REVIEWS

Hepatitis C and Renal Disease: An Update

Catherine M. Meyers, MD, Leonard B. Seeff, MD, Catherine O. Stehman-Breen, MD, MS, and Jay H. Hoofnagle, MD

• **Hepatitis C is both a cause and a complication of chronic renal disease. Chronic infection with hepatitis C virus (HCV) can lead to the immune complex syndromes of cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN). The pathogenetic mechanisms for these conditions have not been defined, although they are clearly caused by the chronic viral infection. Management of HCV-related cryoglobulinemia and MPGN is difficult; antiviral therapy is effective in clearing HCV infection in a proportion of patients, but these conditions can be severe and resistant to antiviral therapy. Hepatitis C also is a complicating factor among patients with end-stage renal disease and renal transplants. The source of HCV infection in these patients can be nosocomial. Screening and careful attention to infection control precautions are mandatory for dialysis units to prevent the spread of hepatitis C. Prevention of spread is particularly important in these patients because HCV infection is associated with significant worsening of survival on dialysis therapy, as well as after kidney transplantation. Furthermore, therapy for hepatitis C is problematic, only partially effective, and associated with significant side effects in this population. There are significant needs in both basic and clinical research in the pathogenesis, natural history, prevention, and therapy for hepatitis C in patients with renal disease.** ***Am J Kidney Dis*** **42:631-657.**

INDEX WORDS: Hepatitis C virus (HCV); cirrhosis; cryoglobulinemia; glomerulonephritis; dialysis; renal transplantation; interferon alfa; ribavirin; peginterferon; randomized controlled trials.

BOTH HEPATITIS C and chronic renal disease are common and potentially serious medical problems in the United States and throughout the world. In recent years, it has become clear that these 2 conditions are linked in several important ways. Some forms of renal disease are precipitated by hepatitis C virus (HCV) infection. In addition, persons with renal disease are at increased risk for acquiring HCV because of their frequent exposure to blood from transfusions or exposure to HCV-contaminated medical equipment during hemodialysis or at the time of renal transplantation.

Despite these known associations, the role of hepatitis C in the course, morbidity, and mortality of renal disease is not well established and often not considered in the care of persons with kidney disease. Furthermore, advances in knowledge about hepatitis C have not been applied fully to cohorts of patients with renal disease.

The critical need for more information on the pathogenesis, natural history, control, and treatment of hepatitis C in persons with renal disease was highlighted at The National Institutes of Health Consensus Development Conference on Management of Hepatitis C, held in June 2002. In response to these needs, the Division of Kidney, Urologic and Hematologic Diseases and the Division of Digestive Disease and Nutrition of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) organized a 2-day research workshop on hepatitis C and renal disease, focusing on outlining current knowledge and defining needs for future research. The meeting summarized information on hepatitis C in the general population and addressed the problems of hepatitis C in the end-stage renal disease (ESRD) population, concerns regarding dialysis patients, potential therapeutic options, and renal transplantation in HCV-infected patients.

From the Divisions of Kidney, Urologic and Hematologic Diseases; and Liver Disease Research Branch, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, The National Institutes of Health, Bethesda, MD; Departments of Medicine; and Epidemiology, University of Washington; and the Department of Veterans Affairs, Puget Sound Healthcare System, Seattle, WA.

Received March 19, 2003; accepted in revised form June 10, 2003.

Summary of a workshop held October 21 to 22, 2002, in the Lister Hill Auditorium, The National Institutes of Health, Bethesda, MD.

Address reprint requests to Jay H. Hoofnagle, MD, NIH/NIDDK, Bldg 31, Rm 9A27A, 31 Center Dr, Bethesda, MD 20892. E-mail: hoofnaglej@extra.niddk.nih.gov

0272-6386/03/4204-0004$30.00/0

doi:10.1053/S0272-6386(03)00828-X

HCV

Dr Marian Major, Center for Biologics Evaluation and Research, US Food and Drug Administration, Rockville, MD

HCV is a small double-shelled virus consisting of a lipid envelope (E) with virally encoded glycoproteins (E1 and E2) and an inner nucleocapsid (core) that contains a positive-sense single-stranded RNA genome consisting of 9,500 nucleotides.[1] HCV has well-defined structural (core, E1, and E2) and nonstructural ([NS]; P7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) components. The nonstructural proteins encode several proteases, a virus-specific helicase, and an RNA-dependent RNA polymerase responsible for replication of the genome. HCV isolates are classified into 6 distinct clades (genotypes 1 to 6) based on sequence homology. The virus circulates in serum as quasispecies with wide genomic variation, particularly in the envelope proteins E1 and E2.

HCV does not replicate in cell culture, but mammalian cell expression systems have been developed for the in vitro study of viral replication. Most helpful has been a subgenomic replicon system that allows assessment of replication and screening of antiviral agents.[2,3] This system does not support full viral production and therefore cannot assess transmission and protective immunity, elements critical to vaccine development. Because there are no reliable small-animal models for HCV, studies of infectivity have relied on the chimpanzee, the only reliable animal model for HCV infection and disease.

Exposure of chimpanzees to infectious inocula is followed by the appearance of HCV RNA in serum within 1 to 2 weeks.[4] Viral levels increase rapidly and serum alanine aminotransferase (ALT) values generally become abnormal as HCV levels peak 4 to 8 weeks after exposure. Antibody to HCV (anti-HCV) arises late, and the initial antibody response is targeted mostly against HCV core, NS3, and NS4 proteins; low levels of anti-E1 and anti-E2 generally arise later. Recovery is marked by loss of HCV RNA and resolution of disease activity, whereas chronicity is marked by persistence of viremia. The immunologic basis for viral clearance and immunity in hepatitis C has yet to be fully defined.[1] Studies in chimpanzees and limited data in humans indicate that immunity from reinfection in hepatitis C is not absolute. Reinfection occurs with different HCV genotypes, the previously infected strain, or the same quasispecies. Anti-HCV, including anti-E1 and anti-E2, is only weakly protective, and the presence of anti-E1/E2 correlates poorly with recovery and immunity. To date, candidate vaccines using recombinant E1 and E2 have provided only partial immunity to reinfection and disease.[5] Perhaps more critical are the cellular immune responses to HCV during infection.[4] Recovery from infection has correlated best with an early, vigorous, and broadly based $CD4^+$ and $CD8^+$ immune response against HCV peptides. Accordingly, approaches to stimulate $CD4^+$ and $CD8^+$ responses are attractive avenues to the development of effective HCV vaccines. Thus, for the near future, approaches to control this disease will have to depend on public health measures, rather than a specific HCV vaccine.

NATURAL HISTORY AND COURSE OF HEPATITIS C

Dr Leonard Seeff, Division of Digestive Diseases and Nutrition, NIDDK, Bethesda, MD

Acute hepatitis C is often mild and associated with few, if any, symptoms. Fulminant or severe cases are rare. The major complication of acute HCV infection is chronic hepatitis, which occurs in up to 70% of cases. Neither clinical, laboratory, nor serological features of acute infection predict whether infection will resolve or persist.[6]

The overall chronicity rate of hepatitis C is 70%, but lower rates have been reported in specific cohorts.[7,8] In children and young healthy women, chronicity rates have been only 50% to 60%,[9-11] whereas in older individuals and African Americans, rates are higher. Two studies have shown chronicity rates greater than 90% in African-American men.[7,12] In addition, acute icteric hepatitis C is associated with a lower rate of chronicity than anicteric asymptomatic disease.[6,11] Defining chronicity also can be problematic. During the acute illness, HCV RNA levels fluctuate, and some patients are intermittently negative by current assays despite ultimately developing chronic disease with high viral levels.[12] At present, continued presence of HCV RNA for 6 months after (estimated) onset defines chronic infection; and subsequent spontaneous loss of virus is unusual.

The natural history of chronic hepatitis C has been the subject of many studies, but remains only partially defined.[6] The initial onset of acute infection often is not recognized. Evolution from acute to chronic hepatitis ensues without clinical symptoms, and chronic hepatitis continues for decades before clinically apparent end-stage liver disease emerges, if it does at all.[12,13] The major long-term complication of chronic hepatitis C is hepatic fibrosis, which can eventuate in cirrhosis, portal hypertension, and hepatic failure. Patients with cirrhosis also are at high risk for hepatocellular carcinoma.

Three strategies have been used to define the natural history of hepatitis C and quantify risks for morbidity and mortality: (1) retrospective, (2) prospective, and (3) combination retrospective/prospective (nonconcurrent prospective) studies.[6] Retrospective studies have suggested that severe consequences can emerge in a high proportion of patients. These studies usually originate from tertiary care centers and may have referral bias, but suggest that 17% to 55% (mean, 42%) of patients develop cirrhosis within 20 years of the estimated onset of infection.[14,15] Conversely, prospective studies reported detection of cirrhosis by the 20-year mark in only 7% to 16% (mean, 11%) of HCV-infected individuals.[6,8,13] Finally, retrospective/prospective studies, which require the ability to identify and recall patients who were involved in a defined outbreak of hepatitis C in the past have identified cirrhosis in only 0.3% to 4% (mean, 2.1%) of patients.[9-11,16] These natural history studies were based largely on patients infected as children or young adults; a similar study that enrolled older people (age ~ 50 years) infected by blood transfusion reported cirrhosis in 15% within 20 years of onset.[8]

Thus, the development of cirrhosis in published studies has ranged from 2% to 42%. Combined data suggest that progression of disease is uncommon and slow in children and young adults, but more rapid in older individuals. These studies have not yet extended beyond the first 2 decades after infection; thus, information regarding lifelong morbidity and mortality is not known other than through modeling.[15] Modeling has been based on the assumption that fibrosis progresses in a linear fashion throughout life, but it is possible that the process may increase exponentially as aging advances or, conversely, that it may plateau and not advance at all.

Several factors correlate with a greater rate of fibrosis progression.[6,15] Viral factors, such as HCV RNA level, viral genotype, or quasispecies diversity, do not appear to be important. Conversely, several host factors are important, including older age, older age at onset of infection, male sex, white race, coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), and other comorbid conditions, such as hemochromatosis, nonalcoholic steatohepatitis, obesity, and diabetes. Among environmental factors, chronic alcoholism undoubtedly contributes to progression of liver disease, but the lowest level of alcohol intake that accelerates progression has not been defined. How chronic renal disease and its complications, management, and therapy affect the natural history of hepatitis C is now the focus of several retrospective and prospective studies.

THERAPY FOR HEPATITIS C

Dr Charles Howell, University of Maryland, Baltimore, MD

Interferon alfa was first shown to have activity against chronic hepatitis C in the mid-1980s, and by 1991, it was licensed for use in this disease.[17] The basis for approval was the demonstration that a 24- to 48-week course of interferon could lead to a sustained loss of HCV RNA, normalization of ALT levels, and resolution of the liver disease. Early studies provided the definition of a sustained response as the absence of detectable HCV RNA at least 6 months after stopping therapy. Long-term follow up of patients who achieved a sustained virological response (SVR) indicated that more than 95% continued to have undetectable HCV RNA, normal ALT levels, and improved liver histological characteristics, which in some cases returned to normal.[18,19]

Unfortunately, the SVR rate to monotherapy with interferon alfa was poor, with rates of only 6% to 12% after a 24-week course and 12% to 20% after a 48-week course of treatment. A major advance in therapy came with the addition of ribavirin to interferon therapy, which led to increases in SVR rates to as high as 38% to 43%.[20,21] In post hoc analyses, genotype was the strongest predictive factor; responses were only

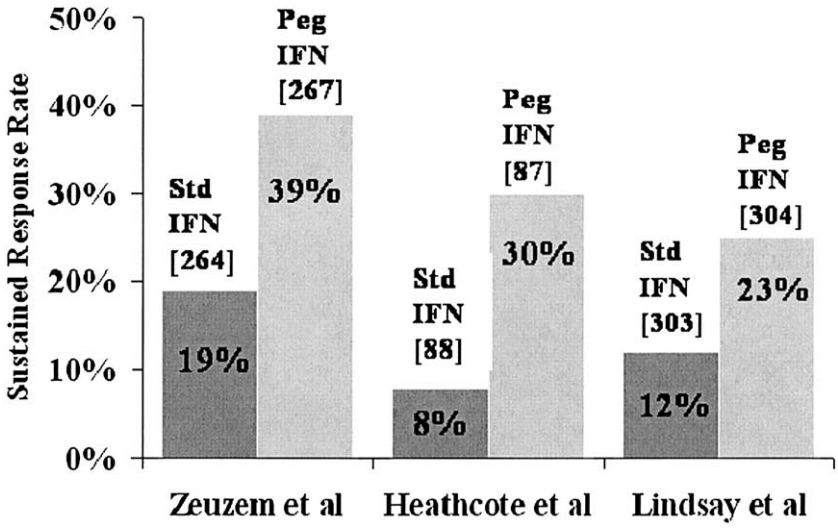

Fig 1. SVR rates in 3 large controlled trials comparing 48-week courses of peginterferon (Peg IFN) with standard interferon alfa (Std IFN) monotherapy. Trials compared standard interferon alfa-2a (5 MU thrice weekly) with peginterferon alfa-2a (180 μg/wk)[23,24] or peginterferon alfa-2b (1.5 μg/kg/wk) with standard interferon alfa-2b.[25] Numbers of patients in each group are listed in brackets.

28% to 31% in patients with genotype 1 compared with 64% to 66% in those with genotypes 2 and 3. Furthermore, patients with genotypes 2 and 3 responded equally well to 24- and 48-week courses of combination therapy.[20,21]

A more recent advance in therapy for hepatitis C was the introduction of pegylated forms of interferon (peginterferon). Pegylation refers to the covalent attachment of a large inert molecule of polyethylene glycol (PEG) to a protein to yield a molecule that retains biological activity, but has delayed absorption and clearance, allowing for weekly rather than daily or thrice-weekly administration.[22] Delayed clearance also led to greater, more potent, and longer lasting antiviral effects. Two forms of peginterferon have been developed: peginterferon alfa-2a (Pegasys; Hoffmann-LaRoche, Nutley, NJ), which has a 40-kd branched PEG moiety, and peginterferon alfa-2b, which contains a small, linear, 12-kd molecule of PEG (PegIntron; Schering Plough Corp, Kenilworth, NJ).

SVR rates from 3 large, randomized, controlled trials of peginterferon monotherapy are shown in Fig 1.[23-25] All patients received 48 weeks of therapy with peginterferon alfa-2a (135 or 180 μg/wk), peginterferon alfa-2b (1.0 or 1.5 μg/kg/wk), or standard interferon alfa-2a or alfa-2b (3 million units [MU] thrice weekly). All 3 studies showed the superiority of peginterferons, with response rates 2 to 3 times greater than with standard interferons.

More recently, the combination of peginterferon and ribavirin has been compared with both peginterferon monotherapy and combination therapy using standard interferon (Fig 2). Overall response rates to a 48-week course of combination therapy were 54% using peginterferon alfa-2b and 56% using peginterferon alfa-2a compared with 47% and 44% using standard interferon and ribavirin.[26,27] SVR rates to peginterferon combination therapy correlated with genotype; SVR rates were 76% to 82% in patients with non-1 genotypes and only 42% to 46% in those with genotype 1. Patient age, body weight, HCV RNA level, and degree of fibrosis correlated with response rate, but to a lesser extent than genotype.

