HEPATITIS C: 2001

Willis C. Maddrey, M.D.
Professor of Internal Medicine
Executive Vice President for Clinical Affairs
The University of Texas
Southwestern Medical Center

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Professor of Internal Medicine
Executive Vice President for Clinical Affairs
The University of Texas Southwestern Medical Center

Clinical and Research Interests:

- Viral Hepatitis
- Autoimmune Hepatitis
- Alcohol-Induced Liver Disease
- Primary Biliary Cirrhosis
- Drug-Induced Liver Disease

Hepatitis C remains the most important cause of chronic liver disease in the United States and many other parts of the world. Estimates from the CDC indicate that approximately 4,000,000 people in the United States are chronically infected with the hepatitis C virus. 8,000 - 10,000 deaths are attributed each year to complications of cirrhosis and hepatocellular carcinoma caused by hepatitis C. The development of a reliable test (anti-HCV) to detect the presence of the hepatitis C virus has led to remarkable advances in understanding of the prevalence, natural history, and multiple manifestations of chronic hepatitis C.

HEPATITIS C

- Caused by one of six known hepatitis viruses
- Accounts for 20% of all cases of acute hepatitis
- Most patients asymptomatic until irreversible liver damage has occurred
- Most common cause of chronic liver disease in US

  -- Leading cause of liver transplantation

  -- Associated with increased risk of liver cancer
- Responsible for 8,000-10,000 deaths/year

  -- Without effective intervention, this number expected to triple in next 10-20 years.

In less than a decade it has been shown:

1. That hepatitis C was the most important virus causing post-transfusion hepatitis and that testing blood donors for hepatitis C and removing these individuals from the donor pool made the blood supply remarkably safer. Hepatitis C from blood transfusions is now an exceedingly rare event.

2. That most patients diagnosed with hepatitis C are young and middle-aged adults with most diagnoses occurring in patients between the ages of 30 and 49 years.

3. That chronic hepatitis C is more prevalent in African-Americans and Hispanics than in whites.

4. That users of illicit drugs who share needles almost all become infected with HCV, often acquiring the virus within the first several months of drug use.

5. That many patients who had increases in serum aminotransferase levels hitherto considered insignificant actually have chronic hepatitis C and that hepatitis C is among the leading causes of elevated aminotransferase levels in asymptomatic individuals.

6. That chronic hepatitis is the leading cause of cirrhosis, which leads to liver transplantation.

7. That the natural history of chronic hepatitis C is usually one of slow progression with much of the liver damage occurring in an insidious fashion below the level of clinical recognition.

8. That chronic hepatitis C induced cirrhosis is an important - likely the most important precursor to the development of hepatocellular carcinoma in the United States.

9. That effective therapy based on the use of interferon leads to favorable sustained biochemical and virologic responses in some patients. Use of combination therapy of interferon and ribavirin has been associated with an almost 30%-40% sustained virologic response which is defined as no detectable HCV-RNA six months after the completion of therapy.

10. That the development of long-acting pegylated interferon will allow once a week injection, facilitate weight based dosing, and in combination with ribavirin will become the standard of treatment in 2001.

11. That further potentially useful therapeutic approaches include the use of protease inhibitors, helicase inhibitors, and the potential use of ribozymes and antisense oligonucleotides.

12. That prospects for an effective vaccine in the near future are not bright.

FEATURES OF HEPATITIS C VIRUS:

HCV is a lipid-enveloped single stranded RNA virus of the Flaviviridae family. The genome for HCV has been cloned, and consists of approximately 10,000 nucleotides in a single open reading frame encoding a large polyprotein that subsequently processes into at least 10 proteins.

There are several (at least 6) rather distinctive genotypes of hepatitis C, and there is considerable variation in genotype distributions around the world. Specific genotypes appear to differ somewhat as to the natural history of the liver disease which develops. Genotype has a major influence on the likelihood of response to interferon or interferon-ribavirin therapy (Zein).

In addition, HCV rapidly changes under immune pressure with the development of multiple quasispecies thereby creating in an individual patient a heterogeneous population of viruses (Farci). These quasispecies result from minor viral variations which are sufficient to change the virus in some ways but do not interfere with the ability to replicate. These random errors occur at a high rate with some sites highly conserved and others especially prone to variability (hypervariable regions). A patient may have several quasispecies at any time and the profile may shift dramatically during attempts at therapy. Quasispecies may vary in resistance to treatment and in determining the course of the disease. The genotypic and rapid emergence of quasispecies has added to the major problems (thus far insurmountable) in the development of an effective vaccine.

EPIDEMIOLOGY AND TRANSMISSION:

Hepatitis C is most readily transmitted as a blood borne disease and is spread primarily through percutaneous and mucosal exposures (McQuillan). Many patients have been identified with advanced liver disease from hepatitis C in whom the only risk factor likely to have been responsible for acquisition of hepatitis C was a blood transfusion before 1990 when widespread and subsequently mandatory testing of blood for anti-HCV was introduced. Patients who have used illicit drugs and have shared needles, even casually and on few occasions many years before, are at extremely high risk. 50% - 60% of new drug abusers are infected within 6 months of beginning drug use, and 90% are infected by a year.

It is apparent that there are routes of transmission of hepatitis C other than use of illicit drugs or transfusion which have not been as well defined. For example, the utensils used for body-piercing, tattoos, and acupuncture have the potential to transmit HCV if proper

precautions regarding sterilization are not taken. There are similar concerns of transmission for individuals who share razors and toothbrushes with infected persons. Of more recent vintage is the observation that the "straws" used for intranasal cocaine administration may have blood on the tip and thereby when shared become a vehicle for transmitting hepatitis C (Conry-Cantilena).

There is some evidence that hepatitis C can be transmitted (albeit rather inefficiently) by close personal contact such as is found in sexual relationships. Individuals who have had multiple sexual partners appear to be at increased risk, although it is uncertain which of several often associated activities leads to transmission. Fortunately the risk of sexual transmission is apparently quite low (much less than 5%) in monogamous relationships in the United States, and it is quite unusual to find the sole sexual partner of a person infected with hepatitis C to have evidence of the disorder. Individuals who have hepatitis C and who have multiple partners should be advised to pay special attention to safe sexual practices. In situations in which sexual partners are found to be hepatitis C positive, it is often helpful to obtain a detailed history looking for evidence of other risk factors such as previous experience with the use of illicit drugs.

In a few instances (less than 5 percent), an infected mother may transmit hepatitis C to her neonate. This low rate of maternal to fetal transmission is in contrast to the >90% transmission to a neonate from a mother who has chronic hepatitis B and is HBeAg positive. It appears that mothers who are infected with HIV and HCV are more likely to transmit HCV. It is recommended that a baby born to a mother who has chronic hepatitis C should be tested for the presence of the virus at one year of age by which time maternally acquired antibodies are no longer present. There is no evidence that any form of gamma globulin is of use in preventing transmission of hepatitis C. The method of birth (vaginal versus Caesarean section) does not appear to affect the likelihood of transmission. There have been no recorded instances of transmission of hepatitis C by breast feeding.

