Consensus Statement of HCV Task Force of the Indian National Association for Study of the Liver (INASL). Part II: INASL Recommendations for Management of HCV in India

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The estimated prevalence of hepatitis C virus (HCV) infection in India is between 0.5 and 1.5% with hotspots showing much higher prevalence in some areas of northeast India, in some tribal populations and in certain parts of Punjab. Genotype 3 is the most prevalent type of infection. Recent years have seen development of a large number of new molecules that are revolutionizing the treatment of hepatitis C. Some of the new directly acting agents (DAAs) like sofosbuvir have been called game-changers because they offer the prospect of interferon-free regimens for the treatment of HCV infection. These new drugs have not yet been approved in India and their cost and availability is uncertain at present. Till these drugs become available at an affordable cost, the treatment that was standard of care for the whole world before these newer drugs were approved should continue to be recommended. For India, cheaper options, which are as effective as the standard-of-care (SOC) in carefully selected patients, are also explored to bring treatment within reach of poorer patients. It may be prudent to withhold

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Abbreviations: ALT: alanine amintraonsferase; ANC: absolute neutrophil count; anti-HCV: antibody to HCV; AST: aspartate aminotransferase; CH–C: Chronic Hepatitis C; CKD: chronic kidney disease; CTP: Child-Turcotte-Pugh; EIA: enzyme immunoassay; ETR: end-of-treatment response; EVR: early virological response; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HCV: hepatitis C virus; HIV: Human immunodeficiency virus; IFNa: interferon alfa; INASL: Indian National Association for Study of the Liver; PCR: polymerase chain reaction; Peg-IFNa: pegylated interferon alfa; RBV: Ribavirin; RVR: rapid virological response; SOC: standard of care; SVR: sustained virological response; ULN: upper limit of normal
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treatment at present for selected patients with genotype 1 or 4 infection and low levels of fibrosis (F1 or F2), and for patients who are non-responders to initial therapy, interferon intolerant, those with decompensated liver disease, and patients in special populations such as stable patients after liver and kidney transplantation, HIV co-infected patients and those with cirrhosis of liver. (J Clin Exp Hepatol 2014;4:117–140)

Hepatitis C virus (HCV) infection is estimated to affect 0.5%–1.5% of Indian population. The management of chronic hepatitis C (CH–C) has evolved over the last two decades resulting in significantly improved of response rates. Initial treatment regimen with conventional interferon alfa (IFNα) alone in dose of 3 million Units (MU) thrice weekly for 24 or 48 weeks had dismal results, with sustained virological response (SVR) rates of 6% and 13–19% respectively. The response rates improved with the addition of ribavirin (RBV) and SVR rates with IFN-α/RBV combination therapy were 33% and 41% with 24 and 48-week therapy respectively. However, it was with the introduction of pegylated interferon alfa (Peg-IFNα), that response rates improved dramatically. The SVR rates with Peg-IFNα/RBV combination therapy are around 50% for genotype 1 and 80% for genotype 2/3 infections.[1,2] In the case of genotype 2/3, SVR rates of as high as 84–95% have been reported from some Southeast Asian countries.[3]

Currently, there are several comprehensive and up-to-date guidelines, issued by leading authorities such as AASLD and EASL, for the management of CH–C.[4–7] However, there are many special issues which merit attention prior to the implementation of any such guidelines for the management of CH–C in India. The first issue is that the most prevalent HCV genotype in India is genotype 3, unlike in western countries. Genotypes 2/3 have usually been considered to respond better to Peg-IFNα/RBV combination therapy. Hence, genotypes 2 and 3 have usually been grouped together for therapeutic strategies with recommendation for a shorter duration of treatment (24 weeks or even 16 weeks) and use of a fixed and lower RBV dose (800 mg/d). However, genotype 3 has some distinct characteristics including association with significant steatosis, a more rapid progression to fibrosis[8] and higher incidence of hepatocellular carcinoma.[9] Unlike genotype 2, where Telaprevir monotherapy reduces the levels of HCV-RNA in chronic HCV, it has limited activity in genotype 3.[10] Moreover, it is now known that SVR rate with Peg-IFNα/RBV combination therapy in patients with genotype 3 HCV infection is lower than that with genotype 2 infection.[11,12] The steatosis associated with genotype 3 HCV infection is associated with higher rates of viral relapse, irrespective of viral load, even after a rapid virological response (RVR) has been achieved.[13] It is therefore important that genotype 3 be dealt with separately, rather than being lumped together with genotype 2 as an "easy-to-treat genotype", which has been the practice in published guidelines hitherto. Secondly, the newer directly acting agents [DAA], which have been recommended as the standard of care in the newer guidelines, are yet to become available in India. Finally, in a resource-poor country like India, the vast majority of patients are not covered by insurance and the expensive therapy for HCV is not funded by the state. Many patients with CH–C are unable to afford therapy with Peg-IFNα. In such a setting the additional costs of newer advances like IL28B genotype testing and addition of directly acting agents (DAAs) may make the cost prohibitive for many patients.

The members of the INASL task force are very well aware that this consensus statement is likely to get time-barred very soon. We are prepared for the need to update these recommendations in the near future, as soon as the newer DAAs appear in the Indian market. This would happen, preferably, after Indian physicians and experts have had time to get a feel of the new DAAs based regimes in real-life rather than in licensing-study mode and once various players have sorted out their pricing policies for India.

We have focused on genotype-3 HCV recommendations, which have not received proper attention in the genotype-1 dominated consensus statements from other associations. As probably the last interferon-based consensus likely to be published, we have tried to make it practical and comprehensive with regards to interferon usage.

Finally, India is a very price-sensitive market and faces significant cost-constraints. Simultaneously, there is pressing need to ensure penetration of effective antiviral therapy to the 99.8% of the population that is in need of antiviral therapy against HCV but is not able to afford it. Hence, we have attempted to explore cost-effective though less-than- ideal options while proposing Indian guidelines. Use of standard interferon in appropriately selected patients as well as continued use of Peg-IFNα/RBV dual therapy has been discussed; perhaps, both may retain a place in India even after the availability of DAAs in the Indian market.

These considerations have prompted the Indian Association for Study of the Liver (INASL) to set up an HCV Task Force to formulate consensus guidelines for management of CH–C, relevant to the Indian scenario. This report summarizes the deliberations in the INASL HCV task force

consensus meeting for the formulation of HCV management guidelines in the Indian context.

These guidelines have been developed using data collected from Indian centers by the INASL HCV Task Force and from PubMed searches.[14] These recommendations have been formulated after scrutinizing Indian data as well as existing international publications on the individual issues. The task force adopted the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system for evaluating evidence.[15] The detailed description of GRADE system is given in part 1 of this paper. In brief, based on the available data, the recommendations have been graded as strong (1) or weak (2), and the quality of evidence supporting these have been graded as high (A), moderate (B), low-quality (C) or very low quality (D).

LABORATORY TESTING

Investigations for patients with HCV infection include serological assays for antibodies to hepatitis C (anti-HCV) and molecular assays for detection of viral RNA. In addition, investigations for stage of hepatic fibrosis may also be considered.

Serological Assays

Presence of anti-HCV antibodies indicates prior exposure to HCV infection. However, the assay may be negative early in acute HCV infection, in immunosuppressed individuals (including those with human immunodeficiency virus [HIV] infection and organ transplant recipients who are receiving immunosuppressive drugs) or years after resolution of HCV infection.[16,17] Anti-HCV antibodies can be detected by rapid immunoassays, enzyme-linked immunosorbent assays (ELISA), or chemiluminescent immunoassays. Quality of some of the test kits for anti-HCV may be a reason for concern.[18,19]

Rapid Immunoassay

Rapid immunoassay tests use a unique combination of modified HCV antigens conserved across all genotypes from the putative core, NS3, NS4 and NS5 regions of the virus. In one study, the sensitivity and specificity of rapid immunoassay has been shown to be comparable to FDA-approved lab conducted HCV antibody tests.[20] However, some studies have demonstrated that rapid tests cannot be solely relied upon in screening patients from high-risk population in India.[21,22]

Enzyme Linked Immunosorbent Assay

This tests the presence of antibodies against HCV core, NS3 and NS5 regions. A study in North India has demonstrated the value of blood banks screening using two ELISA kits concurrently to improve detection of contaminated blood.[23]

Enhanced Chemiluminescence Immunoassay

ECi, a quantitative assay based on chemiluminescent reaction, can also be used.[24] The performance of these tests is similar to that of the usual ELISAs.

