied between 17 and 34 percent. Measurements of HCV RNA by validated reverse transcription-polymerase chain reaction (RT-PCR), available from a study comprising 80 patients with cirrhosis,[4] showed a low 1-month response (HCV RNA undetectable: 22 percent in cirrhosis vs. 45 percent in noncirrhosis) and a high rate of breakthrough (loss of HCV RNA response during therapy: 43 percent in cirrhosis vs. 27 percent in noncirrhosis); the relapse rate after therapy appeared similar for cirrhosis and noncirrhosis (about 50 percent). In multivariate analysis, the presence of cirrhosis was an independent predictive factor for both the initial response and the breakthrough phenomenon.

These observations point to a diminished responsiveness to interferon in cirrhosis, but also to a more than 50 percent probability of sustained response in those maintaining a virological response during therapy.

The effects of interferon monotherapy on clinical events in cirrhosis type C have been assessed in one prospective and two large retrospective studies comprising 703 patients.[5–7] In these studies, the main focus has been on the efficacy of interferon monotherapy to reduce the incidence of HCC. The results of the three studies are summarized in the table.

TABLE 1a. Study Population Cirrhosis Type C, IFN Therapy and HCC

Study	Patients Total	Treatment		Sustained Response*		Followup years (x)	Reference
		Untreated	IFN Treated	n	(%)		
I	329	136	193	14	(7)	5	7
II	284	91	193	39	(20)	3	6
III	90	45	45	7	(16)	4	5
Total	703	272	431	60	(14)	4	

* After interferon therapy

TABLE 1b. Number of Patients Developing HCC With and Without IFN Therapy

Study	Untreated		IFN Treated			
			Sustained Response		Nonresponse	
	n	(%)	n	(%)	n	(%)
I	16	(12)	0		7	(4)
II	9	(10)	0		5	(3)
III	17	(38)	0		2	(5)
Total	42	(15)	0	(0)	14	(4)
Patients at risk	272		60		371	

These results may lead to the conclusion that interferon therapy is associated with a decreased incidence of hepatocellular carcinoma, with a particular strong effect in those who go into a sustained remission. However, multivariate analysis of prognostic factors by the Cox regression model in study 1 failed to show that interferon was among the variables independently correlated with the incidence of hepatic carcinoma; moreover, the estimated 5-year probability of HCC occurrence was—after adjustment for clinical and serologic differences at entry—similar for IFN-treated and untreated patients. Statistical analysis, including multivariate methods in study 2, also did not show a preventive effect in nonresponders, but responders to IFN therapy had a significantly reduced incidence of hepatocellular carcinoma.

The large multicenter European retrospective study[1,7] also addressed the effect of interferon monotherapy on survival. The probability of survival was—according to univariate analysis—significantly higher in patients treated with interferon than in those not receiving this drug. However, untreated patients were older and had more severe liver disease than IFN-treated patients at entry to the study, and multivariate analysis failed to show a significant independent prognostic effect of IFN

therapy on survival. These observations show that beneficial effects of interferon therapy are not convincingly documented for the large majority of patients with cirrhosis, but they also suggest a clinically important reduction in complications of cirrhosis for those with a sustained response to therapy.

In an attempt to enhance the sustained response rate of antiviral therapy, alpha interferon has been combined with ribavirin, an oral nucleoside analogue. A meta-analysis of individual data of patients participating in small randomized controlled trials or open protocols[8] included data on 18 individuals with compensated cirrhosis who had completed 6 months of combination therapy and 6 months of followup. The sustained response rate was—with 21 percent—more than a twofold increase in comparison to interferon monotherapy in a similar group of patients. This observation suggests that the diminished responsiveness to interferon in cirrhosis might be partly overcome by combination therapy.

Decompensated Cirrhosis

The prognosis of decompensated cirrhosis type C was estimated in 65 patients from the compensated cirrhosis study[1] who remained tumor-free; the time point of the first episode of ascites, clinical jaundice, variceal bleeding, or hepatic encephalopathy was taken as T=0. The probability of survival after the onset of decompensation was 50 percent at 5 years.

The efficacy of interferon monotherapy in decompensated cirrhosis has been poorly documented, as such patients were usually excluded from randomized trials. Several investigators have anecdotal data which suggest that improvement was associated with low-dose interferon therapy in an occasional patient. More data on benefits and risks of interferon therapy are needed in this category of patients before its use can be recommended, particularly for patients who are candidates for liver transplantation.

The efficacy of liver transplantation to ameliorate life expectancy has been assessed in two consecutive series comprising 334 patients with hepatitis C infection after liver transplantation.[9,10] Despite the persistence of viremia in over 95 percent of patients, the reported 5-year survival rate was 70–80 percent; survival rates were similar for patients receiving liver transplants for end-stage cirrhosis type C, patients with non-C cirrhosis infected at the time of transplantation, and patients with non-B, non-C cirrhosis. Persistent HCV infection led to graft loss in less than 10 percent of patients; the progressive nature of the disease suggests that HCV-infected patients may experience more problems than non-C patients with longer followup. These observations show that liver transplantation should be considered the treatment of choice for decompensated cirrhosis type C.

Summary

In compensated cirrhosis type C, the incidence of complications appears reduced in sustained responders to interferon therapy. Therefore, interferon therapy should aim at a rapid virological response and continuation of therapy in only those maintaining a virological response; combination of interferon with ribavirin may be more effective than interferon monotherapy. For patients with decompensated cirrhosis, liver transplantation is the treatment of choice.

References

1. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, Nevens F, Solinas A, Mura D, Brouwer JT, Thomas H, Njapoum C, Casarin C, Bonetti P, Fuschi P, Basho J, Tocco A, Bhalla A, Galassini R, Noventa F, Schalm SW, Realdi G. Morbidity and mortality in compensated cirrhosis C: a follow-up study of 384 patients. Gastroenterology. In press.

