Management of Hepatitis C

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INTRODUCTION

The hepatitis C virus (HCV) was identified in 1989, and it is a major public health problem and a leading cause of chronic liver disease.[1] All over the world, hepatitis C is the principle cause of death from liver disease and the leading indication for liver transplantation.[2] The prevalence of HCV globally is 3% and approximately 170 million people are infected. The spectrum of liver disease caused by it includes acute hepatitis (although rare), chronic hepatitis, liver failure, cirrhosis and hepatocellular carcinoma (HCC). In majority of patients acute HCV infection is asymptomatic. In almost all the patients, within 1–2 weeks of exposure the HCV-RNA can be detected in the serum, while anti-HCV may take 4–6 weeks.

The first 6 months is usually considered as an acute phase of infection and during this phase spontaneous clearance is still a possibility. Approximately 50–80% of the patients of acute hepatitis develop chronic infection, while 20–50% of patients achieve spontaneous resolution. Among patients with chronic hepatic C, approximately 20% can be expected to develop cirrhosis; of these, 6% of the patients will decompensate to end-stage liver disease (ESLD) and an additional 4% will develop HCC. Chronic hepatitis C is a chronic viral infection that can be cured by antiviral therapy.[2]

VIROLOGY

Hepatitis C virus belongs to the Flaviviridae family and is the sole member of the genus, Hepacivirus. It is a spherical single-stranded enveloped RNA

virus.[3] The genome of HCV contains an open reading frame (ORF). The ORF encodes one large viral polyprotein precursor and is flanked upstream by a 5' untranslated region (UTR) that functions as an internal ribosome entry site (IRES). Internal ribosome entry site directs the viral RNA to its docking site on the endoplasmic reticulum in the host cells and mediates initiation of HCV polyprotein translation and downstream by a 3' UTR, which is critical for initiation of new RNA strand synthesis.[2]

The large polyprotein generated by translation of the HCV genome undergoes post translation modification into at least 11 viral proteins including both structural (C, E1, E2) and non-structural proteins (NS2, NS3, NS4A, NS4B, NS5A and NS5B). The structural proteins and non-structural proteins are separated by the short membrane peptide P7 (Viroporin), which forms an ion channel essential for efficient assembly and release of viral particles.[2] High degree of genetic variability is an important feature of HCV genome. In the viral genome, various regions have different mutation rates. E1 and E2 regions are the most variable, while 5' UTR and 3' UTR are highly conserved. As a result, different mutants of the parent strain co-exist as quasi-species in a single infected individual.[1] Large differences have been noted in the HCV genome between strains from different geographical regions allowing the virus to be classified into 6 major genotypes. In India genotype 3 predominates in north, east and west India whereas genotype 1 is more frequent in south India.[1]

EPIDEMIOLOGY

Global Distribution

Globally, it was estimated that in 2005, more than 185 million people had HCV antibodies (prevalence of 2.8%)

Areas with high prevalence (>3.5%) included:

- Central and East Asia
- North Africa
- The Middle East

Moderate prevalence (1.5–3.5%) was noted in:

- South and Southeast Asia
- Sub-Saharan Africa
- Andean, Central, and Southern Latin America
- The Caribbean
- Oceania
- Australasia (Australia, New Zealand, New Guinea, and neighboring Pacific islands)
- Western, Central, and Eastern Europe

Low prevalence (<1.5%) was noted in:

- The Asia Pacific
- Tropical Latin America
- North America

Distribution of Genotypes

Genotype	Distribution
1 a & b	USA, Europe
2	Globally
3 a & b	India, Thailand, Australia
4	North Africa, Middle East
5	South Africa
6	South East Asia

TRANSMISSION[3–5]

Mode of transmission of HCV can be divided into:

1. Percutaneous (main route—90% of transmission)
   - Blood transfusion
   - Injection drug abusers
   - Needle-stick inoculation (seroconversion after accidental needle puncture is ~3%)
   - Hemodialysis
   - Organ transplantation
2. Non-percutaneous (uncommon)
   - Sexual contact (~5% of transmission)
   - Perinatal exposure (~5% of transmission)
   - Intranasal cocaine abuse

More than 80% of Indian patients with chronic HCV infection are either transfusion recipients or have undergone hemodialysis (Table 1).[5] Since blood banks have been mandatorily asked to check for hepatitis C only in 2001–2002, anybody who has received blood transfusion prior to that is at high risk. Casual household contacts including intimate ones like kissing (exposure to saliva) have been shown to be inefficient mode of transmitting virus.