Hepatitis C Virus Core-antigen

Detection of HCV core-antigen, a protein with highly conserved sequence, by enzyme-immunoassays may be a simpler alternative to RNA detection.[25] Its major role may be in identification of blood donors who are in the pre-seroconversion window. It has been shown to be more cost-effective than nucleic acid testing for early diagnosis of HCV infection. Its cost has been estimated to be around 3–4 times lesser than the in-house reverse transcription-polymerase (RT-PCR) assays and 9–10 times less than that of the United States Food and Drug Administration approved RT-PCR assays.[26] HCV core antigen-ELISA may be an alternative to detect active HCV infection where HCV RNA testing may not be feasible.[27]

Hepatitis C Virus RNA testing

HCV nucleic acid detection relies on either amplification of the detection signal or amplification of the nucleic acid target. The branched DNA method (bDNA assay) for signal amplification detects HCV RNA and has a lower limit of quantification of 615 IU/mL. This level of sensitivity is generally inadequate for measuring response to antiviral therapy where the goal is viral eradication. Quantitative assays using RT-PCR methods have a lower limit of detection of 50 IU/mL (Amplicor v2.0® and Cobas v2.0®, Roche). A broader dynamic range allows for better quantification of HCV RNA at the highest levels of viremia prior to initiation of treatment.

HCV RNA testing is recommended for:

- For confirmation of viremia if anti-HCV test is positive.
- For confirmation of a strong suspicion of HCV infection where HCV antibodies may be negative e.g. acute HCV infection with exposure to HCV within the last 6 months, immunocompromised patients or in those with HIV infection.
- The diagnosis of HCV infection in babies born to HCV positive mothers since antibody testing may be fallacious due to presence of maternal anti-HCV antibodies up to 18 months of age. During this period HCV RNA should be done to confirm the diagnosis.[28,29]
- At baseline, prior to commencing treatment at baseline and for monitoring of viral kinetics during therapy and to guide therapy.

HCV RNA testing should be done using a sensitive method (lower limit of detection of <50 IU/ml) and the results should be expressed in a standardized format as IU/mL.

Hepatitis C Virus Genotype Testing

Genotype testing is pivotal to determine the duration and dosage of therapy with Peg-IFNα/RBV and in predicting the efficacy of the treatment. While a variety of techniques are used, the gold standard for HCV genotyping is nucleotide sequencing, which can be done by using core (C), envelope (E1), or the non-structural (NS5) regions which can be amplified by polymerase chain reaction. Most diagnostic assays commonly target the 5′ untranslated region (5′UTR).

However, some genotype 6 variants found in Southeast Asia have 5′UTR sequences identical to those of genotype 1a or 1b.[30,31] Hence, currently used 5′UTR-based assays are unlikely to be very accurate in high-diversity areas.[32] There are a large number of subtypes in India and commercial assays geared for detection of subtypes prevalent in western countries may have not be very effective in detecting subtypes indigenous to the Indian population.

Interleukin-28B Polymorphisms

Host genetic factors have long been suspected to play a role in predicting outcome and treatment response in HCV infection. There has been increasing data regarding the significance of the interleukin-28B (IL-28B) polymorphism not only in the response to treatment but also in spontaneous clearance of acute HCV infection. Multiple studies have shown that patients with the CC genotype at the single nucleotide polymorphism (SNP) rs12979860 polymorphic site have higher sustained virologic response (SVR) rates than patients with the CT or TT genotype. Similarly, patients with the TT genotype at the SNP rs8099917 polymorphic site have higher SVR rates than patients with the GT or GG genotype. In one study from India, the favorable CC genotype of the SNP rs12979860 has been found to be more frequent suggesting a possible better response to therapy for HCV in India.[33]

Assessment of Fibrosis and Role of Liver Biopsy

Assessment of hepatic fibrosis is important, as it establishes the status of hepatic injury and is helpful in taking the decision to start therapy as well as in predicting outcome of therapy. Assessment of liver fibrosis can be done by liver biopsy or by non-invasive means. Noninvasive tests for fibrosis fall into two categories: serologic panels of tests and radiologic tests. Serological markers include the aspartate aminotransferase-platelet ratio index (APRI) ratio, which can be easily calculated using data available from routine laboratory tests, or commercially available serum marker systems such as the FibroTest/FibroSure, Hepascore, FibroSpect, and the European Liver Fibrosis Study Group panel.

The most widely used imaging modality is transient elastography (Fibroscan®). It uses ultrasound for measuring liver stiffness, which correlates with the amount of hepatic fibrosis. Other commonly used tests include magnetic resonance elastography, acoustic radiation force impulse imaging, supersonic imaging and real-time shear wave elastography.

Liver biopsy remains the gold standard for assessment of fibrosis. However, it is invasive, is subject to sampling error, has intra-observer and inter-observer variation and carries a risk of complications. In view of their good response to therapy, patients with genotype 3 usually do not need a biopsy unless they are HIV-infected or another source of liver disease is suspected in view of the good response to therapy. There is also debate on the role of biopsy in HCV genotype 1. Where possible, non-invasive methods can be used instead of liver biopsy to assess the severity of liver disease. A liver biopsy may be especially useful in patients with a known or suspected dual etiology like alcoholism, autoimmune disease or concurrent hepatitis B virus (HBV) infection.

Evaluation for Other Causes of Liver Disease

Co-infection with HBV and HIV should be tested for by appropriate tests. Other conditions associated with liver injury, such as alcohol, autoimmune or metabolic liver disease, or steatohepatitis should also be assessed. Details of such investigations are beyond the scope of this paper.

TREATMENT OF CHRONIC HEPATITIS C

Indications for Therapy

All patients with compensated liver disease due to CH–C who have evidence of HCV replication and no contraindications to therapy should be considered for treatment. The decision to initiate or not to initiate antiviral treatment should not be based only on alanine aminotransferase (ALT) levels, since significant liver disease may exist even in patients with persistently normal ALT.[34]

The standard-of-care (SOC) for hepatitis C, till recently, has been combination therapy with Peg-IFNα/RBV. However, the treatment of HCV is rapidly evolving. The latest guidelines from AASLD and EASL in 2014 have already incorporated DAAs in the management of patients with CH–C. The newly approved DAA are yet to reach the Indian market. It may be prudent to consider deferring treatment pending the availability of newer agents in India in patients who can wait for therapy eg. those with no or minimal fibrosis and those with poor likelihood of response to SOC therapy (e.g. previous treatment failures, genotype 1, HCV–HIV co-infections, etc.). However, in patients with advanced fibrosis (fibrosis score F3 or F4), compensated cirrhosis or significant extrahepatic manifestations (symptomatic cryoglobulinemia or HCV immune complexes nephropathy) or in those likely to have good response to IFNα/RBV (eg. genotype 3 CH–C), it may not be advisable to wait and treatment should be started.

While most standard guidelines have classified algorithms based on genotype 1 and genotype 2/3, INASL guidelines have focused on the management algorithm based on genotype 3 and "other genotypes". The reason for such recommendations is a predominance of genotype 3 in India and the fact that genotype 2 is rare in India.