Fortunately there have been few well-documented instances of transmission of hepatitis C in medical settings, either from patient to physician or vice versa. However, even a few is cause for concern. There are increased risks of transmission in certain situations, such as for surgeons who may cut themselves while performing procedures in an infected patient. Exposure to wire sutures or the sharp edges found on resected bone present special risks.

CDC studies have suggested a higher incidence of hepatitis C in patients from lower socioeconomic groups although the interpretations of these observations are uncertain. There are many patients in whom it is not possible to establish with any certainty how hepatitis C virus was acquired.

RECOMMENDATIONS TO AVOID HCV TRANSMISSION

- Avoiding household transmission
  - -- No sharing of toothbrushes or razors
  - -- Cover open wounds
  - -- No need to avoid close contact with family members
  - -- No need to avoid sharing meals or utensils or washing clothing separately
- Pregnancy not contraindicated
  - -- Risk of transmission to baby <5%
  - -- Breast-feeding considered safe
  - -- Interferon: not recommended during pregnancy
  - -- Ribavirin: contraindicated
- Needle-exchange programs
- Avoiding tattooing, acupuncture, and body-piercing under unsterile conditions

PREVALENCE OF HEPATITIS C:

The number of new cases of acute hepatitis C occurring each year appears to be dropping likely through mandatory testing of blood and blood products, and possibly through increased awareness of hepatitis C in users of illicit drugs and participation in needle exchange programs. The latest CDC estimates would indicate that there are at present 25,000 to 35,000 new cases a year in the United States as compared to estimates of 150,000 to 175,000 a year at the beginning of the 1990s. The CDC estimates that there are approximately 3.9 million persons infected with the hepatitis C virus in the United States with an overall prevalence of 1.8%. (Alter, 1999) The majority of infected individuals are in the 30 to 49 year age group. Chronic infection is estimated to be present in 74% (2.7 million) of the 3.9 million infected individuals, 73.7% of patients with hepatitis C in the United States have genotype 1.

It is estimated that the number of patients who present with decompensated liver disease from hepatitis C infections acquired 20 or more years ago, will increase dramatically over the next several years as the cohort of already infected patients move through life. Suggested explanations for the cohort effect of hepatitis C include entry into the pool of patients of many who used illicit drugs even if only occasionally, beginning in the 1960s and 1970s as well as those who were transfused prior to 1990.

CDC SCREENING RECOMMENDATIONS

GROUP 1: ROUTINELY TESTING INDICATED

Risk History (Lifetime)

- Persons who injected illegal drugs, even once
- Clotting factor recipients (pre-1987)
- Transfusion or solid organ recipients (pre-July 1992)
- Persons notified that they received blood from donor who later tested HCV-positive
- Long-term dialysis patients
- Persons with evidence of liver disease
- Health care workers exposed to anti-HCV antibody – positive blood
- Infants >12 months old born to HCV-positive women*

GROUP 2: GROUPS WHO MAY BE AT INCREASED RISK

- Intranasal cocaine and other noninjection illegal drug users
- Persons with history of tattooing and body piercing
- Recipients of transplanted tissue (eg, corneal, musculoskeletal, skin, ova, sperm)
- Long-term sexual partners of HCV-pcsitive persons (risk is slight)

GROUP 3: ROUTINE TESTING NOT NECESSARY

Risk History (Lifetime)

- Men whc have sex with men
- Health care workers
- Pregnant women
- Household contacts of infected persons

CDC = Centers for Diseases Control and Prevention; HCV = hepatitis C virus;

IMPACT OF IDENTIFICATION AND REMOVAL OF INDIVIDUALS WHO ARE ANTI-HCV POSITIVE FROM THE BLOOD DONOR POOL:

What is established is that following the mandatory testing of blood donors, there has been a remarkable decrease in the number of patients who acquire hepatitis C through transfusion of blood products. Post-transfusion hepatitis C is now a rare event. Through educational programs emphasizing the risks of sharing needles in the transmission of HIV, hepatitis B and hepatitis C, there appears to be a favorable impact on transmission of these viral diseases among users of illicit drugs.

PROGRESSION FROM ACUTE TO CHRONIC HEPATITIS:

A major problem for patients who acquire hepatitis C virus is the remarkable frequency with which the acute infection does not resolve and leads to chronic infection. Whereas immunocompetent adults who acquire hepatitis B have only a 1% to 7% chance of becoming a chronic carrier of hepatitis B, patients who develop acute hepatitis C appear to have a 75% or more likelihood of retaining the hepatitis C virus. Factors that determine whether or not the patient progresses from acute to chronic disease needs to be further elucidated. Once chronic hepatitis C develops, there is scant evidence that spontaneous remission ever occurs. In many (but not all) followup studies, cirrhosis develops in 20% to 30% of patients with chronic hepatitis C within 20-30 years.

Preliminary studies suggest that recognition of hepatitis C during the acute phases of the illness may have important therapeutic implications. It is possible (even likely) that institution of interferon (or interferon-ribavirin) therapy immediately upon recognition of acute hepatitis C may prevent viral retention. However, it is often difficult to recognize acute hepatitis C. Only a few of these patients have evidence of jaundice, abdominal pain

or other signs suggesting an acute liver disease. The majority of patients who are discovered to have hepatitis C are already well into a chronic phase at the time of diagnosis.

Interestingly there have been few, if any, cases of acute liver failure (fulminant hepatitis) which can be reliably attributed to hepatitis C virus. There are reports of a fulminant course if a patient who has chronic hepatitis C acquire superinfections with hepatitis A (Vento).

A STEALTHY AND OFTEN RATHER SILENT CLINICAL COURSE:

HCV generally has a relatively unannounced clinical onset, then quietly sets up residence within liver cells and leads to ongoing chronic hepatitis (Tong 1995, Tong 1996, Seeff). The chronic hepatitis is often present with few if any symptoms. Many individuals are surprised (and often devastated) when told of the presence of hepatitis C following further evaluation of an elevated aminotransferase level found at the time of attempting to donate blood or obtain life insurance. The symptoms of chronic hepatitis C, when present, are usually quite non-specific. Many patients are asymptomatic whereas others experience at most slight to moderate fatigue. However in some, the fatigue associated with hepatitis C is sufficient to limit activities. The chronic hepatitis may remain clinically silent and stealthily progress to cirrhosis over many years.