PATHOGENESIS

The exact mechanism of hepatocellular injury in HCV infection is unknown. Currently, it is believed that host immune responses to HCV-infected hepatocytes play a major role in the pathogenesis of chronic hepatitis C.[4] In

Table 1.
Risk Factors and Odds of Being Infected[6]

Risk factor	Odds of being infected with hepatitis C
Intravenous drug use	49.6
Blood transfusion	10.9
Pierced ears or body parts	2.0
Having been struck or cut with a bloody object	2.1
Immunoglobulin injection	1.6

the pathogenesis of HCV infection, the pivotal role is played by the cellular immune response and the importance of humoral immune response is less clear. Being a RNA virus, in 60–80% of patients, it is able to escape innate and adaptive immune surveillance and establishes itself as an agent of chronic hepatitis. Cytotoxic lymphocytes in an attempt to eradicate the virus, contribute to the liver injury. On the other hand, strong multispecific T-lymphocyte reaction against HCV proteins is associated with viral clearance. The functions of both CD4+ and CD8+ lymphocyte are important for this outcome. The progression of inflammation and fibrosis in individual patients of chronic infection are determined by the genetic and environmental factors. Micro-RNAs are now widely believed to play an important role in the pathogenesis of HCV.

In some immunocompromised HCV patients (HIV-positive and organ transplant recipients), fibrosing cholestatic hepatitis may develop. This is thought to result from direct viral hepatotoxicity of infected cells, since the viral levels are very high due to immunosuppressed state.[2] This is rapidly progressive and leads to ductopenic liver failure.

NATURAL HISTORY[2] (FIGURE 1)

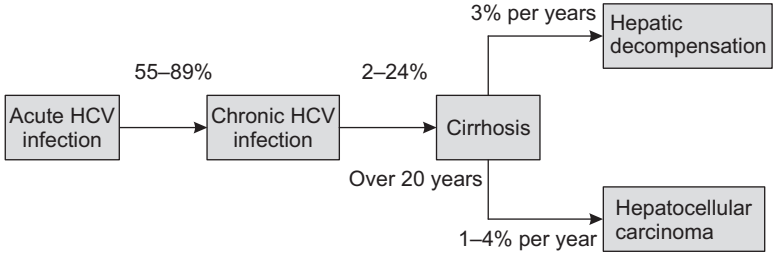


Figure 1. Natural history of hepatitis C.

A systematic review of 111 studies analyzing natural history estimated that the prevalence of cirrhosis 20 years after infection was 16% (95% CI 14–90%).[7]

Studies of patients who acquired acute hepatitis C from a blood transfusion generally describe no increase in all-cause mortality if the follow-up is <25 years.[8,9] In one of these studies, all-cause mortality was similar among 222 hepatitis C-related cases compared to 377 controls (67% vs 65%), although liver-related mortality was increased (4.1% vs 1.3%). This suggests that not all patients who become chronically infected will develop significant liver disease following acute infection.[8]

In contrast, patients who present with chronic hepatitis, show a more aggressive course of the disease with high risk of developing cirrhosis, decompensation and HCC. In one series from the United States, 131 patients with chronic post-transfusion hepatitis C were evaluated over a mean of 22 years after transfusion: 23% had chronic active hepatitis, 51% had cirrhosis, and 5% had HCC.[10]

A study of 384 patients with compensated cirrhosis due to HCV found that the risk of developing hepatic decompensation was 3.9% per year.[11] 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).

In another report of 200 consecutive patients with decompensated cirrhosis at baseline, the probability of survival after diagnosis of decompensated HCV-related cirrhosis was 51% at 5 years.[12] Overall mortality was 43% after a mean of 34 months. Ascites was the most frequent form of decompensation (48%).

The natural history of advanced fibrosis or cirrhosis was also examined in a large prospective trial (the Hepatitis C Antiviral Long-term Treatment against Cirrhosis Trial; HALT-C) that included 1050 patients with either advanced fibrosis (60%) or cirrhosis (40%).[13] Among the patients with advanced fibrosis followed for 4 years for progression to cirrhosis, the incidence of cirrhosis was 9.9% per year. Over 8 years of follow-up, there were 679 adverse clinical outcomes (Child-Turcotte-Pugh [CTP] score of ≥7, variceal hemorrhage, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, definite or presumed HCC, liver transplantation, or death). The most common adverse clinical outcomes were CTP score ≥7 and HCC. Adverse clinical outcomes were more common among patients with cirrhosis compared with those with advanced fibrosis (7.5% vs 3.3% per year). Death or liver transplantation occurred in 12.2% of patients with advanced fibrosis and in 31.5% of patients with cirrhosis during follow-up. Once a patient developed a CTP score ≥7, the rate of subsequent clinical events increased to 12.9% per year with a mortality rate of 10% per year.