Contraindication to Interferon/Ribavirin Therapy

The various absolute contraindications include decompensated liver disease (Child Pugh score 9 or more), uncontrolled depression, psychosis, epilepsy, uncontrolled autoimmune disease, pregnancy or in those planning pregnancy, severe concurrent medical disease like poorly controlled hypertension, diabetes mellitus, heart failure and chronic obstructive pulmonary disease.

Relative contraindications include abnormal hematological parameters (hemoglobin (Hb) < 10.0 g/dL, baseline neutrophil count <1500/mm^3, or a baseline platelet count <90,000/mm^3), serum creatinine >1.5 mg/dl, significant coronary artery disease and untreated thyroid disease, previous intolerance or hypersensitivity to IFNα and age >70 years. Therapy can be individualized on a case-to-case basis in elderly patients.

Consensus Statement: Indications of Therapy of Hepatitis C

1. ***All treatment naive patients with compensated liver disease due to HCV should be considered for therapy (Strength-2, Level of evidence-A)***.
2. ***For elderly (≥70 years) patients and those with mild disease, indication and timing of therapy can be individualized (Strength-2, Level of evidence-B).***
3. ***Early therapy should be considered for patients with advanced fibrosis or significant extra-intestinal manifestations irrespective of genotype (Strength-1, Level of evidence-A)***.
4. ***Therapy can be deferred in patients with no or mild fibrosis, especially so in patients other than genotype 2/3 (Strength-1, Level of evidence-B)***.

Assessment Prior to Treatment

Prior to starting Peg-IFNα/RBV treatment, the following checklist should be completed:

- A detailed history and physical examination is essential. In addition detailed history of alcohol consumption and drug abuse need to be evaluated. Detailed cardiac, pulmonary and psychiatric evaluation should be done, if indicated.
- Baseline complete hemogram and liver biochemistry [including include alanine aminotransferase (ALT) and aspartate aminotransferase (AST) alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase (GGT), prothrombin time or INR, albumin], renal function and thyroid function. Other tests which may be recommended are, iron studies, vitamin D, alpha-fetoprotein and autoantibody studies.
- Serum HCV RNA (quantitative) and HCV genotyping/serotyping.
- IL-28B genotyping is not recommended for routine use, may be done in selected patients to prognosticate treatment response and help in decisions regarding treatment duration.
- Liver biopsy is not required if patients are willing for treatment or have established cirrhosis. Liver biopsy may be appropriate if patients are not convinced about the treatment or want to wait for new treatment.
- Cardiac and pulmonary evaluation, if indicated.
- Psychiatric evaluation, if indicated.
- In women of child bearing age urine pregnancy test is required.

Consensus Statement: Evaluation Prior to Starting Therapy of Hepatitis C

5. ***The initial screening test for HCV testing is anti-HCV serology (Strength-1, Level of evidence-A)***.
6. ***In patients who are immunosuppressed or are suspected to have acute HCV infection, anti HCV test may be negative and HCV RNA testing should be done to confirm the presence of infection (Strength-1, Level of evidence-A)***.
7. ***Prior to starting treatment, the following should be done***:
   a. ***Full medical history and clinical examination***
   b. ***Laboratory tests including complete hemogram, liver biochemistry, renal function, thyroid function, iron studies and autoantibodies (Strength-1, Level of evidence-prognosis B)***.
8. ***Liver disease severity should be assessed prior to therapy. Patients with cirrhosis should be identified as their response to therapy and prognosis are different and they require surveillance for HCC (Strength-1, Level of evidence-A)***.
9. ***Fibrosis stage can be assessed by noninvasive methods like liver stiffness measurement and panels of biomarkers. Liver biopsy is required where there is uncertainty regarding severity or etiology (Strength-1, Level of evidence-B)***.
10. ***Prior to treatment of HCV, quantitative HCV RNA should be checked at baseline. HCV RNA detection and quantification should be done by sensitive assay (low limit of detection ≤50 IU/ml) (Strength-1, Level of evidence-A)***.
11. ***HCV genotyping is recommended prior to starting therapy to guide the appropriate regimen and duration of therapy (Strength-1, Level of evidence-A)***.
12. ***IL-28B is not a prerequisite but may be done on case to case basis (Strength-1, Level of evidence-C)***.

Monitoring During Treatment

Monitoring during treatment is aimed at: i) monitoring for treatment efficacy, which would help in deciding duration of therapy depending on virological response; and ii) monitoring for adverse effects of treatment.

Patients should be followed at 2 weekly intervals for the first 8 weeks and subsequently after every 4 weeks till completion of therapy.

- At each visit, patients should be assessed for side effects including flu like symptoms, fatigue, depression, sleep disorder, irritability, dyspnea, headache injection site reaction and for infections, autoimmune reactions, hearing and visual disturbances and interstitial lung disease.
- Patients should be observed for signs of depression and psychiatric evaluation should be done, if indicated. There should be reinforcement of advice regarding need for contraception during therapy.
- Patients with obesity should be counseled regarding weight reducing strategies by diet, exercise and medical therapies
- Complete blood count at 1, 2, 4 weeks and every 4 weeks thereafter.
- Liver biochemistry and renal function every 4 weeks.
- Thyroid function should be done every 12 weekly.
- Serum HCV RNA should be tested at baseline, week 4, week 12, week 24, end of treatment and 24 weeks after end of therapy. Follow-up testing should be done using the same method as used for baseline testing.

Achieving SVR has generally been taken as a cure of HCV infection. SVR is defined as absent HCV RNA in serum using a sensitive test 6 months after the completion of therapy for HCV. Some reports, including data from India, have shown that while SVR is durable in most patients, some patients do have late relapse, with reappearance of HCV RNA among individuals who had treatment-induced SVR; long-term follow up may be particularly important in patients with HCV-related liver cirrhosis.[35] Some reports of recurrence of HCV RNA after SVR may be due to differing sensitivities of the assays used by different investigators. However, a recent meticulously performed study has shown that an SVR almost always signals durable loss of the hepatitis C virus and improvement of associated liver disease, and hence indicates apparent cure.[36]

Consensus Statement: Monitoring of Patient on Peg-IFNα/Ribavirin Therapy

13. ***Treatment toxicities should be assessed at the end of weeks 1, 2 and 4 of therapy and 4-weekly intervals thereafter (Strength-2, Level of evidence-C).***
14. ***Serum HCV RNA should be tested at baseline, week 4, week 12, week 24, end of treatment and 24 weeks after end of therapy (Strength-1, Level of evidence-A).***
15. ***The goal of treatment is eradication of HCV infection (Strength-1, Level of evidence-A).***
16. ***Achieving SVR usually equates to cure of infection (Strength-1, Level of evidence-A).***

Post-treatment Follow-up

Patients who achieve SVR can be retested for ALT and HCV RNA at 48 weeks post treatment. Patients who are negative can be taken as cured. Thyroid function should be assessed after 1 year of therapy. Patients with cirrhosis need surveillance for HCC and portal hypertension.

Consensus Statement: Post-treatment Follow-up

17. ***Patients with SVR should be tested for ALT and HCV RNA at 48 weeks post treatment (Strength-2, Level of evidence-C).***
18. ***Patients with cirrhosis need surveillance for HCC and complications of portal hypertension (Strength-1, Level of evidence-B).***

Predictors of Response to Antiviral Therapy

Response to treatment of CH–C with IFNα or Peg-IFNα and RBV can be predicted by a number of factors at the baseline and 'on therapy' factors. Some of them are enumerated in Table 1. In a multi-national evaluation of outcomes of antiviral treatment with Peg-IFNα and RBV in more than 7000 treatment naöve patients afflicted with CH–C (PROPHESYS cohort), a number of factors were found to predict response to therapy.[37] Some of the well-established predictors of response to therapy and their associated strength in predicting SVR are described below.

