Study Of Long Term Outcome Of Interferon Therapy In Hepatitis C Virus Positive Hemodialysis Patients After Renal Transplantation

Essay

Submitted for partial fulfillment of master degree in internal medicine

by

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<tr>
<td>AASLD</td>
<td>American Association for the Study of Liver Diseases</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>Anti-LKM</td>
<td>liver/kidney Microsomes</td>
</tr>
<tr>
<td>bDNA</td>
<td>Branched DNA</td>
</tr>
<tr>
<td>CAPD</td>
<td>Continuous Ambulatory Peritoneal Dialysis</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>CPT</td>
<td>Child-Pugh-Turcotte</td>
</tr>
<tr>
<td>CRF</td>
<td>Chronic Renal Failure</td>
</tr>
<tr>
<td>EIA-2</td>
<td>Enzyme Immunoassay</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked Immunosorbent Assay</td>
</tr>
<tr>
<td>ESRD</td>
<td>End-Stage Renal Disease</td>
</tr>
<tr>
<td>ETR</td>
<td>End of treatment response</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>Granulocyte-Macrophage Colony-Stimulating Factor</td>
</tr>
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</table>
GN  Glomerulonephritis
HAI  Histologic Activity Index
HBV  Hepatitis B Virus
HCC  Hepatocellular Carcinoma
HCV  Hepatitis C Virus
HD   Hemodialysis
HIV  Human Immune Deficiency Virus
HOA  Hypertrophic osteoarthropathy
HRS  Hepatorenal Syndrome
IF   Interstitial Fibrosis
IFN  Interferon
IFNa Interferon-alfa
IFN-gamma Interferon gamma
IL-10 Interleukin-10
IRES Internal Ribosome Entry Site
ITP Autoimmune Thrombocytopenic Purpura

K/DOQI Kidney Disease Outcomes Quality Initiative

KDIGO Kidney Disease Improving Global Outcomes

kDa Kilodaltons

LP Lichen Planus

MELD Model of End-Stage Liver Disease

MG Myasthenia Gravis

MN Membranous Nephropathy.

MO Month

MPGN Membranoproliferative Glomerulonephritis

NAT Nucleic acid test(ing)

NHL Non-Hodgkins Lymphoma

NODAT New-onset diabetes after transplantation

NIH National Institutes of Health

PCR Polymerase Chain Reaction
PCT  Porphyria Cutanea Tarda
PD   Peritoneal Dialysis
PEG/RBV Peg-Interferon and Ribavirin
PEG-IFN Pegylated Interferon
RBV  Ribavirin
RdRP RNA dependent RNA polymerase
RIBA Recombinant Immunoblot Assay
RRT  Renal Replacement Therapy
RT   Renal Transplantation
RTMA Renal Thrombotic Microangiopathy
SBP  Spontaneous Bacterial Peritonitis
SR   Sustained Response
TA-1 Thymosin alfa-1
TLR  Toll-like Receptors
WHO World Health Organization
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Aim Of Work
Aim of the work:

I reviewed the literature concerning the outcome of Interferon therapy in HCV positive infected hemodialysis patients after renal transplantation.
Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. The rising prevalence of treated end stage renal disease (ESRD) can be attributed primarily to the increase in the number of patients who start renal replacement therapy (RRT) each year, and to a smaller extent, increased survival of patients with ESRD.

Prevalence of CKD:

The National Kidney Foundation - Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) workgroup has defined CKD as the presence of markers of kidney damage for ≥ 3 months, as defined by structural or functional abnormalities of the kidney with or without decreased glomerular filtration rate (GFR), These markers of kidney damage include: pathological abnormalities, abnormalities in the composition of blood or urine, or abnormalities in imaging tests (K/DOQI guidelines 2002).

Classification of chronic kidney disease by stage and the estimated prevalence within the United States of each stage as (largely determined by the National Health and Nutrition Examination Survey performed in 1999 to 2004) (Coresh J et al, 2007) is as follows:
- Stage 1 disease is defined by a normal GFR (greater than 90 mL/min per 1.73 m2) and persistent albuminuria (1.8 percent of the total United States adult population).
- Stage 2 disease is a GFR between 60 to 89 mL/min per 1.73 m2 and persistent albuminuria (3.2 percent).
- Stage 3 disease is a GFR between 30 and 59 mL/min per 1.73 m2 (7.7 percent).
- Stage 4 disease is a GFR between 15 and 29 mL/min per 1.73 m2 (0.21 percent)
- Stage 5 disease is a GFR of less than 15 mL/min per 1.73 m2 or end-stage renal diseases (2.4 percent).
**Preparation and initiation of renal replacement therapy:**

It is important to identify patients who may eventually require renal replacement therapy since adequate preparation can decrease morbidity and perhaps mortality. Early identification enables dialysis to be initiated at the optimal time with a functioning chronic access and may also permit the recruitment and evaluation of family members for the placement of a renal allograft prior to the need for dialysis. Once it is determined that renal replacement therapy will eventually be required, the patient should be counseled to consider the advantages and disadvantages of hemodialysis (in-center or at home), peritoneal dialysis (continuous or intermittent modalities), and renal transplantation (living or deceased donor). The 2006 K/DOQI guidelines recommend that patients with a GFR less than 30 mL/min per 1.73 m2 should be educated concerning these issues (*K/DOQI Guidelines 2006*).

Kidney transplantation is the treatment of choice for end-stage renal disease. A successful kidney transplant improves the quality of life and reduces the mortality risk for most patients, when compared with maintenance dialysis. Referral to a transplant program should occur once renal replacement therapy is thought to be required within the next year (*Knoll G et al, 2005*).

**Hepatitis C virus and chronic kidney disease:**

Patients with chronic kidney disease (CKD) on renal replacement therapy especially hemodialysis (HD) continue to have a higher prevalence of hepatitis C virus (HCV) infection than the general population. The prevalence of anti-HCV seropositivity in patients undergoing regular dialysis in developed countries ranges between 7% and 40% (*Finelli L et al, 2005*).

A detrimental effect of HCV on survival in dialysis patients and renal transplant recipients has been confirmed (*Fabrizi F et al, 2002*).
Important insights gained in the last decade include more accurate diagnostic testing for HCV in CKD and prevention of nosocomial HCV transmission (Fabrizi F et al, 2002).

Despite these advances, the management of hepatitis C virus-infected patients with CKD is complex and there are several issues, such as the role of antiviral therapy in dialysis patients and post-renal transplant that remain unresolved. In addition, at least some patients develop CKD as an extrahepatic manifestation of HCV.
Hepatitis C Virus
Hepatitis C Virus

HCV is closely related to flaviviruses and pestiviruses. Its genetic organization and protein products classify it in the flaviviridae family, although its diversity is great enough for it to be classified as a separate genus. HCV is not related to any of the other known hepatitis viruses; however, the recently described hepatitis G virus is a distant relative (Major ME et al, 1997).

Viral Genome and Replication:

The HCV genome is a positive-sense RNA molecule of approximately 9500 nucleotides. There are highly conserved 5' and 3' untranslated regions flanking an approximately 9000 nucleotide single open reading frame which encodes a large polyprotein of about 3000 amino acids. This protein undergoes posttranslational processing by host and viral enzymes to form the structural and nonstructural proteins and enzymes of the virus (Major ME et al, 1997).

Prevalence:

According to the World Health Organization (WHO) data at 2002, about 3% of the general population is infected by HCV, thus indicating that approximately 200 to 300 million individuals may be affected. One million new cases of infection are reported annually, where HCV is believed to be more prevalent than the hepatitis B virus (HBV) infection (Cooreman MP et al, 1996).

Nearly 4 million persons are infected in the United States, while it is estimated that annually 30,000 new acute infections occur. This number is predicted to triple in the next 10 to 20 years if no effective intervention is implemented (National Institutes of Health 1997).

Hepatitis C virus is endemic in most parts of the world; however, there are significant geographic and temporal differences in the incidence and prevalence of
HCV infection. Industrialized countries in North America, Northern and Western Europe, and Australia have noted a lower prevalence. Nations with relatively low rates of HCV are Germany (0.6%), Canada (0.8%), France (1.1%), Australia (1.1%), Poland (1.9%), Japan (1.5–2.3%), and the United States (1.8%). The largest percentage of infected subjects is recorded in Northern and Central Africa (e.g., Cameroon: 32% and Central Africa: 24%), as well in the Pacific area, where the prevalence reaches 75% on certain islands (Shepard CW et al, 2005).

**Prevalence in Egypt:**

Egypt has a population of 72.5 million at 2006 and the national prevalence rate of HCV antibody positivity has been estimated to be 13% (Deuffic-Burban S et al 2006).

**Genotypes:**

Worldwide, at least 6 major genotypes of the HCV have been identified, each comprising multiple subtypes. Hepatitis C virus genotypes 1, 2, and 3 have a worldwide distribution, while their relative prevalence varies from one geographic area to another. Hepatitis C virus subtypes 1a and 2b are the most common genotypes in the United States, while also being predominant in Europe. The subtype 1b is responsible for up to 73% of HCV infection in Japan. Hepatitis C virus subtypes 2a and 2b are relatively common in North America and Europe, while 2c is found commonly in Northern Italy. Intravenous drug abusers in Europe and the United States have the HCV genotype 3a. Hepatitis C virus genotype 4 appears to be prevalent in North Africa and the Middle East and genotypes 5 and 6 in South Africa and Hong Kong (Zein NN, 2000).
Transmission:

The majority of patients infected with HCV acquired the disease through intravenous drug use or blood transfusion, the latter of which has become rare since routine testing of the blood supply for HCV was begun in 1990.

Perinatal transmission: Vertical transmission of HCV occurred in fewer than 10 percent of most unselected HIV-negative pregnant populations. The risk of vertical transmission was higher when the mother was co-infected with HIV and had a demonstrable HCV viremia during pregnancy or delivery. Transmission from non-viremic mothers with or without HIV coinfection was uncommon (Thomas SL et al, 1998).

The following HCV risk factors were identified (Murphy EL et al, 2000):

Intravenous drug use, Blood transfusion, Sex with an intravenous drug user, Having been in jail more than three days, Religious scarification, Having been struck or cut with a bloody object, Pierced ears or body parts, Immunoglobulin injection or Hemodialysis.
The Clinical Features:

ACUTE HEPATITIS C

The course of acute hepatitis is highly variable and ranges in severity from a transient, asymptomatic infection to severe or fulminant disease. The disease may be self-limited and resolve, run a relapsing course, or lead to chronic infection. In a typical, clinically apparent course of acute resolving viral hepatitis (Fig. 1), the *incubation period* varies from 15 to 120 days (mean of 50), largely on the basis of the viral etiology and exposure dose. During this phase, virus becomes detectable in blood, but serum aminotransferase and bilirubin levels are normal, and antibody is not detected (*Hoofnagle JH*, 2007).

The *preicteric phase* of illness is marked by the onset of nonspecific symptoms such as fatigue, nausea, poor appetite, and vague right upper quadrant pain. Viral-specific antibody first appears during this phase. The preicteric phase typically lasts 3 to 10 days, but this phase may last longer and even constitute the entire course of illness in patients with subclinical or anicteric forms of acute hepatitis. Viral titers are generally highest at this point, and serum aminotransferase levels start to increase. The onset of dark urine marks the *icteric phase* of illness, during which jaundice appears and symptoms of fatigue and nausea worsen. Typically, acute viral hepatitis is rarely diagnosed correctly before the onset of jaundice. If jaundice is severe, stool color lightens, and pruritus may appear. Anorexia, dysgeusia, and weight loss may also occur. Physical examination usually shows jaundice and hepatic tenderness. In more severe cases, hepatomegaly and splenomegaly may be present. Serum bilirubin levels (total and direct) rise, and aminotransferase levels are generally greater than 10 times the upper limit of normal, at least at the onset. During the icteric, symptomatic phase, levels of hepatitis virus begin to decrease in serum and liver. The duration of clinical illness is variable; it typically lasts 1 to 3 weeks. Recovery is first
manifested by return of appetite and is accompanied by resolution of the serum bilirubin and aminotransferase elevations and clearance of virus. *Convalescence* can be prolonged, however, before full energy and stamina return. Neutralizing antibodies usually appear during the icteric phase and rise to high levels during convalescence (*Hoofnagle JH*, 2007).

![Acute Viral Hepatitis](image)

**Figure 1:** Typical course of acute viral hepatitis (*Hoofnagle JH*, 2007).
CHRONIC HEPATITIS C

Symptoms:
Most patients with chronic infection are asymptomatic or have only mild nonspecific symptoms the most frequent complaint is fatigue; other less common manifestations include nausea, anorexia, myalgia, arthralgia, weakness, and weight loss (Merican I et al, 1993) The symptoms of chronic HCV infection do not reliably reflect disease activity. Abdominal pain, itching, and dark urine were the only complaints that were significantly more common among the HCV patients, although they were present in only a small number of patients (Shakil AO et al, 1995).

Complication of chronic hepatitis C:
A-Cirrhosis:
Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages at which point the only option may be liver transplantation. However, reversal of cirrhosis (in its earlier stages) has been documented in several forms of liver disease following treatment of the underlying cause. Patients with cirrhosis are susceptible to a variety of complications and their life expectancy is markedly reduced. Cirrhosis and chronic liver disease accounted for more than 25,000 deaths and 373,000 hospital discharges in the United States in 1998 according to a report from The National Center for Health Statistics (Gordon, E et al, 1998).

Clinical Manifestation:
Patients with cirrhosis may present in a variety of ways.
1- They may have stigmata of chronic liver disease discovered on routine physical examination such as:
- Spider angiomata (also referred to as spider telangiectasias) are vascular lesions consisting of a central arteriole surrounded by many smaller vessels. They are
most frequently found on the trunk, face, and upper limbs (*Pirovino M et al, 1988*).

- Palmar erythema is an exaggeration of the normal speckled mottling of the palm, and is also believed to be caused by altered sex hormone metabolism (*Erlinger et al, 1991*).

- Clubbing and hypertrophic osteoarthropathy: Clubbing is present when the angle between the nail plate and proximal nail fold is greater than 180 degrees. When severe, the distal finger has a drum stick appearance. Hypertrophic osteoarthropathy (HOA) is a chronic proliferative periostitis of the long bones that can cause considerable pain. Clubbing is more common in biliary causes of cirrhosis (particularly primary biliary cirrhosis) while hypertrophic osteoarthropathy can be seen with various causes of liver disease (*Mills PR et al, 1981*).

- Hepatomegaly: The cirrhotic liver may be enlarged, normal sized, or small. While the presence of a palpable liver may indicate liver disease, a non-palpable liver does not exclude it. When palpable, the cirrhotic liver has a firm and nodular consistency.

- Splenomegaly: it is common especially in patients with cirrhosis from nonalcoholic etiologies (*Soper NJ et al, 1982*). It is believed to be caused primarily by congestion of the red pulp as the result of portal hypertension. However, splenic size does not correlate well with portal pressures, suggesting that other factors may be contributing (*Erlinger et al, 1991*).

- Ascites: it is the accumulation of fluid in the peritoneal cavity. In one study, the absence of flank dullness was the most accurate predictor against the presence of ascites; the probability of ascites being present was less than 10 percent in such patients (*Cattau EL Jr et al, 1982*).

- Caput medusae: The veins of the lower abdominal wall normally drain inferiorly into the iliofemoral system while the veins of the upper abdominal wall drain superiorly into the veins of the thoracic wall and axilla. When portal hypertension occurs as the result of cirrhosis, Blood from the portal venous
system may be shunted through the periumbilical veins into the umbilical vein and ultimately to the abdominal wall veins, causing them to become prominent.

- Jaundice: it is a yellow coloring of the skin and mucus membranes that results from increased serum bilirubin. It is usually not detectable until the bilirubin is greater than 2 to 3 mg/dL.