FACTORS INFLUENCING DISEASE PROGRESSION IN CHRONIC HEPATITIS C INFECTION[14]

Host factors: Older age at acquisition, duration of infection, male gender, obesity, hepatic steatosis, insulin resistance and hepatic iron overload.

Environmental factors: Alcohol intake, regular marijuana use.

Host Factors

Several host factors are important in the progression of chronic hepatitis C:

- Genetic polymorphisms of transforming growth factor B1 (TGF B1), and angiotensin II.
- Acquisition of HCV infection after the age of 40–55 may be associated with a more rapid progression of liver injury
- Male sex has been associated with faster fibrosis progression
- Ethnicity and racial differences also affect outcome. Progression may be slower and histology less severe in African Americans
- Patients who acquire the disease from a blood transfusion may be at increased risk for disease progression compared with those infected via other modes
- Patients who have a high body mass index, insulin resistance and hepatic steatosis are at increased risk for the development of fibrosis progression.
- Daily use of marijuana has been associated with development of steatosis and more rapid fibrosis progression
- Regular coffee consumption is associated with a lower rate of disease progression and low HCC risk
- Patients who had a G allele at the rs8099917 locus (i.e., patients who were G/T or G/G) are less likely than patients with the T/T genotype to have significant fibrosis or to have rapid progression of their fibrosis (odds ratios 0.43 and 0.56, respectively)
- Alcohol consumption accelerates the process of fibrosis in liver

Viral Factors

Co-infection with HBV, co-infection with HIV, infection with multiple HCV genotype accelerates liver fibrosis.

CLINICAL FEATURES

Acute Hepatitis C

Incubation period of HCV ranges from 15 days to 160 days (mean, 50 days).[4] More than 75% of acute HCV infections are silent and only 25% manifest as

clinical hepatitis.[4] Patients who develop icteric hepatitis are more likely to clear the virus as compared to those who don't.

Chronic Hepatitis C

There are no features specific for hepatitis C. Most are asymptomatic. Many patients are diagnosed during pre-surgery work-up, blood donation, executive health check-ups, and unexplained thrombocytopenia.

Patients may have non-specific symptoms like fatigue, malaise, anorexia, and arthralgia. Some may present with the complications of liver cirrhosis like jaundice, ascites, bleeding gastroesophageal varices, pedal edema, hepatic encephalopathy, coagulapathy, palmar erythema, and spider angioma. Some patients may present with HCC.

Extrahepatic Manifestation of Hepatitis C Virus Infection[2]

About 1–2% of patients suffering from HCV infection may develop extrahepatic manifestations.

The proven associations are with autoimmune hepatitis, diabetes mellitus, lichen planus, essential mixed cryoglobulinemia, B cell non-Hodgkin's lymphoma (lymphoplasmocytic lymphoma), monoclonal gammopathies, porphyria cutanea tarda.

Other possible associations are: Chronic polyarthritis, idiopathic pulmonary fibrosis, non-cryoglobulinemic nephropathies, sicca syndrome, thyroid cancer, renal cell carcinoma, and vitiligo.

DIAGNOSIS

The diagnostic approach for hepatitis C involves identifying infection and then assessing the need to treat and the duration of therapy.

- Screening test—Anti-HCV (HCV RNA preferred in patients with chronic kidney disease)
- Confirmatory test—HCV RNA
- Viral genotype testing helps to identify patients most likely to respond favorably to therapy (genotype 1 and 4 are most unfavorable) as well as the duration and dosage of therapy
- Liver biopsy:
  a. May be indicated to assess the severity of disease, predict response to therapy.
  b. Liver biopsy generally not required in patients with favorable genotype 2 and 3 as well as in patients who have clinical evidence of cirrhosis/

portal hypertension and/or extrahepatic manifestation of disease, all of whom are offered therapy.

- Non-invasive markers of fibrosis: such as fibroscan or fibrotest

TREATMENT

There have been significant advancements in the treatment of hepatitis C in the recent years. Besides the use of combination therapy with pegylated interferon and ribavirin, several newer drugs (oral direct acting antivirals) have recently emerged which have revolutionized the treatment of Hepatitis C. This chapter will first discuss the established treatment regimens for Hepatitis C, and then will focus on the newer developments that have taken place recently.