1. Viral load: A large multi-centric European study enrolling more than 500 patients each in three different dosage arms of Peg-IFNα2b as well as IFNα2b with varying doses of RBV suggested that SVR rates were higher in those with $<2 \times 10^6$ copies per ml (cpml) vis-à-vis those with $>2 \times 10^6$ cpml at baseline [78% versus 42% across genotypes, $P < 0.01$].[38] However, a multi-centric study of patients treated with Peg-IFNα2a, failed to show significant difference in SVR rates when patients were stratified according to viral loads cut-off of 2×10^6 cpml.[39]
2. Genotype: This is the strongest baseline predictor of response to therapy in CH–C. A large multi-centric European study enrolling more than 500 patients each in three different dosage arms of Peg-IFNα2b as well as IFN2b with varying doses of RBV suggested that SVR rates were higher in those with genotype 2/3 compared with those with genotype 1 [82% vs. 42%, in the high Peg-IFNα2b subgroup, $p < 0.05$].[38] The multi-centric Peg-IFNα2a study also showed that non-genotype 1

Table 1 Predictors of Poor Response to Antiviral Therapy in Chronic Hepatitic C.

Host Factors	Viral factors	Treatment factors
Advanced age	High viral load (>4 × 10^5 IU/mL)	Regimen (IFN monotherapy)
Male gender	Genotypes 1, 4	Inadequate dose and duration
Ethnicity	Presence of Quasispecies	Dose reduction, discontinuation due to adverse effects
Insulin resistance		
Alcohol use		
Bridging fibrosis/ cirrhosis		
Unfavorable IL-28B SNPs		

patients respond better to therapy (OR: 3.25, non-GT-1 vs. GT-1, $P < 0.001$).[39]

3. Degree of fibrosis: Baseline fibrosis predicts not just the probability of achieving SVR, but possibly, the duration of therapy too. A large multi-centric European study enrolling more than 500 patients each in three different dosage arms of Peg-IFNα2b as well as IFNα2b with varying doses of RBV suggested that SVR rates were higher in those with no or minimal fibrosis vis-à-vis those with bridging fibrosis/cirrhosis [57% vs. 44% in the high Peg-IFNα2b arm, $P < 0.05$].[38] The multicentric Peg-IFNα2a study did not show a difference in SVR rates between those with a pre-treatment histological diagnosis of cirrhosis and those with a lesser degree of fibrosis on multi-variate analysis.[39]
4. Duration of therapy and cumulative dose of Peg-IFNα/RBV: For genotype 1, 48 week duration of therapy was observed to be better than 24 week therapy [SVR rates have been shown to be better with standard dose (1–1.2 g/day) RBV than low dose (800 mg/day) RBV.[40] For genotypes 2 and 3, the duration or dose of RBV did not matter, as SVR rates were uniformly high in all the four groups.[40,41] Compliance to therapy with Peg-IFNα and RBV affects the SVR rates, at least in the group of patients who have an intermediate chance of achieving SVR.[42]
5. On therapy viral kinetics: The likelihood of SVR depends on viral kinetics while on therapy. The patterns of virological response are depicted in Table 2. The rapidity of viral decline following initiation of antiviral treatment with Peg-IFNα and RBV is the strongest predictor of response to therapy. Patients who achieve HCV RNA negativity [<50 IU/ml] at week 4 (RVR) and are able to maintain it to week 24, have high SVR rates (85–90%).[43] This phenomenon is observed across genotypes and viral loads, though those with high viral loads are less likely to achieve RVR. The next milestone in viral kinetics is EVR (early virologic response), wherein HCV RNA is negative [<50 IU/ml] at week 12. About 65% of these patients achieve SVR. Those who have not achieved EVR (HCV RNA at week 12, >50 IU/ml or <2 log decline in HCV RNA from baseline) have less than 5% likelihood of developing SVR.
6. Genetic markers: Genetic variations near the IL-28B gene have been associated with response to HCV therapy with Peg-IFNα and RBV.[44–46] The IL-28B gene polymorphisms may have a lesser role to play in the era of DAAs. However, in the initial registration trials using Peg-IFNα, RBV and first generation NS3-4a protease inhibitors (PIs) the prediction of SVR and/or shortened duration of therapy have been well documented.[47]

Therapy of Genotype 3 Chronic Hepatitis C

As has been highlighted earlier, unlike genotype 2, genotype 3 in not really an "easy-to-treat" genotype. Data

Table 2 Patterns of Virological Response of HCV on Therapy.

Timing on therapy	Response	Description
Week 4	Rapid virological response (RVR)	Undetectable HCV RNA
Week 12	Early virological response (EVR)	- Complete EVR (cEVR): Undetectable HCV RNA at 12 weeks of therapy - Partial EVR (pEVR): ≥2 Log_{10} reduction in HCV RNA from baseline at 12 weeks of therapy
	Null response	<2 Log_{10} reduction in HCV RNA from baseline at 12 weeks of therapy
Week 24	Late virological response (LVR)	In patients who had pEVR, undetectable HCV RNA after 24 weeks of therapy
	Partial response	In patients who had pEVR, detectable HCV RNA after 24 weeks of therapy
End of treatment	End of treatment response (ETR)	Undetectable HCV RNA at the end of treatment
24 Weeks after stopping therapy	Sustained virological response (SVR)	Undetectable HCV RNA 24 weeks after stopping therapy
	Relapse	Reappearance of HCV RNA in patients who had ETR
	Breakthrough	Reappearance of HCV RNA on treatment at any time after virological response

Table 3 Management of HCV Genotype 3 Treatment Naive Patients.

	APASL 2012	EASL 2014	AASLD 2014	INASL 2014
First Line therapy	Peg-IFNα (2a or 2b) + RBV 1000 mg < 75 kg, 1200 > 75 kg × 24W	1.Peg-IFNα (2a or 2b) + RBV + Sofosbuvir × 12W	**Regardless of IFNα eligibility** Sofosbuvir + RBV × 24W	DAA not available Peg-IFNα (2a or 2b) + Weight based RBV 15 mg/kg × 24 W
Alternative regimen	–	2. Sofosbuvir + RBV × 24 W 3. Sofosbuvir + Daclatasvir × 12W ± RBV	**IFNα eligible** Sofosbuvir + RBV + Peg-IFNα × 12 W	Conventional IFNα + Weight based RBV 15 mg/kg × 24 W
Treatment not recommended/ not available	–		1. Peg-IFNα/RBV × 24W 2. Monotherapy with Peg-IFNα, RBV, or a DAA Telaprevir-, boceprevir-, or simeprevir-based regimens	DAA not available

RBV, ribavirin; Peg-IFN, pegylated-interferon; DAA, directly acting agents; W, week.

from India also shows that the response rates to Peg-IFNα/RBV therapy in genotype 3 may be lower than those reported for genotype 2/3 from the west. Poorer response to interferon described in Asians has been attributed to an older age and more advanced liver disease at presentation.[48,49] Overall, SVR was achieved by 54% in a study to determine whether Asian race independently predicted SVR. It was highest amongst non-South Asians (79%) compared with South Asians (56%, $P = 0.04$) and Caucasians (50%, $P = 0.001$) despite a predominance of genotype 3 infection amongst the South Asians.[50] However, a recent study, which evaluated treatment response of genotype 3 infected Asian patients, showed no difference in treatment response for Asian versus white European patients.[51]

The initial study of Peg-IFNα/RBV therapy in CH-C genotype 3 from India by Sood et al[52] showed an SVR of 78.9% in low-dose Peg-IFNα and 92.6% in the standard high-dose Peg-IFNα group. Some other studies with smaller number of patients with genotype 3 had also shown a similar SVR of 76–87.5%.[53–56] However, other workers have shown poorer response rates to therapy in genotype 3 CH-C in the Indian population.[57] Tohra et al[58] have reported SVR rate of 67% in 97 treatment-naöve patients with CH-C genotype 3 with Peg-IFNα/RBV for 24 weeks. Similar results have been reported by a multinational study, which included Indian patients, the SVR in genotype 2/3 (80% genotype 3) with SOC therapy was 66.5%.[51] Data of the INASL HCV registry showed a response rate of 677/934 (72.5%) in patients with genotype 3 infection.[14]

Guidelines for treatment of genotype 3 CH-C in India have to balance the need for higher efficacy with relatively lower response rates with alternative lower cost strategies for patients without any risk factors for an adverse outcome.