2. Jouët P, Roudot-Thoraval F, Dhumeaux D, Métreau J-M, and Le Groupe Français pour lEtude du Traitement des Hépatites Chroniques NANB/C. Comparative efficacy of interferon alfa in cirrhotic and noncirrhotic patients with non-A, non-B, C hepatitis. Gastroenterology 1994;106:686–90.

3. Alberti A, Chemello L, Bonetti P, Casarin C, Diodati G, Cavalletto L, Cavalletto D, Frezza M, Donada C, Belussi F, Casarin P, Pozzato G, Ruol A, and the TVVH Study Group. Treatment with interferon(s) of community-acquired chronic hepatitis and cirrhosis type C. J Hepatol 1993;17(suppl 3):123–6.

4. Brouwer JT, Nevens F, Kleter BEM, Elewaut A, Adler M, Brenard R, Chamuleau RAFM, Michielsen P, Pirotte J, Hautekeete ML, Weber J, Bourgeois N, Reesink HW, Geubel AP, Niesters HGM, Hop WCJ, Hansen BE, Kate FJW ten, Bronkhorst CM, Heijtink RA, Fevery J, Schalm SW. Efficacy of interferon dose and prediction of response in chronic hepatitis C: Benelux study in 336 patients [abstract]. J Hepatol 1995;23(Suppl 1):84.

5. Nishiguchi S, Kuroki T, Nakatani S, Morimoto H, Takeda T, Nakajima S, Shiomi S, Seki S, Kobayashi K, Otani S. Randomised trial of effects of interferon-a on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet 1995;346:1051:5.

6. Mazzella G, Accogli E, Sottili S, Festi D, Orsini M, Salzetta A, Novelli V, Cipolla A, Fabbri C, Pezzoli A, Roda E. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. J Hepatol 1996;24:141–7.

7. Fattovich G, Giustina G, Degos F, Diodati G, Tremolada F, Nevens F, Almasio P, Solinas A, Realdi G, Schalm SW, and the European Concerted Action on Viral Hepatitis (Eurohep). Effectiveness of interferon alpha on incidence of hepatocellular carcinoma and decompensation in European patients with cirrhosis type C [abstract]. Hepatology 1996;24(suppl 2):155A.

8. Schalm SW, Hansen BE, Chemello L, Bellobuono A, Brouwer JT, Weiland O, Cavaletto L, Schvarcz R, Ideo G, Alberti A. Ribavirin enhances the efficacy but not the toxicity of interferon in chronic hepatitis C: a meta-analysis of individual European patients. J Hepatol. In press.

9. Gane EJ, Portmann BC, Naoumov NV, Smith HM, Underhill JA, Donaldson PT, Maertens G, Williams R. Long-term outcome of hepatitis C infection after liver transplantation. N Engl J Med 1996;334:815–20.

10. Féray C, Gigou M, Samuel D, Paradis V, Wilber J, David MF, Urdea M, Reynes M, Bréchot C, Bismuth H. The course of hepatitis C virus infection after liver transplantation. Hepatology 1994;20:1137–43.

Treatment of Patients With Normal ALT Levels

Patrick Marcellin, M.D., Ph.D.

Introduction

In the last few years, with large-scale detection of anti-HCV antibodies, it has appeared that a significant proportion of anti-HCV-positive subjects were asymptomatic and had normal serum alanine aminotransferase (ALT) levels, despite the presence of detectable serum HCV RNA. The issue of the treatment of these subjects should be considered, taking into account, on the one hand, the contagiousness, the symptoms, the liver lesions, and the long-term outcome of the disease, and on the other hand, the efficacy and the side effects of therapy and its cost.

Prevalence

The exact prevalence of asymptomatic anti-HCV-positive subjects with detectable serum HCV RNA and normal serum ALT levels is not well known. The prevalence of anti-HCV antibodies in blood donors is 0.3 percent in the United States.[1] Between 39 percent and 69 percent of anti-HCV ELISA- positive subjects have a positive recombinant immunoblot assay (RIBA) and, among the anti-HCV RIBA-positive subjects, 27–59 percent have normal serum ALT levels.[2–4] The proportion of anti-HCV RIBA-positive subjects with normal serum ALT levels who have serum HCV RNA detectable by polymerase chain reaction (PCR) was found to be 54–65 percent.[3–6] Thus, one may estimate that about 10–20 percent of anti-HCV-positive subjects are serum HCV RNA-positive with normal serum ALT.

Contagiousness

These subjects should be informed that they are potentially infectious. Since the risk of sexual transmission seems very low, no recommendation for protected sexual relations is needed. Women should be informed that there is a low risk (less than 5 percent) of vertical transmission. These subjects should be informed that alcohol consumption should be avoided. Finally, these subjects must not donate blood.

Symptoms

Although these subjects are considered to be asymptomatic, as anti-HCV positivity was discovered fortuitously, some of them do report mild symptoms.[3–5,7] These symptoms are non-specific and consist mainly of fatigue, headaches, anxiety and drowsiness; their frequency and intensity do not seem different from those reported by subjects with increased serum ALT levels.

Virologic Characteristics

The mean level of serum HCV RNA, quantified by the branched DNA method, showed no significant difference between subjects with normal ALT levels and those with increased serum ALT levels.[4,8,9] Indeed, high levels of serum HCV RNA, as high as 260×10^6 Eq/mL, may be observed in some of these subjects.[9]

Studies of HCV genotypes have shown no difference in the distribution of the different genotypes in the subjects with normal serum ALT as compared with those with increased serum ALT.[3,4,6,10] Therefore, the majority of these subjects are infected with HCV genotype 1b.