General Measures

1. Attempt to optimize body weight
2. Stop smoking
3. Avoid alcohol
4. Coffee consumption (more than 2 cups/day) has been associated with a reduced risk of hospitalization and mortality from chronic liver disease.[15,16] In addition, high levels of coffee consumption appear to increase sustained virologic responses in those receiving peg-interferon (IFN) and ribavirin. However, these observations do not justify recommending increased consumption of coffee.

Goal of Antiviral Therapy

The goal of antiviral therapy in patients with chronic HCV is to eradicate HCV RNA, which is predicted by attainment of a sustained virologic response (SVR) defined as undetectable HCV RNA in the serum when measured 6 months after the end of treatment (Table 3).[17] A SVR is associated with a 97–100% chance that the patient will remain HCV RNA-negative during long-term follow-up.[18] Sustained virologic response has been associated with decreases in all-cause mortality, liver-related death, need for liver transplantation, HCC rates, and liver-related complications, even among patients with advanced liver fibrosis.

Indications and Contraindications[2]

According to the National Institutes of Health consensus statement on management of hepatitis C, all patients are potential candidates for antiviral therapy. In practice, various issues must be considered prior to treatment with peg-IFN and ribavirin, specifically assessing the risks and benefits of treatment for an individual patient (Table 2).

Table 2.
Contraindications for Interferon

Absolute contraindications for interferon.	Relative contraindications
• Acute pancreatitis • Autoimmune hepatitis • Comorbid conditions that markedly limit life expectancy • History of hypersensitivity to interferon • Pregnancy or unwillingness to use birth control during and for 6 months after treatment • Severe cardiac disease • Severe pulmonary disease • Uncontrolled psychiatric condition • Uncontrolled seizure disorder • Advanced Child C cirrhosis.	• Active alcohol or drug abuse • Active infection • Baseline hemoglobin level <10 g/dl (for ribavirin) • Baseline neutrophil count <1000/ mm^3 • Baseline platelet count <50,000/ mm^3 • Creatinine clearance <50 ml/min (for ribavirin) • Decompensated cirrhosis • Hemoglobinopathy (for ribavirin) • Ophthalmologic disorders (may worsen during therapy) • Other active autoimmune disorders

The Optimal Treatment of Chronic Hepatitis C Virus: Peg-interferon Alfa and Ribavirin

The currently available therapy in India is the combination of a pegylated interferon alfa and ribavirin.

Standard recommendations for dosing and duration of treatment of peg-IFN (PEG) and ribavirin according to viral genotype (Table 4).[6]

Response-guided Therapy

The difference in the viral genotypes solely dictates the course of therapy in the standard treatment recommendations described above. In practice, there is ongoing assessment of virologic response to determine the advisability of continuing therapy when SVR is unlikely. This is to guide whether a prolonged course of peg-IFN and ribavirin may be warranted to decrease the chance of relapse in slow virologic responders, and also to determine whether therapy can be successfully shortened without sacrificing the chances for SVR among those who rapidly respond to peg-IFN and ribavirin (Algorithm).[20]

Monitoring and Side Effects[6]

Before starting therapy, liver biochemistry (LFT), a complete blood count (CBC), and a thyroid stimulating hormone (TSH) level, HCV genotype and serum HCV RNA level, psychiatry fitness and pregnancy test (in women) are required.

Table 3.
Virological Responses during Therapy and Definitions[19]

Virological response	Definition	Clinical utility
Rapid virological response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay	May allow shortening of course for genotypes 2 and 3 and possibly genotype 1 with low viral load
Early virological response (EVR)	≥2 log reduction in HCV RNA level compared to baseline HCV RNA level (partial EVR) or HCV RNA negative at treatment week 12 (complete EVR)	Predicts lack of SVR
End-of-treatment response (ETR)	HCV RNA negative by a sensitive test at the end of 24 or 48 weeks of treatment	
Sustained virological response (SVR)	HCV RNA negative 24 weeks after cessation of treatment	Best predictor of a long-term response to treatment
Breakthrough	Re-appearance of HCV RNA in serum while still on therapy	
Relapse	Re-appearance of HCV RNA in serum after therapy is discontinued	
Non-responder	Failure to clear HCV RNA from serum after 24 weeks of therapy	
Null responder	Failure to decrease HCV RNA by ≥2 logs after 24 week of therapy	
Partial responder	Two log decrease in HCV RNA but still HCV RNA positive at week 24	

Serum ALT level and CBC should be obtained regularly on therapy, and TSH level should be obtained every 3 months, quantitative HCV RNA levels should be drawn at baseline and at weeks 4 and 12. The HCV RNA level should be measured at the end of treatment in all patients. If HCV RNA is undetectable, a level should be repeated 6 months after completion of therapy to determine whether an SVR or relapse has occurred.