A recent study compared response rates to peginterferon combination therapy using different doses of ribavirin (800 versus 1,000 to 1,200 mg) and different durations of therapy (24 versus 48 weeks).[28] The study showed that optimal response rates were achieved with the greater dose of ribavirin and 48 weeks of treatment in patients with genotype 1, but SVR rates were equivalent with either dose of ribavirin and both 24 and 48 weeks of therapy in patients with genotypes 2 and 3 (Fig 3). These results have helped define the current recommended therapeutic regimen for chronic hepatitis C. For patients with genotype 1, treatment should consist of a 48-week course of peginterferon alfa-2a (180 μg) or peginterferon alfa-2b (1.5 μg/kg) weekly combined with 1,000 to 1,200 mg of ribavirin daily (based on body weight $<$ or $\geq$ 75 kg). For

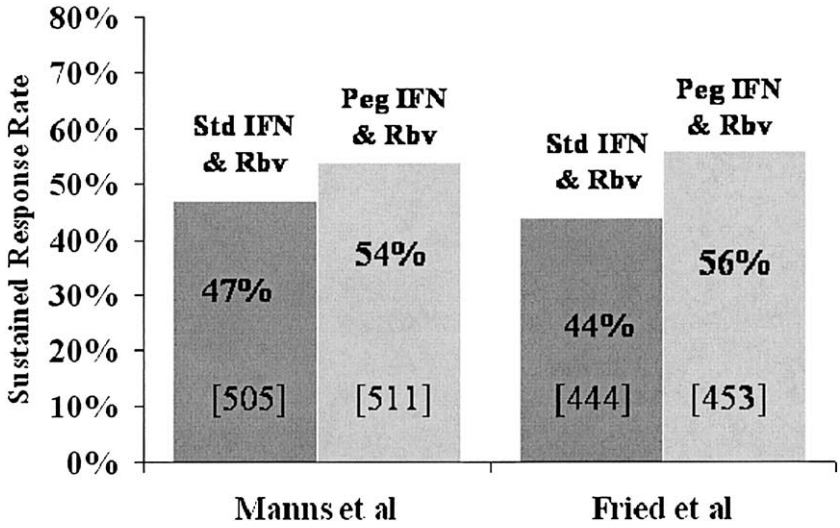

Fig 2. SVR rates in 2 large controlled trials comparing combination therapy using peginterferon (Peg IFN) or standard interferon (Std IFN) with ribavirin (Rbv). Manns et al[26] compared peginterferon alfa-2b (1.5 μg/kg/wk) and ribavirin (800 mg/d) with standard doses of interferon alfa-2b (3 MU thrice weekly) and ribavirin (1,000 to 1,200 mg/d based on body weight). Fried et al[27] used peginterferon alfa-2a (180 μg/wk) and ribavirin (1,000 to 1,200 mg/d) compared with standard doses of interferon alfa-2b and ribavirin. Numbers of patients in each group are listed in brackets.

patients with genotype 2 or 3, a 24-week course of peginterferon combined with 800 mg/d of ribavirin is appropriate.

Both interferon and ribavirin have frequent side effects. In the registration trials of combination therapy, 42% to 45% of patients required dose reduction, and 10% to 19%, early discontinuation of therapy.[26,27] The most common side effects of interferon are fatigue, headache, body aches, fever, nausea, poor appetite, irritability, anxiety, sleep disturbance, and depression. Interferon has myelosuppressive effects and decreases white blood cell and platelet counts by 30% to 40%. Ribavirin causes a dose-related hemolysis, which usually results in a 10% to 15% decrease in hemoglobin levels and can be a major problem in patients with preexisting anemia or hemolysis or those in whom sudden onset of anemia might trigger myocardial or cerebral ischemia. Combination therapy also can have serious adverse events, including bacterial infections, induction of autoimmune disease, and rare instances of renal, pulmonary, cardiac, hepatic, neurological, visual, or auditory injury.

Thus, current optimal therapy for chronic hepatitis C is problematic, but can result in a sustained loss of virus and long-term improvement in liver disease in slightly more than half the

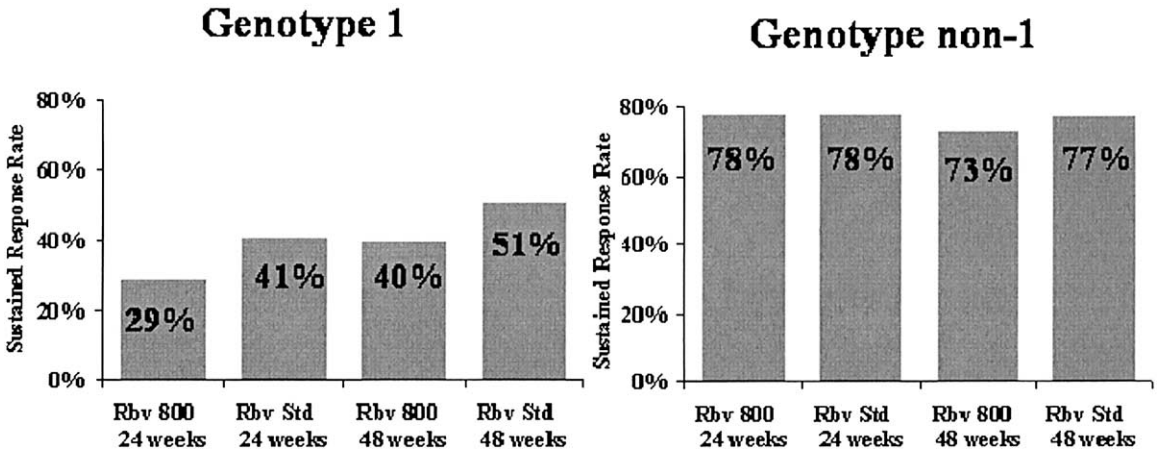

Fig 3. SVR rates by patient genotype (1 versus non-1) in a study comparing 24- to 48-week courses and 2 different ribavirin (Rbv) doses combined with peginterferon alfa-2a.[28] Ribavirin doses were either the standard dose (Std) of 1,000 to 1,200 mg/d based on body weight or a fixed dose of 800 mg/d.

patients. An important shortcoming of therapy is that it is not appropriate for many categories of patients, particularly those with other significant underlying medical conditions, including renal failure. The efficacy and safety of current therapy in patients with ESRD have not yet been shown.

HCV-RELATED CRYOGLOBULINEMIA

Dr Vincent Agnello, Lahey Clinic, Boston, MA

Chronic HCV infection has been associated with extrahepatic manifestations, including cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, lichen planus, seronegative arthritis, keratoconjunctivitis sicca, Mooren's corneal ulcer, and lymphoproliferative disorders.[29] The most frequent is essential mixed cryoglobulinemia.[30] Cryoglobulinemia is defined as the presence of immunoglobulins in serum that precipitate in vitro at reduced temperatures. Hepatitis C is associated most commonly with mixed cryoglobulinemia, in which cryoglobulins consist of complexes of rheumatoid factor (RF) with immunoglobulin G (IgG). Mixed cryoglobulinemia can be classified as type II (monoclonal RF and polyclonal immunoglobulin) or type III (in which both RF and immunoglobulin are polyclonal).[30] Testing unselected patients with cryoglobulinemia has shown that up to 90% have anti-HCV, indicating that the disease is not really essential, but rather related to HCV. Cryoglobulins consist of complexes of RF, IgG, anti-HCV, and HCV virions.[31] The cause of cryoglobulinemia is not well understood; it appears to be excessive proliferation of B cells induced by the chronic antigenic stimulation of HCV infection.[32] The typical RF in type II cryoglobulinemia has an antibody combining site cross-idiotype called WA, suggesting a common antigenic stimulus.[30]

Testing cohorts of patients with hepatitis C indicates that cryoglobulins can be detected in up to 50%, but usually at low levels (cryocrit $<$ 3%).[33] Frank symptomatic cryoglobulinemia occurs in 1% or less of patients and usually is associated with high levels of RF and cryoglobulins. In these patients, typical symptoms are fatigue and palpable purpura, which histologically consists of a leukoclastic vasculitis (with complexes of anti-HCV and HCV in injured tissue). A smaller proportion of patients have arthritis, neuropathy, and/or renal disease or other systemic vasculitic symptoms.[30] Typical renal manifestations of cryoglobulinemia include proteinuria and microscopic hematuria with mild to moderate renal insufficiency, with renal histological evaluation showing membranoproliferative glomerulonephritis (MPGN).[34] Cryoglobulinemia is more common in women than men and typically occurs after years or decades of HCV infection. The systemic illness can be severe and even fulminant. Non-Hodgkin's B-cell and splenic lymphomas can arise in the setting of cryoglobulinemia.[35,36] Whether this represents a frank malignancy as opposed to a nonmalignant proliferation of B cells is not well established, but responses to interferon alfa therapy suggest that these lymphomas arise from chronic HCV-induced antigenic stimulation, not from an autonomous malignant lymphocyte clone.

The cause, natural history, and optimal management of HCV-related cryoglobulinemia remain poorly defined. Central unresolved questions are why patients produce cryoglobulins and how cryoglobulins cause or are associated with tissue injury.

HCV-RELATED GLOMERULAR DISEASE

Dr Charles E. Alpers, University of Washington, Seattle, WA

The principal renal manifestation of HCV infection is MPGN, usually in the context of cryoglobulinemia.[34,37] HCV is probably the major cause of idiopathic MPGN.[37-42] The renal disease is rare in children and typically occurs in patients with long-standing infection, often in association with mild subclinical liver disease. Clinically, patients may have symptoms of cryoglobulinemia, including palpable purpura, arthralgias, neuropathy, and weakness.[30,34] Rarely, the presentation includes severe vasculitis with gastrointestinal, pulmonary, cardiac, or central nervous system involvement. Renal manifestations include nephrotic or nonnephrotic proteinuria and microscopic hematuria.[34,37-44] Renal insufficiency, frequently mild, commonly is identified.

Laboratory testing establishes the diagnosis of HCV-related MPGN. Most patients will have anti-HCV, as well as HCV RNA, in serum. Serum aminotransferase levels are elevated in 70% of patients, and the majority have RF and low levels of complement. Cryoglobulins are detected in 50% to 70% of patients.

Renal histological evaluation typically shows evidence of immune complex deposition in glo-

meruli and changes of MPGN.[34,45] Glomerular capillaries may have marked inflammatory cell infiltrates with both mononuclear cells and polymorphonuclear leukocytes (Fig 4A). Glomeruli show accentuation of lobulation of the tuft architecture and may have a combination of increased mesangial cellularity and matrix, capillary endothelial swelling, splitting of capillary basement membranes, and intracapillary globular accumulations of eosinophilic material representing precipitated immune complexes or cryoglobulins. On electron microscopy, immune complexes are usually subendothelial and may have a finely fibrillar or tactoid pattern suggestive of cryoglobulin deposition (Fig 4B and C).

In noncryoglobulinemic MPGN, histological features are similar, but features of leukocytic infiltration and intracapillary immune aggregates are less apparent or absent. Both subendothelial and mesangial immune complexes can be identified by electron microscopy, typically without distinctive substructure. In both forms of HCV-associated MPGN, mesangial and capillary wall deposition of IgM, IgG, and C3 are usually, but not invariably, shown.

Other forms of glomerular injury have been associated with HCV infection in individual case reports and small series, including membranous glomerulonephritis, IgA nephropathy, postinfectious glomerulonephritis, focal and segmental glomerulosclerosis, fibrillary glomerulonephritis, and immunotactoid glomerulopathy.[40-44] Occasional patients will have small-vessel vasculitis, and necrotizing inflammation of interlobular arteries and arterioles may dominate the biopsy picture.

Recurrence of MPGN in renal allografts has been suspected in a small number of patients.[44] Establishing the diagnosis of MPGN after transplantation is made especially difficult by similarities of the glomerular lesions to transplant glomerulopathy. Patients with HCV also may be at greater risk for rejection than uninfected patients.[46]

The pathogenesis of the glomerular injury in HCV infection is not known. Currently, the injury is believed to result from deposition of circulating immune complexes of HCV, anti-HCV, and RF at the site of injury. There are no adequate animal models of HCV-related glomerulonephritis, and reagents for identifying HCV

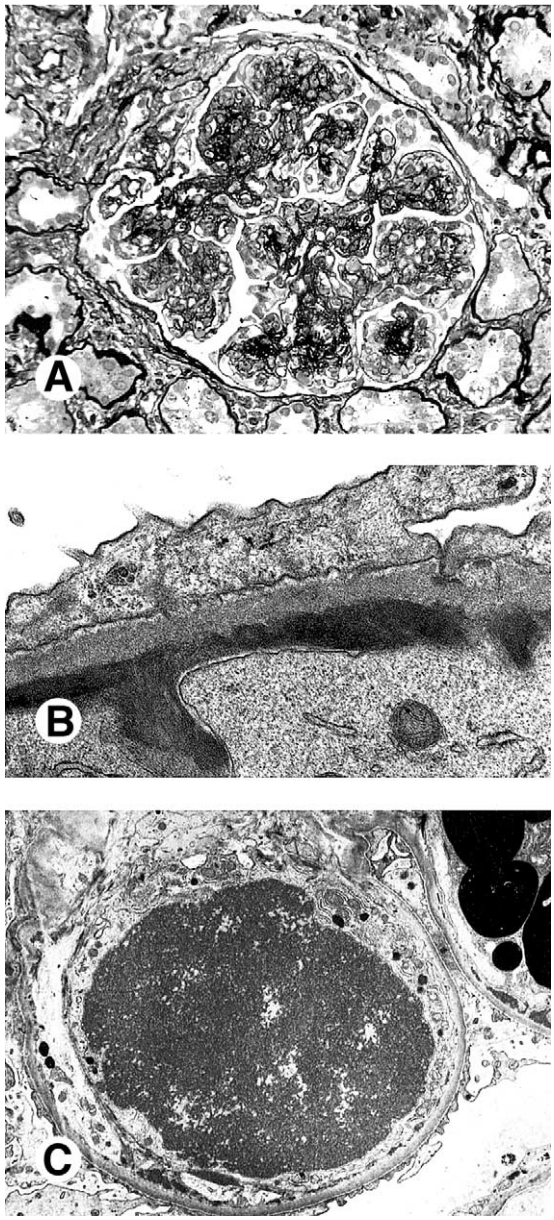

Fig 4. (A) Typical light microscopic findings of HCV-related MPGN, with mesangial hypercellularity, mesangial matrix accumulation, splitting of capillary basement membranes, and leukocyte influx into capillary loops. (Silver methenamine; original magnification ×400.) Electron microscopic demonstrations of (B) subendothelial electron-dense deposits in a glomerular capillary wall with a finely fibrillar pattern typical of cryoglobulins and (C) intracapillary accumulation of electron-dense material characteristic of precipitated cryoglobulins. Glomerular capillary walls contain smaller deposits of immune complexes in subendothelial locations. Histological specimens provided by Dr Charles E. Alpers, University of Washington, Seattle, WA.

antigens and RNA in tissue are limited. Most recently, several mouse models of cryoglobulinemia and MPGN, similar to the human disease, have been identified.[47,48] These models may be useful for the identification of strategies for treatment of this disease.