THE IMPORTANCE OF HEPATITIS C-INDUCED CIRRHOSIS:

There is general agreement that 20%-40% of patients who have chronic hepatitis C will eventually progress to cirrhosis. In many patients cirrhosis is recognized after 20 or more years of infection. There are considerable variations in individual patients. However once cirrhosis develops, the patient is in a precarious state and the frequency of life-threatening complications began to appear. In a follow-up study of 384 European patients who had chronic hepatitis C and compensated cirrhosis, the survival rate was 91% at 5 years and 79% at 10 years. (Fattovich) The 5 year risk of developing hepatocellular carcinoma was 7%, and the 10 year risk of hepatocellular carcinoma was 18%.

There is no question that chronic hepatitis C is a disease associated with considerable morbidity and mortality once cirrhosis develop (Niederau).

EXTRAHEPATIC MANIFESTATIONS OF HEPATITIS C VIRUS INFECTION:

While hepatitis C virus is an infectious disease with a propensity to cause liver injury, the virus does cause a variety of diseases with clinical manifestations apart from liver disease.

CRYOGLOBULINEMIA IN PATIENTS WITH CHRONIC HEPATITIS C:

Hepatitis C is a leading cause of cryoglobulinemia. In this syndrome, patients often present with fatigue, arthralgias, and an erythematous raised rash over the lower legs. In some patients with hepatitis C induced cryoglobulinemia, there is scant or no evidence of liver injury.

Cryoglobulins are found in 40%-50% patients with HCV infection (Cicardi, Akriviadis). There does not appear to be a correlation between HCV genotype and predisposition to develop cryoglobulinemia (Sinico). The type of cryoglobulinemia most often associated with HCV infection is type II, previously called essential mixed cryoglobulinemia, which is composed of polyclonal IgG and monoclonal IgM, and rheumatoid factor against IgG-associated HCV. It has been reported that 50% to 80% of patients with type II cryoglobulinemia are infected with HCV (Luneil). The association of type II cryoglobulinemia and chronic HCV infection may be linked to the ability of the virus to bind to B lymphocytes via CD81 (Pileri). It has been suggested that the binding lowers the activation threshold of the lymphocytes, thereby promoting production of autoantibodies.

Treatment of patients who have cryoglobulinemia and chronic HCV is difficult. Immunosuppressive therapy of all types enhance viral replication and may worsen HCV-related disease. Improvement in cryoglobulinemia correlates with loss of HCV-RNA. Treatment with interferon monotherapy produced a transient response in 33%-65% of patients with cryoglobulinemia (Akriviadis). Ribavirin is often contraindicated in these patients, especially if there is evidence of impaired renal function. Long term interferon therapy offers the greatest likelihood of sustained response (Casato). Pegylated interferon will likely become the standard of care of HCV with cryoglobulinemia allowing prolonged viral suppression.

Furthermore, hepatitis C is an important cause of membranoglomerulonephritis accounting for 10% to 20% of patients with this condition. In membranoglomerulonephritis, as in cryoglobulinemia, it appears that deposition of hepatitis C containing immune complexes causes the disorder. Therefore all patients who present with significant proteinuria should be tested for the presence of anti-HCV. Conversely all patients who have hepatitis C should have a test for urine protein.

PORPHYRIA CUTANEA TARDA AND CHRONIC HEPATITIS C:

There is an increased incidence of hepatitis C virus in patients who have porphyria cutanea tarda (PCT) suggesting the virus may cause or unmask the disease. These patients often have evidence of chronic hepatitis C infection in addition to the characteristic bullae on sun exposed parts of the body. How the hepatitis C virus might lead to the abnormalities in porphyrin metabolism and subsequently to the clinical manifestation of PCT is unknown. Many patients who have PCT are chronic alcoholics. One of the first lines of treatment for PCT is the removal of iron through venesection. These observations are of further interest when it is recalled that alcohol is an important factor in promoting the progression of hepatitis C and that hepatitis C is the only viral induced liver disease which is associated with increased deposition of iron in the liver.

DIABETES MELLITUS AND CHRONIC HEPATITIS C:

Several epidemiologic studies have linked diabetes mellitus and chronic HCV infection (Mason, Knobler, Caronia). In a retrospective analysis of 1,117 patients with chronic viral hepatitis, diabetes was significantly more common among patients with chronic HCV infection (21%) compared with chronic hepatitis B viral infection (12%, P=.004). It was further noted that HCV genotype 2a was disproportionally represented among HCV infected diabetic patients (Mason). The cause of the apparent increase incidence of diabetes mellitus in this situation is unknown, but may be a consequence of insulin resistance secondary to increased levels of tumor necrosis factor.

EXTRAHEPATIC MANIFESTATIONS OF HCV

- Extrahepatic manifestations or syndromes (immunologic origin)
  - -- Essential mixed cryoglobulinemia (especially Type II)
  - -- Membranoglomerulonephritis
  - -- Arthritis
  - -- Keratoconjunctivitis sicca
  - -- Lichen planus
  - -- Porphyria cutanea tarda
  - -- Diabetes Mellitus

HEPATOCELLULAR CARCINOMA

Chronic hepatitis C induced cirrhosis is an important risk factor in the development of hepatocellular carcinoma. The constant stimulation of cell turnover over many years, associated with regeneration and repair, ultimately leads to cirrhosis in at least 20% of patients within 20 years. Hepatocellular carcinoma rarely if ever occurs in a patient who has chronic hepatitis C who does not have cirrhosis. In patients who have HCV-induced cirrhosis, the risk of developing hepatocellular carcinoma is estimated to be 1% to 4% a year. Men appear to be at increased risk. Patients who have chronic hepatitis C and cirrhosis should be regularly monitored by ultrasonography and determination of serum alpha-fetoprotein in order to facilitate detection of early hepatocellular carcinoma.

HEPATITIS C AND HEPATOCELLULAR CARCINOMA (HCC)

- Chronic HCV infection increases risk of HCC (1%-5% after 20 years)
- Most HCV-related HCC occurs in presence of cirrhosis
  - -- Rate of development of HCC after cirrhosis increases to 1%-5%/year
- HCV-related HCC more common in men and in older patients
- Up to 70% of patients with HCC are HCV-infected

DIAGNOSIS:

Hepatitis C is most often diagnosed following discovery of elevated aminotransferase levels. Prior to the availability of serologic tests to detect hepatitis C, many clinicians did not regard slight elevations in aminotransferase levels in asymptomatic patients to be of much consequence. There are surely many causes for slight aminotransferase elevations including obesity and reactions to a variety of therapeutic drugs (including alcohol). However, the prevalence of hepatitis C is high enough to warrant screening all patients who have elevated aminotransferases for the presence of anti-HCV.