Table 4.
Standard Recommendation of Dosing and Duration of Treatment of peg-IFN (PEG) and Ribavirin According to Viral Genotype

Genotype	PEG dose (per week)	Ribavirin dose (mg/day)	Duration (weeks)	SVR (%)
1	180 μg PEG-α-2a or 1.5 μg/kg PEG-α-2b	800–1,400 (weight based)	48	41–42
2	180 μg PEG-α-2a or 1.5 μg/kg PEG-α-2b	800	24	60–84
3	180 μg PEG-α-2a or 1.5 μg/kg PEG-α-2b	800	24	60–84
4	180 μg PEG-α-2a or 1.5 μg/kg PEG-α-2b	1,000–1,200	48	55
5	180 μg PEG-α-2a or 1.5 μg/kg PEG-α-2b	1,000–1,200	48	64
6	180 μg PEG-α-2a or 1.5 μg/kg PEG-α-2b	1,000–1,200	48	63

The most frequent side effects of interferon include flu-like symptoms (in >90% of patients) and alopecia (in 10–30%). Other adverse events include depression and hypothyroidism or hyperthyroidism.

With ribavirin, anemia, cough, pharyngitis, insomnia, dyspnea, pruritus, rash, nausea, and anorexia are the most common side effects.

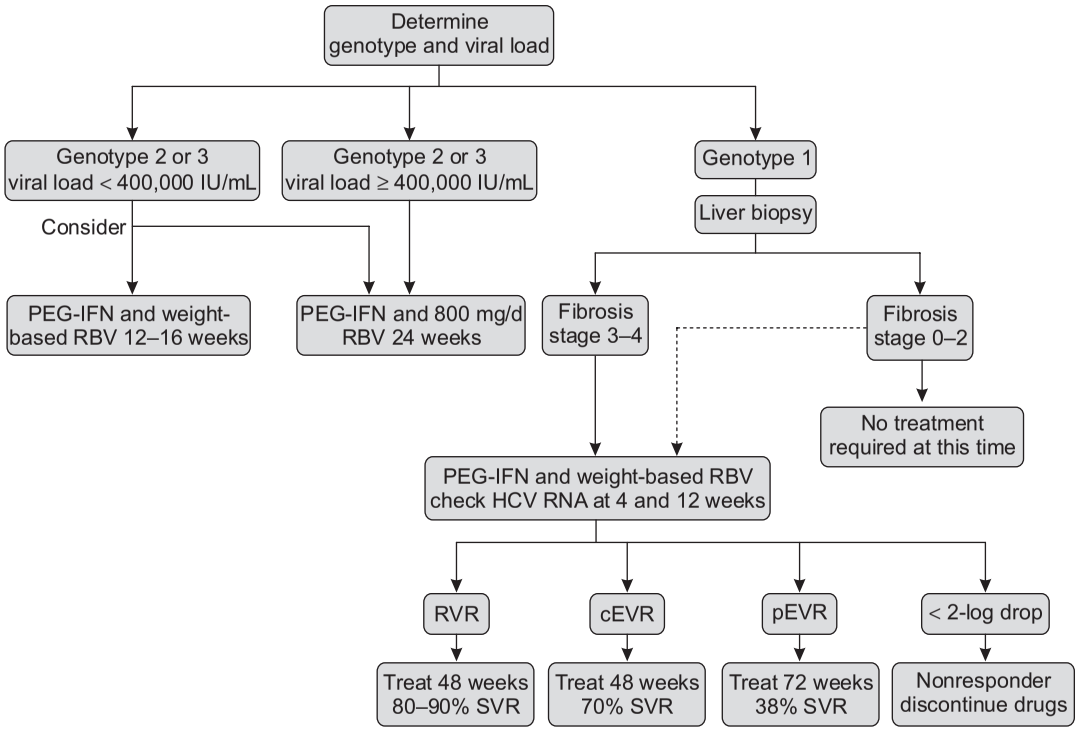
TREATMENT OF HEPATITIS C VIRUS IN SPECIAL POPULATIONS

Cirrhosis and Decompensated Cirrhosis

Patients with decompensated cirrhosis are not candidates for treatment with peg-IFN and ribavirin due to the high rate of morbidity and mortality. However, patients with well-compensated cirrhosis may be treated with these agents, although rates of SVR are somewhat lower than for earlier stages of liver disease. Patients with decompensated cirrhosis with Child-Pugh score of ≥7 and MELD > 14 should be referred for liver transplantation immediately.[10,13,14]

