Review Article

Newer Advances in the Management of Hepatitis C

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Abstract:

HCV (hepatitis C virus) is single-stranded enveloped RNA virus. Chronic HCV infection is one of the leading causes of liver-related deaths in many countries. About 130-170 million peopleare estimated to be infected with the hepatitis C virus (HCV). Main aim of antiviral treatment targets eradication of the virus. Until a few years ago, the combination of pegylated interferon and ribavirin (PEG/RBV) was the only treatment strategy available and the rates of viral clearance response did not surpass 50% in certain genotypes (1 and 4) with these treatments. In 2011, the first direct acting antiviral agents (DAA), boceprevir and telaprevir were approved for treatment of genotype 1, in combination with traditional dual therapy which accomplished to increase the rates of sustained viral response (SVR) in both naive patients and in retreated patients. New, more effective DAAs have been incorporated since 2013. Besides increasing the rates of SVR, these have pan-genomic properties, excellent tolerance and ease of administration being oral drugs. This has led to shorter therapies, lesser toxicities and regimens free of PEG/RBV, which has enabled their almost generalised applicability in all patients with minimal invasive investigations required.

INTRODUCTION

In the 1970s, cases of transfusion-associated hepatitis were reported, which frequently took a chronic, progressive course and could not be attributed to either the hepatitis A virus (HAV), the hepatitis B virus (HBV) or to any other known cause. It was called as non-A, non-B hepatitis (NANBH). It took approximately 20 years until the hepatitis C virus (HCV) was finally identified as the aetiological agent causing NANBH. Initially, interferon-α (IFNα) was used as the first antiviral agent, with regimens lasting up to 72 weeks. However, tolerability and efficacy quite were quite low and the cure rates were less than 20% for these first regimens.[1]

Around 130-170 million people (3% of the world population) are estimated to be infected with the hepatitis C virus (HCV).Of these, 55%-85% will develop chronic hepatitis, 30% will later have cirrhosis, and 2% will have hepatocellular carcinoma(HCC). Chronic infection with HCV is one of the leading causes of liver- related death and it is the primary reason for having a liver transplant in many countries.[2] The estimated prevalence of HCV infection in India is about 0.5– 1.5%.[3] Approximately 12–18 million people are thought to be infected with HCV in India.[4] The prevalence of HCV is 5.2% in Punjab.[5]

Antiviral treatment aims to eradicate the virus which is defined as a viral RNA that is undetectable by highly sensitive methods (lower detection limit of 15 IU/mL). A sustained viral response (SVR) is considered if this RNA remains undetectable 12 weeks after stopping treatment (SVR12).[2]

Many advances in treatment have been made in the treatment of HCV and it became the first curable, chronic viral infection in humans. Iatrogenic transmission (such as blood transfusion), has been reduced owing to effective hygienic measures and screening blood donors and blood products.[6,7] Also, antiviral treatment has been revolutionized leading to viral eradication rate in more than 98% of all patients infected with HCV treated by all-oral drugs.

The treatment lasts for only 8–12 weeks and there are no or only minor side effects.[8]

The WHO proclaimed in 2016 the ambitious goal to reduce new HCV infections by 2030 by 90%, with the ultimate goal of HCV elimination.[9]

Hepatitis C virusbelongs to the flavivirus family and is a linear, single-stranded enveloped RNA virus .

Clinical Course of HCV Infection

The usual route of transmission of HCV is through infected syringes and needles and transfusion of infected blood. In heterosexual couples, sexual transmission of HCV occurs infrequently. It is more common in HIV-positive persons. The risk of mother to child transmission occurs in 4–8% of births to women with HCV infection and in 10.8–25% of births to women with HIV and HCV co-infection.

HCV causes both acute and chronic hepatitis. Acute hepatitis is usually clinically mild and shown by fluctuating elevations of serum aminotransferase levels. Chronic infection with HCV is usually clinically silent and is only very rarely associated with life-threatening disease; likelihood of chronicity is >50 % leading to cirrhosis in >20%.