Liver Histology

The majority of anti-HCV-positive subjects with normal serum ALT show liver lesions to some degree. A review of 11 studies published on a total of 290 cases shows that only 27 percent of those subjects have normal liver histology or non-specific changes.[11] The majority of subjects (54 percent) have chronic hepatitis with mild inflammatory lesions with no or minimal necrosis. However, approximately 19 percent of subjects have chronic hepatitis with moderate activity. Usually, fibrosis is absent or minimal. Cirrhosis is an exception.[12]

Long-Term Outcome

The long-term outcome of anti-HCV-positive subjects with normal serum ALT is not known. The discovery of a relatively long duration of HCV infection in those subjects is consistent with a good prognosis. Most of these subjects seem to have been infected many years before—sometimes 10–20 years before—and the liver lesions are usually very mild. However, there is no followup study available. Further studies are needed to know the long-term prognosis in this population.

Alpha Interferon Therapy

While many studies are in progress on the treatment with alpha interferon of anti-HCV subjects with persistently normal transaminases, final results are available only for a few small studies. In these studies, the response to therapy has been defined by the disappearance of detectable serum HCV RNA by PCR. All studies showed a low rate of sustained response (SR) (see Table 1).

In one study, including patients with chronic hepatitis C with normal or near normal serum transaminase levels, a sustained response to alpha interferon therapy administered at the dose of 5 million units (MU) for a minimum of 6 months, was observed in 10 of the 37 subjects treated.[13] In one study including only patients with persistently normal serum transaminases, negativation of serum HCV RNA was observed in only 2 of 10 patients under therapy and in no patient after interferon therapy.[14] No improvement of liver histological lesions was observed. The poor response to alpha interferon therapy was confirmed by other studies which showed a low rate of SR: 7 out of 40 patients treated had a sustained negativation of serum HCV RNA 6–12 months after therapy.[15–18] It is noteworthy that a relatively high proportion of the subjects treated showed an increase of serum ALT during or after interferon therapy. This proportion seems to be higher than in untreated subjects, suggesting that the immunomodulatory effect of alpha interferon induces, in these patients, an increase of immunologically induced liver lesions.

TABLE 1. Response to Alpha Interferon Therapy In Anti-HCV and Serum HCV RNA-Positive Patients With Normal Serum ALT

	Number of Patients	Treatment Schedule	Negative Serum HCV RNA		
			At End of Treatment	6 Months After Treatment	Increase in ALT
Serfaty (14)	10	3 MU x 6 months	2	0	6
San Giovanni (15)	8	3 MU x 6 months	?	0	6
	9	No treatment	?	0	1
Areias (16)	14	3 MU x 6 months	9	3	?
Rossini (17)	10	3 MU x 12 months	5	2	2
	9	No treatment	0	0	?
Ideo (18)	8	3 MU x 6 months	?	2	6

Conclusion

Many subjects with chronic HCV infection, as demonstrated by detectable serum HCV RNA, have normal serum ALT levels. They are usually asymptomatic. Most of them have a very mild liver disease with a probable good prognosis. Preliminary studies suggest that alpha interferon therapy is of little effectiveness in inducing a complete sustained inhibition of viral replication in these individuals. On the other hand, alpha interferon therapy might, in some patients, induce a reactivation of the liver disease.

References

1. Alter MJ. Epidemiology of hepatitis C in the West. Sem Liver Dis 1995;15:5–14.

2. Esteban JI, Lopez-Talavera JC, Genesca J, et al. High rate of infectivity and liver disease in blood donors with antibodies to hepatitis C virus. Ann Intern Med 1991;115:443–9.

3. Prieto M, Olaso V, Verdù C, Cordoba J, Gisbert C, Rayon M, Carrasco D, et al. Does the healthy hepatitis C virus carriers state really exist? An analysis using polymerase chain reaction. Hepatology 1995;22:413–7.

4. Shakil AO, Conry-Cantelina C, Alter HJ, Hayashi P, Kleiner DE, Tedeschi V, Krawczynski K, et al. Volunteer blood donors with antibody to hepatitis C virus: clinical, biochemical, virologic, and histologic features. Ann Intern Med 1995;123:330–7.

5. McGuiness PH, Bishop GA, Lien A, Wiley B, Parsons C, McCaughan GW. Detection of serum hepatitis C virus RNA in HCV antibody-seropositive volunteer blood donors. Hepatology 1993;18:485–90.

6. Marcellin P, Kilani A, Cymes K, Martinot M, Gournay J, Benhamou JP, Degott C, et al. Virological and histological characteristics in anti-HCV positive subjects with normal transaminases levels (Abstract). Hepatology 1995;22:273A.

7. Healey CJ, Chapmann RWG, Fleming KA. Liver histology in hepatitis C infection: a comparison between patients with persistently normal or abnormal transaminases. Gut 1995;37:274–8.

8. Shindo M, Arai K, Sokawa Y, Okuno T. The virological and histological states of anti-hepatitis C virus positive subjects with normal liver biochemical values. Hepatology 1995;22:418–25.

9. Martinot-Peignoux M, Marcellin P, Gournay J, Gabriel F, Courtois F, Branger M, Wild AM, et al. Detection and quantitation of serum HCV RNA by branched DNA amplification in anti-HCV positive blood donors. J Hepatol 1994;20:676–8.

10. Silini E, Bono F, Cividini A, Cerino A, Bruno S, Rossi S, Belloni G, et al. Differential distribution of hepatitis C virus genotypes in patients with and without liver function abnormalities. Hepatology 1995;21:285–90.