Co-infection with Human Immunodeficiency Virus

The patients of HCV with co-infection of HIV appears to have shortened natural history of hepatitis C as these patients progress more rapidly to



Algorithm. Treatment of hepatitis C virus infection.[2]

cirrhosis compared with hepatitis C infection alone. Along with this there is high incidence of hepatotoxicity associated with antiretroviral therapy in these patients which further complicates the management of HIV infection.[15,21] Ideally, the therapy for HCV infection should be started before antiretroviral therapy for HIV is initiated, especially if CD4 count is >200. When HCV therapy cannot be started first, zidovudine, stavudine, and didanosine should not be used in combination with ribavirin because of the additive risk of mitochondrial toxicity.

Hepatitis C in Renal Disease and Dialysis

In patients with renal disease, there is a possibility of false negative anti-HCV and hence, HCV RNA should be tested especially before renal transplantation. Generally the treatment for hepatitis C in patients with chronic kidney disease is associated with lower response rates and higher rates of adverse events.[16,17] After renal transplant the treatment of chronic hepatitis C has not been recommended due to the risk of developing renal graft dysfunction and rejection.[22] The notable exception are those patients who develop fibrosing cholestatic hepatitis, a rapidly progressive, frequently fatal, liver injury reported in several types of solid organ transplantation.[23]

Cryoglobulinemia and Glomerulonephritis

Patients with hepatitis C and mild manifestations of cryoglobulinemia can be treated with peg-IFN and ribavirin. When patients have progressive vasculitis and organ damage, therapy is focused on gaining immediate control of the vasculitis, utilizing therapies such as corticosteroids, plasma exchange, cyclophosphamide, or rituximab.

Acute Hepatitis C

Approximately 50% of patients with acute hepatitis C will spontaneously resolve the acute infection without treatment. Thus, initially the patients should be followed up with serial quantitative HCV RNA determinations as spontaneous resolution may occur. Persistent high level of viremia or failure of decline in level of viremia in first 12 weeks of presentation suggests that spontaneous resolution is unlikely and treatment should be instituted. Delaying therapy beyond 12–16 weeks appears to be associated with diminished treatment response approaching the expected rates of SVR for chronic HCV. The best treatment regimen remains controversial, although treatment for between 12 weeks and 24 weeks appears optimal.

Treatment-experienced Patients

The decision to board on a repeated course of therapy must be considered by weighing the potential benefits and should be individualized for each patient when options are limited and the chances for success are quite low.[18,19] The extension of therapy to 72 weeks has been shown to decrease relapse rates among genotype 1 slow virologic responders. However, patients who have received inadequate dosage, inadequate duration, non-correction of co-factors, and conventional interferon should be definitely offered adequate therapy.

Role of Maintenance Therapy

Prolonged treatment with peg-IFN alone has been investigated in an attempt to decrease adverse clinical outcomes among patients with advanced fibrosis.

Liver Transplant Recipients

This is an increasing patient group where the treatment is difficult due to the side effects.

Within first few weeks after the transplantation the pre-emptive therapy of all HCV-infected patients is associated with substantial toxicity and a low chance of an SVR. Hence, it is not recommended. The follow-up of the patient expectantly post transplantation and beginning of antiviral therapy when surveillance liver biopsy specimens demonstrate progression of disease, usually to grade 3 inflammation or early fibrosis, is the preferred option.

RECENT ADVANCEMENT IN THERAPIES

Direct-acting Antiviral Agents

The availability of the direct-acting antiviral agents that specifically target critical enzymes in the replication of HCV will transform the treatment of chronic hepatitis C. Several HCV proteins possess well-defined enzymatic activities, including NS2 (a *cis*-acting protease), NS3/4A (serine protease-helicase), NS4B (GTPase), and NS5B (RNA-dependent RNA polymerase) that serve as targets for HCV therapy.

NS3/4A Protease Inhibitors

Linear peptidomimetic—Telaprevir, Boceprevir

Macrocyclic—Danoprevir, Ciluprevir, Vaniprevir

Telaprevir and boceprevir are potent protease inhibitors (already approved in USA), which must be used in combination with peg-IFN and ribavirin to

minimize viral resistance. Telaprevir treatment should incorporate triple therapy beginning with treatment inception while boceprevir regimens should utilize a 4-week lead-in with peg-IFN and ribavirin alone before adding boceprevir. Triple therapy combination with protease inhibitors significantly improves rates of SVR compared with combination therapy with peg-IFN and ribavirin alone. Randomized trials suggest that telaprevir and boceprevir have similar efficacies when compared with placebo although there are no head-to-head trials. Currently, they are used for the treatment of patients with genotype 1.