2- They may have undergone laboratory or radiologic testing or an unrelated surgical procedure that incidentally uncovered the presence of cirrhosis.

3- They may present with decompensated cirrhosis, which is characterized by the presence of dramatic and life-threatening complications, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis (SBP), or hepatic encephalopathy.

![Diagram showing complications of cirrhosis](image)

**Figure 2:** Complications of cirrhosis result from portal hypertension or liver insufficiency. Varices and variceal hemorrhage are a direct consequence of portal hypertension. Ascites results from sinusoidal portal hypertension and can be complicated by infection (spontaneous bacterial peritonitis [SBP]) or renal dysfunction (hepatorenal syndrome [HRS]). Hepatic encephalopathy results from portosystemic shunting (i.e., portal hypertension) and liver insufficiency. Jaundice results solely from liver insufficiency (*Garcia-Tsao G, 2007*).
Table 1: The Two Most Commonly Used Scoring Systems In Cirrhosis: 
(Garcia-Tsao G, 2007)

1. **Child-Pugh-Turcotte (CPT)** score (range, 5–15)

<table>
<thead>
<tr>
<th>Parameters</th>
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<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>Grade 1–2 (or easy to treat)</td>
<td></td>
</tr>
<tr>
<td>Grade 3–4 (or refractory)</td>
<td></td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Grade 1–2 (or induced by a precipitant)</td>
<td></td>
</tr>
<tr>
<td>Grade 3–4 (or spontaneous)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;2</td>
</tr>
<tr>
<td>2–3</td>
<td></td>
</tr>
<tr>
<td>&gt;3</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt;3.5</td>
</tr>
<tr>
<td>2.8–3.5</td>
<td></td>
</tr>
<tr>
<td>&lt;2.8</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (seconds &gt; control)</td>
<td>4–6</td>
</tr>
<tr>
<td>&lt;4</td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td>1.7–2.3</td>
<td></td>
</tr>
<tr>
<td>&gt;2.3</td>
<td></td>
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</tbody>
</table>

CPT classification: Child A: score of 5–6; Child B: score of 7–9; Child C: score of 10–15

2. **Model of End-Stage Liver Disease (MELD)** score (range, 6–40):

\[
[0.957 \times \text{LN (creatinine in mg/dL)} + 0.378 \times \text{LN (bilirubin in mg/dL)} + 1.12 \times \text{LN (INR)} + 0.643] \times 10
\]

In interpreting the MELD Score in hospitalized patients, the 3 month mortality is:

- 40 or more - 100% mortality
- 30-39 - 83% mortality
- 20-29 - 76% mortality
- 10-19 - 27% mortality
- <10 - 4% mortality

INR = international normalized ratio; LN = natural logarithm.
B-Hepatic decompensation:

Cirrhosis is a prerequisite for most of the major complications of liver failure in patients with chronic HCV infection; however, not all patients with cirrhosis develop these complications (Planas R et al, 2004). The most common form of decompensation was ascites, followed by variceal bleeding, encephalopathy, and jaundice (which is almost always a sign of advanced liver disease in patients with chronic hepatitis C).

C-Hepatocellular carcinoma (HCC):

Deaths associated with chronic hepatitis C in the United States are more likely to be due to end stage liver disease rather than HCC. However, HCV accounts for approximately one-third of HCC cases in the United States. Estimates of the risk of developing HCC once cirrhosis has developed have varied from 0 to 3 percent per year in various reports (Hu KQ et al, 1999).

Factors associated with an increased rate of development of hepatocellular carcinoma:

Cirrhosis or advanced fibrosis on liver biopsy, age, male sex, and alcohol abuse. In some retrospective studies, treatment with interferon alfa, even without a sustained virologic response, has been associated with a lower rate of development of liver cancer. Obesity, diabetes, and steatosis on liver biopsy have been associated with more advanced disease in some studies, but it remains unclear whether these factors are the result rather than the cause of the worse disease. Viral genotype and high virus levels have not been linked to an increased rate of cirrhosis or liver cancer (Hu KQ et al, 1999).
Extrahepatic manifestations of hepatitis C virus infection:

The hepatitis C virus (HCV) is a cause of both acute and chronic hepatitis. In addition, several extrahepatic diseases have been associated with chronic HCV infection, and in most cases appear to be directly related to the viral infection. These include (El-Serag HB et al, 2002):

A-HEMATOLOGIC DISORDERS: HCV infection is associated with a number of hematologic disorders including essential mixed cryoglobulinemia, monoclonal gammopathies (which may be associated with multiple myeloma), and lymphoma and less commonly monoclonal gammopathies.

Essential mixed cryoglobulinemia:

Mixed cryoglobulinemia is a lymphoproliferative disorder that can lead to deposition of circulating immune complexes in small to medium sized blood vessels. It often presents with the clinical triad of palpable purpura, arthralgias, and weakness, but can also involve the kidneys, peripheral nerves, and brain.

Unfortunately, not all patients with HCV infection and cryoglobulinemia respond to interferon treatment. In addition, a reduction in cryoglobulin titers is not directly associated with a decrease in serum alanine aminotransferase (ALT) or HCV RNA.

Treatment of patients with cryoglobulinemia due to HCV should be based upon the presence of cryoglobulinemia symptoms rather than the usual criteria used in patients with chronic hepatitis alone (Saadoun D et al, 2006). The response should be assessed by symptomatic improvement of cryoglobulinemia, a reduction in cryocrit, and an increase in serum complement levels. Complete responses may be more common in patients with low pretreatment levels of viremia and with high dose interferon regimens (Casato M et al, 1997).
Monoclonal gammopathies: Hepatitis C may be a risk factor for the development of monoclonal gammopathies (Andreone P et al, 1998).

Lymphoma: Multiple reports have described an association between HCV infection and B-cell non-Hodgkins lymphoma (NHL). The strongest association of HCV infection with lymphoma is in the subset of patients with immunocytoma, a low-grade malignancy that has previously been associated with cryoglobulininemia (Monti G et al, 2005).

B-DIABETES MELLITUS:

HCV infection has been linked to diabetes mellitus in several epidemiologic studies (Zein CO et al, 2005) HCV genotype 2a was overrepresented among the diabetic patients.

Risk factors for the development of diabetes mellitus in HCV infected patients included older age, obesity, severe liver fibrosis, and a family history of diabetes mellitus (Petit JM et al, 2001). Patients undergoing liver transplantation for HCV also appear to be at increased risk, compared to other liver diseases, for developing diabetes mellitus following transplantation (Bigam DL et al, 2000).

The cause of these associations is unknown, but may be due to the following factors (Hadziyannis S et al, 1999):
- Patients with diabetes have more parenteral exposures than the general population, placing them at increased risk for transmission of viruses.
- HCV infection becomes chronic more often than HBV infection.
- HCV has also been linked to insulin resistance without overt diabetes (Moucari R et al, 2008). The insulin resistance may contribute to fibrosis progression, particularly with HCV genotypes 1 and 4 and high serum RNA levels (Moucari R et al, 2008). Insulin resistance may also impair the response to antiviral therapy with interferon and ribavirin.
C-AUTOIMMUNE DISORDERS:

A number of autoimmune disorders have been associated with HCV infection, including autoantibody formation, thyroid disease, sialadenitis, and autoimmune thrombocytopenic purpura.

Autoantibodies:

Autoantibodies are common in patients with chronic HCV infection; antinuclear antibodies, antibodies directed against the Fc portion of IgG (rheumatoid factor), anticardiolipin antibodies, smooth muscle antibodies, or antithyroid antibodies are detected in 40 to 65 percent of patients (Cacoub P et al, 1997). These antibodies are typically present in low titer, and do not appear to influence the presentation or course of infection.

Antibodies to actin and to liver/kidney microsomes (anti-LKM-1) are characteristic of types 1 and 2 autoimmune hepatitis, respectively. These antibodies have been detected in some patients with chronic HCV infection, particularly in Europe (Zauli D et al, 1997).

Thyroid disease:

Thyroid disorders are common in patients with chronic HCV, particularly women (Antonelli A et al, 2004). A separate issue is the development of thyroid disease in patients with HCV infection who are treated with interferon alfa.

Sialadenitis:

A lymphocytic sialadenitis suggestive of Sjögren's syndrome has been described in patients with chronic HCV infection (Ramos-Casals M et al, 2005).
Autoimmune thrombocytopenic purpura:

Anti-HCV antibodies occur in 10 to 19 percent of patients with autoimmune thrombocytopenic purpura (ITP). Some of these patients acquired anti-HCV antibodies passively following use of IVIG with a high titer of anti-HCV antibodies, while others developed actual infection following transfusion of HCV-infected blood products employed for the treatment of ITP (eg, contaminated IVIG). In other cases, ITP developed following the acquisition of HCV infection, or during its treatment (Pawlotsky JM et al, 1995).

Myasthenia gravis:

An association between myasthenia gravis (MG) and hepatitis C virus infection has been suggested in case reports (Eddy S et al, 1999), although a causal association has not been clearly established (Halfon P et al, 1996).

D-OCULAR DISEASE:

HCV infection has been associated with a variety ophthalmologic disorders including dry eyes, corneal ulcers (Mooren's ulcer), uveitis, and scleritis (Jacobi C et al, 2007), and sicca syndrome in patients with HCV-related Sjogren's syndrome (Ramos-Casals M et al, 2005). In addition, ophthalmologic disorders (retinal hemorrhages, cotton wool spots, and rarely retinal artery or vein obstruction) can occur during interferon therapy.

E-RENAL DISEASE:

Glomerular disease may occur in patients with chronic HCV infection. The most common patterns are membranoproliferative glomerulonephritis (usually associated with essential mixed cryoglobulinemia) and, less frequently, membranous nephropathy (McGuire BM et al, 2006). Several series have reported that anti-HCV antibodies are nearly universal in patients with both membranoproliferative disease and cryoglobulinemia; the pathogenesis appears to relate to deposition of immune complexes containing anti-HCV and HCV RNA in the glomeruli.
Interferon alfa is indicated in patients with mixed cryoglobulinemia and membranoproliferative glomerulonephritis. A number of studies have reported a beneficial response to antiviral therapy in this setting, and the reduction in proteinuria correlates with a fall in HCV RNA (Sabry AA et al, 2002).

**F-DERMATOLOGIC DISEASE:**

**Porphyria cutanea tarda:**

Porphyria cutanea tarda (PCT) is a skin disease caused by a reduction of hepatic uroporphyrinogen decarboxylase activity that is characterized by photosensitivity, skin fragility, bruising, and vesicles or bullae that can become hemorrhagic.

**Leukocytoclastic vasculitis:**

A leukocytoclastic vasculitis may occur in conjunction with essential mixed cryoglobulinemia, presenting clinically with palpable purpura and petechiae that usually involve the lower extremities. Other tissues, particularly the lower extremity peripheral nerves, may show similar vasculitic changes involving the vasa nervorum (David WS et al, 1996).

**Lichen planus:**

Lichen planus (LP) is characterized by flat-topped, violaceous, pruritic papules with a generalized distribution. It can also involve mucus membranes, hair, and nails. LP may be mediated through the cellular immune response, although the actual precipitating mechanism is not known (Pilli M et al, 2002).

**Necrolytic acral erythema:**

Necrolytic acral erythema is a pruritic, psoriasis-like skin disease characterized by a sharply marginated, erythematous to hyperpigmented plaques
with variable scale and erosion on the lower extremities. Biopsy specimens showed psoriaform changes, keratinocyte necrosis and papillomatosis. Improvement was observed in a patient who had been treated for HCV with interferon alfa (and subsequent relapse nine months after discontinuation (Abdallah MA et al, 2005).

**G-MUSCULOSKELETAL:**

Hepatitis C-associated osteosclerosis is a rare disorder characterized by a marked increase in bone mass during adult life. While most cases have been reported in patients with a history of intravenous drug abuse, it has also been seen with hepatitis C after blood transfusion (Shaker JL et al, 1999).
Diagnostic Approach to Hepatitis C Virus Infection:

Diagnostic tests for hepatitis C virus (HCV) can be divided into two broad categories:
1- Serologic assays that detect antibody to hepatitis C.
2- Molecular assays that detect or quantify HCV RNA.
Other investigations such as genotype testing and liver biopsy may help to predict prognosis and the response to treatment.

Antibody testing:
Called enzyme-linked immunosorbent assay or ELISA that detects HCV proteins. Ease of use, low variability, ease of automation, and relatively low expense enzyme immunoassay EIA-2 is more sensitive and specific than the earlier assay (Alter HJ, 1992).

The third-generation ELISA test however is more specific and sensitive in patients with CKD. The sensitivity is as high as 95 percent, and the positive predictive value is 88 to 95 percent (Gretch DR, 1997).

Recombinant immunoblot assay RIBA, the test is not more sensitive, but it does confer increased specificity over the screening EIA assay (Lok AS et al, 1997).

Molecular testing:
HCV RNA can be measured qualitatively or quantitatively by either reverse transcription Polymerase chain reaction PCR or branched DNA (bDNA) assays.
Figure -3: Typical serologic course of chronic hepatitis C.

ALT = alanine aminotransferase; HCV = hepatitis C virus;
PCR = polymerase chain reaction, (Hoofnagle JH,2007).

Samples for HCV-RNA testing in dialysis patients should be obtained prior to the HD procedure; heparin used during dialysis sessions can interfere with the PCR technique.

In addition, the HD procedure can lower HCV RNA levels by adsorption of HCV RNA onto the inner surface of dialyzers and destruction of viral particles by the hydraulic pressure exerted by the blood for dialysis (Okuda K et al, 1996).

Anti-HCV in the absence of HCV RNA:

Absence of HCV RNA despite anti-HCV antibodies may be seen in a number of circumstances.

Antibody to HCV may persist after the viral RNA has disappeared, representing patients who had been infected with the virus, but no longer harbor it.
False positive results on antibody tests due to technical reasons, Detection of anti-HCV antibodies that have been passively acquired from blood transfusions, Detection of maternal anti-HCV antibodies in babies.

Viremia may be intermittent, with HCV RNA not being present in the serum at the time of testing. HCV may be sequestered at sites other than the blood stream, such as the liver or peripheral blood mononuclear cells. The number of copies of HCV RNA may be below the limit of detection or there may be other technical problems with the test (Pereira BJ et al, 1997).

Immunocompromised patients such as Patients on hemodialysis and transplant recipients have a much higher rate of false negative EIAs than immunocompetent patients. Thus, HCV RNA testing should be performed in all patients who are immunocompromised and EIA-2 negative if there is clinical suspicion of infection (Lau JY et al, 1993).

HCV Genotyping Testing:
A variety of methods are available to identify genotypes. HCV genotyping is usually unnecessary for diagnosing infection but is useful for guiding the duration of therapy and predicting the likelihood of response (Bukh J et al, 1995).

Liver Biopsy:
Hepatic histologic characteristics include spotty hepatocellular necrosis, chronic inflammatory cell infiltration in the portal areas, and variable degrees of fibrosis. The hepatocellular necrosis is typically eosinophilic degeneration or ballooning degeneration. The necrosis is spotty throughout the parenchyma, but activity is usually greater in the periportal area; the pattern is termed piecemeal necrosis or interface hepatitis. The hepatocellular necrosis seems to be mediated largely by apoptosis in association with cytotoxic lymphocytes.

Chronic inflammatory cells (CD4+ and CD8+ lymphocytes and plasma cells, histiocytes, and macrophages) are found in the areas of necrosis and in sinusoids
but most prominently in the portal areas. Fibrosis occurs insidiously during the course of chronic hepatitis and typically begins in the periportal regions. Ultimately, bands of fibrosis can link up adjacent portal areas or portal and central areas (bridging fibrosis), distort the hepatic architecture, and lead to cirrhosis and portal hypertension (Hoofnagle JH, 2007).