Spontaneous clearance of acute HCV infection occurs within six months of infection in 15–45% of infected individuals even in the absence of treatment and 55–85% of patients will harbour HCV for the rest of their lives (if not treated) and are considered to have chronic HCV infection. In chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years. The other complications of chronic HCV infection are liver failure and HCC (hepatocellular carcinoma). In persons with cirrhosis the risk of HCC is approximately 2–4% per year.[10]

Laboratory Diagnosis

After an initial phase of 1–2 weeks during which no virological or serological markers can be detected, the natural course of HCV infection is characterized by the appearance of HCV RNA, then HCV core p22 Ag in the absence of an antibody response for a further 6–10 weeks. During this serological window, free HCV core antigen(HCVcAg) can be detected in a proportion of individuals. Following the development of the antibody response, HCVc Ag becomes complexed with these antibodies specific for HCV[10]

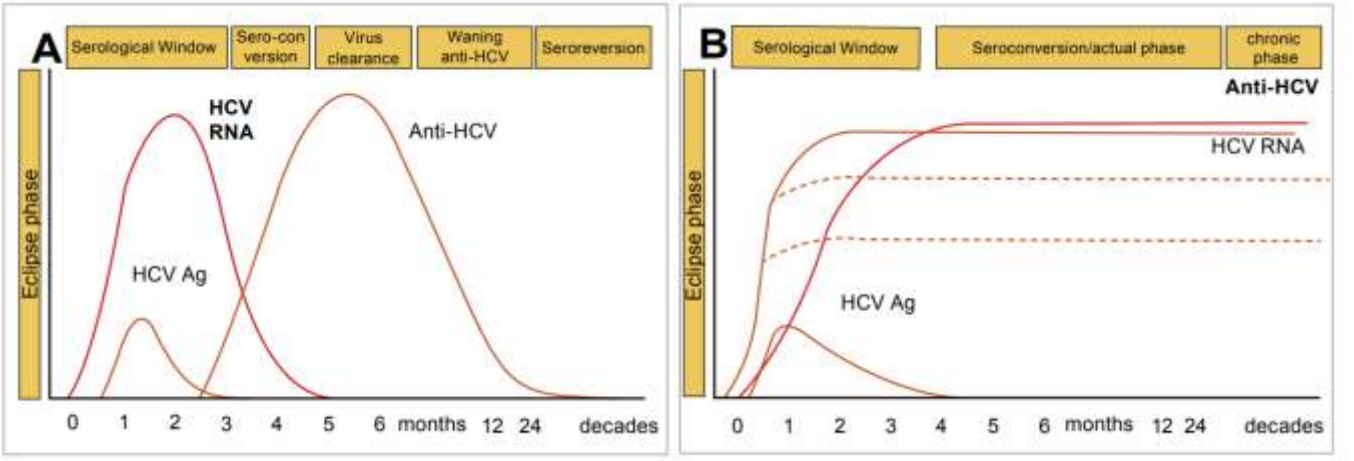


Fig.1: Approximate Time course of virological and immunological markers of HCV infection with (A) Self-resolving HCV infection, and (B) Chronic HCV infection Ref: WHO guidelines; Feb. 2017

The standard method of diagnosis is by detection of anti-HCV antibody. Both rapid diagnostic tests (RDTs) and Immunoassays are available, with comparable sensitivity and specificity. Third generation immunoassays can detect anti-HCV antibodies usually within 6 - 8 weeks of infection. This test does not differentiate between current and past infection. The diagnosis of an individual patient should be confirmed by HCV RNA detection prior to considering treatment as the test may also be false positive in some situations.[10]

Laboratory tests that are routinely included in

the evaluation of patients with Hepatitis C include a serum panel of liver tests [Albumin, totalbilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT)and alkaline phosphatase], prothrombin time and complete blood count. Non invasive tests for detecting liver fibrosis/cirrhosis

AST to Platelet Ratio Index (APRI) and Fibrosis 4 score (FIB-4 scores) are two of the most popular scoring systems for liver fibrosis and have been reported to achieve high accuracy for the diagnosis of advanced fibrosis.[11,12]

APRI score = [(AST Level/ULN)/platelet count (109/L)] *100

FIB-4 score = [age * AST/platelet count (109/L) * √ALT][13,14]

APRI score= 1.0 indicates the absence of cirrhosis and APRI -2.0 indicates the presence of cirrhosis.[15]

For FIB-4 model ,the cut-off of 1.45 and 3.25, respectively, to rule out and rule in advanced fibrosis are used.[16]

Transient elastography (Fibroscan) is a rapid and non-invasive technique that measures liver stiffness. The cut off value for cirrhosis is 12.5 kPa.[17]