Telapravir

Telaprevir is given as 750 mg (two 375 mg tablets) three times per day with food containing adequate quantity of fat. Telaprevir is given from the outset of therapy without a lead-in period of treatment with peg-IFN and ribavirin.

Regimens for Pegylated Interferon + Ribavirin + Telapravir

Treatment-naive Patients or Prior Relapsers

If the HCV RNA is undetectable at 4 weeks and 12 weeks, then triple therapy is given for 12 weeks, followed by another 12 weeks of dual therapy (peg-IFN and ribavirin). However, patients with cirrhosis who are treatment-naïve and have undetectable HCV RNA at 4 weeks and 12 weeks may benefit from 36 weeks of dual therapy instead of 12 weeks, for a total of 48 weeks of therapy. Patients who have a low detectable HCV RNA (1000 IU/mL or less) at week 4, should receive triple therapy for 12 weeks, followed by another 36 weeks of dual therapy, for a total treatment duration of 48 weeks.[24]

Prior Partial or Null Responders

Patients who are prior partial or null responders should be treated with peg-IFN, ribavirin, and telaprevir for 12 weeks, followed by 36 weeks of peg-IFN and ribavirin, for total treatment duration of 48 weeks.

When to Discontinue Treatment

Any patient with an HCV RNA level >1000 IU/mL at week 4 or 12 is unlikely to achieve an SVR, and it is recommended that treatment be stopped in such patients. In addition, treatment should be stopped in patients with detectable HCV RNA (regardless of level) at 24 weeks of treatment. Patients who have virologic breakthrough during treatment (>1 $\log_{10}$ increase in HCV RNA above the nadir) should have their telaprevir discontinued while continuing the

peginterferon and ribavirin. The AASLD recommends against switching from one protease to another in patients who experience virologic breakthrough or who relapse on one protease inhibitor.[19]

Boceprevir

Boceprevir is given as 800 mg (four 200 mg capsules) three times per day starting at week 4 of treatment, following a 4-week lead-in period of treatment with peg-IFN and ribavirin. Boceprevir should be given with food containing adequate amount of fat

Regimens Involving Bocepravir

Treatment-naive Patients

During the first 4 weeks of treatment, patients are treated with dual therapy (peg-IFN and ribavirin). After 4 weeks of treatment, patients are switched to triple therapy (peg-IFN, ribavirin, and boceprevir).[25] The treatment duration is then determined by changes in viral load:

- Undetectable viral load at weeks 8 and 24: Triple therapy is continued through week 28 of treatment. However, if the patient had detectable HCV RNA at 4 weeks, extending treatment to 48 weeks increases sustained virologic response rates
- Detectable viral load at week 8, undetectable viral load at week 24: Triple therapy is continued through week 36 of treatment (4 weeks of dual therapy followed by 32 weeks of triple therapy). After week 36, the patient returns to dual therapy, which is given for an additional 12 weeks, for total treatment duration of 48 weeks.

Previous Partial Responders or Relapsers

During the first 4 weeks, patients are treated with dual therapy (peg-IFN and ribavirin). After 4 weeks of treatment, patients are switched to triple therapy (peg-IFN, ribavirin, and boceprevir). The treatment duration is then determined by changes in viral load:

- Undetectable viral load at weeks 8 and 24: Triple therapy is continued through 36 weeks of treatment.
- Detectable viral load at week 8, undetectable viral load at week 24: Triple therapy is continued through week 36 of treatment. After week 36, the patient returns to dual therapy, which is given for an additional 12 weeks, for total treatment duration of 48 weeks.

Previous Null Responders

Patients should first be treated with 4 weeks of peg-IFN and ribavirin, followed by 44 weeks of peg-IFN, ribavirin, and boceprevir, for a total treatment duration of 48 weeks.

Patients with Compensated Cirrhosis

During the first 4 weeks, patients are treated with peg-IFN and ribavirin. After 4 weeks of treatment, boceprevir is added, and all three drugs are continued for 44 weeks, for total treatment duration of 48 weeks. This is based upon subgroup analyses, which suggest higher efficacy with longer treatment durations in patients with cirrhosis.