11. Marcellin P, Lévy S, Benhamou JP, Erlinger S. Management of the asymptomatic HCV carrier with normal ALT levels. Viral Hepatitis Reviews 1996. In press.

12. Alberti A, Morsica G, Chemello L, Cavaletto D, Noventa F, Pontisso P, Ruol A. Hepatitis C viraemia and liver disease in symptom-free individuals with anti-HCV. Lancet 1992;340:697–8.

13. Van Thiel D, Caraceni P, Molloy PJ, Hassanein T, Kania RJ, Gurakar A, Friedlander L. Chronic hepatitis C in patients with normal or near normal alanine aminotransferase levels: the role of interferon alpha 2b therapy. J Hepatol 1995;23:503–8.

14. Serfaty L, Chazoullières O, Pawlotsky JM, Andreani T, Pellet C, Poupon R. Interferon alpha therapy in patients with chronic hepatitis C and persistently normal aminotransferase activity. Gastroenterology 1996;110:291–5.

15. San Giovanni A, Spinzi GC, Ceriani R, Prada A, Bissoli F, Morales R, Casiraghi L, et al. Randomized control trial of HCV healthy carriers with Interferon (abstract). Hepatology 1995;22:290A.

16. Areias J, Pedroto I, Freitas T, Cerqueira R, Teixeira R, Pinho I, Justiça B et al. Hepatitis C virus carriers with normal ALT activity: viremia, genotype and effect of interferon therapy. Gastroenterology 1996;110:A1144.

17. Rossini A, Ravaggi A, Biasi L, Callea F, Agostinelli E, Gazzola GB, Cariani E, Radaeli E. Virological response to interferon (IFN) treatment of HCV carriers with normal ALT. Hepatology 1996;24:401A.

18. Ideo G, Bellobuono A, Tempini S, Mondazzi L, Bellati G, Zanetti AR. Poor efficacy of alpha interferon treatment in patients affected by chronic hepatitis C with normal or near normal ALT levels. Gastroenterology 1996;110:A1215.

Retreatment With Interferon

Alfredo Alberti, M.D.

Interferon alpha is an established treatment for chronic hepatitis C and is currently used to prevent progression of the disease. However, sustained response with virus eradication is achieved only in a minority of treated patients, and most cases show only transient or partial response or do not respond at all. The observation that a large proportion of patients with chronic hepatitis C develop a complete response while treated with reactivation after withdrawal has prompted several researchers to investigate the possibility of achieving more permanent results with a second cycle of interferon. Furthermore, the absence of alternative treatment strategies of proven efficacy has led to attempts at retreatment with interferon also in patients who were nonresponders during the first cycle.

Although several studies of retreatment with interferon alpha in patients with chronic hepatitis C have appeared in the literature, a comprehensive analysis of their results is hampered by the heterogenicity of the patient populations, the type and schedule of interferon used for retreatment, and the time lag between the first and second cycles. All these variables may influence the outcome after retreatment. Furthermore, many studies have been reported only as short abstracts rather than as full papers, and thus have not provided complete information on important issues such as the virologic status of treated patients and the histologic outcomes.

The effects of retreatment with interferon appear to be quite different in previous interferon recipients who did not respond compared with previous interferon recipients who responded and relapsed, and these two categories deserve to be presented separately.

Retreatment With Interferon in Previous Nonresponders

The results available in the literature on retreatment with interferon in patients classified as nonresponders during the first cycle are summarized in the Table 1. Analysis of the data of 11 reports have allowed us to identify 511 nonresponders who were retreated.[1–11] In six studies, patients were treated with 3 million units (MU) thrice weekly for 6 months during the first cycle and were retreated with the same schedule; in two studies, retreatment with an identical schedule was compared with retreatment with a more aggressive schedule (higher dosage and/or longer duration); and in three studies, higher dosages and/or longer duration were used in all retreated cases. In three studies, data were reported on the comparison of retreatment with the same type of interferon vs. a different type of interferon. Overall, 74/511 (14.4 percent) patients had a complete biochemical response during retreatment, but only 6/361 (1.6 percent) had a sustained response lasting for at least 6 months after therapy withdrawal. There was no evidence of significant differences in obtaining a primary response or a sustained response with the use of different retreatment schedules or of different types of interferon. The effect on serum HCV RNA during retreatment was not described in most studies. However, when HCV RNA was evaluated, only trivial effects were observed during retreatment.

TABLE 1. Cumulative Results of Published Studies on Retreatment With Interferon of Patients With Chronic Hepatitis C

Type of Response to 1st Cycle	# Cases	Results of Retreatment: Primary Response	Results of Retreatment: Sustained Response
No complete response	5111	74/511 (14.4%)	6/361 (1.6%)
Retreated with same schedule	162	17/162 (10.4%)	0/134 (0%)
Retreated with higher dose/longer duration	349	57/349 (16.3%)	6/227 (2.6%)
Complete (biochemical) response with relapse after withdrawal	527	430/527 (81.5%)	147/527 (27.8%)
Retreated for 6 months	360	284/360 (78.8%)	61/360 (16.9%)
Retreated for 12 months	167	146/167 (87.4%)	86/167 (51.4%)

Retreatment With Interferon in Previous Responders Who Relapsed

The results of retreatment with interferon in patients who had a complete biochemical response during the first cycle but had relapsed after its withdrawal are summarized in Table 1. A total of 527 patients of this type are described in 10 publications.[5–14] Most of them received 3MU of interferon thrice weekly for 6 months during the first cycle. In four studies, patients were retreated with the same schedule, three studies analyzed retreatment with different schedules as to dosage and/or duration, and three studies compared retreatment with the same or a different type of interferon. Overall, 430/527 (81.5 percent) patients showed again a complete biochemical response during retreatment, and 147/527 (27.8 percent) developed a sustained biochemical response lasting for at least 6–12 months after therapy withdrawal. The rate of primary response and, even more, that of sustained response were significantly improved by a 12-month schedule of retreatment compared with a 6-month schedule. No clear-cut differences in rates of response were noted using the same or a different type of interferon. However, limited data are available on this issue. The behavior of serum HCV RNA was not always reported. When serum HCV RNA was tested, most sustained responders were HCV RNA negative at the end of followup after retreatment.