Histologic scoring systems for chronic liver disease:

KNODELL SCORE:

Also known as the histologic activity index (HAI), is composed of the summation of four individual scores representing periportal and/or bridging necrosis, intralobular degeneration and focal necrosis, portal inflammation, and fibrosis; the score ranges from 0 to 22 (show table 2). Several modifications of the HAI have also appeared, which were designed, in part, to address histologic features specific to the disease under study (Kaplan MM et al, 1997). One modification (referred to as the Ishak score) has six stages of fibrosis, permitting more detailed evaluation of changes in fibrosis compared with the standard Knodell fibrosis score, which has only four stages (Ishak K et al, 1995).

The Knodell score does not account for features specific to different types of viral hepatitis. As an example, the HAI does not account for lymphoid aggregates, bile duct injury, and macrovesicular fat that are often present in chronic hepatitis C (Banner BF et al, 1995).
### Table 2: Knodell score (HAI) of liver biopsy specimens*(Knodell, RG, et al, 1981)*

<table>
<thead>
<tr>
<th>I. Periportal ± bridging necrosis</th>
<th>Score</th>
<th>II. Intralobular degeneration and focal necrosis♦</th>
<th>Score</th>
<th>III. Portal inflammation</th>
<th>Score</th>
<th>IV. Fibrosis</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>0</td>
<td>none</td>
<td>0</td>
<td>No portal inflammation</td>
<td>0</td>
<td>No fibrosis</td>
<td>0</td>
</tr>
<tr>
<td>Mild piecemeal necrosis</td>
<td>1</td>
<td>Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in &lt; 1/3 of lobules or nodules)</td>
<td>1</td>
<td>Mild (sprinkling of inflammatory cells in &lt;1/3 of portal tracts)</td>
<td>1</td>
<td>Fibrous portal expansion</td>
<td>1</td>
</tr>
<tr>
<td>Moderate piecemeal necrosis (involves less than 50 percent of the circumference of most portal tracts)</td>
<td>3</td>
<td>Moderate (involvement of 1/3 to 2/3 of lobules or nodules)</td>
<td>3</td>
<td>Moderate (increased inflammatory cells in 1/3 to 2/3 of portal tracts)</td>
<td>3</td>
<td>Bridging fibrosis (portal-portal or portal-central linkage)</td>
<td>3</td>
</tr>
<tr>
<td>Marked piecemeal necrosis (involves more than 50 percent of the circumference of most portal tracts)</td>
<td>4</td>
<td>Marked (involvement of &gt;2/3 of lobules or nodules)</td>
<td>4</td>
<td>Marked (dense packing of inflammatory cells in &gt;2/3 of portal tracts)</td>
<td>4</td>
<td>Cirrhosis▲</td>
<td>4</td>
</tr>
<tr>
<td>Moderate piecemeal necrosis plus bridging necrosis●</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked piecemeal necrosis plus bridging necrosis●</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multilobular necrosis §</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* HAI score is the combined scores for necrosis, inflammation, and fibrosis.
Degeneration-acidophilic bodies, ballooning; focal necrosis-scattered foci of hepatocellular necrosis.

▲ Loss of normal hepatic lobular architecture with fibrous septae separating and surrounding nodules.

● Bridging is defined as 2 bridges in the liver biopsy specimen; no distinction is made between portal-portal and portal-central linkage.

§ Two or more contiguous lobules with panlobular necrosis.

The combination of these three markers indicates the amount of inflammation in the liver (Franciscus A, 2007):

• 0 = no inflammation
• 1-4 = minimal inflammation
• 5-8 = mild inflammation
• 9-12 = moderate inflammation
• 13-18 = marked inflammation

**METAVIR SCORE:** Was developed in an attempt to address some of the problems with the Knodell score (Bedossa P et al, 1996). In contrast to the Knodell score, which was designed as a generic scoring system for chronic hepatitis, the Metavir score was specifically designed and validated for patients with hepatitis C.

The Metavir score is a semiquantitative classifications system consisting of an activity and a fibrosis score:

- The fibrosis score is assessed on a five point scale (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = numerous septa without cirrhosis, 4 = cirrhosis). Compared to the Knodell fibrosis score (which has only four levels), the Metavir score permits recognition of subtler variation in the degree of fibrosis.

- The activity score was graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). The inter- and intraobserver reliability of the activity and fibrosis score of the Metavir system are similar to the Knodell score (The French METAVIR Cooperative Study Group, 1994).
Antiviral Therapy For HCV Infection

1-Interferon (IFN):
Definition:
Interferons comprise a group of related proteins whose effects include antiviral activity, growth regulatory properties, inhibition of angiogenesis, regulation of cell differentiation, enhancement of major histocompatibility complex antigen expression, and a wide variety of immunomodulatory activities.

Mechanism of action:
It is assumed that increased expression of antiviral genes induced by type 1 interferons is an important factor in the elimination of hepatitis viruses. These antiviral genes are only partially understood with respect to function; they comprise 2', 5' oligoadenylate synthetase, a 60 Kilodaltons (kDa) protein kinase, and the Mx protein homologue (Peters M et al, 1989).

Types of Interferone: They were originally classified according to their source and have subsequently been renamed: Alpha interferon (formerly known as leukocyte interferon) Beta interferon (formerly known as fibroblast interferon) Gamma interferon (formerly known as immune interferon). At least 18 distinct genes are known for the human alpha interferons; in comparison, there is only one gene for beta interferon and one for gamma interferon (Lodish H et al, 1995).

Alpha interferons have been extensively studied in the treatment of patients with chronic hepatitis, including hepatitis B, C, and D.
Types of Alpha Interferon:

1- Interferon alfa-2b is produced by recombinant DNA techniques. It is approved in the United States for patients with HCV infection at a dose of 3 million units (MU) subcutaneously three times weekly for up to 24 months.

2- Interferon alfa-2a is also a recombinant alpha interferon. It differs from interferon alfa-2b by a single amino acid. The majority of people produce interferon alfa-2b which probably explains the high rate of antibody formation when interferon alfa-2a is given. Interferon alfa-2a is approved for use in the United States in patients with HCV infection at a dose of 3 MU subcutaneously three times weekly for 12 months.

3- Interferon alfacon-1 or consensus interferon is a non-natural recombinant interferon which was developed by scanning subtypes of alpha interferon and assigning the most frequently observed amino acid at each position to form a consensus molecule. It is approved for use in the United States at a dose of 9 µg subcutaneously three times per week for six months.

4- Interferon alfa-n1 is a mixture of nine interferon subtypes produced from a human B lymphoblastoid cell line. approved by the European Union at a dose of 5 MU subcutaneously or intramuscularly three times weekly for 48 weeks (Lindsay KL, 1997).

Pegylated Interferon Alfa:

A modified form of IFNa, pegylated IFNa or peginterferon alfa, was developed by attaching a polyethylene glycol moiety to interferon alfa. This reduces renal and cellular clearance, and decreases the immunogenicity of the protein. All of these effects tend to enhance the half-life of the drug. While pegylated interferons have demonstrated clear therapeutic advantages in HCV-infected patients without renal failure, there is limited published information about their use in patients on renal replacement therapy and there has been concern about dosing (Gordon CE et al, 2008).
Although current data on pegylated interferon in hemodialysis remain very limited, it appears that hemodialysis has only negligible effects on the clearance of pegylated interferon alfa-2a or alfa-2b (Barril G et al, 2004). However, pegylated interferon treatment of dialysis patients, compared with standard interferon monotherapy, does not seem to provide more benefit in terms of virologic response, and some safety concerns have been expressed. Consequently, standard interferon monotherapy should remain the treatment of choice in hemodialysis patients (Russo MW et al, 2006).

Overview of side effects of IFNa therapy:

**Hematological Side Effects:**

**Anemia:** It is extremely common among patients taking Peg-Interferon and Ribavirin (PEG/RBV) combination therapy for chronic hepatitis C. Standard IFN and RBV therapy is associated with mean maximal Hb decreases within the first 12 weeks of 2.9-3.1 g/dl (Maddrey WC, 1999). The etiology of anemia is multifactorial and is caused by Ribavirin (RBV)-induced hemolysis and IFN suppression of the normal compensatory bone marrow response. IFN is a potent suppressor of all components of the bone marrow and inhibits erythropoiesis as evidenced by an inadequate reticulocyte response to anemia. IFN has also been associated with autoimmune hemolytic anemia.

**Neutropenia:** Treatment with interferon is commonly associated with bone marrow suppression. PEG-IFN has a pharmacokinetic profile associated with more profound marrow suppression than standard IFN.

**Thrombocytopenia:** is common in patients with advanced liver disease. The cause is multifactorial due in part to increased sequestration in the spleen and reduced production of thrombopoietin (a cytokine that regulates megakaryocyte maturation and platelet production) (Kawasaki T et al, 1999).
Flu-like symptoms:

The most common side effects associated with IFN therapy are flu-like symptoms (mainly muscle aches, headaches, and low-grade fevers) which are seen in over 80 percent of patients.

Respiratory tract symptoms:

Including a nonproductive cough and shortness of breath are relatively common with IFN monotherapy, and occur at a similar rate in those treated with PEG/RBV (24 versus 26 percent) (*Manns MP et al, 2001*). The etiology of dyspnea is usually related to the severity of anemia; however, rarely interstitial pneumonia and bronchiolitis obliterans can occur and necessitate immediate discontinuation of PEG/RBV (*Ogata K et al 1994*).

Ophthalmologic disorders:

Ophthalmologic disorders (retinal hemorrhages, cotton wool spots, loss of color vision, and rarely retinal artery or vein obstruction) can occur during IFN therapy. The most common ocular complication has been the development of a mild to moderate ischemic retinopathy (*Fortin E, 1998*). The incidence of this retinopathy has varied greatly in different reports (2 to 86) percent, Several cases of glaucoma have also been reported in association with IFN therapy, but a causative association remains unproven (*Kwon et al, 2001*).

Glucose metabolism:

Several studies have suggested an association between HCV therapy and diabetes mellitus, although the strength of the association remains unclear (*Noto, H et al, 2006*).
Pregnancy:

Counseling both male and female patients about the risks of pregnancy while on PEG/RBV therapy, and for six months after discontinuing treatment, is critically important. IFN (5 to 10 mU) caused abortion in pregnant rhesus monkeys, and there are no adequate and well-controlled studies in pregnant women. IFN is therefore not advisable in pregnancy (Boskovic R et al, 2005).

Autoimmune disease exacerbation:

including psoriasis, vitiligo, rheumatoid arthritis, lichen planus, sarcoidosis, dermatitis herpetiformis, and type 1 diabetes mellitus. Thus, IFN should be used with caution in patients with known autoimmune disease and is contraindicated in patients with known autoimmune hepatitis (Ramos-Casals M et al, 2005).

Hair loss:

Reversible hair loss occurs in approximately 20 percent of patients as a result of IFN (Tosti A et al, 1992).

Thyroid dysfunction:

Thyroid abnormalities requiring therapy develop in approximately 1 to 7 percent of patients treated with IFN, hyperthyroidism develops more commonly than hypothyroidism by an approximate ratio of 6:1 (Kryczka W et al, 2001). Thyroid dysfunction is associated with the dose and duration of therapy and is more likely if patients have preexisting antithyroid antibodies, suggesting that IFN exacerbates underlying thyroid autoimmune disease (Fernandez-Soto L et al, 1998).

Migraine headaches:

Migraine headaches develop in fewer than 2 percent of patients receiving combination therapy (Bräu N et al, 2003).
**Hearing loss:**

Sudden hearing loss and tinnitus have been described with IFN and PEG IFN plus ribavirin combination therapy. The mechanism is unclear but may be related to direct ototoxicity of interferon, autoimmunity, or hematologic changes (*Formann E et al, 2004*).

**2-Ribavirin (RBV):**

**Definition:**

Ribavirin is a nucleoside analog which has a broad spectrum of antiviral activity.

**Mechanism of action:**

It inhibits the replication of RNA viruses in cell culture.

Its mode of action is not completely understood, but several mechanisms may be involved:

- Depletion of intracellular triphosphate pools through direct inhibition of inosine monophosphate dehydrogenase.
- Inhibition of the 5' cap structure of viral mRNA
- Inhibition of the viral dependent RNA polymerases
- Altering the balance between proinflammatory (Th1-like) and anti-inflammatory (Th2-like) cytokines (*Ning Q et al, 1998*).
- Inducing mutations into viral RNA (*Crotty S et al, 2000*).

**Side effects:**

Anemia: due to hemolysis, RBV use may be associated with a persistent cough without any objective airway disease.

RBV produced significant embryonal or teratogenic effects in every animal species studied. Thus, it is contraindicated in pregnancy, and any woman that becomes pregnant on RBV should immediately notify their physician, and receive
appropriate counseling about teratogenicity and the option for therapeutic abortion. Dermatologic complications include rashes (Schalm SW et al, 1997).

3-New therapies for hepatitis C virus infection:

The search for new therapies for chronic hepatitis C is ongoing. Although current therapies are primarily based on the use of type 1 interferon, several major research efforts are now underway aimed at production of specific targeted anti-HCV compounds. These approaches focus on HCV encoded proteins that are vital to the replication and life cycle of the virus. Targets include the HCV encoded serine protease, the HCV encoded helicase, the HCV encoded RNA dependent RNA polymerase (RdRP), and the HCV RNA internal ribosome entry site (IRES). In addition, efforts to stimulate the host immune response by cytokine activation with non-interferon based therapies are also underway.

A-MODEIFIED CONVENTIONAL THERAPIES:

Albuferon: A form of interferon alfa genetically fused to albumin is undergoing clinical testing. Possible advantages compared to other forms of interferon that were identified in preclinical studies are its very long half-life and improved side-effect profile (Zeuzem S et al, 2008).

Ribavirin derivatives and related drugs: Ribavirin has several antiviral effects, which may contribute to its efficacy as adjunctive therapy in HCV. Several ribavirin derivatives are currently undergoing development. These include levovirin (the L isomer of ribavirin) and viramidine (a prodrug of ribavirin that has a three-fold longer residence time in the liver and may be less likely to cause hemolysis) (Lin CC et al, 2003).
**B-IMMUNE-AUGMENTING TREATMENTS:**

Several treatments are in development that are aimed at modulating the immune system to improve the efficacy of antiviral treatments.

**Thymosin:** Thymosin, an extract of the thymus gland, promotes T-cell maturation and natural killer cell activity.

**Interleukin 10:** Interleukin-10 (IL-10) is a cytokine that downregulates proinflammatory immunologic responses, providing a rationale for its use in chronic hepatitis C. However, clinical development has been halted because of safety concerns.

**Interleukin 11:** Interleukin 11 inhibits production of Th-1 cytokines, which are considered to contribute to hepatocellular injury caused by HCV. A pilot study of recombinant human IL-11 in 20 subjects found an improvement in the degree of histologic injury while mean serum ALT levels decreased significantly (Lawitz EJ, et al, 2004).

**Resiquimod:** Resiquimod is a small molecule that signals through toll-like receptors (TLR7) causing induction of cytokines including interferon alfa, IL-12 and tumor necrosis factor. Certain polymorphisms in TLR7 have been associated with protection from HCV-induced hepatic inflammation and fibrosis (Schott E, et al, 2007).

**Therapeutic vaccination:** Vaccines designed to augment the immune response to HCV are in development. A pilot study of one candidate vaccine (designed to elicit a t-cell response) suggested a possible benefit on liver histology and improvement in serum aminotransferases (Nevens F et al, 2003). Another vaccine (based upon immunization with HCV antigens expressed in dendritic cells) also showed promise in an mouse model (Kuzushita N et al, 2006).
Preventive vaccination: A phase 1 trial of a candidate vaccine demonstrated safety and a significant antibody and lymphocyte proliferation response in healthy volunteers (Vajdy M et al, 2006). A T-cell HCV vaccine was protective against acute infection in chimpanzees (Folgori A et al, 2006). A third vaccine (based upon recombinant HCV-like particles produced in insect cells) also controlled HCV challenge in a chimpanzee model (Elmowalid GA et al, 2007).