DIAGNOSTIC TESTS FOR HCV INFECTION

TEST	USE
Anti-HCV antibody (EIA)	Initial diagnosis
Supplementary RIBA	Resolve a doubtful EIA result, particularly false-positive in low-risk populations
Qualitative PCR for HCV RNA	Resolve indeterminate RIBA and confirm ongoing infection with viremia
Quantitative HCV RNA tests	Determine level of serum HCV-RNA

EIA = enzyme immunoassay; RIBA = recombinant immunoblot assay;

PCR = polymerase chain reaction; bDNA = branched DNA

Second generation EIA tests provide a highly accurate inexpensive, automated way to screen patients for hepatitis C. The test is 92% to 95% sensitive using HCV-RNA as the standard.

In patients who have elevated aminotransferase levels and a history of behavior that suggests a possible (or likely) exposure to hepatitis C, a positive anti-HCV test almost always indicates the presence of hepatitis C. However if a positive test is found in an asymptomatic blood donor in whom there are no risk factors, only 25% to 60% of these individuals who test positive on the initial screening test are subsequently shown to have hepatitis C. It is in this latter group that supplemental tests including radioimmunoblot assay (RIBA) are useful. In the RIBA test which is considered a supplemental test, there are immunoassays against individual epitopes of the hepatitis C virus. Many clinicians bypass use of RIBA and proceed directly to determination of HCV-RNA.

RT-PCR and bDNA techniques are available to measure the presence and, in certain circumstances, to quantitate the amount of hepatitis C virus. There are a number of RT-PCR based tests on the market and these vary in the primers used. The advantage of the RT-PCR test relates to sensitivity. Disadvantage of the RT-PCR based tests have included the variability in the performance and lack of reproducible results. The bDNA technology, which employs a signal amplification technology, has proven quite reliable. However, the disadvantage of this approach is that it is not as accurate at detecting low levels of virus as are RT-PCR methods.

AVAILABLE HCV RNA TESTS

- Polymerase chain reaction (PCR

  -- Qualitative and quantitative types

  -- Qualitative most sensitive and specific to detect HCV viremia

  -- Quantitative to measure actual viral load

- Branched DNA amplification (bDNA)

  -- Quantitative, but less sensitive than PCR method

  -- Diminished sensitivity limits usefulness; concentrations <2 x 10^5 Eq/mL undetectable

  -- Easier to perform, less variability in results

CHRONIC HEPATITIS C IN PATIENTS WHO HAVE NORMAL AMINOTRANSFERASE LEVELS:

Normal aminotransferase levels are found at least intermittently in 30% to 50% of patients who have chronic hepatitis C. It is acknowledged that patients who have hepatitis C and normal aminotransferase levels generally (although not invariably) have less liver disease than those who do not have elevations. However, significant on-going liver injury may occur even in those in whom ALT values remain within the normal range or are only slightly elevated and progressive fibrosis may occur (Mathurin).

ROLE OF LIVER BIOPSY:

Liver biopsy is important in the evaluation of chronic hepatitis C in providing an accurate determination of the stage of the liver injury. Once a patient with chronic hepatitis C develops cirrhosis, there are considerable short and long-term risks of hepatic decompensation. Clinicians are often surprised when there is evidence of more extensive liver disease on liver biopsy than was clinically suspected in a patient who has chronic hepatitis C. The insidious nature of the disorder and the clinically quiet development of necrosis and fibrosis can lead to a clinically silent cirrhosis. It must be noted that there is no such thing as "benign cirrhosis". Any patient who has the structural rearrangements of

the liver found in cirrhosis with the resultant changes in blood flow is at considerable risk of decompensation. The development of cirrhosis is the most important negative milestone. A further occasional dividend of liver biopsy in patients who have hepatitis C is in the identification of disorders other than hepatitis C that may be present.

HISTOLOGIC FINDINGS IN PATIENTS WITH CHRONIC HEPATITIS C:

There is a continuum of liver disease in patients with chronic hepatitis C, which ranges from mild inflammation to severe advanced cirrhosis. In mild disease the inflammation is localized to the portal triad and the adjacent periportal regions. In moderate disease, in addition to the portal and periportal necrosis, areas of interlobular focal necrosis are often evident. As the disease progresses, increasing fibrosis develops with the end result of cirrhosis in some patients. In addition patients with chronic hepatitis C often have increased fat in the liver and may have evidence of excessive iron deposition.

FACTORS THAT INFLUENCE PROGNOSIS IN PATIENTS WITH CHRONIC HEPATITIS C:

Proposed explanations for the variability in the course of hepatitis C in individual patients are many:

- The genotype of the virus influences the rate of progression of the liver disease and the response to therapy. There are 6 major genotypes. Approximately 70% of patients in the United States are genotype 1 (1a and 1b). Patients who have genotype 1 appear to be more likely to have progressive liver disease than do those who have genotype 2 and 3. However it must be noted that decisions regarding prognosis and/or the need for treatment in individual patients should not at present be influenced by genotype.

- Age at the time of acquisition of hepatitis C appears important. There is some evidence that liver disease is more progressive in patients who acquire chronic HCV after age 40.

- The histologic stage of disease is of great importance in determining prognosis. Once cirrhosis develops, the patient is at considerable risk of developing decompensated liver disease and for developing hepatocellular carcinoma.

- Women appear to respond more favorably to treatment than do men.

- Viral levels as measured by serum HCV-RNA are important in that patients who have high viral levels respond generally less well than those who have lower levels. In part, the variation in viral load may relate to the underlying immune status of an individual. Some differences in viral load have been attributed to the viral genotype Patients most bereft of defenses would be expected to have higher viral loads and also to respond less well to therapy.

- The immune status is important in determining the course of chronic hepatitis C in that immunosuppressed patients do not respond as well to treatment with interferon as do immunocompetent individuals. Patients who have had combined infections of chronic hepatitis C and hepatitis B or HIV generally have responded less well to treatment than those who have HCV alone. Formerly patients who had co-infection with HIV and HCV were seldom treated for HCV because of the higher likelihood that HIV presented the far greater risk to health. With the recent development of protease inhibitors and other drugs for the treatment of HIV infections, it is necessary to reconsider whether patients who are on an effective multi-drug treatment program and have achieved effective suppression of HIV should be treated for chronic HCV.

The issue of hepatic iron concentration as a prognostic indicator is one in which there has been considerable interest and great uncertainty. It has been established that hepatic iron stores are increased to a greater extent in chronic hepatitis C than in other types of chronic viral hepatitis. Furthermore, phlebotomy in patients who have hepatitis C and porphyria cutanea tarda (PCT) often leads to an improvement not only of the PCT but also in a reduction in serum aminotransferase levels. It remains to be established if therapeutic phlebotomy will prove effective in making patients more responsive to interferon. Preliminary results do not suggest any major advantage.