A Randomized Trial of Interferon Retreatment in Patients With Chronic Hepatitis C

In our unit, we recently completed a randomized trial of retreatment with interferon in patients with chronic hepatitis C.[15] Ninety patients were included, having received a complete first cycle of interferon with either a “low dose” regimen (3 MU thrice weekly for 6 months) or a “high dose” regimen (6 MU thrice weekly for 4–6 months followed by 3 MU to complete a 12-month period of treatment). Patients who did not complete the first cycle were not included in the retreatment study. Twenty-five patients were nonresponders to the first cycle, whereas 65 did respond but relapsed after withdrawal. Patients who had received the “low dose” schedule as the first cycle were retreated with either the same schedule or with the “high dose” schedule according to a 2:3 randomization list; all patients who had received the

TABLE 2. Results of Retreatment in Nonresponders to First Cycle (25 cases)

1st Cycle ® 2nd Cycle	Response to 2nd Cycle		
	Absent	Transient	Sustained
Schedule A* ® Schedule A (9 cases)	100%	0%	0%
Schedule A ® Schedule B† (8 cases)	75%	25%	0%
Schedule B ® Schedule B (8 cases)	100%	0%	0%
All cases (25 cases)	92%	8%	0%

TABLE 3. Results of Retreatment in Relapsers after First Cycle (65 cases)

1st Cycle ® 2nd Cycle	Response to 2nd Cycle		
	Absent	Transient	Sustained
Schedule A ® Schedule A (12 cases)	0%	83%	17%
Schedule A ® Schedule B (22 cases)	0%	59%	41%
Schedule B ® Schedule B (31 cases)	19%	75%	6%
All cases (65 cases)	9%	71%	20%

* Schedule A: 3MU thrice weekly for 6 months.
† Schedule B: 6MU thrice weekly for 6 months followed by 3 MU thrice weekly for 6 months.

"high dose" schedule were retreated with the same regimen. The results obtained, assessed in an intent-to-treat analysis, are described in Table 2 for previous nonresponders and in Table 3 for previous relapsers. Sustained response was defined as a complete alanine aminotransferase (ALT) response, maintained up to week 52 after therapy. None of the nonresponders showed a sustained response when retreated independently of the treatment schedule. On the other hand, a sustained biochemical response was observed in 20 percent of retreated relapsers.

Among relapsers, those who received the "low dose" regimen as a first cycle achieved better response rates when retreated, reaching 41 percent sustained response in the group retreated with the "high dose" regimen. All patients showing a sustained ALT response were found HCV RNA negative in serum at the end of followup. Multivariate analysis indicated that the following variables were independently associated with sustained response after retreatment: (1) a negative serum HCV RNA test at the end of first cycle; (2) the use of an increased dose/duration regimen during retreatment; and (3) preretreatment ALT and GGT levels. On the other hand, sustained response was found independent of liver histology, the HCV genotypes and levels of serum HCV RNA measured before retreatment. Interestingly, only patients who had developed a complete biochemical and virologic response during the first cycle (normal ALT and negative HCV RNA at the end of therapy) developed a sustained response with retreatment, in agreement with other data in the literature.[10]

Main Conclusions

Retreatment with interferon appears to be a valid option for patients with chronic hepatitis C who already have been treated with 3 MU for 6 months and have shown a complete biochemical and virologic response with relapse after withdrawal. These patients should be retreated for at least 12 months, with an expected rate of sustained response of 40–60 percent. Patients showing biochemical but not virologic response during the first cycle usually respond again when retreated, but eradication of the infection is rarely achieved. Whether these patients may benefit from long-term maintenance therapy with interferon alone[16] remains to be defined, and the effectiveness of such strategy will need to be compared with that of interferon-ribavirin combination therapy. The same conclusion is valid for patients who relapse after having received 3–6 MU of interferon for at least 12 months, because in these cases retreatment with interferon alone often restores the biochemical response but virus eradication is rarely achieved.

Patients who do not develop a complete biochemical response when treated with 3 MU of interferon thrice weekly for at least 6 months do not seem to benefit from retreatment with interferon alone. For these patients, other strategies need to be explored.

References

1. Van Thiel DH, Friedlander L, Malloy P, et al. Retreatment of hepatitis C interferon nonresponders with larger doses of interferon with or without phlebotomy. Gastroenterology 1994;106(Suppl):1002.

2. Bresci G, Parisi G, Banti S, et al. Re-treatment of interferon resistant patients with chronic hepatitis C with interferon alpha. J Viral Hepatitis 1995;2:155.

3. Giudici Cipriani A, Ponassi I, Varagona G, et al. Retreatment of patients with chronic hepatitis C non responder to a first interferon course: analysis of a large patient cohort. Hepatology 1996;24:273A.

4. Chow Wc, Marcellin P, Boyer N, et al. Interferon retreatment in chronic hepatitis C patients after a standard course of interferon therapy. Hepatology 1996;24:274A.

5. Horiike N, Kurose K, Ohkura I, et al. Retreatment with interferon in chronic hepatitis C. J Hepatol 1994;21:1155.

6. Kakumu S, Yoshioka K. Retreatment with interferon in patients with chronic hepatitis C. J Hepatol 1994;21:483.

7. Marcellin P, Pouteau M, Boyer N, et al. Retreatment with recombinant interferon alpha in patients with chronic hepatitis C. J Infect Dis 1993;167:780.