Hepatitis C immunoglobulin: Unlike hepatitis B, no effective immunoglobulin prophylaxis exists for hepatitis C. Studies evaluating HCV-specific immunoglobulins in vivo have produced conflicting results. One possible explanation is that non-neutralizing antibodies contained in the polyclonal preparations may interfere with the function of neutralizing antibodies (Zhang P et al, 2007).

T-cell receptor gene transfer: Studies of viral persistence in HCV suggest that ineffective T cell immunity may be partially responsible for chronic infection. Laboratory experiments suggest the possibility of transferring genes into T cells that stimulate the T cell to recognize HCV (Meyer-Olson D et al, 2004).

C-TREATMENTS TARGETING THE HCV GENOME:

Protease inhibitors: NS3/4a serine protease inhibitors are in preclinical development or early clinical trials. Of these, telaprevir has been best studied in humans. Given alone or in combination with pegylated interferon, it demonstrated potent suppression of HCV RNA levels patients with chronic HCV genotype 1 (Kieffer TL et al, 2007). Other protease inhibitors continue to be evaluated, (bocepravir) reduced HCV RNA levels in patients who were refractory to pegylated interferon (Sarrazin C et al, 2007), (valopicitabine) exhibited consistent antiviral activity in a phase I/II study involving 48 patients (Rodriguez-Torres M et al, 2005).
D-TREATMENTS AIMED AT REDUCING FIBROSIS:

Many of the clinical consequences of HCV infection are due to the development of cirrhosis. Treatments aimed at reducing or reversing fibrosis (without necessarily having an antiviral effect) are in development.

**Interferon gamma:** Interferon gamma (IFN-gamma) is a cytokine secreted primarily by T-cells (CD4+ T cells, CD8+ T cells, and natural killer cells). Animal models suggest that IFN-gamma can inhibit the proliferation of hepatic stellate cells and reduce collagen synthesis (Pockros PJ et al, 2007).

**Vitamin E:** In a pilot study, the antioxidant vitamin E impaired fibrogenesis, presumably by an effect on hepatic stellate cells (Houglum K et al, 1997). Furthermore, in two small controlled studies it was associated with a significant reduction in the serum alanine aminotransferase concentration. Vitamin E has no effect on viral replication. (Von Herbay A et al, 1997).

**Caspase inhibitors:** is an inhibitor of caspases, proteases that mediate apoptosis. A pilot study found that short-term treatment reduced serum aminotransferase levels but had no effect on HCV RNA (Pockros PJ et al, 2007).

E-TREATMENTS AIMED AT BLOCKING HCV ENTRY INTO CELLS: Cellular receptors responsible for entry of HCV into cells have been identified (Gardner JP et al, 2003) offering potential targets for agents aimed at blocking HCV entry.
F-PROBABLY INEFFECTIVE THERAPIES:

Amantadine, an influenza antiviral drug, has been studied as monotherapy and in combination with other anti-HCV treatments. Most studies have suggested that amantadine alone or in combination with interferon is ineffective in the treatment of chronic HCV (Thuluvath PJ et al, 2004). A possible benefit has been suggested in studies of triple therapy with interferon plus ribavirin plus amantadine in patients who had not previously responded to prior interferon-based therapy (Teuber G et al, 2003). Studies of triple therapy in patients who had never been treated have produced conflicting results (Ferenci P et al, 2006).

G-OTHERS:

A variety of other modalities have been tried in the treatment of chronic hepatitis C with generally discouraging results. These include: Cytokines and immunomodulators, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-12 levamisole, interleukin-2, and monotherapy with thymic extracts, such as thymosin alfa-1 (TA-1) (although thymic extracts have been approved in many countries) (Pockros PJ et al, 2003). Antioxidants, such as N-acetylcysteine (Idéo G et al, 1999). Hypericin, a natural derivative of the common St. John's wort plant (Jacobson JM et al, 2001). Miscellaneous drugs include ursodeoxycholic acid and pentoxifylline (Takano S et al, 1994) given alone or in combination with interferon. Nonsteroidal anti-inflammatory drugs have the potential for enhancing the effects of interferon and have thus been evaluated as combination therapy. However, studies evaluating this approach have produced discordant results (Muñoz AE et al, 2000).
Treatment Guidelines:

The 1997 National Institutes of Health (NIH) Consensus Conference recommended that patients with normal serum ALT should not be treated with interferon even if there is evidence of chronic hepatitis on liver biopsy. A revised consensus statement from 2002 suggested that many factors should be considered in deciding upon treatment including the genotype, findings on liver biopsy, patient motivation, symptoms, severity of co-morbid illness, and age (The National Institutes of Health, 2002).

Similarly, a 2004 guideline issued by the American Association for the Study of Liver Diseases (AASLD) suggested that the decision to initiate therapy in patients with persistently normal aminotransferase values should be individualized based upon the severity of disease, the potential for side effects, the likelihood of response, and the presence of co-morbid conditions (Strader DB et al, 2004).

National Institutes Of Health (NIH) Guidelines: Guidelines for the selection of patients for treatment with interferon monotherapy were initially proposed at the National Institutes of Health (NIH), the guidelines were revised in 2002 to include a broader range of potentially eligible patients.

The Consensus Panel recommended that all patients with chronic hepatitis C should be considered as potential candidates for antiviral therapy. Treatment should be recommended for patients who are at increased risk for progression to cirrhosis. Such patients are characterized by the presence of measurable HCV, a liver biopsy showing portal or bridging fibrosis, and at least moderate inflammation and necrosis; the majority of these patients have persistently elevated serum ALT values.
NIH comments in particular settings:

- **Mild liver disease**: Patients who have persistent elevation in serum ALT but do not have fibrosis and have minimal necroinflammatory changes are likely to have only slow disease progression. Such patients can be monitored periodically. However, the decision to treat should be individualized.

- **Advanced liver disease**: In patients with advanced fibrosis or compensated cirrhosis the response is lower than in patients without cirrhosis. The main treatment option for such patients is liver transplantation.

Guidelines issued by the American Association for the Study of Liver Diseases (AASLD) are consistent with the NIH guidelines but provide additional details. The (AASLD) recognizes three categories of patients:

**Persons for whom therapy is widely accepted**:

- At least 18 years of age.
- Abnormal serum ALT values.
- Liver biopsy with chronic hepatitis with significant fibrosis.
- Compensated liver disease (total serum bilirubin <1.5 g/dL; INR <1.5; albumin >3.4 g/dL; platelet count >75,000 k/mm(3); and no evidence of hepatic encephalopathy or ascites).
- Acceptable hematological and biochemical indices (hemoglobin >13 g/dL for men and >12 g/dL for women; neutrophil count >1.5 k/mm (3); creatinine < 1.5 mg/dL).
- Willing to be treated and to conform to treatment requirements.
Persons for whom therapy should be individualized

- With persistently normal ALT values.
- Who failed prior treatment (nonresponders and relapser) consisting of either interferon given alone or in combination with ribavirin, or consisting of peginterferon given alone.
- Current users of illicit drugs or alcohol.
- Liver biopsy evidence of either no or only mild fibrosis (portal fibrosis: Metavir score <2; Ishak score <3).
- Acute hepatitis C.
- Coinfection with HIV.
- Less than age 18 years.
- Chronic renal disease (on or not on hemodialysis).
- Decompensated cirrhosis.
- Recipient of a liver transplant.

Persons in whom therapy is contraindicated

- With major, uncontrolled depressive illness.
- Who received a renal, heart, or lung transplant.
- With autoimmune hepatitis.
- Untreated hyperthyroidism.
- Pregnant or unwilling/unable to comply with adequate contraception.
- Severe concurrent disease such as severe hypertension, heart failure, significant coronary artery disease, poorly controlled diabetes, obstructive pulmonary disease.
- Younger than 3 years.
- Known hypersensitivity to drugs used to treat HCV.

Dosage of initial therapy:

Consistent guidelines published by the (AASLD) recommend combination therapy with pegylated interferon plus ribavirin, which is superior to interferon monotherapy and to standard interferon/ribavirin combination therapy in patients with chronic HCV who are considered to be appropriate candidates for therapy. Combination therapy should be administered for 48 weeks using standard doses of
ribavirin in patients with genotype 1 or 4 (1,000 mg for those ≤ 75 kg in weight and 1,200 mg for those more than 75 kg). Quantitative HCV RNA should be determined before the initiation of therapy and at week 12. Treatment can be discontinued in those who do not achieve an early virologic response at week 12, although the decision should be individualized depending upon how well therapy has been tolerated, the severity of the underlying liver disease, and demonstration of some degree of biochemical and/or virologic response. In contrast, 24 weeks of therapy using a lower dose of ribavirin (800 mg daily in divided doses) appears to be as effective as longer courses of therapy (using the standard higher dose of ribavirin) in patients infected with genotype 2 and 3 (Strader DB et al, 2004).

**Standard interferon in the treatment of chronic hepatitis C virus infection:**
The NIH Consensus suggested standard response definitions as follows (Farrell GC et al, 1998):

- **End of treatment response (ETR)** is defined as a normal serum ALT concentration (biochemical response) or the absence of detectable HCV-RNA (virologic response) at the end of treatment.

- **A sustained response (SR)** is defined as a biochemical or virologic response at the end of treatment and throughout an observation period of at least six months following the discontinuation of interferon therapy.

- **A histologic response** has not been well defined since the time at which post-treatment liver biopsies have been performed has varied from study to study.

Most studies have defined histologic response as a two point or greater reduction in the histology activity index score (Knodell histological score for inflammatory components only) (Knodell RG et al, 1981).
Hepatitis C In Dialysis
Hepatitis C In Dialysis

Prevalence In Dialysis Patients:

The prevalence of anti-HCV antibody among patients on dialysis is consistently higher than in healthy populations, suggesting that dialysis patients may be at higher risk of acquiring HCV infection. The reported incidence, however, varies based in part upon the type of laboratory assay used (Pereira BJ et al, 1997).

Pooled data from studies in which dialysis patients were tested by both (ELISA1 and ELISA2) revealed that ELISA2 identified more than twice the number of patients with HCV antibodies than ELISA1 (Pereira BJ et al, 1997).

Using second generation anti-HCV tests, the prevalence of anti-HCV antibodies among dialysis patients has been reported to be 25 to 36 percent in the United States, 2 to 63 percent in Europe and 22 to 55.5 percent in Asia (Natov SN et al, 1996).

As shown in (Table 3), information on the prevalence and incidence of HCV infection in patients on long-term dialysis in developing countries is limited but single-center surveys show continued high prevalence and incidence rates (Hmaied F et al, 2006).

This probably reflects nosocomial transmission of HCV in the HD environment, incomplete anti-HCV screening of blood and blood products, and a higher prevalence of HCV in the general population (Martin P et al, 2008).
Table 3: (Martin P et al, 2008) HCV infection among patients undergoing long-term dialysis in developing countries: prevalence rates.

<table>
<thead>
<tr>
<th>Country</th>
<th>Anti-HCV positives</th>
<th>Reference year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moldavia</td>
<td>75% (111/148)</td>
<td>1999</td>
</tr>
<tr>
<td>Egypt</td>
<td>80% (169/210)</td>
<td>2000</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>43.4% (86/198)</td>
<td>2004</td>
</tr>
<tr>
<td>Iran</td>
<td>24.8% (74/298)</td>
<td>2005</td>
</tr>
<tr>
<td>Turkey</td>
<td>19% (83/437)</td>
<td>2005</td>
</tr>
<tr>
<td>Morocco</td>
<td>76% (141/186)</td>
<td>2005</td>
</tr>
<tr>
<td>Tunisia</td>
<td>20% (79/395)</td>
<td>2006</td>
</tr>
<tr>
<td>Brazil</td>
<td>16.4% (180/1095)</td>
<td>2007</td>
</tr>
<tr>
<td>Sudan</td>
<td>23.7% (56/236)</td>
<td>2007</td>
</tr>
</tbody>
</table>

The Prevalence In Egypt:

The prevalence of HCV viremia, using polymerase chain reaction (PCR), is as high as 60% (80 from 133) of patients with end-stage renal disease (ESRD) awaiting renal transplantation (Mahmoud IM et al, 1999).

This inordinately high prevalence had been attributed to an increased likelihood of transmitting the virus by blood transfusions in Egyptian hemodialysis patients as the antibody to HCV (anti-HCV) seroprevalence is 13.6% in Egyptian blood donors (Darwish MA et al, 1993).

In addition, the severe shortage of erythropoietin, which is expensive, rendered repeated blood transfusions almost the only line of treatment for anemia of chronic renal failure.
Infection Routes In Dialysis Units:

Several of the following factors may affect the risk of transmission of HCV to patients and staff in hemodialysis units:

- Transmission of infection to dialysis staff by needle-stick injury
- Physical proximity to an infected patient, a higher risk of seroconversion was found in patients dialyzed at a station adjacent to that of an anti-HCV positive patient as compared to other patients in the same unit (Jadoul M et al, 1993).
- Dialysis machines: the use of dedicated machines and isolated areas for anti-HCV positive patients along with strict enforcement of universal precautions was associated with a decrease in the incidence of seroconversion (Garcia-Valdescasas J et al, 1993). Overall, data suggest that HD machines do not have a significant role in the nosocomial transmission of HCV infection (Froio N et al, 2003). Therefore, it is likely that HCV transmission in hemodialysis settings principally results from environmental contamination and horizontal, patient-to-patient, transmission.
- Dialyzer membranes, hemodialysis ultrafiltrate, and peritoneal fluid: Theoretically, the passage of HCV through intact dialyzer membranes seems improbable as the viral particles have an estimated diameter of 35 nm, much higher than the pores of even the most permeable dialysis membrane. Nevertheless, the passage of the virus into the dialysate compartment could result from any alteration in pore size or disruption of the membrane integrity associated with the process of filter assembly, the dialysis session itself, or with dialyzer reuse. HCV has been found in several organic fluids including ascites; thus, the peritoneal fluid of HCV-infected PD patients may represent a potential infectious risk. Since most studies suggest that HCV RNA is present in the CAPD effluent of some patients, the effluent should be considered infectious material (Castelnovo C et al, 1997).
- Reprocessing of dialyzers.
Risk Factors For HCV Infection In Dialysis Patients:
Identified risk factors for HCV infection among dialysis patients include:

**Number of blood transfusions:**
Anti-HCV-positive HD patients had received significantly more units of blood products than anti-HCV negative patients (Natov SN et al, 1998). Fortunately, since the introduction of erythropoietin and screening of blood products for anti-HCV, the risk of acquiring post-transfusion HCV infection has declined to less than one per 3000 units of blood products transfused (Donahue JG et al, 1992).

**Duration of ESRD:**

**Mode of dialysis:**
Patients on peritoneal dialysis (PD) are at lower risk for HCV infection and, in contrast to hemodialyzed patients, the duration of dialysis does not appear to be a risk factor for acquiring HCV infection (Pereira BJ et al, 1997) the rate of seroconversion was 0.15 per patient-year on HD compared to 0.03 per patient-year on continuous ambulatory peritoneal dialysis (CAPD), the prevalence of HCV infection was 18 and 7 percent among HD and PD patients, respectively (Weinstein T et al, 2001).

**Other factors:**
A history of previous organ transplantation, Intravenous drug abuse, male gender have been reported to have a higher prevalence and significantly higher concentration of serum HCV RNA than females (DuBois DB et al, 1994).
Natural history of HCV in CKD patients (dialysis population):  
Accurate assessment of the natural history of HCV in dialysis patients and renal transplant recipients has been difficult as infection in these patients is typically asymptomatic with an apparently indolent course.