In patients with risk factors for poor outcome and/or lack of RVR, there must be a low threshold for increasing duration of treatment and weight based rather than conventional, fixed 800 mg dose of RBV should be used.

In patients who achieve RVR and do not have any risk factors for poor outcome, the therapy may be shortened to 12–16 weeks, though response rates may be marginally lower than SOC. In a large multinational study, Manns et al[51] compared Peg-IFNα2b (1.5 μg/kg/wk) for 24 weeks (group A); Peg-IFN-α2b (1.0 μg/kg/wk) for 24 weeks (group B); or Peg-IFNα2b (1.5 μg/kg/wk) for 16 weeks (group C), each in combination with weight-based RBV (800–1200 mg/d). SVR rates were 66.5%, 64.3%, and 56.6% in groups A, B, and C. Among patients with undetectable HCV RNA at week 4, SVR rates were 75.3%, 75.9%, and 72.4%, respectively.

Response of Conventional Interferon/Ribavirin Therapy in Genotype 3

With an estimated HCV prevalence of 0.5–1.5% and an estimated 6-18 million infected individuals in a population of >1.2 billion, the burden of CH-C in India is colossal. While Peg-IFNα/RBV is the SOC and DAAs are on the horizon, the vast majority cannot afford any expensive therapy for HCV in India.

With this background, there is always a hunt for alternate cheaper treatment options for Indian patients with CH-C. Acharya et al[59] have published, a multi-centric, prospective, randomized controlled trial comparing conventional IFNα2b 3 MU/day and RBV 1000 mg/day (IR) with IFNα2b 3 MU/day and glycyrrhizin 250 mg/day (IG) in CH-C. While the results of glycyrrhizin arm were disappointing, the SVR rate of 65.7% in the IR arm (67% in genotype 3 CH-C) with standard IFNα -2b 3 MU OD + RBV 1000 mg/day were nearly identical to results reported in genotype-3 patients treated with Peg-IFNα (2a or 2b) +RBV for 24 weeks (SVR 67%) from another north Indian center.[58] In an era where Peg-IFNα/RBV therapy, the SOC till recently, is being threatened by the arrival of newer drugs and the world prepares to move on to newer, more expensive though effective SOC, these results of conventional IFNα must be not be completely ignored in settings of economic constraints. However two factors must be kept

Table 4 Duration of Treatment of Genotype 3 as Per Viral Kinetics.

Week	Interpretation	HCV RNA level				
0	Base line viral load	LVL or HVL	LVL or HVL	HVL	LVL	LVL or HVL	LVL or HVL
4	RVR	HCV RNA+	HCV RNA +	HCV RNA–	HCV RNA–	HCV RNA+	HCV RNA+
12	EVR	HCV RNA + (<2log↓) NR	HCV RNA + (>2log↓) (pEVR)	HCV RNA – (cEVR)	HCV RNA – (cEVR)	HCV RNA – (cEVR)	HCV RNA + (>2log↓) (pEVR)
24	LVR		HCV RNA+	HCV RNA–	HCV RNA–	HCV RNA -	HCV RNA–
Recommendation		Stop at 12W	Stop at 24W	24W Rx (48W if risk factors)[a]	24W Rx; 16W if no risk factors[a]	48W Rx	48W Rx

Note: The sign of '+' means that HCV RNA is still detectable (response to treatment is not complete) and '–' implies that HCV RNA is not detectable (response to treatment is complete). LVL, low viral load; HVL, high viral load; RVR, rapid virological response; cEVR, complete early virological response; pEVR, partial early virological response; LVR, late virological response.
[a]In conditions, where cost economics is an issue, 16 weeks therapy can be considered in patients with low viral load (<4 × 10^5 IU/mL) without any risk factors (advanced fibrosis, cirrhosis, insulin resistance, metabolic syndrome or steatosis).

in mind. Firstly, these were results of daily IFNα rather than the thrice-weekly schedule as was earlier routinely prescribed. Secondly daily schedule of injections not only more than doubles the cost compared to thrice weekly schedule and may increase loss of man-days, which must not be ignored.

Recommendations

The recommended therapy for HCV genotype 3 in India is Peg-IFNα (2a or 2b) along with weight-based RBV for duration of 24 weeks. In patients with low viral load (<4 × 10^5 IU/mL) and who achieve RVR and do not have any risk factors for poor outcome, a shortening of therapy to 16 weeks may be considered though response rates may be marginally lower. Treatment duration should be increased to 48 weeks in patients who do not achieve RVR but achieve cEVR and in those who only achieve pEVR but become HCV RNA negative at 24 weeks. Therapy should be stopped if patients do not achieve EVR or in case of pEVR, the HCV RNA continues to be positive at 24 weeks. INASL consensus recommendations for genotype 3 in comparison with those of APASL 2012, EASL 2014 and AASLD 2014 are shown in Table 3. The decision on duration of therapy as per viral kinetics is shown in Table 4 and an algorithm for management of HCV genotype 3 is shown in Figure 1. As an alternative therapy where cost constraints preclude the use of Peg-IFNα, conventional IFNα and weight based RBV can be used for 24 weeks.

It may be seem discordant and retrograde that while the world is moving on to DAA and the latest AASLD guidelines even write off Peg-IFNα/RBV therapy as "Not Recommended", that the current guidelines for India are even considering conventional IFN in the management of CH–C. This must be seen in the perspective that DAA recommended by the AASLD have yet to reach the Indian shores. Acceptability of DAA will depend on the cost at which they will be marketed in India and its availability will definitely prompt a change in recommendations by INASL to follow evidence based recommendations supported by APASL 2014. For the present situation, in conditions where cost constraints are a barrier to therapy, an inferior therapy may be better than no therapy. In the neighboring country Pakistan, more than 20,000 persons have received therapy with conventional IFNα, which has been funded by the state.[60]

Consensus Statement: Management of genotype 3 in India

19. ***Patients with genotype 3 should be considered for treatment regardless of the stage of the disease as long as the liver disease is compensated (Strength-1, Level of evidence-B)***.
20. ***The combination of Peg-IFNα and RBV for duration of 24 weeks remains SOC for management of HCV genotype 3 (Strength-1, Level of evidence-A)***.

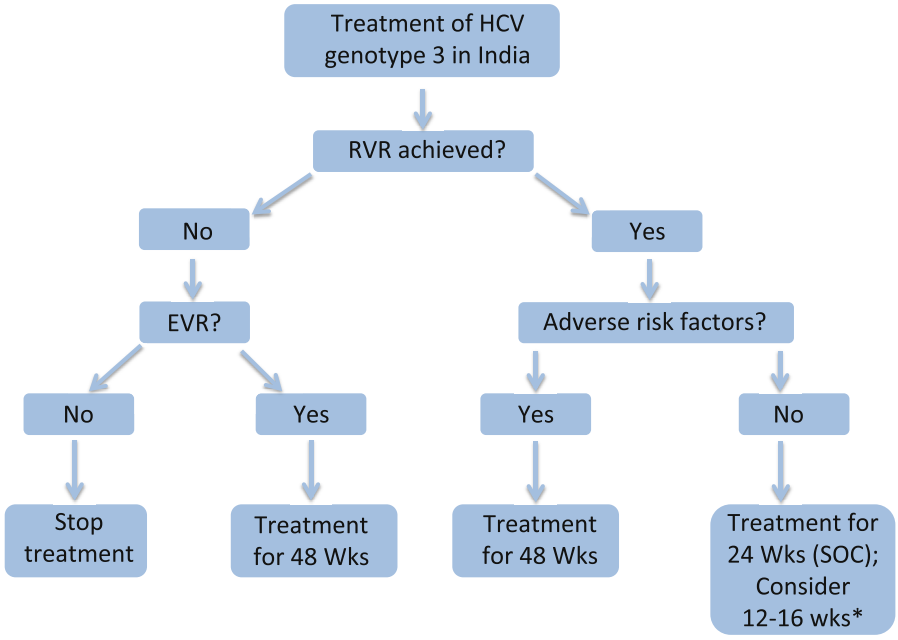

Figure 1 Algorithm for management of HCV genotype 3 with Peg-IFNα/RBV therapy. * Response rate may however be marginally lower than SOC.