THERAPY FOR HCV-RELATED CRYOGLOBULINEMIA AND RENAL DISEASE

Dr Giuseppe D'Amico, San Carlo Hospital, Milan, Italy

Extrahepatic manifestations of chronic HCV infection appear to be caused by an abnormal B-cell response to viral antigens. Therapy therefore can be directed at either the immune response (prednisone or cytotoxic or immunomodulatory agents) or viral replication (interferon and ribavirin).

Controlled trials have shown that antiviral therapy with interferon alfa is associated with improvements in cryoglobulin, RF, and creatinine levels and lessening of symptoms of immune complex disease.[49,50] Unfortunately, relapse after therapy occurs in a large proportion of patients, particularly with interferon monotherapy administered for only 6 months. Long-term remission in cryoglobulinemia can occur with interferon therapy, and response rates are similar in patients with hepatitis C without cryoglobulinemia.[51-54] Greater doses of interferon and combination therapy with ribavirin yield greater response rates, but relapses and nonresponses still occur.[55-57] In some instances in which sustained viral eradication was unsuccessful, long-term maintenance interferon therapy has led to amelioration of disease. Importantly, worsening of vasculitis during interferon therapy has been reported.[58] Results of peginterferon and ribavirin combination therapy have yet to be published, but response rates are likely to be similar to those in patients without cryoglobulinemia.[26,27] In patients unable to tolerate or not responding to interferon therapy, disease amelioration has been achieved in some cases by using ribavirin alone.[59]

There are fewer data regarding antiviral treatment of HCV-related glomerular diseases, largely because they are uncommon and the renal disease complicates therapy. In the initial report of HCV-related MPGN, interferon therapy was reported to improve renal function and decrease proteinuria, but subsequent relapses were common,[34] findings that have been duplicated in other case series.[60-66] Combination therapy also has been used with variable responses.[67,68]

Thus, antiviral therapy can be successful in eradicating HCV in patients with cryoglobulinemia or glomerulonephritis, but sustained responses are uncommon. Furthermore, antiviral therapy can be associated with worsening of renal disease.[69,70] In cases of severe acute systemic vasculitis, anti-inflammatory and cytotoxic drugs and plasma exchange have been used with apparent partial success.[71] For these reasons, corticosteroids and cyclophosphamide continue to be used, particularly when interferon therapy is ineffective.[72] Although these drugs may increase viral titers, they have not been associated with worsening of the underlying hepatic disease. An appropriate approach to treatment of severe acute flares of cryoglobulinemia with glomerulonephritis or vasculitis is combination antiviral therapy using peginterferon and ribavirin for 48 weeks, adding corticosteroids and cyclophosphamide as needed to control severe symptoms. In the most severe cases, plasmapheresis (exchanges of 3 L of plasma 3 to 4 times/wk for 2 to 3 weeks) can be helpful. Recent promising results suggest that monoclonal antibody to B cells (anti-CD20; rituximab) may be helpful in refractory cases.[73]

EPIDEMIOLOGICAL CHARACTERISTICS OF HEPATITIS C IN DIALYSIS UNITS

Dr Miriam Alter, Centers for Disease Control and Prevention, Atlanta, GA

Hemodialysis patients are at particularly high risk for blood-borne infections because of prolonged vascular access and the potential for exposure to infected patients and contaminated equipment. Recent data indicate that 8% to 10% of dialysis patients in the United States have anti-HCV, and the incidence of new cases of hepatitis C has ranged from less than 1% to 3% yearly.[74,75] There is considerable variation in the prevalence of anti-HCV and the incidence of new cases among dialysis centers. Risk factors for spread include a history of transfusion, number of blood products transfused, and number of years on hemodialysis therapy.[76]

Measures to prevent the spread of hepatitis C have been derived at least in part from studies of other blood-borne infections in hemodialysis

units. For instance, previous investigations of outbreaks of hepatitis B almost invariably showed problems in infection control practices.[77] Such factors precipitated the 1977 Centers for Disease Control and Prevention (CDC) Infection Control Recommendations for hemodialysis units. Implementation of these recommendations, followed by the development and availability of a hepatitis B vaccine, led to a marked decline in both the incidence and prevalence of hepatitis B among hemodialysis patients.[77] Transmission of HCV, as with HBV, depends on the presence of chronically infected patients and potential exposure to blood and blood products, and recommendations are similarly based on hemodialysis-specific infection control practices (Table 1). In addition to standard universal precautions, additional practices are recommended because exposure to blood is routinely anticipated.[76,77] These recommendations include special dialysis unit precautions, regular serological testing, active surveillance, and training and education. Recommended precautions include routine use of gloves and restriction of use of common supplies, medications, and carts to deliver them. In addition, there should be strict attention to cleaning and disinfecting items shared between patients and careful disposal of dialyzers and blood tubing after treatments. The CDC has not recommended isolation of HCV-infected patients in dialysis units.[76,77] Similarly, HCV-infected patients need not be excluded from participating in dialyzer reuse programs.

Recommendations for routine biochemical and virological testing in dialysis patients are listed in Table 2.[76,77] Baseline testing should include serum ALT levels and assays for both HBV and HCV infection. For anti-HCV–negative patients, recommended monitoring includes testing ALT levels monthly and anti-HCV every 6 months. Elevations in ALT levels should lead to anti-HCV testing. If ALT levels are persistently abnormal despite the absence of anti-HCV, testing for HCV RNA by qualitative assay (such as polymerase chain reaction) should be considered. Routine HCV RNA testing is expensive and rarely identifies patients not detected by third-generation tests for anti-HCV.[76] Dialysis patients who develop anti-HCV should be reported to local health departments.

The CDC also recommends that dialysis units maintain surveillance records relevant to infection control.[76,77] Patient records should include the location of the dialysis station, machine number, and names of attending staff members. Centralized records should include logbooks or files of serological test results and patient vaccine status. Staff should be designated to review results regularly, and a plan should be developed to investigate new cases. Dialysis units also are encouraged to take advantage of opportunities for training and education, available at http://www.cdc.gov/mmwr/PDF/rr/rr5005.pdf.

HEPATITIS C IN DIALYSIS PATIENTS

Dr Brian Pereira, Tufts-New England Medical Center, Boston, MA

There is considerable variability in the prevalence of anti-HCV and chronic HCV infection in dialysis units worldwide, ranging from as low as 1% to as high as 63%.[78,79] There also is great variability in HCV testing practices in dialysis centers.[78,79] Some nations have introduced routine screening of dialysis patient populations, whereas other countries have been less consistent.[80-83] In the United States, the proportion of dialysis units that test for HCV among patients and staff has been increasing and is now approximately 60%.[84] With the introduction of routine screening and heightened attention to prevention of spread, the incidence of HCV infection has declined in dialysis centers in many countries, but remained high in others (~15%).[80-83] In the United States, the prevalence of hepatitis C in the dialysis population has not changed, and the incidence of new cases of hepatitis C has remained constant, in the range of 1% to 3% per year.[74,85] Conversely, there has been a marked decrease in the incidence of acute hepatitis C in the general nondialysis population. The prevalence of anti-HCV among dialysis patients is still in the range of 8% to 10% and has not changed to an appreciable extent since tests for anti-HCV were first developed in the early 1990s.[79,85,86]

The high prevalence of HCV in dialysis patients is of great concern in view of studies that suggest these patients have a higher mortality than HCV-negative patients.[87,88] Although HCV transmission through blood product transfusion previously was a significant source of infection, current cases are more likely related to nosocomial exposure. Dialysis units with a greater preva-

Table 1. Recommended Infection Control Practices for Hemodialysis Units

Wear disposable gloves when caring for the patient or touching the patient's equipment at the dialysis station; remove gloves and wash hands between each patient or station.
Items taken into the dialysis station should either be disposed of, dedicated for use only on a single patient, or cleaned and disinfected before taken to a common clean area or used on another patient.
Nondisposable items that cannot be cleaned and disinfected (eg, adhesive tape, cloth-covered blood pressure cuffs) should be dedicated for use only on a single patient.
Unused medications (including multiple-dose vials containing diluents) or supplies (eg, syringes, alcohol swabs) taken to the patient's station should be used only for that patient and should not be returned to a common clean area or used on other patients.
When multiple-dose medication vials are used (including vials containing diluents), prepare individual patient doses in a clean (centralized) area away from dialysis stations and deliver separately to each patient. Do not carry multiple-dose medication vials from station to station.
Do not use common medication carts to deliver medications to patients. Do not carry medication vials, syringes, alcohol swabs, or supplies in pockets. If trays are used to deliver medications to individual patients, they must be cleaned between patients.
Clean areas should be clearly designated for the preparation, handling and storage of medications and unused supplies and equipment. Clean areas should be clearly separated from contaminated areas where used supplies and equipment are handled. Do not handle and store medications or clean supplies in the same area or one adjacent to that where used equipment or blood samples are handled.
Use external venous and arterial pressure transducer filters/protectors for each patient treatment to prevent blood contamination of dialysis machines' pressure monitors. Change filters/protectors between each patient treatment and do not reuse them. Internal transducer filters do not need to be changed routinely between patients.
Clean and disinfect the dialysis station (eg, chairs, beds, tables, machines) between patients.
Give special attention to cleaning control panels on the dialysis machines and other surfaces that are frequently touched and potentially contaminated with patients' blood.
Discard all fluid and clean and disinfect all surfaces and containers associated with the prime waste (including buckets attached to the machines).
For dialyzers and blood tubing that will be reprocessed, cap dialyzer ports and clamp tubing. Place all used dialyzers and tubing in leak-proof containers for transport from station to reprocessing or disposal area.

Adapted from the CDC recommendations for preventing transmission of infections among long-term hemodialysis patients.[77]

lence of HCV also have a greater incidence.[80] In addition, patients on peritoneal dialysis and home hemodialysis therapy, who have less exposure to the environment of the dialysis unit, have a lower prevalence of HCV infection.[89-92]

Current CDC recommendations to control the spread of HCV in dialysis units include dialysis unit–specific precautions, as well as routine serological testing and surveillance.[76,77] In view of the unchanging prevalence of HCV infections in the US dialysis patient population and observations that suggest a decreased incidence of HCV in units that implement additional infection control measures, additional strategies to control the nosocomial transmission of HCV in dialysis units should be considered, particularly in units with a high prevalence of infection.[80] Such strategies might include isolation of HCV-positive patients, use of dedicated machines, and a restriction on dialyzer reuse for HCV-infected patients.[80]

NATURAL HISTORY OF HEPATITIS C IN DIALYSIS PATIENTS

Dr Paul Martin, Cedar-Sinai Medical Center, Los Angeles, CA

Assessing the natural history of hepatitis C in patients on hemodialysis therapy is problematic because of unique characteristics of this population. First, ALT levels are frequently normal and appear to be less reflective of the activity of the liver disease in HCV-positive dialysis patients compared with patients without renal disease.[93] Second, anti-HCV testing may not be reliable in dialysis patients because of the blunted humoral immune responses that occur with renal disease. A small proportion of patients with ESRD have HCV RNA in serum, but lack detectable anti-HCV.[94] Third, liver biopsy is the typical gold standard for assessing severity of hepatitis C, but has yet to be applied to a large number of dialysis patients. Finally, chronic hepatitis C has an insidious and prolonged natural history, and the competing mortality of complications of ESRD and hemodialysis may obscure the long-term consequences of hepatitis C.[95]

Cross-sectional studies have provided an overview of the spectrum of liver disease in HCV-positive hemodialysis patients (Table 3).[96-102] Disease activity was reported to be mild to moderate in most series, and a high proportion of patients

Table 2. Schedule for Routine Testing for HBV and HCV Infections in Dialysis Patients

Patient Status	On Admission	Monthly	Semiannual	Annual
All patients	HBsAg,* anti-HBc (total),* anti-HBs,* anti-HCV, ALT			
HBV susceptible, including non-responders to vaccine		HBsAg		
Anti-HBs positive (≥10 mIU/mL), anti-HBc negative				Anti-HBs
Anti-HBs and anti-HBc positive		No additional HBV testing needed		
Anti-HCV negative		ALT	Anti-HCV	

Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen.

*Results of HBV testing should be known before the patient begins dialysis therapy.

Adapted from CDC recommendations for preventing transmission of infections among long-term hemodialysis patients.[77]

had normal ALT levels. Importantly, the proportion of patients with advanced fibrosis or cirrhosis tended to be low. In these studies, the frequency of bridging hepatic fibrosis (stage 3) or cirrhosis (stage 4) ranged from 5% to 32%. In most studies, there were no associations between ALT or HCV RNA levels and severity of histological changes, indicating that liver biopsy is the only accurate means of assessing hepatitis C disease severity.

The natural history of hepatitis C in patients with ESRD on hemodialysis therapy has been the focus of several prospective studies with somewhat brief follow-ups. In a study from Seattle, WA, 220 patients, of whom 34 patients were HCV RNA positive, were followed up for an average of 3 years.[103] Multivariate analysis showed an increased relative risk (RR) for death in HCV RNA–positive patients of 1.78 (95% confidence interval [CI], 1.01 to 3.14). In a multicenter prospective study from Japan, 1,470 patients (19% positive for anti-HCV) from 16 dialysis centers were followed up for an average of 6 years.[87] Mortality was greater in the anti-HCV–positive group (33%) than in controls (23%; Fig 5), and the excess mortality appeared to be accounted for by deaths from cirrhosis (5.5% versus 0%) and hepatocellular carcinoma (8.8% versus 0.4%). The RR for death in anti-HCV–positive patients was 1.57 (95% CI, 1.23 to 2.00). In a study from the United States, 287 anti-HCV–positive and 286 randomly selected dialysis control patients from 14 transplant centers were assessed, with a median follow-up of 7 years.[88] In multivariate analysis, RR for death from all causes in anti-HCV–positive patients was 1.41 (95% CI, 1.01 to 1.97), and for death from liver disease or infection, 2.39 (95% CI, 1.28 to 4.48). Death from liver disease occurred in 14% of anti-HCV–positive and only 2% of anti-HCV–negative controls. These data show that chronic hepatitis C adversely affects survival in patients with ESRD; cirrhosis and liver cancer account for 13% to 14% of deaths.

Table 3. Spectrum of Liver Disease in HCV-Positive Dialysis Patients

Reference	No. of Patients Studied	Normal ALT	Bridging Fibrosis	Cirrhosis
Caramelo et al[96]	33	7 (21)	1 (3)	3 (9)
Pol et al[97]	17	(69)*	NR	2 (12)
Sterling et al[98]	50	48 (96)	6 (11)	6 (11)
Glicklich et al[99]	22	13 (59)	1 (5)	0 (0)
Martin et al[100]	37		3 (8)	9 (24)
Cotler et al[101]	46	34 (74)	2 (5)	4 (9)
Roth et al[102]†	152		7 (5)	7 (5)

NOTE. Values expressed as number (percent).

Abbreviation: NR, not reported.

*Proportion with normal ALT levels from the total cohort of 52 patients, of whom only 17 patients underwent liver biopsy.

†Meeting abstract.