Dialysis patients generally have high morbidity and mortality rates reflecting age and comorbid conditions making the long-term consequences of HCV infection difficult to determine. Routine evaluation of HCV infection is further complicated in CKD by aminotransferase values which are typically lower in the dialysis than in the non-uremic population (Alter MJ et al, 1992).

Treatment Of HCV Infection In ESRD Patients On Maintenance Dialysis:  
The recommended therapy of most patients with chronic HCV infection who do not have renal dysfunction consists of interferon alfa (preferably pegylated interferon) in combination with ribavirin. Ribavirin warnings for patients with renal dysfunction are because its clearance is impaired in these individuals and the drug and its metabolites are not removed by hemodialysis (Glue P, 1999).

Thus, ribavirin is not recommended for patients with a creatinine clearance below 50 mL/min, outside its use in controlled trials (Meyers CM et al, 2003). Similar concerns currently apply to pegylated interferon because of its long half-life. The role of standard, non-pegylated interferon-alfa (IFNa) alone therapy in the treatment of HCV infection in ESRD patients on maintenance dialysis is still evolving.

In a study of 19 HD patients with chronic HCV infection evaluated the effects of treatment with IFNa for six months. Six patients subsequently dropped out because of intolerance of side effects or complications from their primary disease. Benefits with therapy included a decrease to normal of AST and ALT levels by the second month of therapy in all patients, and HCV RNA became
negative in 10 of 13 patients by the end of the treatment period (Raptopoulou-Gigi M et al, 1995).

In a double-blind, controlled trial of dialysis patients, a nonsignificant trend toward biochemical and virological improvement at 12 months was observed among patients given IFNa compared to those given placebo (Fernández JL et al, 1997).

While in a multicenter randomized study of HCV RNA positive HD patients, the Mean ALT values significantly decreased following IFN therapy and remained within normal limits during the follow-up period in all patients in the treatment group, while no changes were observed in the (untreated) control group (Campistol JM et al, 1999). In this study among the patients who underwent renal transplantation, Fifteen patients (10 in the treatment group and 5 in the control group), the mean ALT values during the post-transplant follow-up were significantly lower in patients who had received IFN treatment as compared to those in patients from the control group (P<0.05).

In a meta-analysis of 20 clinical trials, the overall sustained virologic response rate with IFN was 41 percent (95% CI 33 to 49 percent), with a discontinuation rate of 26 percent (95% CI 20 to 34 percent) (Gordon CE et al, 2008). The response rate was increased with a regimen of 3 million units or higher of IFN 3 times weekly. These observations demonstrate that IFN therapy in HD patients results in good biochemical and virological response and appears to exert a beneficial effect on the course of liver disease following renal transplantation, regardless of the virological response (Campistol JM et al, 1999). Other reports, have also documented that IFNa therapy for treatment of HCV-infected ESRD patients on maintenance dialysis, administered prior to renal transplantation, is associated with high rates of sustained biochemical and virological response in the post-transplant period (Kamar N et al, 2003).
Kidney Disease Improving Global Outcomes (KDIGO, 2008) published Clinical Practice Guidelines for management of HCV-infected patients with CKD Stage 5 on maintenance hemodialysis, as follows:

Interferon: Alfa-2a IFN: 3mU SQ 3 times per week
   Alfa-2b IFN: 3mU SQ 3 times per week

Patients with genotypes 1 and 4 should receive 48 weeks of IFN therapy if an early viral response is obtained at 12 weeks (>2 log fall in viral titer). Genotypes 2 and 3 should be treated for 24 weeks.

Ribavirin: is not recommended.

**Pegylated Interferon (PEG-IFN):**

The second therapeutic option for patients on chronic haemodialysis with chronic hepatitis C is to use pegylated interferon.

No significant differences in apparent body clearance of peg-IFNα-2a between patients with normal kidney function and those with significant reductions in kidney function (creatinine clearance > 100 mL/min vs. 20–40 mL/min) have been detected (Hmaied F et al, 2006) However, the pharmacokinetics of pegylated interferon α-2a during hemodialysis may vary reflecting permeability and dialyzer pore size (Barril G et al, 2004).

SVR could be achieved in 64.7% of patients on hemodialysis with chronic hepatitis C by a treatment with peglyated-interferon α-2a. Group A (patients received 135 μg peglyated-interferon α-2a weekly for 48 wk) had a significantly better efficacy compared to the control group B (untreated), but the side effects need to be concerned (Ayaz C et al, 2008).

In a study to evaluate the long-term efficacy of pegylated interferon (PEG-IFNα-2a) in HCV-positive hemodialysis (HD) patients: (Ucmak H et al, 2008) Twenty-five HCV-RNA-positive hemodialysis patients were included into the
study. Twelve patients were allocated to the PEG-IFN treatment group (group 1). Six refused the therapy, and seven were not candidates for kidney transplantation and were allocated to the control group (group 2).

All patients underwent chronic hemodialysis treatment for end-stage renal disease during the study period. Group 1 patients received PEG-IFN alpha-2a at a dose of 135 μg weekly for 48 weeks. The patients were prospectively followed up for a period of 192 weeks. Biochemical and virological responses were evaluated at 144 weeks after the completion of therapy, SVR was achieved in half (50%) of patients at the end of 144 weeks of follow-up.

Predictors of response to IFNα therapy:

Drug administration and duration of treatment

Higher doses of IFNα and longer duration of treatment seem to be associated with higher response rates in hemodialysis patients however, such regimens may result in more adverse effects (Huraib S et al, 1999).

The efficacy and adverse effects of IFNα administered at a dosage of three million units (MU) three times weekly for a period of one year were assessed in 17 hemodialysis patients with biopsy-proven HCV-associated chronic hepatitis. A virological response was observed in 88 and 71 percent of patients at the end of treatment and at six months after completion of therapy, respectively. Severe side effects (marked lethargy and myalgia) prompted the discontinuation of treatment in only one patient (Huraib S et al, 1999).

A regimen of three million units (MU) or 6 MU of recombinant IFN-alfa-2b or natural IFN-alfa administered intramuscularly daily for the first two weeks, followed by three times a week for 22 weeks (six HD patients) was compared to a regimen of 3 MU of IFN-alfa-2b given three times a week for 24 weeks (three HD patients). In the group with daily IFN administration in the first two weeks, three
of the six patients had biochemical and virological response at six months after completion of therapy. However, IFN therapy had to be discontinued in the other three patients due to serious side effects (depression, loss of consciousness and persistence of high-grade fever). No such events occurred in the group that received 3 MU three times a week for 24 weeks (Uchihara M et al, 1998).

Daily or high-dose administration of IFNa has therefore been associated with serious adverse events in hemodialysis patients with chronic hepatitis C virus infection. This increased risk may be due to the pharmacokinetics of IFNa in patients with impaired renal function. Compared to nonuremic patients, hemodialysis patients have one-half the clearance of IFNa, significantly longer half-lives of IFN-alfa-2b, and markedly larger areas under the serum IFN concentration curve. (Rostaing L et al, 1998). These observations question the safety of using daily and high-dose IFNa regimens in hemodialysis patients.

Pretreatment viral load

A low pretreatment viral load has been correlated with a sustained response to IFNa therapy, whereas relatively high HCV RNA levels have been associated with a nonsustained or no response (Umlauft F et al, 1997).

HCV genotype

In the general population, infections with HCV genotype 1 have been associated with a lower response rate to IFN therapy than infections with other HCV genotypes (Davis GL et al, 1997). In hemodialysis patients, however, some studies have failed to find any correlation between HCV genotype and response to IFN therapy (Umlauft F et al, 1997), HCV genotype 1b was associated with a better response to interferon treatment, as compared with HCV genotypes 1a and 2a, which seemed to predict a low response rate (Umlauft F et al, 1997).
Liver histology

The presence of liver cirrhosis on the pretreatment biopsy specimen has been associated with a lower response rate to IFN treatment (Davis GL et al, 1997). Similarly, in HD patients, mild liver pathology has been found to be a predictor of sustained response (National Institutes of Health (NIH), 1997).

Effect of HCV infection upon survival with dialysis or renal transplantation:

In the absence of renal failure, the long-term survival of patients with chronic HCV infection is good, except for those with decompensated cirrhosis. However, once decompensated cirrhosis occurred, the five-year survival fell to 50 percent.

Overall, HCV infection is a poor prognostic factor for survival among patients with end stage renal failure (Terrault NA et al, 2007). This was perhaps best studied in a 2004 meta-analysis of four clinical trials of over 2000 patients in which HCV infection was associated with an increased risk of mortality of 1.57 (95% CI of 1.33 to 1.86) versus uninfected dialysis patients (Fabrizi F et al, 2004). Hepatocellular carcinoma and cirrhosis were also significantly more frequent in HCV-infected patients.

Although the presence of anti-HCV antibodies at the time of renal transplantation may be associated with an increased risk of death, it is not yet known whether survival for anti-HCV positive patients is greater with renal replacement therapy with dialysis or with transplantation.

Some studies suggest that renal transplantation may result in better survival than dialysis among anti-HCV positive patients (Maluf DG et al, 2007). A New England Organ Bank study evaluated the relative risk of death among patients with or without anti-HCV antibodies who were placed on a renal transplant waiting list and either did or did not receive a renal allograft (Pereira BJ et al, 1998). Among
all patients, transplantation was associated with enhanced survival compared to continued dialysis \( (p<0.0001) \). The relative risk of death for transplantation versus dialysis was 4.75, 1.76, 0.31, and 0.84 at follow-up periods of zero to three months, three to six months, seven months to four years, and after four years, respectively. At all time periods, the relative risk of death was similar between those with and without anti-HCV antibodies. Thus, transplantation resulted in a long-term survival benefit among the patients who were anti-HCV positive. Similar findings were noted in another report that compared survival among anti-HCV positive patients who underwent renal transplantation with anti-HCV positive individuals who were acceptable for transplant but had not yet undergone the procedure (Knoll GA et al, 1997). Outcomes were assessed in patients with at least two years of follow-up information. Despite similar comorbid clinical features, patients in whom renal transplantation had been performed had a lower mortality than those remaining on dialysis.

These findings suggest that the possible detrimental effect of transplantation on the course of HCV infection does not outweigh its long-term beneficial effect on survival in ESRD. Thus, anti-HCV positive status alone should not be considered a contraindication for renal transplantation
An approach to evaluation of renal transplant candidates with HCV:

Liver biopsy is essential in the evaluation of liver disease in renal transplant candidates because reliance on clinical and biochemical findings may underestimate its severity. Pretransplant liver biopsy provides useful prognostic information. Patients with minimal to mild chronic hepatitis (stages I and II) can be safely transplanted, and a pretransplant trial of antiviral therapy should be considered. Patients with cirrhosis on biopsy should not be transplanted because of the risk for post-transplant hepatocellular failure. If there is a sustained virologic response to antiviral therapy, and if repeat liver biopsy shows improvement, transplant candidacy can be reconsidered. For cirrhotic patients, combined liver & kidney transplant may be a consideration if they subsequently develop hepatocellular failure. For patients whose histology precludes renal transplantation yet whose hepatic function is too well compensated to require liver transplantation, it may be safer to remain on dialysis. In the event that decompensated cirrhosis develops, combined orthotopic liver and kidney transplantation may be indicated (Fabrizi F et al, 2005).
Suggested algorithm for evaluation and treatment of anti–hepatitis C virus (anti-HCV)-positive patients who are under consideration for kidney transplantation. 1. For patients with HCV-associated glomerulonephritis, strong consideration of HCV treatment is recommended before transplantation to prevent recurrent glomerulonephritis after transplantation. 2. Practices vary by center regarding whether patients with cirrhosis are referred for combined liver-kidney transplantation or considered for kidney transplantation alone. 3. The usual treatment duration is 12 mo. Patients who fail to achieve an undetectable HCV RNA level (<50 IU/ml) after 6 mo of treatment are highly unlikely to achieve SVR with continued treatment and should have treatment discontinued. 4. Patients who wait several years on the transplant waiting list may require retesting of HCV RNA before transplantation to confirm presence/absence of infection. In addition, repeat liver biopsy may be considered if the interval from the previous biopsy is >3

Figure 4: (Terrault NA et al, 2007)

Ant-HCV+ Dialysis Patient

HCV RNA—
(≤50 IU/mL)

→

Normal enzymes
Normal liver function

→

Liver biopsy

No or mild
fibrosis

Treatment optional
Consider if favorable response characteristics: genotype 2 or 3, low HCV viral load (<600,000 IU/mL) or if HCV-associated GN

→

Await kidney transplantation

→

HCV RNA+

→

Clinical or radiologic evidence of cirrhosis

→

Moderate fibrosis

→

Treat before transplantation

→

Peg-IFN or IFN³

May include low-dose RBV in selected patients

→

SVR* No SVR

→

Consider combined kidney/liver transplantation

→

Consider treatment options
May include retreatment or proceeding with kidney transplantation
yr. The ideal interval for follow-up biopsy is not known. For immunocompetent patients, the recommended interval is every 3 to 5 yr (National Institutes of Health HCV Consensus Statement, 2003), and populations with potentially accelerated progression warrant closer monitoring. GN, glomerulonephritis; IFN, interferon; RBV, ribavirin; SVR, sustained virologic response.

Kidney Disease Improving Global Outcomes (KDIGO, 2008) published Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease:

**Table 4:** Levels of strength of recommendations:

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Wording of Recommendation</th>
<th>Basis for Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>An intervention “should” be done</td>
<td>“High” quality evidence and/or other considerations support a strong guideline</td>
</tr>
<tr>
<td>Moderate</td>
<td>An intervention “should be considered”</td>
<td>“Moderate” quality evidence and/or other considerations support a moderate guideline</td>
</tr>
<tr>
<td>Weak</td>
<td>An intervention “is suggested”</td>
<td>“Low” or “Very Low” quality evidence; predominantly based on expert judgment for good clinical practice</td>
</tr>
</tbody>
</table>
Management of HCV-infected patients before and after kidney transplantation:

1. Evaluation and management of kidney transplant candidates:
   - 1.1 All kidney transplant candidates should be evaluated for HCV infection (Strong)
      - In low-prevalence settings, initial testing with EIA and follow-up of positive EIA with Nucleic acid test(ing) NAT should be considered. (Moderate)
      - In high-prevalence settings, initial testing with NAT should be considered. (Moderate)

   - 1.2 HCV infection should not be considered a contraindication for kidney transplantation. (Moderate)

   - 1.3 It is suggested that HCV-infected kidney transplant candidates undergo a liver biopsy before transplantation. (Weak)

     A liver biopsy performed before kidney transplantation is necessary to determine the severity of hepatic injury and thereby to assess the prognosis and management of the patient both before and after transplantation. This recommendation is contrary to the AASLD guideline that recommends liver biopsy for patients with genotypes 1 and 4, but considers it unnecessary for patients infected with genotypes 2 and 3 (https://www.aasld.org/eweb).

   - 1.4 - It is suggested that HCV-infected patients with cirrhosis confirmed by liver biopsy, but clinically compensated liver disease, be considered for kidney transplantation only in an investigational setting. (Weak)
This is based on the fact that there are very limited outcome data regarding transplantation of a kidney alone in HCV-infected recipients with pre-existing compensated cirrhosis of the liver. A retrospective study reported that patients with liver cirrhosis before kidney transplant had a 10-year rate of survival of only 26% ([Mathurin P et al., 1999]). Also, there are no data available to determine whether patients with early cirrhosis on liver biopsy yet well-compensated clinical disease do better if they are transplanted or remain on dialysis. A trial of IFN therapy can be considered for such patients, although regression of fibrosis was demonstrated only in 7.8% of non-CKD patients and in three of four dialysis patients, numbers that are too small to draw any conclusions ([Pol S et al., 2004]).