21. ***The dose of RBV should be weight based (15 mg/kg) rather than a flat dose of 800 mg, especially in patients with baseline factors suggesting low responsiveness, considering relatively poorer response to therapy in Indian patients with genotype 3 infection (Strength-2, Level of evidence-B)***.
22. ***In patients with adverse risk factors, the Peg-IFNα/RBV therapy should be considered for 48 weeks (Strength-2, Level of evidence-B)***.
23. ***For patients without RVR: Consider weight based RBV if not advised earlier and 48 weeks of therapy if EVR is attained (Strength-1, Level of evidence-A)***.
24. ***For patients who have RVR***:
    a. ***In patients with risk factors for poor outcome, 48 weeks therapy with weight based RBV should be considered***.
    b. ***In patients without adverse risk factors abridged therapy may be discussed (Strength-2, Level of evidence-B)***.

Management of Non-genotype 3

While genotype 3 is the commonest, genotype 1 is reported more commonly from south India and there are increasing reports of genotype 4 from south and eastern India.

Management of Genotype 1

Genotype 1 has been more difficult to treat with poorer response to Peg-IFNα/RBV therapy. The response rates of Peg-IFNα/RBV therapy in genotype 1 in India are 50–63.6%.[54,55,61]

The comparative recommendations of INASL consensus, APASL 2012, EASL 2014 and AASLD 2014 are depicted in Table 5. The recommendations of APASL 2012 and EASL 2014 are almost similar with Peg-IFNα/RBV therapy for 48 weeks and although both recommend higher doses of RBV for genotype 1, there are subtle differences in recommendations for dosage of RBV. As regards the recent AASLD recommendations, while Peg-IFNα therapy is still recommended, it is only for a shortened duration of 12 weeks along with sofosbuvir. In the Indian context, due to the absence of DAAs, Peg-IFNα/RBV therapy continues to be recommended till these drugs become available. However, considering the poor response despite 48 weeks of Peg-IFNα therapy, it may be prudent to defer therapy in patients with no significant liver fibrosis, anticipating the availability of DAAs in the near future. However, since the time line for the availability of these drugs or their likely cost remain uncertain, these issues should be discussed with the patient before making any such recommendation.

Therapy for 48 weeks is expensive, particularly in the Indian context. Virologic monitoring can identify optimal duration of treatment in genotype 1, and week 4 complete response (RVR) can be used to shorten the duration of treatment to 24 weeks in those with no predictors for poor outcome. Week 12 HCV RNA showing a drop of ≤ 2 $\log_{10}$ is regularly used to identify those unlikely to respond. Patients who do not achieve undetectable HCV RNA before week 24 have ~50% chance of relapsing after 48 weeks of therapy. Studies show that these slow responders may benefit from extended treatment. Duration of treatment of genotype 1 with dual therapy with Peg-IFNα and RBV as per viral kinetics is shown in Table 6.

Table 5 Management of HCV Genotype 1 in Treatment Naöve Patients.

	APASL 2012	EASL 2014	AASLD 2014	INASL 2014
Interferon Eligible	Peg-IFNα (2a or 2b) + RBV (<75 kg- 1000 mg, > 75 kg- 1200 mg) × 48 W **High viral load**: Peg-ifnα + RBV + BOC/TVR	1. Sofosbuvir + RBV + Peg-IFNα × 12 W 2. Simeprevir × 12W + Peg-IFNα/RBV × 24W (without Q80K polymorphism) 3. Daclatasvir + Peg-IFNα/RBV × 24W	IFNα eligible Sofosbuvir + RBV + PEG-IFN-α × 12W Alternative regime Simeprevir × 12W + Peg-IFNα/RBV × 24W 1. HCV genotype 1b 2. HCV genotype 1a (without Q80K polymorphism)	Peg-IFNα (2a or 2b) + weight based RBV 15 mg/kg × 48W Alternatively Defer therapy in patients without significant fibrosis
Interferon ineligible	–	1. Sofosbuvir + RBV × 24W 2.Sofosbuvir + Simeprevir × 12W 3. Sofosbuvir + Daclatasvir 12–24W ± RBV	**S**ofosbuvir + Simeprevir ± RBV × 12W **Alternative regime** Sofosbuvir + RBV × 24W	
Treatment not recommended/ not available	–	–	Peg-IFNα/RBV with or without telaprevir or boceprevir for 24–48W; monotherapy with Peg-IFNα, RBV, or a DAA	DAA not available

RBV, ribavirin; Peg-IFN, pegylated-interferon; DAA, directly acting agents; W, week.

Consensus Statement: Management of Genotype 1 in India

25. ***In genotype 1 infections, therapy can be deferred for the time being in patients with no or minimal fibrosis in view of the likelihood of availability of DAAs in the near future (Strength-2, Level of evidence-C).***
26. ***In patients with significant fibrosis, treatment with Peg-IFNα (2a or 2b) and weight based RBV may be considered for 48 weeks (Strength-1, Level of evidence-A).***
27. ***In patients who have RVR:***
    a. ***In patients with risk factors for poor outcome- 48 weeks therapy with weight based RBV should be considered.***
    b. ***In patients without risk factors for poor outcome abridged therapy may be considered (Strength-1, Level of evidence-A).***
28. ***Conventional Interferon should not usually be recommended for patients with genotype 1 (Strength-1, Level of evidence-A).***

Management of Other Genotypes

Genotype 2 is an "easier to treat" genotype. The management of genotype 2 is similar to that of genotype 3 and shortening duration of therapy to 16 weeks in patients with HCV genotype 2 may provide SVR similar to that with 24 weeks of treatment (A1).

For **Genotype 4**, similar to genotype 1, the recommended duration of therapy is 48 weeks with standard dose of PEG-IFN-a (2a or 2b) along with higher weight based RBV. In patients without significant fibrosis, deferring of therapy should be considered (B1).

Genotypes 5 and 6 are rare in India and should be managed like genotype 1 (B1).

Optimization and Support of Patients on Dual Therapy (Peg-IFNα/RBV)

A detailed discussion should be done regarding benefits of the treatment, side effects of the drugs and the cost of therapy. Patients with alcohol abuse, substance abuse and psychiatric illness should be referred to psychiatrist prior to initiating treating. Adverse events can have a negative impact on treatment outcome and quality of life. About 10%–14% of patients discontinue treatment due to adverse events. It is therefore important to monitor closely during PEG-IFN-α and provide supportive care during therapy.

Management of Anemia

It is recommended that as a first step RBV dose be reduced by either 200 mg (patients receiving 800–1200 mg/day) or 400 mg (patients receiving 1400 mg/day) in case Hb levels fall below 10.5 g/dl. Reduction of RBV dose by another 200 mg may be done if required and RBV should be discontinued if Hb levels decline to <8.5 g/dl. However, RBV dose

Table 6 Duration of Treatment of Genotype 1 with Dual Therapy with Peg-IFNα and RBV as per Viral Kinetics.