THERAPY FOR HEPATITIS C IN PATIENTS WITH ESRD

Dr Stanilas Pol, Hopital Necker, Paris, France

There have been at least 17 published studies of interferon therapy in patients with ESRD, but none have been of sufficient size and duration to permit definitive recommendations regarding the

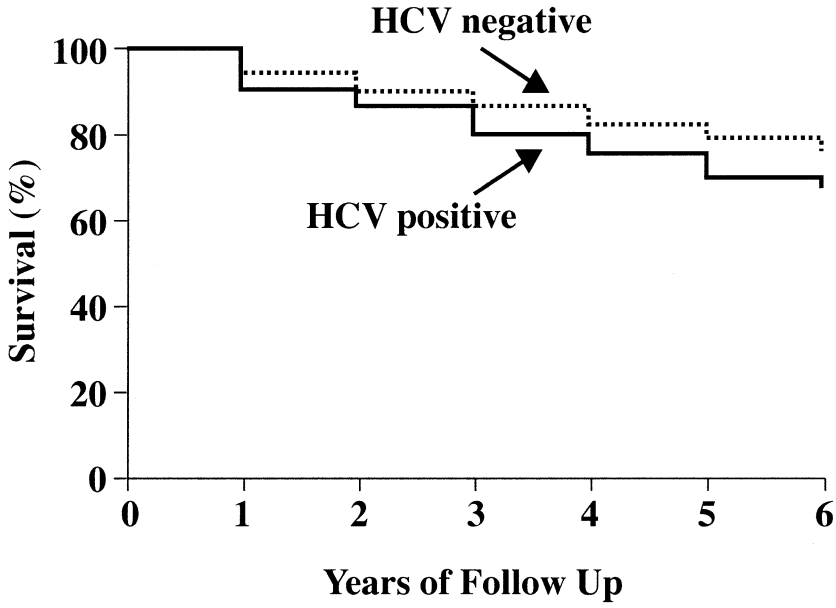

Fig 5. Patient survival during hemodialysis in 276 anti-HCV–positive (solid line) and 1,194 anti-HCV–negative (dotted line) patients on long-term hemodialysis therapy followed up for 6 years. Cumulative survival was significantly less among HCV-infected patients ($P < 0.01$). Modified and reprinted from Nakayama et al.[87]

benefits and risks of therapy.[104-120] In addition, there is virtually no information on the use of peginterferon or interferon-ribavirin combination therapy. Ribavirin is cleared by the kidneys and causes dose-related hemolysis, which makes it contraindicated in patients with kidney disease. For these reasons, studies of therapy in patients with ESRD have used interferon monotherapy.[121]

Published studies of interferon alfa therapy in patients with ESRD in which follow-up information is available on HCV RNA are listed in Table

Table 4. Trials of Interferon Alfa in Patients With Hepatitis C and ESRD

Reference	Year	No. of Patients	Interferon Type	Dose (MU 3 times/wk)	Duration (wk)	ETR Rate (%)	SVR Rate (%)	Discontinue Rate (%)
Koenig et al[104]	1994	37	Alfa	5	16	49	32	38
Okuda et al[105]	1995	15	Alfa-2a	6 → 3	24	NR	53	33
Pol et al[106]	1995	19	Alfa-2b	3	24	53	20	5
Raptopoulou-Gigi et al[107]	1995	19	Alfa-2b	3	24	53	63	32
Chan et al[108]	1997	11	Alfa-2b	3	24	100	27	0
Fernandez et al[109]*	1997	14	Alfa-2b	1.5 → 3	24	36	14	21
Izopet et al[110]	1997	23	Alfa-2b	3	24 or 48	92	52	13
Rodrigues et al[111]	1997	7	Alfa-2b	3	24	43	14	14
Benci et al[112]	1998	10	Alfa-n1	1	48	NR	20	10
Uchihara et al[113]	1998	9	Alfa-2b	3 or 6	24	NR	33	33
Campistol et al[114]*	1999	19	Alfa-2b	3	24	74	42	53
Huraib et al[115]	1999	17	Alfa-2b	3	48	88	71	NR
Tokumoto et al[116]	1999	6	Alfa-n	5 or 10	24	NR	50	NR
Casanovas-Taltavul et al[117]	2001	29	Alfa-n1	3 → 1.5	48	79	59	28
Espinosa et al[118]	2001	13	Alfa-2b	3	48	61	46	23
Degos et al[119]	2001	37	Alfa-2b	3	48	32	19	51
Hanrotel et al[120]	2001	12	Alfa-2a	3	48	75	33	8
Total		260				64	40	26

NOTE. All response rates calculated on the basis of intention to treat.
Abbreviations: IFN, interferon; ETR, end-of-treatment virological response; NR, not reported.
*Randomized, controlled trial.

4. Studies have ranged in size from 6 to 37 patients and used varying formulations of interferon (alfa-2a, alfa-2b, alfa-n1) in varying doses (1 to 10 MU) and varying regimens (usually thrice weekly, but for periods ranging from 16 to 48 weeks). Most studies used a 6-month post-therapy SVR as the end point for successful therapy, but different assays of varying sensitivity and specificity were used to detect HCV RNA. Most, but not all, studies also reported the end-of-treatment virological response rate (absence of HCV RNA during the last week of treatment), and most reported on safety, tolerance, dose modification, and early discontinuation rates.

Overall, 40% of treated patients had an SVR, a rate greater than that usually reported for monotherapy with interferon alfa in patients with hepatitis C without renal disease (6% to 18%). Furthermore, in studies that included controls without renal disease, response rates were similar or greater in patients with renal disease.[109,113] These results suggest that patients with ESRD have a similar, if not better, likelihood of a sustained response to interferon alfa therapy for hepatitis C than patients without renal disease.

Striking in most studies of interferon therapy of patients with ESRD has been a high rate of serious adverse events and high rates of dose modification and early discontinuation (Table 4). Although adverse events were not reported in all studies, the early discontinuation rate ranged from 0% to 51%, averaging 26%. These rates are greater than those reported from most large controlled trials of interferon in patients without renal disease (average, 9% to 19%).[122,123] A large prospective French trial of interferon alfa-2b therapy was terminated early after enrollment of only 37 of 120 patients by the data safety committee because of a high rate of serious adverse events.[119] In this largest study of therapy in patients with ESRD, there was a 57% rate of dose modification and 51% rate of early discontinuation. Severe adverse events included pulmonary edema, cerebral hemorrhage, acute pancreatitis, cardiomyopathy, lymphoma, diplopia, and septic shock after severe graft rejection. These results indicate that side effects of interferon are more common and more severe in patients with renal disease.

Nevertheless, SVRs that have occurred in patients with advanced renal disease appear to be durable and clinically significant. In several studies, follow-up was available after subsequent renal transplantation.[113,115,116,118,121] In patients without an SVR, persistent viremia was detected in all patients undergoing transplantation. Conversely, in 27 of 30 patients (90%) with a 6-month post-therapy SVR, HCV RNA was still undetectable and liver disease appeared inactive during long-term follow-up after transplantation. These results indicate that sustained responses can be achieved in patients with ESRD, and these responses are likely to be clinically significant. The challenge in therapy for hepatitis C in this group is to identify the optimal and safest regimen. At present, therapy for hepatitis C in patients with ESRD is controversial and should be considered only in patients with significant liver disease, minimal other comorbidities, and a reasonable likelihood of prolonged survival and if renal transplantation is contemplated. Patients with acute hepatitis C also are likely to be suitable candidates for treatment. Finally, persistence of HCV RNA despite interferon monotherapy for 8 to 12 weeks should lead to early discontinuation because the chance of an SVR is highly unlikely.[119,120]

PHARMACOKINETICS OF PEGINTERFERON IN ESRD

Dr S. Chris Pappas, Hoffman-LaRoche Inc, Nutley, NJ

Interferon alfa is a natural, 19-kd, nonglycosylated serum protein that circulates in nanomolar concentrations and is induced by exposure to foreign antigens and viruses. Several forms of recombinant interferon alfa (alfa-2a, alfa-2b, alfa-n1) have been developed for human use, and their serum half-life and pharmacokinetics have been analyzed in detail. Interferon is filtered at the glomerulus and undergoes proteolytic degradation during proximal tubular reabsorption.[123-125] Negligible amounts are detectable in urine. Liver catabolism is believed to have a minimal role in turnover, and the molecule most likely is cleared by natural proteases in cells that endocytose interferon that has bound to cell-surface receptors. The serum half-life of interferon alfa averages 6 to 8 hours, and peak levels are detected within 2 to 4 hours of injection. Interferon alfa usually is undetectable 16 to 24 hours after a

Table 5. Pharmacokinetic Parameters of Standard and Pegylated Interferon Alfa

Parameter	Interferon Alfa-2a	Interferon Alfa-2b	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Volume of distribution (L)	~70	~70	~70	~8
Clearance (mL/min)	7,700	6,000	725	60
Absorption half-life (h)	2.3	2.3	4.6	5.0
Elimination half-life (h)	5.1	8.1	40-54	65-80
Time to maximum serum concentration (h)	8-12	8-12	20	80

single injection of 3 to 5 MU: standard doses used in the treatment of chronic hepatitis B and C.

Although interferon is cleared by the kidneys, serum levels and clearance rates of standard interferon alfa are reported to be similar in patients with and without renal disease.[23,24,125] Differences in pharmacokinetics may be seen at greater doses of interferon or in patients with more advanced renal disease.[24] A multiple-dose study reported that the elimination half-life of interferon is increased in patients with ESRD (10 versus 6 hours in patients without renal disease), and the resulting area under the curve (AUC) is greater, suggesting that 65% to 80% of interferon is cleared by the kidney. Greater levels and AUCs of interferon levels in patients with renal disease may account for the greater end-of-treatment and SVR rates to interferon alfa therapy in this patient group.

The 2 peginterferons (alfa-2a and alfa-2b) have different pharmacokinetics (Table 5).[25,126,127] Furthermore, the metabolism of both molecules is complicated because interferon and PEG have different metabolic fates and half-lives, particularly as intact molecules undergo catabolism. Peginterferon alfa-2a is metabolized in the liver and other organs by nonspecific proteases, and metabolic products are excreted in urine.[26,27,128] The PEG moiety is inert and is removed slowly from the body in 50 to 60 days.

In patients with renal disease, peginterferon half-life, time and concentration of peak levels, and AUC are similar down to a creatinine clearance of 20 mL/min (0.33 mL/s). However, there are large interindividual variations in pharmacokinetics and little correlation with creatinine clearance. Products of interferon action, such as 2′5′ oligoadenylate synthetase activity, tend to be lower in patients with renal disease, but only in those with a creatinine clearance less than 40 mL/min (0.67 mL/s).

Studies of patients with ESRD have shown that peginterferon pharmacokinetics are clearly altered.[27] In a study of 4 different once-weekly doses of peginterferon alfa-2a, clearance fraction decreased from 94 mL/h in controls to 63 mL/h in patients with ESRD, whereas peginterferon half-life increased from 52 to 58 hours. In addition, serum concentrations of peginterferon were greater in patients with ESRD. A dose of 135 μg of peginterferon alfa-2a in patients with ESRD gave similar serum concentrations to a dose of 180 μg in patients with normal renal function. On the basis of such pharmacokinetic studies as these, trials of peginterferon in patients with ESRD have been designed using weekly doses of either 135 μg (as opposed to 180 μg) of peginterferon alfa-2a or 0.5 to 1.0 μg/kg (as opposed to 1.0 to 1.5 μg/kg) of peginterferon alfa-2b.

PEGINTERFERON MONOTHERAPY FOR HEPATITIS C IN ESRD

Dr Mark Russo, University of North Carolina, Chapel Hill, NC

High rates of end-of-treatment and SVR to interferon alfa monotherapy in patients with renal disease, coupled with the propensity of liver disease to progress and complicate ultimate renal transplantation, led to attempts to improve therapeutic regimens for this cohort. Although peginterferons have been superior to standard interferons in patients without renal disease, they may not have increased efficacy in patients with renal impairment. The enhanced activity of peginterferon is partially attributable to a more prolonged half-life and decreased renal clearance, advantages that may not be applicable in patients with ESRD. Furthermore, side effects, which often are severe with standard interferon, may be more common, severe, and prolonged with peginterferons. These factors make it imperative that controlled trials of peginterferon be conducted in

patients with advanced renal disease before this therapy is adopted in clinical practice.

A large multicenter trial of peginterferon in 120 patients with ESRD on hemodialysis therapy has been initiated in 7 sites in the United States. Enrollment criteria include the presence of HCV RNA in serum and a liver biopsy showing chronic hepatitis C. Serum ALT levels can be normal or elevated. Patients are randomly assigned to the administration of either 0.5 or 1.0 μg/kg of peginterferon alfa-2b once weekly for 48 weeks. The end point for successful therapy is the absence of HCV RNA 6 months or more after completion of therapy. Information on this trial is available at www.med.unc.edu/wrkunits/2depts/medicine/gi/russo.htm

RIBAVIRIN THERAPY FOR HEPATITIS C IN PATIENTS WITH RENAL DISEASE

Dr Bruce A. Luxon, Saint Louis University School of Medicine, St Louis, MO

In patients without renal disease, the combination of peginterferon and ribavirin is now the standard recommended therapy for chronic hepatitis C. Peginterferon alone is recommended only for patients who have specific contraindications to ribavirin, such as renal disease. Ribavirin is cleared by the kidneys and causes a dose-related hemolysis that can be severe and life threatening in patients with renal disease, most of whom have preexisting anemia and low-grade hemolysis.

The cause of hemolytic effects of ribavirin appears to be related to the metabolic fate of ribavirin within cells. Ribavirin is taken up by an active cell-surface transporter and phosphorylated in the cytoplasm to ribavirin-triphosphate (TP). Red blood cells, being anucleate, can take up and phosphorylate ribavirin, but are unable to dephosphorylate or secrete ribavirin-TP. As a result, ribavirin-TP accumulates in red blood cells and results in depletion of adenosine TP, damage to red blood cell membranes, and subsequent splenic uptake and destruction.

Pharmacokinetic studies show that ribavirin is cleared predominantly in the kidneys, and after a single dose, serum concentrations are 3-fold greater in patients with ESRD than subjects with normal renal function. Hemodialysis does not change serum concentrations; thus, ribavirin accumulates even with adequate dialysis.

Despite the renal clearance and potential for toxicity, several pilot studies of ribavirin therapy in patients with advanced renal disease have been performed. Bruchfeld et al[129] treated 5 patients on hemodialysis therapy and 1 patient on peritoneal dialysis therapy with interferon alfa-2b (3 MU thrice weekly after each dialysis treatment) for 4 weeks, then added ribavirin in a dose of 200 mg/d. Ribavirin doses were adjusted to achieve serum concentrations of 10 to 15 μmol/L, which is typical of patients with normal renal function administered standard doses. The average dose required to achieve these concentrations ranged from 170 to 300 mg/d. Adverse side effects were common; 1 patient died of heart failure, and only 3 patients completed the 28 weeks of therapy. Patients required increased doses of erythropoietin to support hemoglobin levels. Five of 6 patients achieved an end-of-treatment response, but only 1 (16%) had sustained loss of HCV RNA.

Tan et al[130] treated 5 patients on hemodialysis therapy with interferon alfa-2b (3 MU thrice weekly) and low doses of ribavirin (200 mg/d) with a plan to increase the ribavirin dose based on tolerance. Hemoglobin levels decreased in all patients, all required increased doses of erythropoietin, and 4 patients were administered blood transfusions. Two patients developed intolerable side effects and stopped therapy early. Three other patients were able to continue therapy; 2 patients were administered 200 mg of ribavirin thrice weekly and 1 patient was administered 200 mg/d. Four patients became HCV RNA negative on therapy, but posttreatment follow-up was not provided in this preliminary report.