8. Pardo M, Cotonat T, Herrero M, et al. Retreatment of chronic hepatitis C virus infection. Lancet 1994;343:1568.

9. Marcellin P, Boyer N, Pouteau M, et al. Retreatment with interferon alpha of chronic hepatitis C virus infection. Lancet 1994;344:690.

10. Toyoda H, Akano S, Takeda I, et al. Retreatment of chronic hepatitis C with interferon. Am J Gastroenterol 1994;89:1453.

11. Gerken G, Teuber G, Goergen B, et al. Interferon alpha retreatment in chronic hepatitis C. J Hepatol 1995;22:118.

12. Picciotto A, Brizzolara R, Campo N, et al. Two year interferon retreatment may induce a sustained response in relapsing patients with chronic hepatitis C. Hepatology 1996;24:273A.

13. Payen J, Izopet J, Galindo V, et al. A comparison of 3 interferon alpha 2b regimens for retreatment of patients with chronic hepatitis C with prior complete response followed by relapse: a controlled randomized trial. Hepatology 1996;24:273A.

14. Le X, Zhou X, Dai X. Evaluation of interferon alpha 2b for the treatment of relapsed hepatitis C. Hepatology 1996;24:536A.

15. Chemello L, Cavalletto L, Bernardinello E, et al. The effect of a second course of interferon therapy in chronic hepatitis C. Unpublished manuscript.

16. Hoefs JC. Retreatment followed by long term maintenance therapy of HCV patients with prior complete response to interferon followed by relapse. Hepatology 1995;22:117.

Other Options for Treatment of Hepatitis C

Herbert L. Bonkovsky, M.D.

Introduction: Need for More Effective Therapy

The continuing search for more effective modes of therapy for hepatitis C viral (HCV) infection bears witness to the imperfection of current therapy. Although the ultimate therapeutic goal continues to be eradication of all detectable virus, there is a grudging, growing realization that in many patients, this goal is difficult or impossible to achieve. Accordingly, other important and useful goals are being pursued, including, (1) diminution of virus levels in the blood and risk of infectivity, (2) diminution in the activity of hepatic inflammation, (3) diminution of the rate of progression of hepatic fibrosis, and
(4) prevention or delay in the development of cirrhosis and hepatocellular carcinoma.

Several approaches to management of chronic hepatitis C, beyond interferons or ribavirin, have been tested, and the current status of the major approaches is summarized below.

Iron Reduction

It has been known for many years that iron is an element required for replication of virtually all organisms, including virulent microorganisms. Patients with infections or other inflammatory conditions have decreases in serum iron concentrations, due largely to the effects of interleukin-1, an important mediator of the inflammatory response.[1] This hypoferremia is a host defense mechanism that helps to limit infection. Although the effects of iron and limitation of its availability have been studied mainly in bacterial and fungal infections, there is evidence for similar effects in viral infections as well.[2] A role for iron influencing the natural history of viral hepatitis was emphasized by Blumberg and colleagues more than 15 years ago.[3] They observed that patients with hepatitis B viral infection with higher serum iron or ferritin levels had greater likelihood of development of chronic infections than those with lower levels, who more often resolved their infections spontaneously. Several other groups have reported that larger stores of hepatic iron are positively associated with progression of hepatic fibrosis/cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis B.

Increases in levels of serum ferritin, iron, and transferrin saturation also have been noted with high frequencies in patients with chronic hepatitis C,[2] and the higher levels have, in general, been associated with lesser likelihood of response to interferon (IFN) therapy. For example, in nine different studies involving 434 patients, the levels of serum ferritin have been lower in complete responders to IFN than in noncomplete responders. Elevations of serum ferritin or transferrin saturation in such patients is not usually associated with hepatic iron overload. Nonetheless, complete responders to IFN have, on average, lower hepatic iron concentrations than do noncomplete responders. In addition, lack of stainable iron in nonparenchymal cells (especially endothelial cells in portal tracts) has been associated with greater likelihood of complete response of chronic hepatitis C to therapy with IFN.[2] Indeed, the presence of portal iron deposits was as strong a discriminator of response as viral genotype or the level of viral RNA in serum.[4]

Hayashi and colleagues[5] reported that iron reduction alone, by repeated venesection, led to significant improvement in serum alanine aminotransferase (ALT) levels in chronic hepatitis C. Indeed, the levels became normal in 5 of 10 subjects studied. This was confirmed in 12 additional studies involving a total of 306 patients.[2] In addition, in some, iron reduction alone led to a modest, albeit usually not statistically significant, decrease in serum levels of HCV RNA. Addition of IFN after iron reduction led to further and larger decreases in serum HCV RNA levels and to significant improvement in biochemical and virological responses. Of particular interest is a recent study in which previously untreated patients received IFN alone or IFN after iron reduction. A total of 29

percent (6/21) of the former but 59 percent (10/17) of the latter had a complete biochemical response, and this was sustained in 29 percent (5/17) versus 5 percent (1/21) for more than 6 months after therapy was discontinued. Clearly, these results need confirmation in a large multicenter trial. Although the mechanisms underlying a beneficial effect of iron on chronic hepatitis C remain unclear, there is experimental evidence for the following: (1) nonspecific effects of iron to increase oxidative stress enhance peroxidation of lipids and oxidative damage of other cellular components, perhaps with depletion of thiols or other antioxidant protective factors; (2) adverse effects of iron on host immunity, including impairment of function of antigen-presenting cells, impairment of cloning efficiency of T helper-1 and cytotoxic T lymphocyte subsets, impairment of T lymphocyte proliferation and maturation, impairment of proinflammatory T cell responses, and impairment of natural killer cell-dependent lysis of infected cells; and (3) impairment of humoral immunity.