Week	Interpretation	HCV RNA Status					
0	Base line viral load	LVL or HVL	LVL or HVL	LVL or HVL	LVL or HVL	LVL	HVL
4	RVR	HCV RNA +	HCV RNA +	HCV RNA +	HCV RNA +	HCV RNA –	HCV RNA –
12	EVR	HCV RNA + <2log↓ NR	HCV RNA + >2log↓ (pEVR)	HCV RNA + >2log↓ (pEVR)	HCV RNA – (cEVR)	HCV RNA –cEVR	HCV RNA –cEVR
24	LVR		HCV RNA +	HCV RNA -	HCV RNA -	HCV RNA –	HCV RNA –
Recommendation		Stop at 12W	Stop at 24W	72 W Rx	48 W Rx	24W Rx	48 W Rx

Note: The sign of '+' means that HCV RNA is still detectable (response to treatment not complete) and '–' implies that HCV RNA is not detectable (response to treatment is complete).
LVL, low viral load; HVL, high viral load; RVR, rapid virological response; cEVR, complete early virological response; pEVR, partial early virological response; LVR, late virological response.

reduction or discontinuation results in attrition in SVR rates. Erythropoietin (8000–24,000 IU per week) is useful in patients with early onset anemia as a means of preventing RBV dose reduction or treatment discontinuation, especially in patients with advanced fibrosis or compensated liver cirrhosis who may need 48 weeks of therapy.

Management of Neutropenia

If absolute neutrophil count falls below 1500/mm,[3] Peg-IFNα dose may be reduced and may be discontinued if ANC drops <750/mm^3. Use of G-CSF can be considered and although clinical experience shows this to be effective, avoiding IFNα dose reduction, there are no controlled trials demonstrating effectiveness.

Management of Thrombocytopenia

In patients with CH–C, if platelet count is < 50,000/mm^3 on Peg-IFNα2a dose reduction to 90 μg weekly and if platelet count is < 25,000/mm^3, discontinuation of therapy has been suggested. In patients on Peg-IFNα 2b, if platelet count is < 80,000/mm^3, reduction in dose by half and if platelet count is <50,000/mm^3, discontinuation of therapy is suggested. However, it is noteworthy that in patients with advanced fibrosis or compensated liver cirrhosis, low platelet counts at baseline do not change much on IFNα therapy and seldom necessitate dose modification.

Management of Depression

Mild depression can be managed with administration of antidepressants and reduction of dose of Peg-IFNα is usually not required. Antidepressants should be continued for 2–3 months after Peg-IFNα and RBV treatment ends. However, if symptoms become severe, Peg-IFNα may have to be withdrawn.

Management of Flulike Symptoms (Fever, Chills, Myalgias, Arthralgias, Fatigue)

These can be managed with acetaminophen (≤2 g/day), bed rest and increased fluid intake (noncaffeinated) to 8–10 glasses/day.

MANAGEMENT OF HEPATITIS C IN SPECIAL SITUATIONS

Management of Hepatitis C in Liver Transplant Recipients

A vast majority of patients with advanced liver disease have contraindications to the use of Peg-IFNα/RBV therapy, and the results of therapy are generally poor in this group of patients. Post transplantation HCV recurrence is universal and graft re-infection can lead to significant concerns due to graft fibrosis, cirrhosis and decompensation. Successful therapy has been shown to have a positive impact on both graft and patient survival.[62]

As compared to the non-transplant population, HCV disease progression post transplantation is accelerated. Several factors for accelerated HCV recurrence post transplantation have been identified. In general, over immunosuppression is considered to be an important factor for rapid HCV progression, but there is no specific immunosuppression regimen that is proven to prevent or reduce HCV recurrence. Several strategies have been tried to treat HCV recurrence post-transplantation. Pre-emptive therapy in the early post-transplant period is not generally practiced except under a research protocol as it is associated with increased treatment related side effects and is poorly tolerated by patients. Treatment of post-liver transplant HCV recurrence should be instituted in patients with established disease and with histological evidence of fibrosis.

However, early data from India shows that HCV genotype 3 may behave differently to treatment post-transplant compared to genotype 1 (Personal communication, Wadhawan M, Indraprastha Apollo Hospital, New Delhi, India). Early treatment at 6 months post-transplant for genotype 3 has been reported to have high SVR rates especially if RVR is achieved. In this study, forty-three patients with genotype 3 were treated with PEG-IFN and ribavirin at 6 months post-transplant. Five patients had grade-1 fibrosis; all others had no fibrosis. Median HAI was 3 (2–7) at 6 months post-transplant. The

median HCV RNA level was 106 IU/ml (105–108 IU/ml). Twenty patients had been exposed to IFN/Peg-IFN before transplant. Thirty-eight patients achieved RVR, and were continued on therapy. Thirty-three of these 38 achieved SVR. In three patients therapy was stopped despite RVR (severe depressive illness-1, pulmonary tuberculosis on therapy-1, renal failure-1). Two patients achieved ETR but had recurrence at 6 months post-treatment. Erythropoietin was required in a majority of patients (30/37), ten of these patients required blood transfusions. In twenty patients growth factors were used to maintain WBC counts above 2000. In patients who achieved RVR, the SVR rate was 86.8% (33/38).

Unlike in the non-transplant population, the response rate of antiviral therapy with Peg-IFNα with or without RBV is lower in the transplant population. Also post-transplant patients have relatively more side effects and poor tolerance to combination antivirals. The common IFNα-RBV related side effects are anemia and low counts, which need frequent dose adjustments and use of growth factors. RBV dose adjustments are common in view of anemia and renal dysfunction, seen commonly in post liver transplant patients. The likelihood of an SVR in the post-transplant setting with dual therapy is about 30% overall, with better response rates in patients with HCV genotype 2 or 3 than genotype 1.[63–65] There is a need of using newer emerging therapies for recurrent HCV disease in the post-transplant population and the recent AASLD and EASL guidelines for treatment of post liver transplant HCV recurrence are based on newer oral antivirals.[4,5] Till such drugs are available in India, the current management should be based on Peg-IFNα and RBV therapy.

A few changes in the immunosuppression protocol should be followed before starting treatment for HCV post-transplant. Mycophenolate should be stopped before starting therapy due to additive myelosuppression with interferon. The patient should have stable graft function for at least 1 month after stopping mycophenolate before interferon based treatment is started. The levels of calcineurin inhibitor (CNI) should be monitored more frequently while therapy is given. Since rejection rates are higher for up to 6 months after stopping interferon therapy, there is a need to maintain higher CNI levels during this period. Reintroduction of mycophenolate can be considered after stopping interferon if liver functions improve.

Consensus Statement: Management of Patients with Hepatitis C Who Have Undergone Liver Transplantation

29. ***HCV is one of the leading indications for liver transplantation both in India and in the West (Strength-1, Level of evidence-A)***.
30. ***Post-liver transplantation HCV recurrence is universal and can lead to graft dysfunction due to graft fibrosis and cirrhosis (Strength-1, Level of evidence-A)***.
31. ***Patients with post-liver transplant HCV infection should be considered for therapy for histologically proven disease recurrence in the graft (Strength-2, Level of evidence-B)***.
32. ***Pre-emptive treatment for recurrent hepatitis C within 6 months after transplant should be individualized and done within clinical trials (Strength-2, Level of evidence-B)***.
33. ***In genotype 3 cases, early treatment at 6 months can be considered in selected cases (Strength-2, Level of evidence-C)***.
34. ***The preferred regimen in Indian setting presently is 48 weeks of dual therapy with Peg-IFNα (2a or 2b) plus RBV. 24 weeks therapy can be considered in genotype 3 cases if RVR is achieved (Strength-2, Level of evidence-C)***.
35. ***Graft rejection is rare but may occur during or up to six months after Peg-IFNα (2a or 2b) plus RBV treatment (Strength-2, Level of evidence-C)***.
36. ***Over-immunosuppression should be avoided in the early post-transplant period (Strength-2, Level of evidence-B)***.