These results indicate that ribavirin can be administered to patients with ESRD, but only in low doses and with aggressive support for hemolysis and anemia. These studies did not resolve whether ribavirin at these low doses increased response rates. For these reasons, a prospective, randomized, controlled trial of peginterferon with or without low doses of ribavirin has been initiated in 4 centers in the United States. Patients with ESRD on dialysis therapy who have chronic hepatitis C and HCV RNA in serum are eligible. Patients undergo liver biopsy before therapy, but neither histological features nor serum ALT levels are used in enrollment criteria. Patients are randomly assigned to the administration of either

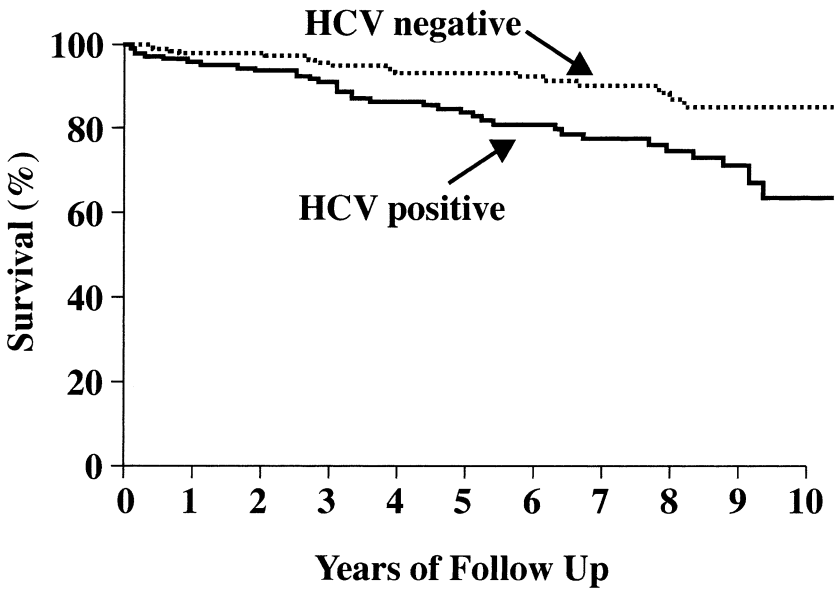

Fig 6. Patient survival after renal transplantation comparing 216 anti-HCV–positive (solid line) and 216 age-, sex-, and immunosuppressive regimen–matched anti-HCV–negative (dotted line) patients followed up for up to 10 years. Survival was significantly decreased among HCV-infected patients (P = 0.001). Modified and reprinted from Mathurin et al.[131]

peginterferon alfa-2a monotherapy (1.0 μg/kg/wk) for 48 weeks or the combination of peginterferon and ribavirin in a dose of 3 mg/kg once weekly, with dosage increases based on tolerance and maintenance of hemoglobin levels at greater than 9.5 g/dL (95 g/L) supported only with erythropoietin. The end point for assessing benefit is a 6-month posttreatment SVR rate.

Thus, ribavirin currently is contraindicated in patients with advanced renal disease and should not be used outside controlled trials. It remains unclear whether low doses of ribavirin can increase the SVR to greater than that achieved with peginterferon alone.

NATURAL HISTORY OF HEPATITIS C AFTER RENAL TRANSPLANTATION

Dr David Roth, University of Miami, Miami, FL

In view of the lack of uniform pretransplantation data collection in HCV-positive patients, such as liver biopsy, viral titers, and viral genotyping, the natural history of HCV in the transplant patient population is difficult to define. Several single-center studies have shown that short-term graft and patient survival are not affected greatly by HCV infection, but long-term (10 to 20 years) survival clearly is worse (Fig 6).[131,132] Analysis of the US Renal Data System (USRDS) database of transplantations performed between 1994 and 1997 indicated an increased RR for death (RR, 1.23; 95% CI, 1.01 to 1.49) in HCV-positive transplant recipients.[133] Excess mortality was attributable to liver disease.

At issue is whether renal transplantation changes the natural history of hepatitis C, what factors are associated with worsening of disease, and which of these can be predicted and modified. In a French study, the presence of cirrhosis before transplantation was an independent predictive factor of poor 10-year survival.[131] Cross-sectional studies suggest that up to 25% of patients with ESRD who are HCV RNA positive have significant fibrosis (bridging fibrosis or cirrhosis; Table 3), but there are no prospective studies of how such patients fare individually after transplantation.[96-100,102] Investigating patterns of posttransplantation liver disease in HCV-positive recipients, several studies have shown a greater incidence of ALT level elevations, an increase in viral replication, and occasional occurrence of fibrosing cholestatic hepatitis and progressive liver disease.[134-137]

To assess the impact of transplantation on hepatitis C, Zylberberg et al[138] compared changes in liver histological characteristics in 28 HCV-positive renal transplant recipients who had undergone 2 or more liver biopsies without intervening antiviral therapy with those among 28 immunocompetent matched controls. Histological characteristics worsened in renal transplant recipients, but changed minimally in controls during an average interval of 7 years. In particu-

lar, hepatic fibrosis worsened in 14 transplant recipients (50%), but only 4 controls (16%; $P < 0.001$), with 6 transplant recipients (21%) developing cirrhosis and 3 transplant recipients (10%) dying of liver disease. This was a retrospective study (and included only 28 of 150 transplant recipients with hepatitis C at this center), but it supported the hypothesis that renal transplantation accelerates the course of chronic hepatitis C.

A prospective study of liver disease in all HCV-positive renal transplant candidates has been initiated at the University of Miami, FL.[102] To date, 152 patients have been enrolled. Almost all patients had genotype 1 (60%, genotype 1a; 30%, genotype 1b). Baseline liver histological evaluation showed that most patients had some degree of inflammation and necrosis, but fibrosis was generally mild, and only 10% had bridging fibrosis or cirrhosis.[102] Approximately 20% of enrolled patients have undergone a follow-up liver biopsy, either posttransplantation or while still on the transplant list. Follow-up biopsies suggested that liver histological state was stable, with little or no evidence of acceleration in progression after renal transplantation (D. Roth, unpublished observations).

Factors that predict progression of hepatitis C in patients without renal disease include older age, male sex, obesity, concurrent alcohol use, and such comorbid conditions as diabetes, hemochromatosis, hepatitis B, and HIV infection.[139] Although there have been few studies of factors that predict progression of hepatitis C in patients with renal transplants, they are likely to be similar.[139-146] Timing of infection may be important because patients who acquire hepatitis C de novo from an infected donor at transplantation often have a rapidly progressive course.[139,140] In addition, both HBV and HIV coinfection appear to worsen the course of hepatitis C after transplantation.[141,142] Degree and form of immunosuppressive therapy (antilymphocyte globulin, azathioprine, mycophenolate mofetil) have major effects on HCV titers after transplantation and consequently may affect disease outcome.[102,135,143,144,147,148] Finally, HCV may have other adverse effects on posttransplantation patients; HCV-infected patients appear to have a greater risk for diabetes mellitus and proteinuria.[149-151] Definitive prospective clinical studies addressing potential adverse effects of different immunosuppressive agents and antirejection regimens in HCV-positive patients are critically needed to provide information on optimal management of HCV-infected patients with ESRD.

RENAL TRANSPLANTATION ISSUES WITH HCV-INFECTED DONORS AND RECIPIENTS

Dr Svetlozar Natov, Tufts-New England Medical Center, Boston, MA

Because HCV is transmitted readily by organ and tissue transplantation, organ procurement organizations routinely screen for anti-HCV. However, tests for anti-HCV do not differentiate between active viremia and resolved hepatitis C, and anti-HCV–positive donors without HCV RNA in serum may not be infectious. Routine testing for HCV RNA (or HCV core antigen) may be more accurate in assessing risk for infectivity, but also are more expensive and have not been adequately standardized or assessed for reliability. Furthermore, testing for HCV RNA is not always available in the time required for cadaveric donation.

The prevalence of HCV infection in cadaveric organ donors has considerable worldwide variation, ranging from 1% to 11%.[152] The US National Collaborative Study (1986 to 1992) estimated that 5.1% of cadaveric organ donors were anti-HCV positive by using the first-generation enzyme immunoassay (EIA-1). Extrapolating to newer assays, the prevalence of anti-HCV (EIA-2) is likely to be 4.2%, and HCV RNA, 2.4%.[152,153] The prevalence of anti-HCV in cadaveric organ donors is severalfold greater than in the healthy blood donor population, probably because of the greater rate of risk factors for parenterally transmitted viral infections in cadaveric donors.[153] Such risk factors include male sex, history of alcohol or injection drug use, blood alcohol level greater than 100 mg/dL, history of multiple sexual partners, or history of HBV or cytomegalovirus infection.[153]

Variable transmission rates of HCV with the use of anti-HCV–positive donors have been reported.[153] A recent summary of published studies on outcomes after receipt of an organ from an anti-HCV–positive donor reported that 35% (range, 0% to 55%) of recipients developed liver disease, 50% (range, 14% to 100%) became anti-HCV positive, and 73% (range, 14% to 96%) developed detectable HCV RNA posttransplantation.[153] Variability in reported out-

comes probably reflected the frequent subclinical nature of HCV infection and lack of uniform follow-up and testing of recipients for HCV RNA.[153] Risk for transmission also may relate to prevalence of HCV RNA in anti-HCV–positive donors.[152] Finally, the method of organ preservation may impact on HCV transmission; pulsatile perfusion, rather than static storage, is associated with a reduction in HCV RNA levels in kidneys harvested from HCV-infected donors.[154]

In view of potential serious long-term complications of HCV transmission, exclusion of HCV-infected donors has been adopted by most organ procurement organizations. The use of HCV-infected donors currently is restricted to life-saving transplants (heart, lung, liver) and requires full disclosure of risks to the recipient.[152] However, policies excluding anti-HCV–positive donors from transplantation result in discarding potentially useful organs, particularly those from donors without HCV RNA.

A rational approach to the use of kidneys from anti-HCV–positive donors is to reserve these organs for recipients who are already infected. Small studies have shown that this approach shortens transplant waiting time and does not adversely affect short-term survival or lead to worsening of preexisting liver disease.[147,155] Potential for reinfection or superinfection with a newly introduced strain or genotype of HCV, particularly in an anti-HCV–positive recipient without HCV RNA, is an additional issue.[147,155,156] An alternative approach is use of anti-HCV–positive organs only in recipients with documented HCV RNA in serum.[152,157,158] This approach requires routine HCV RNA testing of patients awaiting transplantation, but is the most practicable approach to use of organs from HCV-infected individuals. Prospective studies of consequences of transplanting HCV-positive organs in HCV-positive recipients are needed before this policy can be universally adopted.

HCV-RELATED RENAL DISEASE AFTER RENAL TRANSPLANTATION

Dr John Pirsch, University of Wisconsin, Madison, WI

Several different renal diseases have been reported in HCV-infected patients after kidney transplantation, including recurrent or de novo MPGN, membranous nephropathy, minimal change disease, renal thrombotic microangiopathy, acute transplant glomerulopathy, and chronic transplant glomerulopathy.[44,51,151,159-162] MPGN has been reported most commonly, at rates ranging from 5% to 54% in HCV-positive renal transplant recipients.[151,161,162] In such patients, proteinuria or nephrotic syndrome is the most common clinical presentation.[161,163,164] Circulating cryoglobulins are usually, but not always, detected.[151,161,162] However, it should be stressed that the most common cause of proteinuria and renal insufficiency after kidney transplantation, even in HCV-positive patients, is chronic allograft nephropathy, not HCV-related injury.[46,164]

Most studies of patient and graft survival in HCV-positive renal transplant recipients focused on recurrent liver disease as the cause of morbidity and mortality, rather than on recurrent renal disease or graft loss.[83,133,165] Single-center studies, as well as USRDS data, suggest that both graft and patient survival are lower for HCV-positive than HCV-negative patients.[83,85,133,165] Delineation of the effects of recurrent HCV-related renal disease in causing the decreased graft and patient survival has not been possible.

A prospective study of the effect of hepatitis C in cadaveric kidney transplant recipients has been ongoing at the University of Wisconsin since 1991.[166] HCV-positive donor kidneys were given only to high-risk recipients with type 2 diabetes, high cardiovascular risk, lack of dialysis access, or retransplantation. Between 1991 and 2001, a total of 1,368 transplantations were performed, including 115 transplantations using an HCV-positive donor kidney in an anti-HCV–negative transplant recipient, 71 transplantations using a positive donor in a positive recipient, and 43 transplantations using an HCV-negative donor in an HCV-positive recipient. Preliminary results show that patients who received HCV-positive organs had greater mortality rates, but significant comorbidities were the major reason for the increased mortality. Liver failure accounted for only 2% of deaths. Kidney graft survival in HCV-positive transplant recipients, whether they received an HCV-positive or HCV-negative organ, was less favorable than that for HCV-negative transplant recipients. Allograft survival in HCV-negative patients who received HCV-positive organs also was less favorable. Although

trends regarding the incidence of acute rejection and infection in HCV-positive transplant recipients were not markedly different, there appeared to be a greater likelihood of chronic allograft nephropathy in HCV-positive transplant recipients. In addition, there did not appear to be a difference in the incidence of de novo or recurrent glomerulonephritis in HCV-negative and HCV-positive transplant recipients (J. Pirsch, unpublished observations).

Published studies and such large single-center preliminary reports underscore the need for additional investigations routinely assessing the baseline status of HCV-positive transplant candidates and for prospective studies characterizing the impact of HCV donor and recipient status on renal transplantation.

HCV-RELATED RENAL DISEASE AFTER LIVER TRANSPLANTATION

Dr Raymond Chung, Massachusetts General Hospital, Boston, MA

Just as liver disease can complicate the outcome of kidney transplantation, so can renal disease complicate the outcome of liver transplantation in HCV-infected recipients. There have been at least 7 case series or case reports of MPGN and cryoglobulinemia after liver transplantation for chronic hepatitis C.[167-173] In most instances, cryoglobulinemia and MPGN appeared soon after transplantation, averaging 3 months and presenting with proteinuria and nephrotic syndrome. When tested before transplantation, patients were always found to have preexisting cryoglobulins. The natural history of MPGN and cryoglobulinemia after transplantation has not been well characterized. However, some patients develop progressive renal failure or worsening cryoglobulinemia with clinical signs and symptoms of disease.

In a direct comparison of HCV-positive and HCV-negative liver transplant recipients, Kendrick et al[171] found similar absolute and proportional decreases in creatinine clearance in the 2 groups, but a greater frequency of proteinuria (protein $>$ 1 g/d) in HCV-positive (25%) than HCV-negative (5%; $P = 0.05$) transplant recipients. Biopsy-proven MPGN also was more frequent in HCV-positive (4 of 91 patients) than HCV-negative patients (0 of 106 patients).