INTERACTIONS OF ALCOHOL AND CHRONIC HEPATITIS C:

One of the prognostic factors of greatest significance, and one that can be potentially controlled in patients who have chronic hepatitis C, is the use of alcohol (Befrits, Brillanti, Coelho, Corrao, Cromie, Donato, Fong, Mochida, Nalpas, Pares, Pessione, Schiff). There seems no question that patients who have chronic hepatitis C and who are chronic users of alcohol do less well and progress more rapidly to cirrhosis. The additive effects of the injuries produced by alcohol and hepatitis C co-promote the development of cirrhosis. Furthermore, patients who have cirrhosis, and are chronic alcoholics appear to be much more likely to later develop hepatocellular carcinoma.

The recognition that there are additive and likely synergistic relationships between the liver injuries caused by alcohol and hepatitis C virus has been a major theme of the 1990s. Soon after the identification of anti-HCV in 1989 and development of effective tests, it was recognized that the prevalence of anti-HCV was high in chronic alcoholics. The range of anti-HCV positivity in chronic alcoholics with liver disease has been reported to be from 20% to 85%. Furthermore there are reports that 15% to 50% of chronic alcoholics who had evidence of liver disease were positive for HCV-RNA measured by a reverse transcription polymerase chain reaction assay.

The degree of alcohol consumption appears to correlates with the HCV-RNA level. Conversely reduction in alcohol intake leads to a decrease in serum HCV-RNA. A relationship was shown between the extent of alcohol consumption before testing and the level of HCV-RNA.

The combination of long-term alcohol consumption and age promotes the progression of fibrosis. Alcohol promoted increases in fibrosis in patients who have chronic hepatitis C. Alcohol also promotes increased HCV viral titers. The combination of higher viral titers and pro-fibrotic cytokines induced by both alcohol and hepatitis C accelerates progression to cirrhosis and increases the likelihood that hepatocellular carcinoma will develop.

Hepatocellular carcinoma in patients who have chronic hepatitis C is largely confined to patients who have progressed to cirrhosis. The increasing incidence of hepatocellular carcinoma in many parts of the world appears to be in large measure related to chronic HCV infection, and is especially likely to be found in patients who are also chronic users of alcohol.

The synergistic effects of alcohol and HCV in the initiation of hepatocellular carcinoma may relate in part to effects of alcohol (or HCV) on the immune system, on viral replication, or on hepatocellular responses to injury.

In studies of patients receiving interferon therapy for chronic hepatitis C, it has been shown that alcohol consumption (> 60 g/d) decreases the likelihood of a sustained response to therapy. Since sustained treatment responses to interferon in patients with chronic hepatitis C are more likely to occur in patients who have low viral loads, and since alcohol promotes higher viral loads, there is every reason to insist on abstinence from alcohol during treatment for chronic hepatitis C.

Chronic Hepatitis C - Effects of Concomitant Use of Alcohol

- Additive Injuries
- More Rapidly Progressive Disease
- Higher HCV Viral Load

TREATMENT:

Interferon alfa 2b, interferon alfa 2a, and alfacon-1 are approved by the Food and Drug Administration for the treatment of chronic hepatitis C. (Tong) In addition, the combination of interferon alfa-2b and ribavirin is FDA approved. Ribavirin alone has not been demonstrated to be an effective drug in hepatitis C.

INTERFERON-BASED THERAPY:

Interferons are cytokines. The specific mechanism - or more likely mechanisms - by which interferon favorably affects the course of chronic hepatitis C remain to be defined. There are antiviral and antiproliferative actions as well as immune regulatory effects and anti-angiogenesis effects which appear to be of importance.

Indications

Interferon therapy is indicated in patients who are anti-HCV positive, have elevated aminotransferase levels, and have evidence of chronic hepatitis on liver biopsy. Patients who have compensated cirrhosis are candidates for therapy, although it appears the outcome may be less favorable. It is uncertain (and controversial) whether patients who are anti-HCV positive and have normal aminotransferase levels benefit from interferon therapy.

Contraindications to Therapy

Patients who have evidence of decompensated cirrhosis with a history of bleeding from esophagogastric varices, ascites, hepatic encephalopathy, spontaneous sepsis, low platelets or severe leucopenia are not candidates for therapy. Furthermore patients who have a history of a definite autoimmune disease or major depression are not candidates.

Goals of Therapy

The principal goals of therapy in hepatitis C are elimination of all detectable hepatitis C virus, return to normal of serum alanine aminotransferase levels, and reduction of liver inflammation assessed on liver biopsy.

Determinations of Responses to Therapy

Response to therapy is defined biochemically as a return to normal of the serum aminotransferase levels at the end of treatment (ETR) or at the end of long term post-treatment follow-up (sustained response; SR). An additional and more precise marker of treatment effectiveness is to determine the virologic response based on whether the patient has lost serum HCV-RNA six months after completion of a course of therapy suggesting a prolonged, hopefully permanent, response.

Interferon Monotherapy

In initial studies of interferon therapy in patients with chronic hepatitis C, it was established that approximately 40% of patients who received interferon-alfa 2b (3 mu subcutaneously tiw) for 6 months had a return of aminotransferase levels to normal (biochemical response). Unfortunately relapses following cessation of treatment were frequent and only 7% to 20% of patients had a long-term sustained biochemical response. Response-predicting factors were the same as the aforementioned prognostic factors. Patients who were genotype 1 responded less readily. However, a small percentage of these patients did achieve a sustained response.

The biochemical ETR with interferon monotherapy overall was in the 30% to 50% range with a biochemical SR of 15% to 20%. The virological responses with interferon monotherapy are in the range of an ETR of 30% to 40% and SR of 10% to 20%.

Responses were improved when patients received 12-18 months of therapy compared to only 6 months of therapy.

It is of note that virtually every patient who achieved a biochemical or virological response has concomitant evidence of histologic improvement evaluated on paired liver biopsies. Of great interest are those observations which suggest that even in patients who have not had complete biochemical or virological responses, there is often measurable histologic improvement.

From analysis of clinical trials in patients with chronic hepatitis C who received interferon monotherapy, a few general conclusions can be reached. First, the ultimate outcome of interferon therapy in an individual can be predicted by early events. In the vast majority of patients, a response (biochemical and/or virological) will occur by 12 weeks if at all. If a patient has not experienced a biochemical or virological response by 12 weeks, there is no reason to continue therapy.

Clinical trials over the past several years have established that the duration of treatment with interferon monotherapy is more important than the dose in determining a sustained response and that the earlier after institution of interferon therapy that a response occurs, the more likely it is that the response will be sustained. For patients in whom an early response has been detected as defined by return to normal of aminotransferase levels and a return to normal, or almost normal, of the virological markers, it is recommended that therapy continue until 12 months therapy has been given for patients with genotype 1 and 6 months of therapy in those who have genotype 2 or 3.