When to Discontinue Treatment

Treatment should be discontinued if the HCV RNA is 100 IU/ml or greater at week 12 or if HCV RNA is detectable at week 24. In addition, 2011 guidelines from the American Association for the Study of Liver Diseases (AASLD) and 2012 UK consensus guidelines suggest that patients who have virologic breakthrough during treatment (>1 $\log_{10}$ increase in HCV RNA above the nadir) should have their boceprevir discontinued while continuing the peg-IFN and ribavirin.[3] The AASLD recommends against switching from one protease to another in patients who experience virologic breakthrough or who relapse on one protease inhibitor.[19]

Severe adverse events may occur in 10–15% patients with these drugs and mainly are skin rash and anemia. Telapravir is also notorious for causing anorectal pain. The SVR rates are almost 70–80% in genotype 1 naive patients with the triple regimens.

Simepravir

It is a once-daily HCV protease inhibitor which has been recently approved by US FDA for treatment of hepatitis C genotype 1 patients. The dose is 150 mg/day. In the Quest 1 and 2 trial: GT 1, treatment-naïve patients (n = 785), were treated with simeprevir 150 mg or placebo for 12 weeks + peg-IFN/RBV for 24 or 48 weeks as per response-guided therapy. This resulted in SVR rate of 88%. The major advantage is that it was well tolerated with discontinuation due to adverse events being only 3%. The main side effects were an increase in bilirubin and phototoxicity, but there was no anemia. In patients with prior relapse, the SVR rate was 70–80%.

Faldaprevir

It is a newer once-daily HCV protease inhibitor (120–240 mg/day) with similar SVR and side effect profile as simepravir.

NS5B Polymerase Inhibitors

They fall into two general types: Nucleoside analogs and non-nucleoside inhibitors (NNIs).

Table 5.
Direct Acting Antivirals[26]

Characteristics	NS3-4A Protease inhibitors	NS3-4A Protease inhibitors	NS5B Polymerase inhibitors	NS5B Polymerase inhibitors	NS5A inhibitors
	First generation	Second generation	Nucleoside analogs	Non-nucleoside analogs	
Drug	Telaprevir Boceprevir	Simeprevir Asunaprevir Faldaprevir	Sofosbuvir Mericitabine	BMS-791325	Daclatasvir
Potency	Highly variable among HCV genotypes	Highly variable	Moderate consistent across genotypes	Variable among HCV genotypes	High multiple HCV genotypes
Pharmacokinetics	Variable qd-tid	qd	qd	Variable qd-tid	qd
Adverse event	Rash (SJS, TEN), anemia, hyperbilirubinemia appetite loss, renal toxicity, elevation of uric acid	Anemia hyperbilirubinemia	Mitochondrial nuclear interaction (RBV)	Variable	Variable
Barrier to resistance	Low	Low	High	Very low	Low

qd: once a day; tid: three times a day; HCV: hepatitis C virus; RBV: ribavirin; SJS: Stevens–Johnson syndrome; TEN: toxic epidermal necrolysis.

Sofosbuvir

It is a NS5B polymerase inhibitor. It is a prodrug that is metabolized to the active antiviral agent 2'-deoxy-2'-α-fluoro-β-*C*-methyluridine-5'-monophosphate. It has shown excellent clinical efficacy when used either with peg-IFN and ribavirin or with other direct acting antivirals in interferon-free combinations. In the FISSION, POSITRON, FUSION, and NEUTRINO trials, it has resulted in SVR rates between 90%–100% in naïve patients without cirrhosis. The SVR rates are around 60–80% among naïve cirrhotics and for prior treatment failed with 24-week regimen. It has recently got US FDA approval at a dose of 400 mg/day. The most impressive aspect of the drug is its excellent safety profile.

Non-enzymatic Polyprotein Targets

Potent inhibitors of HCV replication directed against NS5A, a non-structural protein with no known enzymatic function, have been identified.

Daclatasvir and Alisporovir are NS5A inhibitors which are undergoing or have just completed phase 3 clinical trials. Table 5 summarizes the characteristics and the targets of the direct acting antivirals.[26]

Progress toward Interferon-free Regimens

The next therapeutic innovation in the treatment will be triple therapy combinations that clearly enhance rates of SVR. The success of interferon-free regimens in recent upcoming trials has completely revolutionized the treatment of Hepatitis C, which perhaps symbolizes the dawn of new era. The progress of all oral therapy for Hepatitis C would be welcome by both clinicians and the patients which will obviate intereferon related side-effects, improve SVR rates, and offer hope of treatment for those who are not candidates for intereferon based regimens. However, till the time these newer therapies are available and affordable in India, intereferon based treatment regimens will continue to hold their place.

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