Cryoglobulinemia can occur with minimal or no symptoms, and its long-term consequences are unknown. Abrahamian et al[167] tested a cohort of HCV-positive and HCV-negative liver transplant patients for cryoglobulins by using a rigorous and reliable technique. Six of 31 HCV-positive patients (19%), but no HCV-negative patients, had cryoglobulins. Among 6 patients with cryoglobulinemia, 3 patients had clinically apparent disease and 1 patient developed progressive renal insufficiency. Another HCV-positive patient without detectable cryoglobulins developed glomerulonephritis and progressed to ESRD.

The potential adverse long-term consequences of cryoglobulinemia in liver transplant patients have led to attempts at therapies using single agents or combinations of interferon alfa, plasmapheresis, cyclophosphamide, and ribavirin, with mixed clinical responses.[59,167,169-171] Reduction in proteinuria and stabilization of renal function have been reported in a few patients, such as those treated with ribavirin as a single agent, but others have developed progressive disease despite therapy.[59,167,169-171] In as much as interferon alfa has not been associated with an increased risk for allograft rejection in liver transplant recipients, a 24- to 48-week course or even maintenance therapy with interferon may be appropriate for transplant recipients with HCV-associated cryoglobulinemia or glomerular disease.[59,167,169-171] Ultimately, renal transplantation may be needed in HCV-positive liver transplant patients, and preliminary results indicate that patient and graft survival in this situation are reasonably good (graft survival rates, 88% at 1 year and 61% at 3 years).[174]

Thus, cryoglobulinemia and MPGN appear to be uncommon, but potentially severe, complications of liver transplantation for chronic hepatitis C. Although published reports indicate that HCV-positive liver recipients with glomerulonephritis are at greater risk for developing ESRD, prospective studies are needed to more accurately define the risk for cryoglobulinemia and MPGN in this patient population.

THERAPY FOR HEPATITIS C AFTER RENAL TRANSPLANTATION

Dr Lionel Rostaing, University Hospital, Toulouse, France

Increasing success rates of therapy for hepatitis C in patients with renal disease and the

knowledge that long-term survival after renal transplantation is compromised have led to attempts to treat hepatitis C after renal transplantation. Initial studies of antiviral therapy in renal transplant recipients administered interferon alfa monotherapy in doses of 1.5 to 6 MU 3 times weekly for 24 or 48 weeks.[175-180] Approximately half the patients had improvements in ALT levels during therapy, and up to 25% had loss of HCV RNA, but only rare patients had a sustained response to treatment. More worrisome was that acute cellular rejection appeared to be increased among interferon-treated patients, and in many series, instances of renal failure and graft loss (despite aggressive immunosuppressive therapy) were common. These reports led to recommendation that patients with renal transplants not be administered interferon alfa.[175-180]

An exception to the proscription against interferon therapy in renal transplant recipients is the occurrence of fibrosing cholestatic hepatitis, a rare but severe form of chronic hepatitis C that occurs most commonly in the setting of severe immunosuppression after solid-organ transplantation. This severe and progressive form of liver dysfunction was originally described in liver transplant recipients with recurrent hepatitis B, but also was reported with HCV infection after liver and renal transplantation.[134,135] A dramatic report of interferon use in 2 renal transplant recipients with fibrosing cholestatic hepatitis suggested that this life-threatening form of HCV-related liver disease can be treated effectively with interferon alfa, and risk for severe rejection in this situation is counterbalanced by risks of the untreated liver disease.[136]

Early studies of ribavirin indicated that monotherapy with this oral nucleoside analogue was associated with improvements in ALT levels and liver histological characteristics in 30% to 50% of patients, although ribavirin has little or no effect on HCV RNA levels.[181,182] In a small open-label study of ribavirin monotherapy (400 to 800 mg/d), 4 of 7 renal transplant recipients with chronic hepatitis C had improvements in ALT levels and slight decreases in HCV RNA levels.[183] In an ongoing study of ribavirin monotherapy in patients with hepatitis C after renal transplantation, improvements were found in ALT levels, but not liver histological characteristics; there also were mild improvements in proteinuria. Dose-dependent hemolysis caused by ribavirin can be severe in patients after solid-organ transplantation.

In several small studies, the oral antiviral agent amantadine was reported to lead to improvements in ALT levels in patients with hepatitis C. Early results of amantadine use in renal transplant recipients suggest it is well tolerated and has some effect on serum ALT levels, but not HCV RNA levels.

Thus, there are no clearly effective therapies for hepatitis C that can be used safely in renal transplant recipients. In view of this limitation, there has been increased focus on the identification of and therapy for hepatitis C in patients with ESRD who are eligible for transplantation. This conundrum makes it even more essential to gather accurate information on the natural history of hepatitis C in patients with renal disease.

SUMMARY RECOMMENDATIONS FOR FUTURE RESEARCH

Hepatitis C is both a cause and complication of chronic renal disease. Chronic infection with HCV is a well-established, but uncommon, cause of glomerulonephritis, occurring largely in the context of cryoglobulinemia. Perhaps more importantly, hepatitis C frequently complicates the course of renal disease and becomes a significant cause of morbidity and mortality, particularly after transplantation. Although there have been major advances in the understanding, management, and therapy for hepatitis C, these advances have not been readily applicable to patients with renal disease. Important needs and challenges remain for future research in hepatitis C and kidney disease. These needs fall into 4 major categories: (1) the pathogenesis, natural history, and optimal management of HCV-related renal disease; (2) epidemiological characteristics and prevention of the spread of hepatitis C in dialysis units; (3) natural history and therapy for hepatitis C in patients with ESRD; and (4) natural history and therapy for hepatitis C after renal transplantation.

Pathogenesis, Natural History, and Management of HCV-Related Renal Disease

The cause of cryoglobulinemia and the pathogenesis and risk factors for the development of glomerulonephritis in patients with chronic hepa-

titis C are not established. Furthermore, tests for cryoglobulinemia and their components have not been standardized and are not always reliable. Better understanding of B-cell abnormalities that accompany chronic hepatitis C and factors that lead to the expansion of clones of cells producing monoclonal RF are needed. In addition, little is known of the natural history of cryoglobulinemia, both before and after the appearance of vasculitic symptoms. Studies also are needed regarding the nature of cryoglobulinemic renal disease and why some cryoglobulins are associated with kidney damage, whereas others are not. The issue of whether noncryoglobulinemic-associated glomerulonephritis can be caused by HCV needs to be resolved. Finally, results of therapy for HCV-related cryoglobulinemia need to be published, and sufficiently large cohorts need to be developed for prospective studies of optimal treatment. Therapy for severe cases of cryoglobulinemia not responsive to interferon therapy are needed, such as the use of monoclonal antibodies to tumor necrosis factor-α or B cells. Many of these goals might be helped by the development of a multicenter cryoglobulinemia working group to collect cases, establish diagnostic criteria, evaluate and follow up patients in a standardized fashion, develop and apply reliable laboratory assays for cryoglobulins and immune complexes, provide resources of immunologic and virological laboratory investigation, and enter patients into prospective clinical trials.

Epidemiological Characteristics of Hepatitis C in Dialysis Units

Better information is needed about the current incidence, prevalence, and risk factors for HCV infection in dialysis patients. It is not clear what proportion of patients with renal disease have acquired HCV infection as a result of the usual risk factors (injection drug use, unsafe sexual practices) as opposed to the management of their renal disease (from blood transfusions, unsafe injection practices, and contaminated equipment used for hemodialysis). The CDC recommendations for screening and infection control practices to prevent and monitor HCV transmission should be widely adopted, including mounting a practical and efficient educational effort to train dialysis personnel in hemodialysis precautions. Algorithms for the diagnosis and management of hepatitis C should be developed by academic societies. Routine screening and monitoring for hepatitis C also would allow for better definition of the natural history of hepatitis C in patients with ESRD.

Natural History and Therapy of Patients With Hepatitis C and ESRD

The rate of progression of fibrosis in hepatitis C in patients with ESRD needs to be more carefully defined, as well as risk factors that predict progression (whether they are the same as in patients without renal disease). The reliability of serum markers in predicting severe hepatic disease and the role of liver biopsy need to be established in patients with kidney disease. Knowledge of the natural history of hepatitis C in dialysis patients is crucial in developing indications for therapy and recommendations regarding transplantation. Although therapy for hepatitis C has advanced considerably in the last 10 years, the applicability of the current regimens for patients with ESRD remains unclear. Prospective, randomized, controlled trials are needed to evaluate the risks and benefits of therapy and identify the optimal regimen for different categories of patients (based on genotype and other predictive factors). Of great need is a simple algorithm to evaluate whether therapy is ineffective early during the course of treatment. Early stopping rules for patients who have little or no likelihood of responding to therapy would be doubly helpful in patients with ESRD. Furthermore, better means of managing side effects in this challenging group are needed. Several industry-sponsored studies of peginterferon with and without ribavirin are currently underway in the United States. Results of these studies are likely to provide a basis for recommendations regarding therapy, which presently cannot be made with any certainty. Studies of therapy also should include long-term follow-up of responders to show whether virological responses are durable and persist even after transplantation.

Natural History, Management, and Therapy for Hepatitis C After Renal Transplantation

Implications of HCV infection for the prognosis of patients undergoing renal transplantation are not well defined. Patient and graft survival appear to be good, at least for the initial 10 years.

Prospective natural history studies are needed to define risk factors for poor outcomes, including serum biochemical and virological markers, histological features, and other factors. Important are the differing effects of various immunosuppressive regimens, the role of liver biopsy, and the reliability of routine serum tests in determining and monitoring the progression of hepatitis C.

Use of kidneys from anti-HCV–positive donors in renal transplantation is controversial. Use of anti-HCV–positive donor kidneys in anti-HCV–negative recipients should be avoided, but their use in patients with ESRD with preexisting HCV RNA may be appropriate. The safety of this strategy needs to be evaluated prospectively before a definitive recommendation on the use of anti-HCV–positive organs can be made.

Therapy for hepatitis C after renal transplantation currently is problematic. Therapy with interferon appears to increase the risk for allograft rejection and graft loss. Ultimately, better tolerated and more effective antiviral agents are needed before treatment trials can start again for hepatitis C after renal transplantation.

REFERENCES

1. Major ME, Rehermann B, Feinstone SM: Hepatitis C viruses, in Howley PM, Knipe D (eds): Field's Virology (ed 4). Philadelphia, PA, Lippincott, Williams & Wilkins, 2001, pp 1127-1161

2. Lohmann V, Korner F, Koch J, Herian U, Theilmann L, Bartenschlager R: Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. Science 285:110-113, 1999

3. Blight KJ, Kolykhalov AA, Rice CM: Efficient initiation of HCV RNA replication in cell culture. Science 290: 1972-1974, 2000

4. Major ME, Mihalik K, Fernandez J, et al: Long-term follow-up of chimpanzees inoculated with the first infectious clone for hepatitis C virus. J Virol 73:3317-3325, 1999

5. Choo QL, Kuo G, Ralston R, et al: Vaccination of chimpanzees against infection by the hepatitis C virus. Proc Natl Acad Sci U S A 91:1294-1298, 1994

6. Seeff LB: Natural history of chronic hepatitis C. Hepatology 36:S35-S46, 2002 (suppl 1)

7. Alter MJ, Kruszon-Moran D, Nainan OV, et al: The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. N Engl J Med 341:556-562, 1999

8. Seeff LB, Hollinger FB, Alter HJ, et al: Long-term mortality and morbidity of transfusion-associated non-A, non-B, and type C hepatitis: A National Heart, Lung, and Blood Institute collaborative study. Hepatology 33:455-463, 2001

9. Vogt M, Lang T, Frosner G, et al: Prevalence and clinical outcome of hepatitis C infection in children who underwent cardiac surgery before the implementation of blood-donor screening. N Engl J Med 341:866-870, 1999

10. Kenny-Walsh E: Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. Irish Hepatology Research Group. N Engl J Med 340:1228-1233, 1999

11. Wiese M, Berr F, Lafrenz M, Porst H, Oesen U: Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in Germany: A 20-year multicenter study. Hepatology 32:91-96, 2000

12. Thomas DL, Astemborski J, Rai RM, et al: The natural history of hepatitis C virus infection: Host, viral, and environmental factors. JAMA 284:450-456, 2000

13. 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 14:969-974, 1991

14. Tong MJ, el-Farra NS, Reikes AR, Co RL: Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 332:1463-1466, 1995

15. Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J: Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J Hepatol 34:730-739, 2001

16. Seeff LB, Miller RN, Rabkin CS, et al: 45-Year follow-up of hepatitis C virus infection in healthy young adults. Ann Intern Med 132:105-111, 2000

17. National Institutes of Health Consensus Development Conference Panel Statement: Management of hepatitis C. Hepatology 26:S2-S10, 1997 (suppl 1)

18. Marcellin P, Boyer N, Gervais A, et al: Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Intern Med 127: 875-881, 1997

19. Lau DT, Kleiner DE, Ghany MG, Park Y, Schmid P, Hoofnagle JH: 10-Year follow-up after interferon-alpha therapy for chronic hepatitis C. Hepatology 28:1121-1127, 1998

20. McHutchison JG, Gordon SC, Schiff ER, et al: Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. N Engl J Med 339:1485-1492, 1998

21. Poynard T, Marcellin P, Lee SS, et al: Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 352:1426-1432, 1998

22. Glue P, Fang JW, Rouzier-Panis R, et al: Pegylated interferon-alpha2b: Pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Hepatitis C Intervention Therapy Group. Clin Pharmacol Ther 68:556-567, 2000

23. Zeuzem S, Feinman SV, Rasenack J, et al: Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med 343:1666-1672, 2000

24. Heathcote EJ, Shiffman ML, Cooksley WG, et al: Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 343:1673-1680, 2000

25. Lindsay KL, Trepo C, Heintges T, et al: A randomized, double-blind trial comparing pegylated interferon

alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology 34:395-403, 2001

26. Manns MP, McHutchison JG, Gordon SC, et al: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomised trial. Lancet 358:958-965, 2001

27. Fried MW, Shiffman ML, Reddy KR, et al: Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 347:975-982, 2002

28. Hadziyannis SJ, Cheinquer H, Morgan TR, et al: Peginterferon alfa-2a (40kD) (PEGASYS) in combination with ribavirin (RBV): Efficacy and safety results from a phase III, randomized, double-blind, multicenter study examining effect of duration of treatment and RBV dose. J Hepatol 36:S3A, 2002 (suppl 1; abstr)

29. El-Serag HB, Hampel H, Yeh C, Rabeneck L: Extrahepatic manifestations of hepatitis C among United States male veterans. Hepatology 36:1439-1445, 2002

30. Agnello V: Mixed cryoglobulinemia and other extrahepatic manifestations of HCV infection, in Liang TJ, Hoofnagle JH (eds): Hepatitis C. San Diego, CA, Academic, 2000, pp 295-313

31. Agnello V, Chung RT, Kaplan LM: A role for hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med 327:1490-1495, 1992

32. De Vita S, De Re V, Gasparotto D, et al: Oligoclonal non-neoplastic B cell expansion is the key feature of type II mixed cryoglobulinemia: Clinical and molecular findings do not support a bone marrow pathologic diagnosis of indolent B cell lymphoma. Arthritis Rheum 43:94-102, 2000

33. Pawlotsky JM, Ben Yahia M, Andre C, et al: Immunological disorders in C virus chronic active hepatitis: A prospective case-control study. Hepatology 19:841-848, 1994