HCV-infected patients with evidence of decompensated liver disease should be evaluated for simultaneous liver kidney transplantation. Transplantation of a kidney alone in this situation is not recommended.

- **1.5 - It is suggested that HCV-infected kidney transplant candidates be considered for treatment with standard IFN before transplantation.** (Weak)

- **1.6 - It is suggested that patients on a kidney transplant waiting list be evaluated for HCV infection.** (Weak)
  - For patients who have never been tested for HCV, it is suggested that testing be performed with EIA in low-prevalence settings (with follow-up of positive results by NAT) and NAT in high-prevalence settings. (Weak)
  - It is suggested that HCV-infected patients not previously known to be viremic be placed on hold status pending full evaluation of the severity of their liver disease. (Weak)
  - It is suggested that patients who had received antiviral treatment before listing and had SVR have testing with NAT repeated at least
annually (Weak); if NAT becomes positive, it is suggested that the patient be put on hold status and have full evaluation of their liver disease. (Weak)

- It is suggested that HCV-infected patients who had prior evaluation with liver biopsy, but either failed or refused antiviral treatment, have repeat liver biopsy every 3–5 years while on the transplant waiting list, depending on their histologic stage. (Weak)

For patients in whom SVR was previously obtained, it is important to perform a NAT annually while on the list to confirm durability of the SVR. Patients who relapse should be placed on hold and referred to a hepatologist for evaluation. Although no data exist on treatment of relapsers with kidney failure, there are data from the general population indicating that these patients can be successfully retreated using a longer course of therapy.

For persistently viremic patients who either failed to achieve SVR or refused IFN therapy, annual re-evaluation should include an assessment of the clinical stability of the liver disease by a hepatologist. Furthermore, it is the judgment of the Work Group that a repeat liver biopsy be performed every 3 years in patients whose baseline liver biopsy (obtained before transplant) showed Metavir Stage 3 and every 5 years for those whose liver biopsy was Metavir Stage 1 or 2. There are no good data to support this recommendation, although it has been demonstrated that liver disease can progress in patients on dialysis (Pereira BJ et al, 1998).

2 Use of kidneys from HCV-infected donors:
   - 2.1 - All kidney donors should be tested for HCV infection. (Strong)
     - Testing with both EIA and NAT (if NAT is available) is suggested. (Weak)
• **2.2 - It is suggested that transplantation of kidneys from donors infected with HCV be restricted to recipients with positive NAT.** (Weak)

To avoid these potential but major complications in uninfected recipients, it is suggested that kidneys from HCV-infected donors should not be used in potential recipients without HCV viremia. However, kidneys from donors infected with HCV can be used in potential recipients with evidence of active HCV viremia at the time of transplantation.

This recommendation is based on the following observations:

1. Studies have shown that the use of kidneys from HCV infected donors in recipients already infected with HCV may shorten waiting times and neither affect short-term survival nor invariably lead to progressive liver disease ([Morales JM et al, 2000](#)). In contrast, a registry analysis demonstrated that recipients of kidneys from HCV infected donors was associated with a higher rate of mortality, regardless of the anti-HCV antibody status of the recipient ([Bucci JR et al, 2002](#)).

2. Large registry analysis indicates that the use of kidneys from anti-HCV-positive deceased donors in HCV-infected recipients is associated with superior patient survival compared to remaining on dialysis ([Abbott KC et al, 2004](#)).

The risks and effects of superinfection with an HCV genotype from the donor that is different from the genotype of the potential HCV-infected recipient are unknown. A new genotype superinfection through transplantation has been reported in two single center investigations. Although one of the studies reported that elevated transaminase levels did occur, ([Widell A et al, 1995](#)), the other found no impact on patient or graft survival ([Natov SN et al, 1999](#)).
3: Use of maintenance immunosuppressive regimens:

- All conventional current maintenance immunosuppressive regimens can be considered for use in HCV-infected kidney transplant recipients. (Weak)

By virtue of their mechanisms of action, immunosuppressive therapies have the potential to have a permissive effect on HCV kinetics after transplantation. This may result in differing effects of the various immunosuppressive agents on viral replication, progressive liver disease, extrahepatic manifestations, and patient and graft outcomes after kidney transplantation in HCV-infected recipients. In addition, diminished drug clearance in the setting of hepatic dysfunction may affect blood levels of commonly used immunosuppressive agents that are metabolized in the liver, such as cyclosporin and tacrolimus. At the present time, there are relatively few studies that examine the impact of immunosuppression on HCV-related outcomes in kidney transplant patients. Although there are studies in liver transplant recipients, the data from these studies cannot be readily extrapolated to the kidney transplant population. Effective immunosuppressive treatment of HCV-infected kidney transplant recipients, therefore, requires consideration of the safety and efficacy of current agents balanced against their potential adverse effects.

Available evidence indicates that all conventional, current maintenance immunosuppressive agents can be used in kidney transplant patients infected with HCV. Viral replication is increased after transplantation in the setting of chronic immunosuppression use, although it is not clear whether or how this impacts liver disease, or patient, or graft survival in kidney transplant recipients (Mahmoud IM et al, 1999).

For example, studies in HCV-infected liver transplant recipients suggest that treatment with corticosteroid boluses for acute rejection may result in up to a 100-
fold increase in HCV RNA concentrations, increased frequency of acute hepatitis, and decreased time to recurrence of disease (Lake JR, 2003) However, this has not been established in kidney transplant patients with HCV infection.

As far as mycophenolic acid-based therapies in HCV-infected transplant recipients are concerned, there is growing evidence for the rationale of using this adjunctive agent to spare exposure to the potential toxicities of calcineurin inhibitors and steroids, although specific data are limited in this regard. Studies in HCV-infected nontransplant patients suggest that mycophenolic acid therapies may have an inhibitory effect on viral replication, but this has not been established in transplant recipients (Zekry A et al, 2004).

On the other hand, there is no convincing evidence of a specific deleterious effect of mycophenolic acid therapy on either graft or patient outcomes in kidney transplant recipients with HCV infection (Abbott KC et al, 2003). In fact, a retrospective registry analysis indicates that mycophenolate mofetil was associated with favorable outcomes, even after adjustment for all possible confounding factors (Abbott KC et al, 2003) Trials in liver transplant patients have confirmed the potential clinical outcome benefit associated with mycophenolate mofetil.

Regarding calcineurin inhibitors, emerging evidence from retrospective studies suggests that cyclosporin, but not tacrolimus, may inhibit HCV viral replication. However, this remains to be validated in kidney transplant patients. Also, the available studies suggest that tacrolimus is more diabetogenic than cyclosporin in most transplant recipients. Among HCV infected kidney transplant recipients, the risk of New-onset diabetes after transplantation (NODAT) appears to be especially high in patients being treated with tacrolimus. For patients developing hyperglycemia in the setting of tacrolimus use, conversion to a cyclosporin-based regimen should be considered.
Among antibody therapies commonly used for induction or for treating acute rejection, unfavorable outcomes have been frequently reported in the literature concerning liver transplant patients with HCV infection. In contrast, preliminary registry data of 3706 patients from the United States indicate that antibody induction is associated with improved patient and graft outcomes in HCV-infected kidney transplant recipients (Luan FL et al, 2008).

There are limited data on the use of sirolimus in HCV infected kidney transplant recipients. This is another area in which more information would be needed before specific recommendations could be made. On the basis of the available although sparse evidence, and even though most immunosuppressive agents increase viral replication, these therapies can all be used in kidney transplant patients with HCV infection (Roth D et al, 1996).
Outcome Of Kidney Transplantation In Chronic Hepatitis C Virus Infected Patients
Hepatitis C Virus After Renal Transplantation

Hepatitis C virus (HCV) has been implicated in the pathogenesis of renal disease in native as well as transplanted kidneys. In native kidneys, HCV has been associated with membranoproliferative glomerulonephritis (MPGN), with or without mixed cryoglobulinemia, and membranous nephropathy (MN). Among renal transplant recipients with HCV infection, both recurrent glomerular disease and de novo MPGN and MN can occur (Periera BJ et al, 1995).

HCV infection may be more commonly associated with glomerular disease in renal transplants than in native kidneys. One possible mechanism is that immunosuppressive therapy to prevent rejection increases the titer of HCV RNA (Periera BJ et al, 1995). The higher number of HCV particles may lead to an alteration in the ratio of antibody to antigen in immune complexes, resulting in decreased clearance and increased deposition of viral complexes in the kidney (Roth D et al, 1995).

HCV Associated renal disease post-transplantation:

The most common manifestations are proteinuria, MPGN, and membranous nephropathy.

Post-transplant proteinuria:

Proteinuria has been used as a marker of disease in the renal allograft among anti-HCV positive transplant recipients (Mahmoud IM et al, 2004).

The HCV positive renal transplant recipients compared to HCV-negative patients were more likely to have nephrotic syndrome (36 versus 12 percent), persistent microhematuria (73 versus 35 percent), and MPGN (45 versus 6 percent). These observations indicate that proteinuria in HCV-infected renal
transplant recipients may or may not indicate HCV associated disease in the renal allograft (Cruzado JM et al, 2001).

**Membranoproliferative glomerulonephritis:**

As in native kidneys, MPGN with or without mixed cryoglobulinemia has been described in association with HCV in the renal allograft. MPGN is a frequent finding in patients with proteinuria and hematuria. It can occur as recurrent or de novo disease; in addition, chronic transplant glomerulopathy can have a membranoproliferative pattern on histologic examination. The presence of HCV-associated MPGN is associated with a worse long-term renal outcome (Cruzado JM et al, 2001).

**Membranous nephropathy:**

Membranous nephropathy (MN) in renal transplant recipients has been associated with HCV infection. However, it is unclear if there is an etiologic relationship. HCV infection was preferentially associated with MN rather than MPGN. The clinical presentation and outcomes of HCV-associated MN (persistent heavy proteinuria and progressive deterioration of renal function) were similar to post-transplant idiopathic de novo MN (Hammoud H et al, 2001).

**Renal thrombotic microangiopathy:**

A renal thrombotic microangiopathy (RTMA) may be observed in HCV-infected renal transplant recipients, particularly among those with anticardiolipin antibodies. This association was suggested in a report of 18 anti-HCV positive patients, five developed RTMA between 5 and 120 days after transplantation. Anticardiolipin antibodies were found in all five patients of these patients, but in only one of the thirteen without a microangiopathy. The hypothesis that anticardiolipin antibodies, HCV infection, and renal thrombosis were correlated was also supported by the observation that normal anticardiolipin antibody titers were found in the seven HCV-negative transplant recipients who presented with RTMA/hemolytic uremic syndrome during the same time period and served as a control group (Baid S et al, 1999).
Acute transplant glomerulopathy:
May be an atypical variant of acute cellular rejection, has a high prevalence among HCV-positive renal transplant recipients (Cosio FG et al, 1996).

Chronic transplant glomerulopathy:
Usually believed to be a glomerular manifestation of chronic rejection, has been reported in association with HCV infection (Gallay BJ et al, 1995).

Diagnosis:
The diagnosis is usually established by renal biopsy., the major differential is with the MPGN pattern of the transplant glomerulopathy induced by chronic allograft rejection. Both disorders present with mesangial cell proliferation and glomerular basement membrane splitting and are often indistinguishable on light microscopy, electron microscopy typically shows large electron-dense immune complex deposition in the glomerular basement membrane in MPGN and only subendothelial accumulation of electron-lucent material in transplant glomerulopathy.
Outcome of Kidney Transplantation in Chronic Hepatitis C Virus Infected Patients

HCV infection is the main cause of chronic liver disease and the fourth cause of death among renal transplant recipients (Campistol JM et al, 1999). The severity of liver disease correlates poorly with serum aminotransferase levels. It has been estimated that 42–60% of HCV-positive hemodialysis patients are carriers of active chronic hepatitis. (Rostaing L et al, 1998).

Although long term studies indicate a less favorable patient and graft survival among HCV-positive recipients, transplantation continues to be the better option for most patients, because mortality on hemodialysis is even higher (McHutchison JG et al, 1998).

It has been shown that immunosuppressive therapy facilitates viral replication and progression of liver disease (McHutchison JG et al, 1998). However, because post-transplant alpha-IFN therapy cannot be instituted due to the high rate of rejection associated with the immunologic properties of the treatment, and because ribavirin is not indicated during hemodialysis because of the possibility of severe hemolytic anemias related to cumulative doses of the drug, pretransplant alpha-IFN monotherapy represents the current approach to treating patients with chronic HCV hepatitis (Casanovas-Taltavull T et al, 2001).

The efficacy of interferon alfa therapy in chronic hepatitis C has been shown in many randomized controlled trials, and its use currently is recommended in anti-HCV positive patients with abnormal serum aminotransferases and well compensated chronic hepatitis on biopsy (lindsay KL, 1997).
Normalization of serum ALT is defined as a biochemical response to treatment, and clearance of HCV RNA from serum is defined as a Virological response. A complete biochemical and virological response by the end of the treatment is defined as end of treatment response ETR and at 6 or 12 months as a sustained response SR (Anonymous, 1997). Two therapeutic regimens using identical dosing (3 million units of interferon alfa administered subcutaneous three times weekly) but different duration of treatment (either 6 or 12 months) have been studied (Lindsay KL, 1997).

Six month treatment courses resulted in biochemical and virological ETR rates of 40 to 50% and 30 to 40% and biochemical and virological SR of 15 to 20% and 10 to 20% (Anonymous, 1997). The biochemical and virological response were accompanied by histological improvement.

Twelve month treatment regimens did not produce higher biochemical or virological ETR but did increase SR rates to 20 to 30% (Anonymous, 1997).

As shown in (table 5), the initial response of dialysis and transplant patients to interferon alfa treatment has been encouraging with most patients showing a decrease in serum ALT levels and an improvement in liver histology:
Table 5: Initial Response to Interferon Alfa Treatment in Dialysis and Transplant Patients with Chronic Hepatitis C (Natov S.N et al 2003):

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Population</th>
<th>N</th>
<th>Decrease in Serum ALT(%)*</th>
<th>Improvement in Liver histology(%)*</th>
<th>Clearing of Serum HCV RNA (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harihara et al,1994</td>
<td>Tx</td>
<td>3</td>
<td>67</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Koeing et al,1994</td>
<td>HD</td>
<td>37</td>
<td>71</td>
<td>NA</td>
<td>65</td>
</tr>
<tr>
<td>Rao and Anderson,1995</td>
<td>HD+Tx</td>
<td>10</td>
<td>100</td>
<td>80</td>
<td>NA</td>
</tr>
<tr>
<td>Pol et al,1995</td>
<td>HD</td>
<td>19</td>
<td>85</td>
<td>NA</td>
<td>53</td>
</tr>
<tr>
<td>Rostaing et al,1995</td>
<td>Tx</td>
<td>16</td>
<td>100</td>
<td>NA</td>
<td>0</td>
</tr>
<tr>
<td>Casanovas et al,1995</td>
<td>HD</td>
<td>10</td>
<td>90</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Durate et al,1995</td>
<td>HD</td>
<td>5</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Raptopoulou-Gigi et al,1995</td>
<td>HD</td>
<td>19</td>
<td>100</td>
<td>NA</td>
<td>77</td>
</tr>
<tr>
<td>Ozgur et al,1995</td>
<td>Tx</td>
<td>5</td>
<td>100</td>
<td>100</td>
<td>NA</td>
</tr>
<tr>
<td>Rodrigues et al,1997</td>
<td>HD</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>50</td>
</tr>
<tr>
<td>Yasumura et al,1997</td>
<td>Tx</td>
<td>6</td>
<td>100</td>
<td>NA</td>
<td>33</td>
</tr>
<tr>
<td>Umlauft et al,1997</td>
<td>HD</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
<td>73</td>
</tr>
<tr>
<td>Rostaing et al,1998</td>
<td>HD</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>90</td>
</tr>
<tr>
<td>Hanafusa et al,1998</td>
<td>Tx</td>
<td>10</td>
<td>80</td>
<td>NA</td>
<td>20</td>
</tr>
</tbody>
</table>

* Among patients who had an abnormal test before treatment and who completed the course of treatment.