AFRICAN-AMERICAN PATIENTS WITH HCV INFECTION:

African-Americans have been relatively under represented in all clinical treatment trials in patients with chronic hepatitis C. Evaluations of overall data suggested that there might be differences in the nature and course of HCV infection as well as a lower response to treatment among African-Americans. These observations have led to a careful analysis of data from several trials. It has been determined that African-Americans are much more likely to have genotype 1 (88%-96%) than Caucasians and much less likely to have genotype 3 (Reddy, Shiffman, McHutchison). These differences in genotype may explain in part the earlier perception of a decreased likelihood of sustained responses.

In the two large multicenter trials comparing interferon monotherapy to interferon/ribavirin combination therapy, only 53 of the 1,744 patients enrolled were black. 50 of these patients were specifically African-American. These patients in the trials were older, heavier, and had a higher hepatic activity index score than non African-Americans. These factors likely explain the apparent differences in responses. In general black patients had lower end of treatment (15% vs. 44%, P=.001) and sustained (11% vs. 27%, P=.01) virologic response rates compared with Caucasian patients regardless of therapeutic regimen. African-American patients had significantly higher (P=.014) sustained virologic response rates with combination therapy than with monotherapy. The combination of

interferon/ribavirin therapy led to a sustained response rate of 21% in these patients. It is of note that no African-American patient had a response to interferon monotherapy whereas 20% -23% achieved sustained virologic responses when treated with 24 or 48 weeks of interferon/ribavirin combination therapy (McHutchison). Therefore, further attention needs to be paid to evaluation of treatment regimens in African-American patients. The disparities in response are likely mainly related to the higher prevalence of genotype 1.

Another issue came to attention during the evaluation of chronic hepatitis C in African-Americans in that the incidence of hepatocellular carcinoma among black men was 60.1 per 100,000 during 1991-1995, whereas it was only 2.8 per 100,000 among Caucasians during this same period (El-Serag).

LONG-TERM FOLLOW-UP:

There is increasing evidence from clinical trials using 12 -18 months of interferon monotherapy, that in patients who maintain a complete biochemical and virologic response for 6 months following cessation of therapy, more than 90% maintained the response for at least 3 - 5 years and demonstrated increasing improvement in histology.

SIDE EFFECTS OF INTERFERON:

Flu-like symptoms are generally more pronounced following the first few injections of interferon and tolerance to interferon often develops within 2-3 weeks. Many patients take interferon at bedtime and use acetaminophen to minimize side effects. The gastrointestinal side effects of nausea, anorexia and occasional diarrhea are generally mild. Decreases in white blood cell and platelet counts relate to the antiproliferative effects of interferon and usually are manageable with rapid recovery following dose reduction or temporary reduction in interferon dose in 10% to 40% of patients and discontinuation of therapy in 5% to 10%. Depression is frequent especially early in the course of treatment. There have been reports of suicidal ideation and rare instances of suicide. Interferon based therapy is contraindicated in patients who have severe depression and a history of suicidal ideation. Fluoxetine or similar anti-depression agents may be helpful in these patients.

Interferon therapy has been reported to exacerbate a wide variety of autoimmune disorders, and if used in patients who have suspected autoimmune disorders, the patient must be carefully monitored. Interferon has been associated with exacerbation of psoriasis and exacerbation of sarcoidosis.

Thyroid problems, usually hypothyroidism, develop in a few patients receiving interferon. The thyroid problems may become clinically significant and thyroid replacement therapy may be needed. It is advisable to obtain a TSH level before beginning therapy in order to provide a baseline for later assessment.

Side Effects of Interferon Therapy

- Systemic, Flu-like
  - Fever
  - Chills
  - Headache
  - Myalgias
  - Fatigue
- Gastrointestinal
  - Anorexia
  - Nausea
  - Vomiting
  - Diarrhea
- Endocrine
  - Hypothyroidism
  - Hyperthyroidism (rare)
- Hematologic
  - Leucopenia
  - Thrombocytopenia
- Alopecia
- Neuropsychological
  - Depression
  - Irritability
  - Cognitive Changes
- Hypertriglyceridemia

INTERFERON-RIBAVIRIN COMBINATION THERAPY:

In trials evaluating combination therapy of interferon alfa-2b and ribavirin, the results in patients who had initially responded to interferon and subsequently relapsed, and in naive patients, showed a virologic sustained response rate of almost 40%. Patients with genotype 1, the major genotype in the U.S., have a decreased sustained virologic response rate (approximately 28%). The responses in patients who had genotype 2 or 3 were invariably more favorable.

The use of combination therapy of interferon with ribavirin has greatly improved the likelihood of achieving a sustained therapeutic response when compared to interferon monotherapy.

Ribavirin is a synthetic nucleoside analog that structurally resembles guanosine. The drug was initially evaluated in patients with hepatitis C following demonstration of its favorable antiviral activity on other RNA viruses including respiratory syncytial virus. Ribavirin monotherapy had a favorable effect on serum aminotransferase levels but has little if any effect on HCV-RNA levels (DiBisceglie). However, when given in combination with interferon, marked synergistic effects were found.

The mechanism of inhibition of hepatitis C virus by ribavirin remains uncertain. It is likely that there are actuarial and immunomodulary activities. It has been suggested that ribavirin depletes intracellular phosphate pools and may inhibit hepatitis C viral polymerase.

Dose, Duration, and Side Effects of Interferon-Ribavirin Therapy

The interferon component of combination therapy is administered subcutaneously at 3mu three times a week. The dose of interferon may have to be reduced if the patient develops drug-related marked decreases in platelet or white blood cells, or if severe depression occurs, especially if there is any indication of suicidal ideation .

Ribavirin is given orally at a recommended dose of 1200 mg a day (divided dose) to patients who weigh >75 kg, and 800 mg a day for those who weigh ≤75kg. Dose reductions are indicated if significant decreases in hemoglobin resulting from drug-induced hemolysis occurs. If the hemoglobin levels fall to <10g/dl, the dose should be reduced to 600mg, and if the hemoglobin falls to <8.5g/dl the drug should be discontinued. There is increasing evidence that a ribavirin dose of 600-800mg/day may suffice. Ribavirin therapy must be administered with great caution to any patient who has evidence of unstable or significant cardiac disease which might be adversely affected by a fall in hemoglobin.

Ribavirin is contraindicated in a patient who has anemia (hemoglobin < 10g/dl), active or significant cardiovascular disease, or renal failure. Most of the drug-induced fall in hemoglobin occurs within the first month of therapy and the mean maximum drop is 2.6-2.8g/dl (Maddrey 1999).