Treatment of Hepatitis C

The combination of pegylated interferon and ribavirin (PEG/RBV) were the only treatment strategies available until a few years ago. Which was given for 24 or 48 weeks depending on the genotype and in genotypes 1 and 4. However, the rates of viral response did not surpass 50%and were only slightly higher in the other genotypes. The identification of new therapeutic targets was made possible with better understanding of the replication cycle of HCV. In 2011 The first direct acting antiviral agents (DAA), boceprevir and telaprevir, for treatment of genotype 1 in combination with traditional dual therapy was approved.[18,19]This strategy managed to increase the rates of SVR in both naive patients and in retreated patients but had greater toxicity, drug interactions and cost, as well as being less safe in patients with advanced disease, in which this treatment can trigger decompensation or even death.[20]

Since 2013 the addition of new more effective DAA, with pan-genomic properties and have excellent tolerance, has increased the rates of SVR (even up to 100%). Including Other advantages like shorter therapies, lesser toxicity and regimens free of interferon and/or RBV. Which has enabled their almost generalised applicability in all patients.[21]

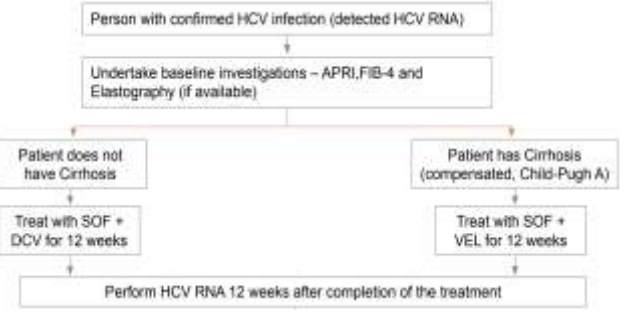
. The main disadvantage of these new drugs is their high cost. This requires selection and prioritization of patients to receive them, via strategies established by the various national organizations, in accordance with the recommendations of scientific societies.[2]

Who needs treatment?

Any individual diagnosed to have infection with hepatitis C virus (viremia +) needs treatment. The duration of treatment will depend on whether the patient is treatment naive or treatment experienced (to peg IFN, DAAs, etc); on whether the patient is cirrhoticor non-cirrhotic and presence of decompensation (ascites, variceal bleeding, hepatic encephalopathy, or infection(s). [10]

What drugs to use?

In India, Directly Acting Antivirals (DAAs) are the recommended first line treatment. The combination of the DAAs and the duration of treatment will depend on presence or absence of cirrhosis and on the genotype of the virus. The following algorithm guides on selection of regimen and the duration in treatment naive patients. [10]



SOF, Sofosbuvir ; DCV, Daclatasvir ; VEL , Velpatasvir

Fig: Algorithm for guidance on selection of regimen and duration of treatment in hepatitis C naive patient.

Regimens recommended[10]

Regime type	Category of patients	Regime recommended	Duration of Treatment
I	Patient without cirrhosis(uncomplicated)	Sofosbuvir(400mg) & Daclatasvir(60mg)*	84 days (12 wks)
II	Patient with cirrhosis- compensated (Child-Pugh A)	Sofosbuvir(400mg) + Velpatasvir(100mg)	84 days(12 wks)
III	Patient with cirrhosis- decompensated (Child-Pugh B and C)**	Sofosbuvir(400mg) + Velpatasvir (100mg) & Ribavirin(600-1200mg**)	84 days(12 wks)
		In Ribavirin intolerant patients - Sofosbuvir(400mg) + Velpatasvir(100mg)	168days (24 wks)

*dose adjustments in PLHIV, renal insufficiency, etc. ** Refer to the Model Treatment Center (MTC)

Dosage of recommended DAAs[10]

Name of drug	Dosage
Sofosbuvir	400 mg once a day
Daclatasvir	60mg once a day
Sofosbuvir + Velpatasvir	Sofosbuvir(400mg) + Velpatasvir (100mg) once a day
Ribavirin	800-1200 mg (to be decided based on weight, hemoglobin level, renal function and presence of cirrhosis)

Side Effects of Drugs Used in Treatment[10]

Sofosbuvir with or without ledipasvir: Both drugs have been well tolerated by patients. Fatigue, headache, insomnia and nausea are the most common adverse events reported. Bradyarrhythmias areassociated with sofosbuvir in patients taking amiodaronetherefore it is contraindicated in these patients.

Daclatasvir : fatigue, headache and nausea, when in combination with sofosbuvir with or without ribavirin.

Sofosbuvir with Velpatasvir : Headache, fatigue, anemia, nausea, insomnia, diarrhea, weakness, rash and depression.