ALT=alanine aminotransferase, HCV=Hepatitis C Virus
HD=Hemodialysis patients, Tx=Transplant recipients

In a study performed by **Huraib S & Co-workers, 2001**, Patients who are anti-HCV positive before renal transplantation have a significantly increased risk of post-transplant liver disease. A prospective controlled study was conducted to evaluate the post-transplant outcome of renal graft candidates with HCV associated chronic hepatitis (n = 30). Patients were randomly assigned to either of two groups. All patients on enrollment underwent liver biopsy, which showed mild to moderate hepatitis activity (mean 4.1, range 2-6). Half the patients received interferon-alpha
(IFN-a) administered at a dosage of 3 million units three times weekly for 1 year. Liver biopsy was repeated for treated patients at the end of IFN-a treatment. Of these, 11 patients received renal transplant (group A). The other half did not receive IFN-a and to date 10 patients have been transplanted (group B). Renal transplant recipients were prospectively followed for a period of 12 months and a follow-up liver biopsy was also done at the end of this period (end of study). Biochemical and virological responses were evaluated and the histologic activity index (HAI) scoring according to Knodell was assessed. The mean pretreatment serum HCV RNA level was 1.14 ± 0.84 and 1.0 ± 0.89 mEq/ml for groups A and B, respectively (bDNA assay sensitivity threshold is <0.2 mEq/ml). HCV RNA became undetectable in 4 patients of group A. At the end of study period the mean quantitative HCV RNA titers were 1.43 ± 4.07 and 15.18 ± 11.08 mEq/ml in groups A and B, respectively (p < 0.0001). In group A, the mean HAI score decreased from 4.27 ± 1.19 to 1.64 ± 0.67 after IFN-a treatment (p < 0.0001). This score was maintained till the end of the study period with a mean of 1.82 ± 0.6. Mean HAI score of group B on enrollment was 3.9 ± 1.2 and at the end of study increased to 5.5 ± 1.35 (p = 0.01). There was statistically significant difference (p value less than 0.0001) between the HAI scores at the end of the study period between the two groups. These results demonstrate that interferon therapy while on dialysis is associated with less viremia and decreased progression of chronic liver disease in renal transplant patients with hepatitis C.

In a clinical trial conducted by Casanovas-Taltavull T & Co-workers 2001, a total of 29 noncirrhotic hemodialysis patients with chronic hepatitis C virus (HCV) infection (based on long-term rise in ALT, HCV serology, HCV RNA by polymerase chain reaction methods, and histological evidence) were included. Tolerability to IFN treatment, pre and post-transplantation therapeutic results, and long-term outcome were recorded. IFN regimen consisted of 3 million units (MU) times per week after hemodialysis sessions for 6 months, followed by 1.5 MU after each hemodialysis session for an additional 6 months. All patients gave informed
In all, 28 patients completed IFN treatment. One patient died of heart failure at 3 months during the course of treatment, IFN therapy was fairly well tolerated. Adverse effects due to IFN toxicity, renal disease, or causes related to the immunological properties of IFN were observed in 24% of patients. At the end of treatment, ALT had normalized in 23/28 patients (82.1%), and HCV RNA had cleared in 23/28 patients (82.1%). During follow-up, HCV RNA was persistently negative in 18 patients (64%, including transplant recipients). A total of 14 patients (nine HCV RNA negative) received a kidney transplant. Mean follow-up after the procedure was 41 ± 28 months. In all, 12 patients had a functioning graft, one had acute vascular rejection, and one died of carcinoma. All transplanted patients maintained normal ALT levels, and eight remained HCV RNA negative.

In a study that was carried out by González-Roncero F & Colleagues, 2003, data from all HCV-infected patients (n = 38) undergoing renal transplantation from a cadaveric donor between January 1997 and June 2002 were retrospectively reviewed. Thirteen of the 38 patients had been treated with alpha-IFN during the pretransplant period.

Sustained viral clearance (HCV-RNA negative) up to the time of kidney transplantation was achieved in seven patients, whereas in the remaining six, IFN treatment was withdrawn due to a lack of response and/or adverse events.

Controls were HCV-negative renal transplantation recipients operated during the same period (n = 273).

The diagnosis of HCV hepatitis was established by positive anti-HCV antibodies (ELISA or second-generation RIBA) and the presence of HCV-RNA by polymerase chain reaction (PCR). In all patients receiving alpha-IFN, a liver
biopsy was obtained before instituting therapy. Histologic examination showed chronic active hepatitis and mild to moderate inflammatory activity.

Patients received alpha-IFN for a mean of 10 months (range 6–18), at a mean dose of 6 million units per week by subcutaneous injection (divided into two or three doses administered after the dialysis session).

In the remaining 25 patients, alpha-IFN therapy was not indicated for different reasons, including absence of significant inflammatory activity in the liver biopsy (n = 9), underlying autoimmune disease contraindicating alpha-IFN administration, patient refusal to undergo liver biopsy or to be treated with alpha-IFN, or urgent need of kidney transplantation.

Post-transplant assessment of biochemical profile, viral replication, and survival of both the recipient and the graft were carried out.

At the end of the study (2.5 years follow-up) the seven patients in whom alpha-IFN therapy was effective, showed persistent clearance of viral replication after kidney transplantation, no case of HCV-RNA positivity has been documented. All patients show excellent clinical courses of liver disease.

These data confirm that pretransplantation alpha-IFN monotherapy may be effective to produce disappearance of viral replication in HCV-infected patients who are candidates for kidney transplantation. HCV-RNA clearance can be maintained in the post-transplant period despite interactions with immunosuppressive agents.

*Cruzado JM & Colleauges, 2003* conducted a study, the purpose of which was to examine the effect of pretransplant interferon administration on the occurrence of post-transplant de novo glomerulonephritis in hepatitis C virus (HCV)-positive renal allografts. From December 1992 to December 2000, 78
HCV-positive patients received a renal allograft. Fifteen out of 78 received pretransplant interferon for 1 year. Hepatitis C virus was investigated by serology and qualitative polymerase chain reaction (PCR). Hepatitis C virus-related de novo glomerulonephritis (membranoproliferative or membranous) was suggested by proteinuria (>1.5 g/24 h) and/or microhematuria and always diagnosed by renal biopsy. Of 15 HCV-positive recipients who received pretransplant interferon, 10 (67%) became HCV-RNA negative at the time of transplantation and only one out of the 15 (6.7%) developed de novo glomerulonephritis (this patient was HCV-RNA positive at transplantation). Among non-interferon-treated allograft recipients, 28.7% had negative HCV-RNA and 12 out of 63 (19%) developed de novo glomerulonephritis (9, membranoproliferative; 3 membranous), all 12 having positive HCV-RNA at transplantation (p < 0.0001). In conclusion, pretransplant interferon may reduce the occurrence of post-transplant HCV-related de novo glomerulonephritis. These results suggest that the indication for pretransplant interferon should be extended to treat all HCV-RNA positive candidates for renal transplantation.

In another clinical trial that conducted by Kamar N et al, 2003, among 55 anti-HCV positive/HCV RNA positive hemodialysis patients who were treated with Alpha-IFN (9 MU/wk during 6 or 12 mo), 21 of them (38%) had a sustained virologic response. Of these, 16 (76%) underwent renal transplantation (RT) 38 mo (range, 2 to 57 mo) after Alpha-IFN therapy. There were 13 men and 3 women aged 46 yr (range, 27 to 68 yr). At RT, HCV serology was still positive in 15 patients, and HCV viremia was negative in all patients.

Immunosuppression relied on anticalcineurin agents with or without steroids and/or antimetabolites; in addition, 12 of them received induction therapy with antithymocyte globulins. At the last follow-up after RT, at 22.5 mo (range, 2 to 88 mo), HCV viremia remained negative in all patients. Moreover, HCV RNA was
not present in peripheral blood mononuclear cells when assessed in eight patients. HCV serology was found to be still positive in 13 patients.

Three patients presented with acute rejection, one presented with a suppurative lymphocele, one died from a sepsis, and four presented with a cytomegalovirus infection. None of them developed posttransplant diabetes mellitus & they concluded that hemodialysis patients waiting for a RT need to be treated with Alpha-IFN because when HCV RNA clearance occurred, they experienced no relapse after transplantation despite chronic immunosuppressive treatment.

In a clinical trial conducted by Mahmoud IM and Co-workers, 2005, the inclusion criteria comprised HD/renal transplant candidates who had their sera positive for HCV RNA and a biopsy proven chronic hepatitis between June 1994 and May 1996 in the Mansoura Urology and Nephrology Center. Exclusion criteria were age < 18 years, positive HBsAg, histopathological evidence of cirrhosis or the presence of any contraindication to transplantation.

The studied HD patients represented two different eras in the management of chronic hepatitis C in the center. Before June 1995, renal transplant candidates with minimal to moderate chronic hepatitis were treated conservatively with monthly checking of liver function tests.

Those patients underwent renal transplantation after transaminases had been normal for at least 6 successive months.

From June 1995 on, a policy to treat such patients with a standard course of IFN was adopted. Patients who met inclusion criteria were, therefore, classified into an IFN (treatment) group and a control group. The pre-transplant characteristics as well as post-transplant clinical course of treated patients were compared with those of control patients.
The efficacy of the drug was judged by testing for complete liver function profile every month and for HCV RNA by PCR at the end of 6 months’ treatment and a second time just before transplantation. None of the patients had a liver re-biopsy at anytime during the follow-up period.

All patients of both groups received live related kidney transplants from anti HCV-negative donors. Serum transaminases were normal at the time of transplantation in all patients of both groups.

All patients, were primarily immunosuppressed with triple drug therapy consisting of prednisolone, azathioprine (anti metabolities) and cyclosporin A.

Pre-Transplant Characteristics were as follows, Patients of both groups were matched with respect to age, gender, number of transfused blood units, history of schistosomiasis and mean values of pre-treatment ALT levels. However, patients in the IFN group had a significantly (p = 0.04) longer time on HD compared to the control group. None of the patients in both groups had a previous renal transplant.

The overall scoring of all liver biopsies gave a Knodell score of 4.7 ± 1.6 (range 2–9), a mean grading of inflammation of 3.3 ± 1.5 (range 1–8) and a mean staging of fibrosis of 1.4 ± 0.9 (range 0–3). None of the studied patients exhibited chronic hepatitis with severe activity or cirrhosis in pre-transplant liver histopathology. Patients in the two studied groups were matched in terms of Knodell scores, activity grading and staging fibrosis (table 6). Minimal activity index (1–3) was encountered in 10 (55%) of the IFN group and in 17 (53%) of the control group while mild activity index in 8 (45%) and 15 (47%) respectively (p = 0.8).
Table 6: Pre-transplant characteristic of patients in the IFN and control group<sup>a</sup>

<table>
<thead>
<tr>
<th>Pre-transplant characteristics</th>
<th>IFN group (n=18)</th>
<th>Control group (n=32)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>31.9±6.5</td>
<td>31.3±7.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Male gender</td>
<td>15(83%)</td>
<td>23(72%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Transfused blood units</td>
<td>5±3</td>
<td>8±7</td>
<td>0.1</td>
</tr>
<tr>
<td>Time on HD, Months</td>
<td>39±25</td>
<td>27±16</td>
<td>0.04</td>
</tr>
<tr>
<td>History of schistosomiasis</td>
<td>5(28%)</td>
<td>10(31%)</td>
<td>1</td>
</tr>
<tr>
<td>Pre-treatment ALT</td>
<td>71±11</td>
<td>80±9</td>
<td>0.4</td>
</tr>
<tr>
<td>Knodell score (0-22)</td>
<td>4.5±1.6(2-8)</td>
<td>4.8±1.7(2-9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Activity grading (0-18)</td>
<td>3.1±1.5(2-7)</td>
<td>3.4±1.6(1-8)</td>
<td>0.3</td>
</tr>
<tr>
<td>Staging fibrosis (0-4)</td>
<td>1.4±0.9(1-3)</td>
<td>1.3±0.9(0-3)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data for continuous variables are presented as mean ± SD, for discrete variables as fraction positive(percentage).

<sup>b</sup> Mann-Whitney test for continuous variables and X<sup>2</sup>/Fisher’s exact tests for discrete variables

Flu-like syndrome (fever, arthralgias, myalgias) developed in 5 patients (28%) and responded well, in all of them, to acetaminophen. Two other patients (11%) had their basal dry body weight decreased by 2.8 kg (4%) and 2.4 kg (3%) during the 6-month treatment course. Body weights, however, returned to pre-treatment figures 6 and 8 weeks after discontinuation of the drug. IFN was discontinued in 2 patients (11%) after 2 and 3 months treatment due to leukopenia (< 2,000/mm<sup>3</sup>) persisting despite 50% dose reduction. The leukocytic counts returned to normal levels after discontinuation of the drug.

The drug was well tolerated in the rest of the patients. Serum ALT levels decreased to normal range in response to IFN therapy in all patients of the treatment group within 1–3 months of treatment. This biochemical response was maintained in all of them until the time of transplantation. HCV RNA turned negative in 10 patients (55%) of the IFN group and in none of the control group.
Neither of the 2 patients who failed to continue a 6-month IFN therapy has cleared the virus. None of the initial responders to IFN therapy underwent a virological relapse before transplantation. The duration between the completion of IFN therapy and transplantation ranged between 3 and 12 months (5 ± 2 months, mean ± SD).

The means of post-transplantation follow-up periods were 41.5 ± 15 months (range 12–60) and 50 ± 16 months (range 16–75) for the IFN group and the control group, respectively.

Two patients of the IFN group had virological relapses at 6 and 9 months post-transplantation. All patients in the control group remained viremic until the last followup.

Serum transaminases remained normal in all patients of the IFN group until the last follow-up. In contrast, biochemical evidence of acute and chronic hepatitis was observed in 5 (p = 0.03) and 13 (p = 0.002) patients, respectively, of the control group (table 7). No patients from either group developed decompensated, fulminant or cholestatic liver disease.

**Table 7:** Post-transplant liver function (ALT behavior) of patients in the IFN and control groups

<table>
<thead>
<tr>
<th>Post-transplant liver function</th>
<th>IFN group (n=18)</th>
<th>Control group (n=32)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistently normal ALT</td>
<td>18(100%)</td>
<td>13(40.6%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Transient ALT elevation</td>
<td>0(0%)</td>
<td>1(3.1%)</td>
<td>1</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>0(0%)</td>
<td>5(15.6%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>0(0%)</td>
<td>13(40.6%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are presented as fraction positive (percentage).  
<sup>b</sup> X² and Fisher’s exact tests.
The two studied groups of patients had comparable mean serum creatinine levels at 1 and 2 years post-transplantation. However, patients of the control group had significantly higher serum creatinine values at 3, 4, and 5 years post-transplantation as well as at the last followup.

All patients in both groups survived the post-transplant follow-up period. In contrast, 8 patients (25%) of the control group and 1 patient (5.6%) of the IFN group developed chronic graft failure and returned to HD (p =0.08). All graft losses in the two groups were due to CAN.

The time to graft loss was 48 months and 44 ± 10 months post-transplantation for the IFN group and control group respectively (p = 0.7). The Kaplan-Meier test revealed a 100% graft survival rate in the first and second post-transplant years in both groups. Graft survival rates were 100, 86 and 86% at 3, 4 and 5 years, respectively, in the treated group compared with 90, 82 and 61% in the control group (p = 0.4).