The duration of combination therapy is determined by the early response and is influenced by genotype. In patients receiving interferon monotherapy, a determination of HCV-RNA at 12 weeks of therapy gave a reliable indication of whether the treatment would be effective in that situation. If HCV-RNA was detectable, there was no reason to continue treatment. However, with combination therapy, the 12 week measurement proved to be less predictive and 15% achieved a loss of HCV-RNA during a subsequent 12 weeks of therapy. Furthermore from multicenter trials, it was determined that patients who had genotype 1 should be treated for 48 weeks, whereas patients who have genotypes 2 or 3 achieved as much benefit from 24 weeks of therapy as from 48 weeks.

A further consideration when using combination therapy is that ribavirin has established teratogenic and embryocidal potential. It is mandatory that patients (male and female) practice effective contraception during and for 6 months following treatment.

During therapy patients should be regularly monitored using standard hematologic tests (weeks 1, 2, 4, and then monthly), and regular pregnancy tests. On occasion a liver panel helps monitor progress. Determination of HCV-RNA at 16 - 24 weeks is useful in determining the likelihood of response.

Interferon-Ribavirin Combination Therapy in Naive Patients with Chronic Hepatitis C

Following the favorable results from small trials of interferon-ribavirin combination therapy, two large multicenter trials were carried out to determine the safety and efficacy of the approach. In the trial in the United States, 912 patients were randomized into 4 groups to receive IFN/placebo for 24 weeks, IFN/placebo for 48 weeks, or IFN/RB for 24 weeks. The incidence and range of side effects in patients receiving combination therapy of interferon alfa-2b and ribavirin appear to be similar to that found with interferon monotherapy with two important exceptions. Ribavirin caused a near universal dose dependent hemolytic anemia which usually became manifest within the first month of therapy. Dose reduction of the ribavirin was necessary in up to 10% of patients. Furthermore ribavirin is fully established to be teratogenic. Patients of both sexes must be strongly advised to practice effective contraception during and for several months following treatment. It is necessary to follow patients on combination therapy carefully throughout treatment in order to detect decreases in hemoglobin which may be dangerous. Patients who have active cardiac disease should not receive combination therapy.

YEAR 2000 STANDARD OF CARE:

Through the year 2000, interferon/ribavirin combination therapy was fully established to be the standard of care for patients who have chronic hepatitis C. These observations include treatment naive patients, interferon relapses, and nonresponders to interferon monotherapy (McHutchison, Poynard, Davis 1998, Bacon 1999 & 2000).

The addition of ribavirin to interferon increased end of treatment response, and the likelihood of achieving sustained response. ETR rates increase from 29% with 48 weeks of interferon monotherapy to 51% with interferon/ribavirin combination therapy. Furthermore relapse rates among patients with an end of treatment response were reduced by more than half, from 45% to 20% (McHutchison/Poynard).

It has been established that genotype is the most important predictor of response. There is no question the patients who have genotype 1 are relatively more resistant to therapy than are those who have genotype 2 and 3. It has been established that the patients who had genotype 1 derive greatest benefit when therapy is continued for a total of 48 weeks whereas those who have genotypes 2 or 3 infection achieve equivalent responses at 24 weeks of treatment (McHutchison/Poynard 1999).

Sustained Virologic Response Rates by Genotype

HCV Genotype	Interferon* 24 Weeks	Interferon/ Ribavirin 24 Weeks	Interferon/ 48 Weeks	Interferon/ Ribavirin 48 Weeks
1	2%	17%	9%	29%
2 or 3	15%	66%	31%	65%

* Interferon alfa-2b

McHutchison/Poynard, 1999

Increasing emphasis is being given to body weight as a key predictor of response to treatment. A retrospective analysis of data from treatment-naïve patients enrolled in trials of interferon/ribavirin have led to recognition that a sustained virologic response to interferon 3 MU TIW for 48 weeks recurred in only 9% of patients greater than 95 kilograms vs. 32% of those less than 55 kilograms.

Adherence to Therapy

In a further retrospective analysis, it was reported that patients who received at least 80% of their total interferon dose, and at least 80% of the ribavirin dose for at least 80% of the expected duration of therapy, achieved a sustained response rate of 48% vs. only 20% among those who received lower doses for shorter duration (McHutchison 2000). These observations suggest that in the future patient weight will become a factor in determining dose of therapy.

THE STANDARD OF THERAPY 2001:

The most recent advance in therapy of chronic hepatitis C has been the development of long-acting pegylated interferons. The addition of polyethylene glycol (PEG) to standard interferons markedly prolongs the half-life of the drug, thereby allowing once a week administration. Even though the side effect profile of PEG-IFN is quite similar to that of 3 times a week dosing of standard interferon, the convenience of the long acting drug has already proven to be more acceptable to patients. In addition the use of pegylated forms of interferon allows further movement towards weight based dosing. Further, an advantage of the use of pegylated interferon is that there are more constant levels of interferon in the blood, and presumably within the liver, thereby keeping replicating viruses under continuous pressure during the replicative cycle.

Two formulations of pegylated interferons entering the market place. The first is a pegylated form of interferon alfa-2b (Pegintron) and the second a pegylated form of alfa-2a (Pegasys). The treatment trial results for both agents are becoming available.

PEG-IFN ALFA-2b

With peginterferon alfa-2b, a trial was carried out in 1219 treatment naïve patients who were randomized to receive doses of 0.5, 1.0, or 1.5 μg/kg of pegylated interferon alfa-2b for 48 weeks and the results were compared to that with the use of standard interferon alfa-2b (Trepo). At all dose levels, results from PEG-IFN were superior to those from standard interferon. The highest end of treatment responses were achieved by patients treated with 1.5 μg/kg peginterferon alfa-2b (49%). Patients treated with 1.0 μg/kg

peginterferon alfa-2b had a sustained response rate of 25%, and those treated with 1.5 μg/kg at a sustained response rate of 23%. In the group of patients treated with standard interferon alfa-2b, the sustained response rate was only 12%.

An important observation from review of all available studies of PEG-IFN was that response rates were higher among those patients who received at least 80% of the expected dose of peginterferon alfa-2b for greater than 80% of the recommended duration. In patients who achieved the 80/80 targets, the overall sustained response rate was 29% with 1.0 μg/kg and 27% with 1.5 μg/kg.

Based on data from all trials of treatment of hepatitis C, an intent to treat analysis has been carried out. The well known problems many patients have with interferon (and with ribavirin) lead to treatment modifications or discontinuations in 10%-20% of patients. It is therefore useful to evaluate the results obtained in those patients who can tolerate most of a full course of treatment.