34. Johnson RJ, Gretch DR, Yamabe H, et al: Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med 328:465-470, 1993

35. Hermine O, Lefrere F, Bronowicki JP, et al: Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. N Engl J Med 347:89-94, 2002

36. Silvestri F, Pipan C, Barillari G, et al: Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders. Blood 87:4296-4301, 1996

37. D'Amico G: Renal involvement in hepatitis C infection: Cryoglobulinemic glomerulonephritis. Kidney Int 54: 650-671, 1998

38. Tarantino A, Campise M, Banfi G, et al: Long-term predictors of survival in essential mixed cryoglobulinemic glomerulonephritis. Kidney Int 47:618-623, 1995

39. Fabrizi F, Martin P, Ponticelli C: Hepatitis C virus infection and renal transplantation. Am J Kidney Dis 38:919-934, 2001

40. Pouteil-Noble C, Maiza H, Dijoud F, MacGregor B: Glomerular disease associated with hepatitis C virus infection in native kidneys. Nephrol Dial Transplant 15:S28-S33, 2000 (suppl 8)

41. Fabrizi F, Pozzi C, Farina M, et al: Hepatitis C virus infection and acute or chronic glomerulonephritis: An epidemiological and clinical appraisal. Nephrol Dial Transplant 13:1991-1997, 1998

42. Stehman-Breen C, Alpers CE, Couser WG, Willson R, Johnson RJ: Hepatitis C virus associated membranous glomerulonephritis. Clin Nephrol 44:141-147, 1995

43. Markowitz GS, Cheng JT, Colvin RB, Trebbin WM, D'Agati VD: Hepatitis C viral infection is associated with fibrillary glomerulonephritis and immunotactoid glomerulopathy. J Am Soc Nephrol 9:2244-2252, 1998

44. Baid S, Cosimi AB, Tolkoff-Rubin N, Colvin RB, Williams WW, Pascual M: Renal disease associated with hepatitis C infection after kidney and liver transplantation. Transplantation 70:255-261, 2000

45. Agnello V: Mixed cryoglobulinaemia after hepatitis C virus: More and less ambiguity. Ann Rheum Dis 57:701-702, 1998

46. Cosio FG, Roche Z, Agarwal A, Falkenhain ME, Sedmak DD, Ferguson RM: Prevalence of hepatitis C in patients with idiopathic glomerulopathies in native and transplant kidneys. Am J Kidney Dis 28:752-758, 1996

47. Pickering MC, Cook HT, Warren J, et al: Uncontrolled C3 activation causes membranoproliferative glomerulonephritis in mice deficient in complement factor H. Nat Genet 31:424-428, 2002

48. Taneda S, Segerer S, Hudkins KL, et al: Cryoglobulinemic glomerulonephritis in thymic stromal lymphopoietin transgenic mice. Am J Pathol 159:2355-2369, 2001

49. Ferri C, Marzo E, Longombardo G, et al: Interferon-alpha in mixed cryoglobulinemia patients: A randomized, crossover-controlled trial. Blood 81:1132-1136, 1993

50. Misiani R, Bellavita P, Fenili D, et al: Interferon alfa-2a therapy in cryoglobulinemia associated with hepatitis C virus. N Engl J Med 330:751-756, 1994

51. Morales JM, Pascual-Capdevila J, Campistol JM, et al: Membranous glomerulonephritis associated with hepatitis C virus infection in renal transplant patients. Transplantation 63:1634-1639, 1997

52. Polzien F, Schott P, Mihm S, Ramadori G, Hartmann H: Interferon-alpha treatment of hepatitis C virus-associated mixed cryoglobulinemia. J Hepatol 27:63-71, 1997

53. Cresta P, Musset L, Cacoub P, et al: Response to interferon alpha treatment and disappearance of cryoglobulinaemia in patients infected by hepatitis C virus. Gut 45:122-128, 1999

54. Dammacco F, Sansonno D, Han JH, et al: Natural interferon-alpha versus its combination with 6-methylprednisolone in the therapy of type II mixed cryoglobulinemia: A long-term, randomized, controlled study. Blood 84: 3336-3343, 1994

55. Casato M, Agnello V, Pucillo LP, et al: Predictors of long-term response to high-dose interferon therapy in type II cryoglobulinemia associated with hepatitis C virus infection. Blood 90:3865-3873, 1997

56. Zuckerman E, Keren D, Slobodin G, et al: Treatment of refractory, symptomatic, hepatitis C virus related mixed cryoglobulinemia with ribavirin and interferon-alpha. J Rheumatol 27:2172-2178, 2000

57. Calleja JL, Albillos A, Moreno-Otero R, et al: Sustained response to interferon-alpha or to interferon-alpha plus ribavirin in hepatitis C virus-associated symptomatic mixed cryoglobulinaemia. Aliment Pharmacol Ther 13:1179-1186, 1999

58. Gordon AC, Edgar JD, Finch RG: Acute exacerbation

of vasculitis during interferon-alpha therapy for hepatitis C-associated cryoglobulinaemia. J Infect 36:229-230, 1998

59. Pham HP, Feray C, Samuel D, et al: Effects of ribavirin on hepatitis C-associated nephrotic syndrome in four liver transplant recipients. Kidney Int 54:1311-1319, 1998

60. Moses PL, Krawitt EL, Aziz W, Corwin HL: Renal failure associated with hepatitis C virus infection. Improvement in renal function after treatment with interferon-alpha. Dig Dis Sci 42:443-446, 1997

61. Matsumoto S, Nakajima S, Nakamura K, et al: Interferon treatment on glomerulonephritis associated with hepatitis C virus. Pediatr Nephrol 15:271-273, 2000

62. Mazzaro C, Panarello G, Carniello S, et al: Interferon versus steroids in patients with hepatitis C virus-associated cryoglobulinaemic glomerulonephritis. Dig Liver Dis 32:708-715, 2000

63. Johnson RJ, Willson R, Yamabe H, et al: Renal manifestations of hepatitis C virus infection. Kidney Int 46:1255-1263, 1994

64. Sarac E, Bastacky S, Johnson JP: Response to high-dose interferon-alpha after failure of standard therapy in MPGN associated with hepatitis C virus infection. Am J Kidney Dis 30:113-115, 1997

65. Laganovic M, Jelakovic B, Kuzmanic D, et al: Complete remission of cryoglobulinemic glomerulonephritis (HCV-positive) after high dose interferon therapy. Wien Klin Wochenschr 112:596-600, 2000

66. Yamabe H, Johnson RJ, Gretch DR, et al: Membranoproliferative glomerulonephritis associated with hepatitis C virus infection responsive to interferon-alpha. Am J Kidney Dis 25:67-69, 1995

67. Garini G, Allegri L, Carnevali L, Catellani W, Manganelli P, Buzio C: Interferon-alpha in combination with ribavirin as initial treatment for hepatitis C virus-associated cryoglobulinemic membranoproliferative glomerulonephritis. Am J Kidney Dis 38:E35, 2001

68. Sabry AA, Sobh MA, Sheaashaa HA, et al: Effect of combination therapy (ribavirin and interferon) in HCV-related glomerulopathy. Nephrol Dial Transplant 17:1924-1930, 2002

69. Ohta S, Yokoyama H, Wada T, et al: Exacerbation of glomerulonephritis in subjects with chronic hepatitis C virus infection after interferon therapy. Am J Kidney Dis 33:1040-1048, 1999

70. Suzuki T, Yonemura K, Miyaji T, et al: Progressive renal failure and blindness due to retinal hemorrhage after interferon therapy for hepatitis C virus-associated membranoproliferative glomerulonephritis. Intern Med 40:708-712, 2001

71. Roithinger FX, Allinger S, Kirchgatterer A, et al: A lethal course of chronic hepatitis C, glomerulonephritis, and pulmonary vasculitis unresponsive to interferon treatment. Am J Gastroenterol 90:1006-1008, 1995

72. D'Amico G, Fornasieri A: Cryoglobulinemia, in Brady HR, Wilcox CS (eds): Therapy in Nephrology and Hypertension (ed 2). Philadelphia, PA, Saunders, 2003, pp 147-151

73. Sansonno D, De Re V, Lauletta G, Tucci FA, Boiocchi M, Dammacco F: Treatment of mixed cryoglobulinemia resistant to interferon-alpha with an anti-CD 20 monoclonal antibody. Blood 101:3818-3826, 2003

74. Niu MT, Coleman PJ, Alter MJ: Multicenter study of hepatitis C virus infection in chronic hemodialysis patients and hemodialysis center staff members. Am J Kidney Dis 22:568-573, 1993

75. Fabrizi F, Martin P, Dixit V, et al: Quantitative assessment of HCV load in chronic hemodialysis patients: A cross-sectional survey. Nephron 80:428-433, 1998

76. Centers for Disease Control and Prevention: Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Recomm Rep 47:1-39, 1998

77. Centers for Disease Control and Prevention: Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep 50:1-43, 2001

78. Geerlings W, Tufveson G, Ehrich JH, et al: Report on management of renal failure in Europe, XXIII. Nephrol Dial Transplant 9:S6-S25, 1994 (suppl 1)

79. Tokars JI, Alter MJ, Miller E, Moyer LA, Favero MS: National surveillance of dialysis associated diseases in the United States—1994. ASAIO J 43:108-119, 1997

80. dos Santos JP, Loureiro A, Cendoroglo Neto M, Pereira BJ: Impact of dialysis room and reuse strategies on the incidence of hepatitis C virus infection in haemodialysis units. Nephrol Dial Transplant 11:2017-2022, 1996

81. Cendoroglo Neto M, Draibe SA, Silva AE, et al: Incidence of and risk factors for hepatitis B virus and hepatitis C virus infection among haemodialysis and CAPD patients: Evidence for environmental transmission. Nephrol Dial Transplant 10:240-246, 1995

82. Lin DY, Lin HH, Huang CC, Liaw YF: High incidence of hepatitis C virus infection in hemodialysis patients in Taiwan. Am J Kidney Dis 21:288-291, 1993

83. Pereira BJ, Levey AS: Hepatitis C virus infection in dialysis and renal transplantation. Kidney Int 51:981-999, 1997

84. Tokars JI, Miller ER, Alter MJ, Arduino MJ: National surveillance of dialysis-associated diseases in the United States, 1997. Semin Dial 13:75-85, 2000

85. US Renal Data System: USRDS 2002 Annual Data Report. The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2002, p 564

86. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ: The risk of transfusion-transmitted viral infections: The Retrovirus Epidemiology Donor Study. N Engl J Med 334: 1685-1690, 1996

87. Nakayama E, Akiba T, Marumo F, Sato C: Prognosis of anti-hepatitis C virus antibody-positive patients on regular hemodialysis therapy. J Am Soc Nephrol 11:1896-1902, 2000

88. Pereira BJ, Natov SN, Bouthot BA, et al: Effects of hepatitis C infection and renal transplantation on survival in end-stage renal disease. The New England Organ Bank Hepatitis C Study Group. Kidney Int 53:1374-1381, 1998

89. Bruguera M, Sanchez Tapias JM: Epidemiology of hepatitis C virus infection. Nephrol Dial Transplant 15:S12-S14, 2000 (suppl 8)

90. Barril G: Hepatitis C virus-induced liver disease in dialysis patients. Nephrol Dial Transplant 15:S42-S45, 2000 (suppl 8)

91. Gilli P, Soffritti S, De Paoli Vitali E, Bedani PL: Prevention of hepatitis C virus in dialysis units. Nephron 70:301-306, 1995

92. Pascual J, Teruel JL, Liano F, Ortuno J: Home hemodialysis protects against hepatitis C virus transmission. Nephron 64:314, 1993

93. Furusyo N, Hayashi J, Kanamoto-Tanaka Y, et al: Liver damage in hemodialysis patients with hepatitis C virus viremia: A prospective 10-year study. Dig Dis Sci 45:2221-2228, 2000

94. Hinrichsen H, Leimenstoll G, Stegen G, Schrader H, Folsch UR, Schmidt WE: Prevalence and risk factors of hepatitis C virus infection in haemodialysis patients: A multicentre study in 2796 patients. Gut 51:429-433, 2002

95. Wolfe RA, Ashby VB, Milford EL, et al: Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 341:1725-1730, 1999

96. Caramelo C, Ortiz A, Aguilera B, et al: Liver disease patterns in hemodialysis patients with antibodies to hepatitis C virus. Am J Kidney Dis 22:822-828, 1993

97. Pol S, Romeo R, Zins B, et al: Hepatitis C virus RNA in anti-HCV positive hemodialyzed patients: Significance and therapeutic implications. Kidney Int 44:1097-1100, 1993

98. Sterling RK, Sanyal AJ, Luketic VA, et al: Chronic hepatitis C infection in patients with end stage renal disease: Characterization of liver histology and viral load in patients awaiting renal transplantation. Am J Gastroenterol 94:3576-3582, 1999

99. Glicklich D, Thung SN, Kapoian T, Tellis V, Reinus JF: Comparison of clinical features and liver histology in hepatitis C-positive dialysis patients and renal transplant recipients. Am J Gastroenterol 94:159-163, 1999

100. Martin P, Carter D, Fabrizi F, et al: Histopathological features of hepatitis C in renal transplant candidates. Transplantation 69:1479-1484, 2000

101. Cotler SJ, Diaz G, Gundlapalli S, et al: Characteristics of hepatitis C in renal transplant candidates. J Clin Gastroenterol 35:191-195, 2002

102. Roth D, Cirocco R, Reddy R, et al: Ten year prospective study of hepatitis C virus infection in kidney transplant recipients. Am J Transplant 2:260A, 2002 (abstr)

103. Stehman-Breen CO, Emerson S, Gretch D, Johnson RJ: Risk of death among chronic dialysis patients infected with hepatitis C virus. Am J Kidney Dis 32:629-634, 1998

104. Koenig P, Vogel W, Umlauft F, et al: Interferon treatment for chronic hepatitis C virus infection in uremic patients. Kidney Int 45:1507-1509, 1994

105. Okuda K, Hayashi H, Yokozeki K, Kondo T, Kashima T, Irie Y: Interferon treatment for chronic hepatitis C in haemodialysis patients: Suggestions based on a small series. J Gastroenterol Hepatol 10:616-620, 1995

106. Pol S, Thiers V, Carnot F, et al: Efficacy and tolerance of alpha-2b interferon therapy on HCV infection of hemodialyzed patients. Kidney Int 47:1412-1418, 1995

107. Raptopoulou-Gigi M, Spaia S, Garifallos A, et al: Interferon-alpha 2b treatment of chronic hepatitis C in haemodialysis patients. Nephrol Dial Transplant 10:1834-1837, 1995

108. Chan TM, Wu PC, Lau JY, Lok AS, Lai CL, Cheng IK: Interferon treatment for hepatitis C virus infection in patients on haemodialysis. Nephrol Dial Transplant 12:1414-1419, 1997

109. Fernandez JL, Rendo P, del Pino N, Viola L: A double-blind controlled trial of recombinant interferon-alpha 2b in haemodialysis patients with chronic hepatitis C virus infection and abnormal aminotransferase levels. Nephrologists' Group for the Study of HCV Infection. J Viral Hepat 4:113-119, 1997

110. Izopet J, Rostaing L, Moussion F, et al: High rate of hepatitis C virus clearance in hemodialysis patients after interferon-alpha therapy. J Infect Dis 176:1614-1617, 1997