Antioxidants and Anti-inflammatory Agents

Other approaches to treatment, such as the use of N-acetyl cysteine (NAC), or other -SH donors, are based upon the knowledge that, in chronic hepatitis C (as in other liver diseases), oxidative stress increases and plasma and liver GSH concentrations decrease. Oral NAC (1800 mg/d), although having little effect alone, enhanced the response to IFN.[6] Favorable effects of vitamin E a-tocopherol) on oxidative stress and activation of the cascade of fibrogenesis were reported recently. In a few small studies, similar effects have been reported for aspirin, other nonsteroidal anti-inflammatory drugs, pentoxyfylline, and colchicine. Similar nonspecific effects probably account for the improvements in serum ALT levels reported in chronic hepatitis C patients treated with many other concoctions, including traditional Chinese remedies and extract of snap cucumber. Whether such improvements in blood tests will be associated with diminution in the rate of progression to bridging fibrosis, cirrhosis, or hepatocellular carcinoma is currently unknown but is clearly an important issue.

Hydrophilic Bile Salts

Supplemental (tauro-) ursodeoxycholic acid has led to improvements in serum ALT levels, in both the absence and the presence of IFN.[7] These effects seem to be related to the beneficent effect of hydrophilic bile salts on many chronic inflammatory conditions involving the liver.

Cytokines and Other Immunomodulating Agents

Cytokines and other immunomodulating agents have also undergone limited trials in chronic hepatitis C. Effects of granulocyte/monocyte colony stimulating factor (GM-CSF) have generally been disappointing: it is expensive, poorly tolerated, and without beneficial effect except perhaps in a rare patient who develops severe neutropenia due to IFN, in whom GM-CSF may permit continuation of higher doses of IFN. In one reasonably large (110 patients), doubly masked, randomized trial, thymosin alpha-1 plus IFN was compared with placebo and IFN alone.[8] A complete serum ALT response was reported in 42 percent of those treated with the combination, compared with 3 percent in those treated with placebos and 17 percent in those treated with IFN alone. The reason for the unusually low latter percentage was not clear, nor were long-term followup data available.

Other antiviral agents recently studied have included amantadine[9] and isoprinosine.[10] The former showed promise (and is currently the subject of further trials), whereas the latter did not. Several inhibitors of the HCV protease and RNA polymerase are under development by pharmaceutical companies. Results of their use are awaited with much interest.

Summary

In summary, several therapies, in addition to IFN and ribavirin, have beneficial effects in chronic hepatitis C. It seems likely that, as has been the case for HIV infection, combinations of these

treatments will prove to be superior to monotherapy of chronic hepatitis C. Additional organized, controlled trials of therapy are urgently needed.

References

1 Dinarello CA. Interleukin-1. Rev Infect Dis 1984;87:1372–4.

2. Bonkovsky HL, Banner BF, Rothman AL. Iron and chronic viral hepatitis. Hepatology. In press.

3. Blumberg BS, Lustbader ED, Whitford PL. Changes in serum iron levels due to infection with hepatitis B virus. Proc Natl Acad Sci USA 1981;78:3222–4.

4. Ikura Y, Morimot H, Johmura H, Fukui M, Sakurai M. Relationship between hepatic iron deposits and response to interferon in chronic hepatitis C. Am J Gastroenterol 1996;91:1367–73.

5. Hayashi H, Takikawa T, Nishimura N, Yano M, Isomura T, Sakamoto N. Improvement of serum aminotransferase levels after phlebotomy in patients with chronic active hepatitis C and excess hepatic iron. Am J Gastroenterol 1994;89:986–8.

6. Beloqui O, Prieto J, Suarez M, Gil B, Qian CH, Garcia N, Civeira MP. N-acetyl cysteine enhances the response to interferon-a in chronic hepatitis C: a pilot study. J Interferon Res 1993;13:279–82.

7. Angelico M, Gandin C, Pescarmona E, Rapicetta M, del'Vecchio C, Bim A, Spada E, Baroni CD, Capocaccia L. Recombinant interferon-a and ursodeoxycholic acid versus interferon-a alone in the treatment of chronic hepatitis C: a randomized clinical trial with long-term follow-up. Am J Gastroenterol 1995;90:263–9.

8. Sherman KE, Sjogren MH, Creager RL, Freeman S, Lewey S, Root S, Davis D, Weber FL, Ishak K, Goodman ZB. Thymosin a 1 +interferon combination therapy for chronic hepatitis C: results of a randomized controlled trial [abstract]. Hepatology 1996;24:402A.

9. Smith JP. Treatment of chronic hepatitis C with amantadine-hydrochloride [abstract]. Gastroenterology 1996;110:A1330.

10. Par A, Bero T, Brasch G, Gogl A, Lamaras G, Mehesfalvi E, Ozsvar Z, Paal M, Szipocs I, Telegdy L. Isoprinosine therapy in chronic hepatitis C (multi-center placebo-controlled double-blind prospective study) [Hungarian]. Orvosi Hetilap 1993;134:1015–9.

Cost-Effectiveness Analysis

Raymond S. Koff, M.D.

Neither ideal treatment for chronic hepatitis C nor effective immunoprophylaxis is currently available. For patients with established chronic hepatitis C, treatment success using interferons, with or without adjunctive therapy, has been achieved in only a proportion of patients.[1] Treatment of patients with chronic hepatitis C also has been tempered by the inconvenience of administration of interferon by injection, by the high frequency of side effects associated with interferon use, and by the need for prolonged therapy in most patients. Furthermore, variability in the natural history of untreated chronic hepatitis C,[2–4] as reflected in major differences in reported rates of progression to cirrhosis and end-stage liver disease, has raised questions about the selection of patients for treatment and the timing of such treatment.