PEG-IFN ALFA-2a

The results of trials of peginterferon alfa-2a have been reported in two large studies. In one study, 531 patients were randomly assigned to receive either 180 μg/kg of peginterferon alfa-2a once a week for 48 weeks (267 patients), or 6 μg/kg units of alfa-2a subcutaneously 3 times a week for 12 weeks followed by 3 μg/kg units 3 times a week for 36 weeks (264 patients) (Zeuzem). All patients were assessed at week 72 for sustained virologic response. In the peginterferon group, 223 of the 267 patients completed treatment and 206 completed followup. An intention to treat analysis was carried out and the end of treatment response rates were 69% in patients who received pegylated interferon alfa-2a as compared to 28% in patients who received standard interferon alfa-2a (P=0.001). At week 72, 39% of those receiving pegylated interferon had a sustained virologic response vs. 19% in the those receiving standard treatment (P=0.001). Serum aminotransferase levels returned to normal more often in the peginterferon group than in the interferon group (45% vs. 25%, P=0.001). Histologic improvement was observed in 63% of the patients with paired liver biopsy specimens in the peginterferon group and 55% of those with paired specimens in the standard interferon group.

Independent factors associated with the sustained virologic response based on a multiple regression analysis were age less than 40, no cirrhosis or bridging fibrosis on liver biopsy, body surface area equal or less than 2 m^2, HCV-RNA level less than 2 million copies/mL, pretreatment alanine aminotransferase greater than 3 x ULN, and HCV genotype other than type 1. It is of note that in this study, 63% of patients were genotype 1a and 1b and 25% were genotype 3.

An additional study of peginterferon alfa-2a were carried out in patients who had chronic hepatitis C and cirrhosis (Heathcote). 271 patients were randomized to receive either 3 million units of interferon alfa-2a 3 times weekly (88 patients), 90 μg of peginterferon alfa-2a once weekly (96 patients), or 180 μg of peginterferon alfa-2a once weekly. The patients were treated for 48 weeks and were followed for an additional 24 weeks. In an intention to treat analysis, HCV-RNA was undetectable at week 72 in 8% of patients treated with interferon alfa-2a, 15% of those treated with 90 μg of peginterferon alfa-2a, and 30% in those treated with 180 μg of peginterferon alfa-2a. The differences between the results obtained with regular interferon and 180 μg of peginterferon alfa-2a were significant (P=0.001). At week 72 alanine aminotransferase concentrations had returned to normal at 15%, 20%, and 34% of patients in the three respective treatment groups. Improvement in histologic response as defined by decrease in at least 2 points on the 22 point histological activity index were 31%, 44%, and 54% respectively. The patients were further evaluated based on a variety of characteristics. Unfavorable prognostic factors included infection with genotype 1, and a higher viral load (greater than 2 million copies/ml) before initiating therapy. Both regimens were well tolerated.

PEG-INTERFERON AND RIBAVIRIN COMBINATION THERAPY

Studies of pegylated interferon suggests that response rates with both formulations are roughly double those found with standard interferon treatment. However the open question is how much further improvement will be gained from the addition of ribavirin to peginterferon. Studies using combination PEG-interferon/ribavirin are underway with both formulations. Ribavirin is known to enhance response rates in interferon regimens in general as well as to promote durable responses. It is likely that peginterferon/ribavirin therapy will become the standard treatment for the foreseeable future.

In a phase 3 open label trial, Manns presented the results of 1,530 treatment naïve patients who were randomized to receive either peginterferon alfa-2b 1.5 μg/kg weekly for 4 weeks, followed by 0.5 μg/kg qw for 4 weeks in combination with 1,000 mg of ribavirin for patients less than 75 kg, or 1,200 mg of ribavirin for patients greater than 75 kg (Manns). This regimen was compared to peginterferon alfa-2b 1.5 μg/kg weekly plus ribavirin 800 mg per day for 48 weeks and to interferon 3 million units 3 times a week plus ribavirin 1,000 mg per day for patients less than 75 kg or 1,200 mg for patients greater than 75 kg.

The results showed that those who received higher doses of interferon alfa-2b (1.5 μg/kg) had an end of treatment response of 62% and a sustained virologic response of 54%. The lower dose of pegylated interferon alfa-2b (0.5 μg/kg) plus ribavirin produce response rates similar to that observed with standard combination therapy. Patients who had genotype 1 had a 42% sustained virologic response rate when given the 1.5 μg/kg pegylated interferon alfa-2b plus 800 mg per day of ribavirin. The sustained response was nearly universal (82%) in patients who had genotype 2 or 3 infection.

WEIGHT-BASED DOSING OF RIBAVIRIN

There have been further studies to establish whether weight based dosing of ribavirin should be considered. Multiple regression analysis showed an increased probability of response to peginterferon/ribavirin with increasing dose per kg of ribavirin. It was determined that patients who received 1.5 μg/kg peginterferon alfa-2b in combination therapy of at least 10.6 mg/kg of ribavirin had a sustained response rate of 61%.

Virologic Response Optimized by Weight-Based Ribavirin Dosing

	Ribavirin Dose (mg/kg)	
	10.6	> 10.6
Interferon 3 MU TIW	27%	47%
Peginterferon alfa-2b 1.5 μg/kg	50%	61%

Furthermore the concept previously established of evaluating those individuals who were able to tolerate at least 80% of the recommended dosages for 80% of the expected duration showed that there was a sustained viral response rate of 72% over all in patients who completed their therapy. Patients who had genotype 1 had a 63% sustained viral response rate, and those who had genotype non-1 had a 94% response rate (McHutchison, 2000).

In evaluating adverse events in these trials it was found that fever, nausea, and injection site reactions were more frequent in patients who received peginterferon at 1.5 μg/kg ribavirin than in those who received standard therapy. The major problems with interferon remain neutropenia, thrombocytopenia, and depression. The major side effect of ribavirin remains the dose related hemolytic anemia.

Therefore, all lines of evidence suggest that the upcoming standard of care for chronic hepatitis C will be the use of pegylated interferon plus ribavirin. It is further evident that weight based dosing, both of interferon and of ribavirin, should prove important in

optimizing therapy and improving responses. However, it must be recognized that side effects continue to be frequent and in a number of patients, dose reduction of one or both drugs, or even discontinuation, will be necessary.

FUTURE THERAPEUTIC APPROACHES:

A major advance has been reported in the past several months with the development of a system in which there is efficient initiation of hepatitis C virus replication in cell culture (Blight). Having a cell-based system to study novel interventions may well speed the evaluation of new approaches. There is great hope that hepatitis C specific protease inhibitors or helicase inhibitors will soon be available and prove to be useful. There is also interest in therapeutic approaches using specially designed ribozymes and antisense oligonucleotides. Hopefully the next great breakthrough will be a vaccine – first a preventive vaccine, and subsequently a treatment vaccine. There remains much to do, and even more to expect.

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