111. Rodrigues A, Morgado T, Areias J, et al: Limited benefits of INF-alpha therapy in renal graft candidates with chronic viral hepatitis B or C. Transplant Proc 29:777-780, 1997

112. Benci A, Caremani M, Menchetti D, Sasdelli M, Giusti PB: Low-dose leukocyte interferon-alpha therapy in dialysed patients with chronic hepatitis C. Curr Med Res Opin 14:141-144, 1998

113. Uchihara M, Izumi N, Sakai Y, et al: Interferon therapy for chronic hepatitis C in hemodialysis patients: Increased serum levels of interferon. Nephron 80:51-56, 1998

114. Campistol JM, Esforzado N, Martinez J, et al: Efficacy and tolerance of interferon-alpha(2b) in the treatment of chronic hepatitis C virus infection in haemodialysis patients. Pre- and post-renal transplantation assessment. Nephrol Dial Transplant 14:2704-2709, 1999

115. Huraib S, Tanimu D, Romeh SA, et al: Interferon-alpha in chronic hepatitis C infection in dialysis patients. Am J Kidney Dis 34:55-60, 1999

116. Tokumoto T, Tanabe K, Ishikawa N, et al: Effect of interferon-alpha treatment in hemodialysis patients and renal transplant recipients with chronic hepatitis C. Transplant Proc 31:2887-2889, 1999

117. Casanovas-Taltavull T, Baliellas C, Benasco C, et al: Efficacy of interferon for chronic hepatitis C virus-related hepatitis in kidney transplant candidates on hemodialysis: Results after transplantation. Am J Gastroenterol 96:1170-1177, 2001

118. Espinosa M, Rodriguez M, Martin-Malo A, et al: Interferon therapy in hemodialysis patients with chronic hepatitis C virus infection induces a high rate of long-term sustained virological and biochemical response. Clin Nephrol 55:220-226, 2001

119. Degos F, Pol S, Chaix ML, et al: The tolerance and efficacy of interferon-alpha in haemodialysis patients with HCV infection: A multicentre, prospective study. Nephrol Dial Transplant 16:1017-1023, 2001

120. Hanrotel C, Toupance O, Lavaud S, et al: Virological and histological responses to one year alpha-interferon-2a in hemodialyzed patients with chronic hepatitis C. Nephron 88:120-126, 2001

121. Fabrizi F, Poordad FF, Martin P: Hepatitis C infection and the patient with end-stage renal disease. Hepatology 36:3-10, 2002

122. Wills RJ: Clinical pharmacokinetics of interferons. Clin Pharmacokinet 19:390-399, 1990

123. Bino T, Madar Z, Gertler A, Rosenberg H: The kidney is the main site of interferon degradation. J Interferon Cytokine Res 2:301-308, 1982

124. Hirsch MS, Tolkoff-Rubin NE, Kelly AP, Rubin RH: Pharmacokinetics of human and recombinant leukocyte interferon in patients with chronic renal failure who are undergoing hemodialysis. J Infect Dis 148:335, 1983

125. Rostaing L, Chatelut E, Payen JL, et al: Pharmacokinetics of alphaIFN-2b in chronic hepatitis C virus patients undergoing chronic hemodialysis or with normal renal function: clinical implications. J Am Soc Nephrol 9:2344-2348, 1998

126. Martin P, Mitra S, Farrington K, Martin NE, Modi MW: Pegylated 40 kDa interferon alfa-2a Pegasys is unaffected by renal impairment. Hepatology 32:370A, 2000 (abstr)

127. Modi MW, Fulton JS, Buckman DK, Wright TL, Moore DJ: Clearance of pegylated (40kDa) interferon alfa-2a Pegasys is primarily hepatic. Hepatology 32:371A, 2000 (abstr)

128. Lamb M, Marks IM, Wynohradnyk L, Modi MW, Preston RA, Pappas SC: Peginterferon alfa-2a 40 kDa Pegasys can be administered safely in patients with end-stage renal disease. Hepatology 34:326A, 2001 (abstr)

129. Bruchfeld A, Stahle L, Andersson J, Schvarcz R: Ribavirin treatment in dialysis patients with chronic hepatitis C virus infection—A pilot study. J Viral Hepatitis 8:287-292, 2001

130. Tan AC, Brouwer JT, Glue P, et al: Safety of interferon and ribavirin therapy in haemodialysis patients with chronic hepatitis C: Results of a pilot study. Nephrol Dial Transplant 16:193-195, 2001

131. Mathurin P, Mouquet C, Poynard T, et al: Impact of hepatitis B and C virus on kidney transplantation outcome. Hepatology 29:257-263, 1999

132. Hanafusa T, Ichikawa Y, Yazawa K, et al: Hepatitis C virus infection in kidney transplantation and a pilot study of the effects of interferon-alpha therapy. Transplant Proc 30:122-124, 1998

133. Batty DS Jr, Swanson SJ, Kirk AD, Ko CW, Agodoa LY, Abbott KC: Hepatitis C virus seropositivity at the time of renal transplantation in the United States: Associated factors and patient survival. Am J Transplant 1:179-184, 2001

134. Gane E, Pilmore H: Management of chronic viral hepatitis before and after renal transplantation. Transplantation 74:427-437, 2002

135. Munoz De Bustillo E, Ibarrola C, Colina F, et al: Fibrosing cholestatic hepatitis in hepatitis C virus-infected renal transplant recipients. J Am Soc Nephrol 9:1109-1113, 1998

136. Toth CM, Pascual M, Chung RT, et al: Hepatitis C virus-associated fibrosing cholestatic hepatitis after renal transplantation: Response to interferon-alpha therapy. Transplantation 66:1254-1258, 1998

137. Chazouilleres O, Kim M, Combs C, et al: Quantitation of hepatitis C virus RNA in liver transplant recipients. Gastroenterology 106:994-999, 1994

138. Zylberberg H, Nalpas B, Carnot F, et al: Severe evolution of chronic hepatitis C in renal transplantation: A case control study. Nephrol Dial Transplant 17:129-133, 2002

139. Bouthot BA, Murthy BV, Schmid CH, Levey AS, Pereira BJ: Long-term follow-up of hepatitis C virus infection among organ transplant recipients: Implications for policies on organ procurement. Transplantation 63:849-853, 1997

140. Ok E, Unsal A, Celik A, et al: Clinicopathological features of rapidly progressive hepatitis C virus infection in HCV antibody negative renal transplant recipients. Nephrol Dial Transplant 13:3103-3107, 1998

141. Rostaing L, Izopet J, Cisterne JM, et al: Impact of hepatitis C virus duration and hepatitis C virus genotypes on renal transplant patients: Correlation with clinicopathological features. Transplantation 65:930-936, 1998

142. Pouteil-Noble C, Tardy JC, Chossegros P, et al: Co-infection by hepatitis B virus and hepatitis C virus in renal transplantation: Morbidity and mortality in 1098 patients. Nephrol Dial Transplant 10:S122-S124, 1995 (suppl 6)

143. Pereira BJ, Milford EL, Kirkman RL, Levey AS: Transmission of hepatitis C virus by organ transplantation. N Engl J Med 325:454-460, 1991

144. Roth D, Zucker K, Cirocco R, et al: A prospective study of hepatitis C virus infection in renal allograft recipients. Transplantation 61:886-889, 1996

145. Natov SN, Lau JY, Ruthazer R, Schmid CH, Levey AS, Pereira BJ: Hepatitis C virus genotype does not affect patient survival among renal transplant candidates. The New England Organ Bank Hepatitis C Study Group. Kidney Int 56:700-706, 1999

146. Izopet J, Rostaing L, Sandres K, et al: Longitudinal analysis of hepatitis C virus replication and liver fibrosis progression in renal transplant recipients. J Infect Dis 181: 852-858, 2000

147. Morales JM, Campistol JM, Castellano G, et al: Transplantation of kidneys from donors with hepatitis C antibody into recipients with pre-transplantation anti-HCV. Kidney Int 47:236-240, 1995

148. Rostaing L, Izopet J, Sandres K, Cisterne JM, Puel J, Durand D: Changes in hepatitis C virus RNA viremia concentrations in long-term renal transplant patients after introduction of mycophenolate mofetil. Transplantation 69: 991-994, 2000

149. Bloom RD, Rao V, Weng F, Grossman RA, Cohen D, Mange KC: Association of hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus. J Am Soc Nephrol 13:1374-1380, 2002

150. Hestin D, Guillemin F, Castin N, Le Faou A, Champigneulles J, Kessler M: Pretransplant hepatitis C virus infection: A predictor of proteinuria after renal transplantation. Transplantation 65:741-744, 1998

151. Roth D, Cirocco R, Zucker K, et al: De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. Transplantation 59: 1676-1682, 1995

152. Natov SN, Pereira BJ: Transmission of viral hepatitis by kidney transplantation: Donor evaluation and transplant policies. Transpl Infect Dis 4:124-131, 2002

153. Pereira BJ, Wright TL, Schmid CH, et al: Screening and confirmatory testing of cadaver organ donors for hepatitis C virus infection: A U.S. National Collaborative Study. Kidney Int 46:886-892, 1994

154. Zucker K, Cirocco R, Roth D, et al: Depletion of

hepatitis C virus from procured kidneys using pulsatile perfusion preservation. Transplantation 57:832-840, 1994

155. Mandal AK, Kraus ES, Samaniego M, et al: Shorter waiting times for hepatitis C virus seropositive recipients of cadaveric renal allografts from hepatitis C virus seropositive donors. Clin Transplant 14:391-396, 2000

156. Widell A, Mansson S, Persson NH, Thysell H, Hermodsson S, Blohme I: Hepatitis C superinfection in hepatitis C virus (HCV)-infected patients transplanted with an HCV-infected kidney. Transplantation 60:642-647, 1995

157. Morales JM, Campistol JM, Andres A, et al: Policies concerning the use of kidneys from donors infected with hepatitis C virus. Nephrol Dial Transplant 15:S71-S73, 2000 (suppl 8)

158. Pereira BJ, Levey AS: Hepatitis C infection in cadaver organ donors: Strategies to reduce transmission of infection and prevent organ waste. Pediatr Nephrol 9:S23-S28, 1995 (suppl 1)

159. Baid S, Pascual M, Williams WW Jr, et al: Renal thrombotic microangiopathy associated with anticardiolipin antibodies in hepatitis C-positive renal allograft recipients. J Am Soc Nephrol 10:146-153, 1999

160. Gallay BJ, Alpers CE, Davis CL, Schultz MF, Johnson RJ: Glomerulonephritis in renal allografts associated with hepatitis C infection: A possible relationship with transplant glomerulopathy in two cases. Am J Kidney Dis 26:662-667, 1995

161. Cruzado JM, Carrera M, Torras J, Grinyo JM: Hepatitis C virus infection and de novo glomerular lesions in renal allografts. Am J Transplant 1:171-178, 2001

162. Hammoud H, Haem J, Laurent B, et al: Glomerular disease during HCV infection in renal transplantation. Nephrol Dial Transplant 11:S54-S55, 1996 (suppl 4)

163. Virgilio B, Palminteri G, Maresca MC, Brunello A, Calconi G, Vianello A: Proteinuria at five years after kidney transplantation: The role of anti-HCV-positive state. Transplant Proc 33:3639-3640, 2001

164. Nampoory MR, Johny KV, Costandi JN, et al: High incidence of proteinuria in hepatitis C virus-infected renal transplant recipients is associated with poor patient and graft outcome. Transplant Proc 33:2791-2795, 2001

165. Meier-Kriesche HU, Ojo AO, Hanson JA, Kaplan B: Hepatitis C antibody status and outcomes in renal transplant recipients. Transplantation 72:241-244, 2001

166. Pirsch J, Becker BN, Becker YT, et al: HCV-related kidney disease after kidney transplantation. Am J Transplant 3:299A, 2003 (abstr)

167. Abrahamian GA, Cosimi AB, Farrell ML, Schoenfeld DA, Chung RT, Pascual M: Prevalence of hepatitis C virus-associated mixed cryoglobulinemia after liver transplantation. Liver Transpl 6:185-190, 2000

168. Burstein DM, Rodby RA: Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. J Am Soc Nephrol 4:1288-1293, 1993

169. Davis CL, Gretch DR, Perkins JD, et al: Hepatitis C: associated glomerular disease in liver transplant recipients. Liver Transpl Surg 1:166-175, 1995

170. Gournay J, Ferrell LD, Roberts JP, Ascher NL, Wright TL, Lake JR: Cryoglobulinemia presenting after liver transplantation. Gastroenterology 110:265-270, 1996

171. Kendrick EA, McVicar JP, Kowdley KV, et al: Renal disease in hepatitis C-positive liver transplant recipients. Transplantation 63:1287-1293, 1997

172. Pascual M, Thadhani R, Chung RT, et al: Nephrotic syndrome after liver transplantation in a patient with hepatitis C virus-associated glomerulonephritis. Transplantation 64:1073-1076, 1997

173. Safadi R, Shouval D, E'id A, Ilan Y, Tur-Kaspa R, Jurim O: Hepatitis-C-associated cryoglobulinemia after liver transplantation. Transplant Proc 29:2684-2686, 1997

174. Molmenti EP, Jain AB, Shapiro R, et al: Kidney transplantation for end-stage renal failure in liver transplant recipients with hepatitis C viral infection. Transplantation 71:267-271, 2001

175. Harihara Y, Kurooka Y, Yanagisawa T, Kuzuhara K, Otsubo O, Kumada H: Interferon therapy in renal allograft recipients with chronic hepatitis C. Transplant Proc 26:2075, 1994

176. Thervet E, Pol S, Legendre C, Gagnadoux MF, Cavalcanti R, Kreis H: Low-dose recombinant leukocyte interferon-alpha treatment of hepatitis C viral infection in renal transplant recipients: A pilot study. Transplantation 58:625-628, 1994

177. Magnone M, Holley JL, Shapiro R, et al: Interferon-alpha-induced acute renal allograft rejection. Transplantation 59:1068-1070, 1995

178. Hanafusa T, Ichikawa Y, Kyo M, et al: Long-term impact of hepatitis virus infection on kidney transplant recipients and a pilot study of the effects of interferon alpha on chronic hepatitis C. Transplant Proc 27:956-957, 1995

179. Rostaing L, Izopet J, Baron E, Duffaut M, Puel J, Durand D: Treatment of chronic hepatitis C with recombinant alpha 2b interferon in kidney transplant recipients: Preliminary results and side effects. Transplant Proc 27:948-950, 1995

180. Tokumoto T, Tanabe K, Ishikawa N, et al: Effect of interferon-alfa treatment in renal transplant recipients with chronic hepatitis C. Transplant Proc 30:3270-3272, 1998

181. Cattral MS, Hemming AW, Wanless IR, et al: Outcome of long-term ribavirin therapy for recurrent hepatitis C after liver transplantation. Transplantation 67:1277-1280, 1999

182. Gane EJ, Tibbs CJ, Ramage JK, Portmann BC, Williams R: Ribavirin therapy for hepatitis C infection following liver transplantation. Transpl Int 8:61-64, 1995

183. Garnier JL, Chevallier P, Dubernard JM, Trepo C, Touraine JL, Chossegros P: Treatment of hepatitis C virus infection with ribavirin in kidney transplant patients. Transplant Proc 29:783, 1997