Treatment success has been measured predominantly with biochemical and/or virological surrogates, i.e., normal serum ALT and negative HCV RNA at the end of treatment and after 6–12 months of followup, and occasionally by assessment of early post-treatment histopathological features. Endpoints such as enhanced survival or improvements in perceived quality of life resulting from the avoidance of end-stage liver disease have yet to be demonstrated in treated patients. In fact, prospective, long-term studies of clinical outcomes and associated health care costs in interferon-treated patients are unavailable.

In the absence of these data, the potential beneficial influence of interferon treatment on life expectancy in chronic hepatitis C and the cost-effectiveness of interferon treatment have been studied by the techniques of decision analysis. Cost-effectiveness analyses have been performed, independently by several groups, by developing computer models simulating outcomes over many decades and identifying management costs associated with and without interferon treatment. Published data on transitional probabilities of clinical events over time in treated vs. nontreated patients and identification of expenses for physician followup, laboratory testing, and hospital stays have been utilized in these simulations to project these measures to clinically and economically meaningful long-term ones.[5–9] A number of these estimates are shown in Table 1, expressed as marginal cost-effectiveness ratios.

These studies, published largely in abstract form, although differing in a number of details of their assumptions, decision and sensitivity analyses, generally support the notion that a 6–12 month course of interferon treatment in patients with chronic hepatitis C, with or without cirrhosis, increases life expectancy. Furthermore, the costs per year of life gained compare favorably with other generally accepted medical therapies and surgical interventions. As might be anticipated, the models suggest that cost-effectiveness decreases in patients over 60 years of age but are still comparable to other accepted therapies in these age groups.

TABLE 1. Cost-Effectiveness of Interferon Treatment		
Reference	Descriptor	Dollars/Life-Year Gained
Dusheiko et al.,[5] 1995	Chronic hepatitis without cirrhosis (25-35 years old) (6 months treatment)	$825
Bennett et al.,[6] 1995	Mild chronic hepatitis without cirrhosis (35 year old) (6 months treatment)	$1,199
Kim et al.,[8] 1996	Chronic hepatitis (40 year old) (6 months treatment)	$5,500
	Chronic hepatitis (60 year old) (6 months treatment)	$36,800
	Chronic hepatitis (40 year old) (12 months treatment)	$8,900
	Chronic hepatitis (60 year old) (12 months treatment)	$52,700
Bennett et al.,[9] 1996	Empiric treatment	$9,290
	Selective strategies (favorable HCV RNA level and genotype)	$1,200

Considerable clinical effort has been directed at identifying factors predictive of a favorable response to treatment in the hope that use of such factors to select highly responsive patients for treatment would increase the cost-effectiveness of treatment. Among recognized predictive factors, level of viremia, HCV genotype, and initial histology are probably the most important. The cost-effectiveness of selection for treatment on the basis of these factors also has been studied using the techniques of decision analysis. In each analysis,[7,9] cost-effectiveness was increased by a selective strategy. However, empiric treatment had a cost-effectiveness well within the generally accepted range and would not miss any potential responders.[9] In contrast, a selective strategy would exclude relatively large numbers of patients who would respond to treatment.

The limitations of economic modeling in chronic hepatitis C notwithstanding,[10] these studies have provided another perspective on the potential value of treatment strategies. Given the absence of prospective, long-term studies that include cost data, and the fact that concerns about cost are dominating decisions about treatment, further economic modeling of treatment strategies may serve to aid in allocating resources for maximal collective health benefits. Important questions remain to be answered about the accuracy of transitional probability assumptions; quality of life assessments; indirect costs (e.g., loss of productivity); time span of modeling; benefits and costs of different interferon dosages and dose schedules, including maintenance therapy; utility of adjunctive therapy; and the influence of lower discount rates on these cost-effectiveness analyses.

References

1. Poynard T, Leroy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996;24:778–89.

2. Yano M, Kumada H, Kage M, et al. The long-term pathological evolution of chronic hepatitis C. Hepatology 1996;23:1334–40.

3. Seeff LB, Buskell-Bales Z, Wright EC, et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. N Engl J Med 1993;327:1906–11.

4. Crowe J, Doyle C, Fielding JF, et al. Presentation of hepatitis C in a unique uniform cohort 17 years from inoculation [abstract]. Gastroenterology 1995;108:A1054 (Abstract).

5. Dusheiko GM, Roberts JA. Treatment of chronic type B and C hepatitis with interferon alfa: an economic appraisal. Hepatology 1995;22:1863–73.

6. Bennett WG, Inoue Y, Beck JR, Pauker SG, Davis GL. Justification of a single 6-month course of interferon (IFN) for histologically mild chronic hepatitis C [abstract]. Hepatology 1995;22:290A.

7. Younossi ZM, McHutchison JG. Interferon treatment of chronic HCV infection: an economic analysis of different strategies [abstract]. Gastroenterology 1996;110:A47.

8. Kim WR, Poterucha JJ, Gross JB, Dickson ER, Evans RW. Cost-effectiveness of 12-months of interferon-alfa treatment for chronic hepatitis C [abstract]. Gastroenterology 1996;110:A1233.

9. Bennett WG, Wong JB, Koff RS, et al. What is the optimal pre-treatment evaluation of chronic hepatitis C [abstract]? Hepatology 1996;24:384A.

10. Koff RS, Seeff LB. Economic modeling of treatment in chronic hepatitis B and chronic hepatitis C: promises and limitations. Hepatology 1995;22:1880–2.