Dose adjustment of ribavirin

Dose adjustment of ribavarin is required in patients with anemia. Haemoglobin level below 10 g/dL needs ribavirin dose reduction from 800–1200 mg/day (depending on the patient's weight and HCV genotype) to 600 mg/day and a patient whose haemoglobin level falls below 8.5 g/dL should discontinue ribavirin therapy.[10]

Contraindications to treatment with Ribavirin[10]

Absolute Contraindication	Relative Contraindication
• Pregnancy or unwillingness to use contraception	• Abnormal haematological indices:
• Breastfeeding women	◦ Hemoglobin <10 g/dL
• Severe concurrent medical disease, including severe infections	◦ Neutrophil count <1.5x10⁹/L
• Poorly controlled cardiac failure	◦ Platelet count <90x10⁹/L
• Chronic obstructive pulmonary disease	• Serum creatinine >1.5 mg/dL
• Previous ribavirin hypersensitivity	• Haemoglobinopathies (sickle cell disease or thalassaemia)
• Co-administration of didanosine	• Significant coronary artery disease

Management of Cirrhotic Patients after HCV clearance in SVR 12

In non-cirrhotic patients who have achieved an SVR 12 after 12 weeks of completing the treatment, HCV infection can be considered curedand no follow-up is required. A periodic clinical assessment as needed is done forpatients with a history of excessive alcohol drinking, obesity, type 2 diabetes, hypertension.

In patients with cirrhosis who have achieved cured (successful treatment), long-term post-SVR follow-up studies have demonstrated that there is a persistence of risk of developing HCC, although it is less compared to untreated patients or patients who did not achieve an SVR. Therefore, these patients with liver cirrhosis who have achieved SVR should remain under surveillance for HCC every 6 months by ultrasound, and for oesophageal varices by endoscopy if varices were present at pre-treatment endoscopy.

Reinfection : is around 1-8% following successful HCV among patients at high risk, such as PWIDs or men who have sex with men, etc. Following SVR 12, the monitoring for HCV reinfection should be recommended in these patients with ongoing risk behaviour.[10]

Treatment of patients with co-morbidities and in special situations

Treatment of Patients with Decompensated Cirrhosis

DAAs can cause severe complications when prescribed to persons with decompensated cirrhosis .This includes presence of ascites, jaundice, history of hepatic encephalopathy and variceal bleed or Child-Pugh score ≥7 [Class B and C]. Therefore, they should be used only in settings where specialized care for managing such cases is available. Following regimens would be used to treat these patients. [10]

DAAs in the treatment of Compensated Cirrhosis

	All Genotype
Ribavirin tolerant	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based RBV** x 12 weeks
Ribavirin intolerant	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) x 24 weeks

SOF: sofosbuvir; VEL: velpatasvir; RBV: ribavirin. * to be managed at model treatment center (MTC), **Ribavirin should be administered orally with food twice daily, with the dose determined according to body weight (1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight ≥75 kg). Ribavirin should be started at

lower dose (600 mg per day) then gradually increase to the maximum tolerated dose.[10]

Management of Treatment Experienced Patients

These patients need to be treated at a specialized centre for further evaluation, especially analysis for resistance associated substitutions (RAS), endoscopy, imaging (TPCT, CEMR, etc), etc. HCV genotype estimation should be done in all patients.

DAAs in the Management of Treatment Experienced Cirrhotic and Non-cirrhotic Patients[10]

Treatment failure regimen	No cirrosis / Compensated cirrhosis	Non-Genotype 3	Genotype 3
Peg IFN+RBV Or SOF+RBV	No cirrhosis	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) x 12 weeks	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) x 12 weeks
	Compensated cirrhosis	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) x 12 weeks	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin* x 12 weeks
SOF+DCV/LDV	No cirrhosis	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin x 24 weeks	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin x 24 weeks
	Compensated cirrhosis	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin x 24 weeks	Daily fixed-dose combination of SOF (400 mg) + VEL (100 mg) + weight-based ribavirin x 24 weeks

SOF: sofosbuvir; RBV: ribavirin, VEL: velpatasvir.

*Ribavirin should be administered orally with food twice daily, with the dose determined according to body weight.
(1000 mg daily in patients with a body weight of <75 kg and 1200 mg daily in patients with a body weight ≥75 kg).
Ribavirin should be started at lower dose (600 mg per day) then gradually increase to the maximum tolerated dose.