The authors concluded that IFN-Alpha 2b is well tolerated and highly effective among HD patients who are candidates for renal transplantation. Patients who were treated with IFN had a significantly better liver function with less frequent modifications of their immunosuppressive regimens compared with non-treated patients. Furthermore, the frequencies of chronic graft dysfunction and proteinuria were significantly higher in non-treated patients. Thus treating HCV-positive HD patients with chronic hepatitis of any degree of activity with an effective antiviral therapy before transplantation is recommended.

In a clinical trial performed by Ozdemir BH & Co-workers, 2007, the aim of this study was to identify the influence of chronic HCV infection on development of interstitial fibrosis (IF) in renal allografts and to evaluate if pretransplant interferon-alpha (IFN-alpha) therapy has an effect on IF. The development of IF and graft outcome were compared between anti-HCV positive (n = 28) and anti-
HCV negative (n = 30) recipients. The influence of IFN-alpha therapy on IF and graft survival was compared between anti-HCV positive recipients who received pre-transplant IFN-alpha therapy (n = 15, group 1) and anti-HCV positive recipients who did not receive IFN-alpha therapy (n = 13, group 2). Recipients with anti-HCV antibodies had higher incidences of IF and shorter graft survival than did recipients without anti-HCV antibodies (p < 0.05 for both). Development of IF was higher in group 2 recipients, and patients in group 1 had longer graft survivals (p < 0.05 for both). Patients with positive HCV-RNA had higher grades of tubular TGF-beta1 expression than did patients with negative HCV-RNA (p < 0.05). Expression of tubular TGF-beta1 was lower in group 1 patients when compared with group 2 patients (p < 0.001). In conclusion, the authors suggested that HCV infection may have a triggering effect on the development of IF in renal allografts by augmenting renal expression of TGF-beta1.
Post-transplantation Treatment of HCV Positive Kidney Transplant Recipients

Treatment of HCV in kidney transplant recipients is not routinely recommended (*Morales JM et al, 2000*) because of concerns about IFN precipitating acute rejection.

Therefore, the decision to treat a kidney transplant recipient with IFN-based antiviral therapy must be individualized. Acute rejection has been reported in several published studies in HCV-infected kidney transplant recipients, with rates varying from 15 to 64% (*Baid S et al, 2000*). However, there are clinical circumstances in which a risk–benefit assessment may favor treatment, and some data suggest that certain transplant recipients will benefit from treatment with IFN monotherapy or IFN plus ribavirin combination therapy (*Shu KH et al,2004*).

HCV associated glomerulonephritides can recur after kidney transplantation and cause progressive renal dysfunction, and antiviral therapy may be needed to prevent graft loss (*Ozdemir BH et al, 2006*). In addition, patients with advanced fibrosis (bridging fibrosis or cirrhosis) or severe cholestatic hepatitis warrant consideration of treatment to prevent death as a result of liver-related complications.

Based on these results, it was recommended not to use IFN in kidney transplant recipients until the mechanism of IFN-associated graft rejection was better understood (*Rostaing L et al, 1996*).

Several factors have been proposed to minimize the risk for acute rejection during antiviral therapy. Treatment in the first year after transplantation may increase the risk for acute rejection, which is already highest during this time (*Baid S et al, 2003*).
Antiviral therapy may be safer if given years after transplantation and in patients with stable graft function and no history of rejection (Luciani G et al, 2003).

In addition, patients should be on a stable immunosuppressive regimen and have therapeutic drug levels of immunosuppressive drugs at the time of IFN treatment.

Finally, the use of ribavirin, a drug with immunomodulatory potential, may positively modulate the risk for acute rejection (Kamar N et al, 2003).

Kidney Disease Improving Global Outcomes (KDIGO,2008) published Clinical Practice Guidelines for Management of HCV related complications in kidney transplant recipients:

- 1 - It is suggested that HCV infected kidney transplant recipients more than 6 months after transplant have their liver disease evaluated at least annually. (Weak)

- 2 - For HCV-infected kidney transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks, monotherapy with standard IFN is suggested. (Weak)

- 3 - It is suggested that HCV-infected kidney transplant recipients be screened for the development of hyperglycemia after transplantation. (Weak)

- 4 - It is suggested that HCV-infected kidney transplant recipients be tested at least every 3–6 months for proteinuria. (Weak)

It is suggested that patients who develop new onset proteinuria (either urine protein/creatinine ratio>1 or 24-h urine protein greater than 1 g on two or more occasions) have an allograft biopsy with immunofluorescence and electron microscopy included in the analysis. (Weak)
• 5 - Because of the risk of rejection, it is suggested that kidney transplant recipients with HCV-associated glomerulopathy not receive IFN-based therapy, unless it is determined that the benefits of therapy outweigh the risks of treatment. (Weak)

Treatment of hepatitis C after kidney transplantation with combined interferon alpha-2b and ribavirin:

1- There is little experience with combined interferon and ribavirin therapy in this group of patients. Four consenting RT recipients (transplanted from 1999 to 2002) who developed acute de novo HCV infection {Circulating HCV RNA was detected by polymerase chain reaction (PCR). HCV genotyping was performed using a line-probe assay and the viral load was quantified either by a branched-chain DNA assay or by quantitative PCR} were treated with a combination of interferon-alpha 2b (3 MU s.c. thrice weekly) and ribavirin (1000 mg or 1200 mg p.o. daily depending on body weight) for a period of 24–48 weeks depending on treatment response (Tang S et al, 2003).

Sustained virologic and biochemical remission were achieved in three patients infected with HCV genotypes 1a, 2, and 6a, respectively (Table 8).

The median time from treatment onset to ALT normalization was 8 weeks. The fourth patient was a non-responder infected with genotype 1b. Dose-dependent hemolysis was the most frequent side-effect. No patient developed allograft dysfunction.

This experience indicates that the judicious use of combined interferon and ribavirin can be considered in selected RT recipients with severe acute hepatitis C infection (Tang S et al, 2003).
Table 8. Demographic data and treatment outcome.

<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age/ Sex</th>
<th>HCV genotype</th>
<th>Treatment duration (weeks)</th>
<th>Time to ALT normalization (weeks)</th>
<th>Follow up duration *(months)</th>
<th>ALT Levels (IU/l) at week*</th>
<th>Serum creatinine (µl/l) at week *</th>
<th>Serum HCV RNA by PCR at week*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/M</td>
<td>1a</td>
<td>48</td>
<td>12</td>
<td>42</td>
<td>0 24 48 72 96</td>
<td>0 24 48 72 96</td>
<td>+ - - - -</td>
</tr>
<tr>
<td>2</td>
<td>34/M</td>
<td>2</td>
<td>48</td>
<td>4</td>
<td>36</td>
<td>270 24 31 39 39</td>
<td>39 168 182 178 165 163</td>
<td>+ - - - -</td>
</tr>
<tr>
<td>3</td>
<td>44/M</td>
<td>6a</td>
<td>48</td>
<td>8</td>
<td>15</td>
<td>188 14 11</td>
<td>93 109 110</td>
<td>+ - - - -</td>
</tr>
<tr>
<td>4</td>
<td>55/M</td>
<td>1b</td>
<td>24</td>
<td>NR</td>
<td>16</td>
<td>125 116 94</td>
<td>102 116 124</td>
<td>+ + + +</td>
</tr>
</tbody>
</table>

NR, non responder.

* Calculated from the date of commencing antiviral treatment.

2- Total of 14 patients received antiviral therapy, all of whom had stable graft function, raised aminotransferases and positive HCV viremia at the start of treatment. Eight patients received ribavirin alone for a period of six months to two yr, in doses of 400-800 mg daily. Five patients received IFN-alpha therapy for a period of two months to 1.5 yr, in doses of 1.5 million units daily or three million units thrice weekly with ribavirin. One patient received pegylated IFN 50 microg once weekly in combination with ribavirin. The response was seen in terms of biochemical and virological improvement at the end of study period.

In patients treated with ribavirin alone (n = 8), mean alanine aminotransferase (ALT) levels before and after treatment were significantly different (198.4 +/- 147.6 and 104.8 +/- 66.5 IU/L respectively; p < 0.05). ALT levels normalized completely in three patients at the end of treatment, improved in three patients and deteriorated in two. Only in one of eight patients on ribavirin alone, HCV-RNA became negative after six months of treatment while in the rest (n = 7) HCV-RNA continued to be positive. In subjects on IFN plus ribavirin (n =
6), the mean ALT levels decreased significantly (from 280.2 +/- 114.9 IU/L at baseline to 71 +/- 49 IU/L at end of therapy; p < 0.05). Two patients had sustained remission (33.3%) on IFN plus ribavirin (persistently negative HCV-RNA), two patients relapsed after initial remission and in two patients treatment was stopped after two months because of graft dysfunction. Totally four patients developed graft dysfunction at some time during the course of IFN therapy (66.6%), but it was discontinued in only two (33.3%). All patients regained normal creatinine levels after discontinuation of IFN, although one patient developed chronic allograft nephropathy as shown by kidney biopsy. Four patients in IFN group developed leucopenia. Two patients developed severe anemia one of whom required blood transfusion and one developed severe flu-like syndrome requiring stoppage of therapy (Sharma RK et al, 2006).

They concluded that Ribavirin monotherapy in renal transplant recipients with chronic hepatitis C infection results in good biochemical response but is not associated with virological clearance. IFN in combination with ribavirin is effective in two-thirds of patients after a minimum therapy of six months, but it is poorly tolerated, results in graft dysfunction in significant number of patients, and relapse can occur after stopping treatment (Sharma RK et al, 2006).
SUMMARY & CONCLUSION
Summary and Conclusion

Patients with chronic kidney disease (CKD) on renal replacement therapy especially hemodialysis (HD) continue to have a higher prevalence of hepatitis C virus (HCV) infection than the general population.

Dialysis patients generally have high morbidity and mortality rates reflecting age and comorbid conditions making the long-term consequences of HCV infection difficult to determine. The recommended therapy of most patients with chronic HCV infection who do not have renal dysfunction consists of interferon alfa (preferably pegylated interferon) in combination with ribavirin. Ribavirin warnings for patients with renal dysfunction are because its clearance is impaired in these individuals and the drug and its metabolites are not removed by hemodialysis.

IFN therapy in HD patients results in good biochemical and virological response and appears to exert a beneficial effect on the course of liver disease following renal transplantation, also documented that IFNa therapy for treatment of HCV infected ESRD patients on maintenance dialysis, administered prior to renal transplantation, is associated with high rates of sustained biochemical and virological response in the post-transplant period.

Although the presence of anti-HCV antibodies at the time of renal transplantation may be associated with an increased risk of death, Some studies suggest that renal transplantation may result in better survival than dialysis among anti-HCV positive patients.

HCV infection may be more commonly associated with glomerular disease in renal transplants than in native kidneys. One possible mechanism is that immunosuppressive therapy to prevent rejection increases the titer of HCV RNA.
Among renal transplant recipients with HCV infection, both recurrent glomerular disease and de novo MPGN and MN can occur.

Because post-transplant alpha-IFN therapy cannot be instituted due to the high rate of rejection associated with the immunologic properties of the treatment, and because ribavirin is not indicated during hemodialysis because of the possibility of severe hemolytic anemias related to cumulative doses of the drug, pretransplant alpha-IFN monotherapy represents the current approach to treating patients with chronic HCV hepatitis.

The efficacy of interferon alfa therapy in chronic hepatitis C has been shown in many randomized controlled trials, and its use currently is recommended in anti-HCV positive patients with abnormal serum aminotransferases and well-compensated chronic hepatitis on biopsy.

Pretransplantation alpha-IFN monotherapy may be effective to produce disappearance of viral replication in HCV-infected patients who are candidates for kidney transplantation. HCV-RNA clearance can be maintained in the post-transplant period despite interactions with immunosuppressive agents.

The authors concluded that Patients who were treated with IFN had a significantly better liver function with less frequent modifications of their immunosuppressive regimens compared with non-treated patients. Furthermore, the frequencies of chronic graft dysfunction and proteinuria were significantly higher in non-treated patients. Thus treating HCV-positive HD patients with IFN therapy before transplantation is recommended.
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الملخص العربي

مرضى الفشل الكلوي المزمن الذين يعالجون بالعلاجات البديلة للكلى وخاصة الاستئصال الديموم يصابون
بأعلى معدل انتشار من عودة التهاب الكبد الفيروسي سي عن عامة الناس.

ويتكون العلاج المولود به لبعض مرضى التهاب الكبد الفيروسي سي المزمن الذين لا يعانون من خلل بالكلي
من عقار الأنتي فيروزون مع عقار الزيفابريين، ويمكن خطورة الزيفابريين لمرضى الكلى في ضعف
استخلاصه في هؤلاء المرضى كما أن العقار ومشتقاته لا يزال بالاستئصال الديموم.

علمياً تثبت أن العلاج بعقار الأنتي فيروزون لعلاج مرضى التهاب الكبد الفيروسي سي المصابون بالفشل الكلوي
المزمن وعالجون بالاستئصال الديموم إذا أخذ قبل زراعة الكلى يكون مصاباً لمعدلات عالية من
الاستجابة الكيميائية الحيوية والفيروسية في الفترة ما بعد زراعة الكلى.

و بالرغم من وجود أجسام مضادة لفيروس الالتهاب الكبدي سي في وقت زراعة الكلى قد يرتبط بخطر
الموت، إلا أن بعض الدراسات تقترح بأن زراعة الكلى قد تؤدي إلى تحسن في العمر المفترض من
استصفاء الكلى بين المرضى الإيجابيين لفيروس الالتهاب الكبدي سي.

ترتبط الأصابة بالالتهاب الكبدي الفيروسي سي كثيراً بمرض كبيبات الكلى في زارعى الكلى عند في الكلى
الطبيعي، وذلك لاحتمال أن الأدوية المثبطة للمناعة اللازمة لمنع الرفض تزيد من تركيز الحامض الربيوزي
النووي للفيروس.

ثبت علمياً أن العلاج بالأنترفيروزون بعد زراعة الكلى لا يمكن استخدامه بسبب النسبة العالية لرفض الكلي التي
تم زراعتها إرتباطها بالخواص المناعية للعقار ولأن عقار الزيفابريين لا يوصف لمرضى الاستئصال
الكلى بسبب إمكانية فقر الدم الانحلالي الحاد المتعلق بالجراعات المتراكمة من العقار، لذا فإن العلاج بعقار
الأنتي فيروزون ماقل زراعة الكلى يمثل الأتجاه العلمي الحديث لعلاج المرضى المصابين بالتهاب الكبد
ال كبدي الفيروسي سي.

كفاءة عقار الأنتي فيروزون في الإلتهاب المزمن لفيروس سي قد ثبتت في الكثير من التجارب كما أن استخدامه
الحالي ينصح به للمرضى الإيجابيين للفيروس الذي يعانون من أعراض كبد غير طبيعية و حالة الالتهاب
الكبدي مستقرة في عينة الكبد.
خُص الباحثون والعلماء أن المرضى الذين تم علاجهم باستخدام عقار الأنتيرفيرون أن وظائف الكبد أفضل وأن تعديل بروتوكولات الأدوية المثبطة للمناعة وأن معدلات خلل الكلى المزروعة المزمن و الزلال البولي أقل بكثير مقارنة بالمرضى الذين لم يعالحوا بهذا العقار.

يوصى الباحثون والعلماء في مجال زراعة الكلى بعلاج مرضى الفشل الكلوي المصابون بالالتهاب الكبدي الفيروسي بعقار الأنتيرفيرون قبل زراعة الكلى.
دراسة طويلة الاجل لنتائج علاج انترفيرون في الالتهاب الكبدي سي لمرضى الغسيل الدموي بعد زراعة الكلى

والذي توطنه للحصول على درجة الماجستير في الباطنة العامة

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2009