Treatment experienced patients: a study demonstrated that Sofosbuvir/ velpatasvir/ voxilaprevir (SOF/VEL/VOX) is an efficacious and safe option as rescue therapy among NS5A - experienced Asian HCV patients.[22]

Treatment of HIV and HCV Co-infection

The treatment of persons with HIV and HCV co-infection have been simplified with the use of DAAs. SVR rates with DAA based therapy among persons with HIV co-infection are higher than 95%, There are fewer Drug-Drug Interactions (DDIs) between DAAs and ARV medicines. Therefore HIV/HCV co-infected patients are not considered as a special or difficult-to treat patient population anymore.

First initiate treatment for HIV and achieve HIV suppression before starting HCV treatment. Circumstances where it may make sense to treat HCV infection first and then initiate therapy for HIV include persons with moderate-to-severe fibrosis at risk of rapid liver disease progression if the HIV infection is not associated with significant immunosuppression at the time of treatment. Also, because of the short duration of HCV treatment, the risk of DDIs between HCV and HIV medicines and the increased risk of ART-related hepatotoxicity in the presence of HCV infection, treating HCV infection first can simplify subsequent ART. [10]

Persons with HBV/HCV co-infection

HBV and HCV co-infection can cause an accelerated disease course and HCV is considered to be the main driver of disease. These patients can be treated with antiviral therapy for HCV and SVR rates are likely to be similar to those in HCV-mono infected persons. However, There is always a risk of reactivation of HBV During treatment and after HCV clearanceand this may require treatment with concurrent anti-HBV antiviral therapy. [10]

Persons with TB/HCV co-infection

Screening for active TB should be part of the clinical evaluation of patients being considered for HCV treatment because people at increased risk of infection with HCV are also often at increased risk of infection with TB. If the patient does not have any one of the following symptoms – current cough, fever, weight loss or night sweats – TB can be reasonably excluded; otherwise, the patient should undergo further investigations for TB. Concurrent treatment of HCV infection and TB should be avoided as most of the DAAs interact with metabolic pathways in the liver, which increases and/or decreases the drug level of DAAs when co-administered with antimicrobial medicines such as rifabutin, rifampin and rifapentine. Active TB should generally be treated before commencing therapy for HCV. Also, it is important to monitor liver function tests in persons with HCV infection being treated for TB as the risk of

anti-mycobacterial -induced hepatotoxicity is higher in patients with TB/HCV co-infection than in those with TB mono infection, although the risk of severe hepatotoxicity is rare. Because of many DDIs between DAAs and second-line antimicrobials, concurrent treatment of HCV infection and multidrug-resistant TB is complicated. Baseline liver function tests for individuals with chronic liver disease are encouraged prior to initiating treatment for latent TB infection.

There are limited data on the management of persons coinfected with HCV, HIV and TB, but such cases need sound clinical judgement in order to reduce the additive side-effects, pill burden and DDIs. [10]

Women of child-bearing age

Women with childbearing potential should be counselled that they require effective contraception during treatment and for six months after completion of therapy because none of the DAAs have been evaluated among pregnant women. Safety of these drugs in pregnancy has not been established. DAAs are contraindicated in pregnant women and those with child bearing potential unless effective contraception (i.e. two forms of contraception) can be guaranteed during treatment. Ribavirin is associated with fetal abnormalities. Pre-treatment pregnancy tests should be conducted prior to treatment initiation.[10]

Patients with chronic kidney disease(CKD) on hemodialysis

Patients with a creatinine clearance (CrCl) of 30-80 mL/min, that is moderate chronic kidney failure may follow the general recommendations. No dose adjustment is necessary for sofosbuvir, simprevir, ledipasvir .

No efficacy or safety data are available for patients with a CrCl< 30 mL/min.

Patients on hemodialysisshould receive treatment free of interferon and RBV, though no safety data are available with the use of DAA.[2]

Conclusion

With direct acting antiviral (DAAs) drugs, the management of patients with chronic hepatitis C has radically changed owing to their high rates of SVR and improved safety profile. This has led to the reduction of the risk of progression to cirrhosis and a lower incidence of complications even in established cirrhosis.

Inorder to achieve elimination of hepatitis C, improvement in screening, access to antiviral treatment and reduction of new infections are essential. This includes cheap, rapid and simple tests to diagnose HCV infection. Other strategies include local and national screening programmes, lowering the costs of drug and developing simple management algorithms that enable unspecialized physicians and even nurses to initiate and guide treatment of HCV infection.

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