Management of Hepatitis C in Human Immunodeficiency Virus Co-infection

Individuals co-infected with HIV-HCV are at three times greater risk of progression to cirrhosis or decompensated liver disease than those infected with HCV alone.[66] Eradication of HCV with therapy is associated with a regression of liver fibrosis and improved survival in HIV/HCV co-infected patients.[67]

The tolerance of antiretroviral agents is poorer in the presence of underlying chronic HCV, with a greater risk of hepatotoxicity.[68] Successful treatment of HCV is followed by a reduced risk of antiretroviral-related hepatotoxicity.[69] The safety, efficacy, and tolerability of Peg-IFNα and RBV for the treatment of HCV in HCV–HIV co-infected patients was assessed in 4 pivotal studies reported in 2004.[70–73] The data on management of HCV–HIV co-infection from India is particularly scarce. In the INASL registry data, 22 of the 34 patients with CD4 counts >200 were treated with Peg-IFNα (2a or 2b) with RBV. The SVR rates were 16% (1/6) in genotype 1/4 and 56% (9/16) in genotype 2/3 while the drug was discontinued due to adverse effects in 18% (4/22).

Selection of Hepatitis C Virus–Human Immunodeficiency Virus Co-infected Patients for HCV Treatment

The indications for HCV treatment in co-infected patients are identical to those in patients with HCV mono-infection. Patients with decompensated cirrhosis should not be treated and should be evaluated for liver transplantation. Favorable genotype and advanced stage of fibrosis influence the selection of treatment candidates. Therefore,

treatment should be strongly considered in patients with high likelihood of achieving SVR.[74]

Antiretroviral Therapy in Human Immunodeficiency Virus–Hepatitis C Virus Co-infection

With the advent of newer DAA, the AASLD-2014 guidelines have recommended the use of Sofosbuvir and Simeprevir as in the regimen without HIV co-infection and the antiretroviral drugs are accordingly limited considering the drug interactions. In HIV/HCV co-infected patients with low CD4 counts, prioritization of antiretroviral therapy (ART) may facilitate subsequent treatment of HCV. As Peg-IFNα induces leucopenia, when possible patients with CD4 counts <200 cells/mm^3, control of HIV replication and increase of CD4 counts with HAART should precede HCV therapy. Chances for complete HCV clearance are greater in patients with CD4 counts >350 cells/mm^3.[75] Selection of ART in patients planned for treatment of CH–C is a key issue. The concomitant administration of RBV and didanosine may result in mitochondrial toxicity leading to hepatomegaly/steatosis, pancreatitis, and lactic acidosis. The concomitant zidovudine use enhances the risk of RBV-associated anemia and should be avoided.[76]

Consensus Statement: Management of Patients with Hepatitis C Virus and Human Immunodeficiency Virus Co-infection

37. ***All HCV–HIV co-infected patients should be considered for treatment (Strength-1, Level of evidence-A)***.
38. ***HCV therapy is strongly considered patients who are likely to achieve an SVR: i.e. all those with Genotype 2/3 and patients with Genotype 1/4 infection with low viral load regardless of histology (Strength-2, Level of evidence-B)***.
39. ***Initial treatment of HCV is HIV infected should be Peg-IFNα plus weight based RBV for 48 weeks at doses recommended for HCV mono-infected patients irrespective of Genotype. If no EVR is achieved by week 12, HCV treatment should be discontinued (Strength-2, Level of evidence-B)***.
40. ***Patients with Genotype 2/3 with low viral load in whom RVR is achieved at 4 weeks may be treated with 24 weeks of therapy but this can increase the relapse rates (Strength-2, Level of evidence-B)***.
41. ***In patients with CD4 counts <200 cells/mm^3 or in presence of opportunistic infections it is preferable to initiate ART and delay HCV therapy until CD4 counts improve (Strength-2, Level of evidence-B)***.
42. ***Although ART should be initiated for most HIV–HCV co-infected patients regardless of CD4 count. In ART-naive patients with CD4 counts >500 cells/mm^3. It may be better to defer ART until completion of HCV treatment because if side effects develop it will be difficult to determine which drug was responsible (Strength-2, Level of evidence-B)***.
43. ***ART and HCV therapy may be started simultaneously if CD4 counts are >350 cells/mm^3 because the therapy itself and higher CD4 counts may slow the progression of liver disease (Strength-2, Level of evidence-C)***.
44. ***Didanosine, stavudine, and zidovudine should be avoided during Peg-IFNα and RBV therapy (Strength-2, Level of evidence-B)***.
45. ***HIV infected patients with decompensated liver disease (CTP class B or C) should not be treated with Peg-IFNα and RBV and should be evaluated for liver transplantation (Strength-2, Level of evidence-B)***.
46. ***With the approval and availability of new pangenotypic DAA the treatment regimens without Peg-IFNαand RBV are possible. Hence, patients with F0-2 fibrosis may be candidates for delaying therapy in anticipation of near-future availability of newer regimens (Strength-2, Level of evidence-B)***.

Management of Hepatitis C Virus in Pediatric Age Group

In neonatally acquired infection spontaneous clearance has been reported to be 25% at 7.3 years and overall clearance of 28% at 10 years.[77] European Pediatric Hepatitis C Network found 20% of vertically transmitted HCV infection to clear spontaneously in follow up.[78]

Hepatitis C virus is reported to have mild course during childhood. Although liver biopsies in HCV infected children may show mild chronic hepatitis, only 1–2% progress to develop cirrhosis and require liver transplantation during their childhood.[79] Follow up studies have shown minimal progression of liver disease in 5–20 years of follow up.[79–82]

Unlike in adults few randomized controlled trials are available of HCV treatment in children. The overall reported SVR rates in children are 35.6% with standard interferon, 42.8% with Peg-IFNα monotherapy, 46.8% with standard IFNα with RBV combination and 69% with Peg-IFNα and RBV combination.[83] Sood et al[84] reported SVR rates of 70% with Peg-IFNα2b and RBV in thalassemic children between 3 and 15 years of age with transfusion acquired chronic HCV infection.

Both available type of Peg-IFNα 2a and 2b have been shown to be equally effective in children. The dose of Peg-IFNα 2a is 180 μg/1.73 m^2 body surface area/week and alpha 2b is 60 μg/m^2 of body surface/week as subcutaneous injection. The dose of RBV is 15 mg/kg in two divided doses.

Growth retardation both in height and weight has been reported up to 63% of children while on treatment, but most of them catch up growth after completion of treatment.[85,86] Although the combination of Peg-IFNα and RBV is found to be most efficacious in treatment of HCV in children, considering that it is a slowly progressive disease, and there may be easier treatment option may be

available in future, it is a matter of debate whether treatment can be delayed in children.

Consensus Statement: Management of Hepatitis C in Pediatric Age Group

47. ***Peg-IFNα 2a or Peg-IFNα 2b can be used in doses of 180 μg/1.73 m^2 body surface area/week and 60 μg/m^2 of body surface/week weekly along with RBV in a dose of 15 mg/kg/day (Strength-1, Level of evidence-A)***.
48. ***However, deferring of therapy should be considered in view of prospect of newer DAA antiviral therapies (Strength-1, Level of evidence-B)***.

Management of Hepatitis C in End-stage Renal Failure (ESRD) and Renal Transplant Recipients

In patients with CH–C and ESRD, altered drug pharmacokinetics, increased susceptibility to drug-related toxicity, the requirement for renal transplantation, and a modified course of disease make their treatment difficult. Since these patients are difficult to treat post kidney-transplantation and IFNα may be contraindicated in latter group of patients unless there is fibrosing cholestatic hepatitis (FCH) or severe vasculitis, all efforts should be made to treat these patients prior to kidney transplantation.[87]

Interferon Monotherapy (Conventional IFN-α)

Four meta-analysis on the use of conventional IFNα in patients with ESRD showed SVR rates of 33–41% and withdrawal rates of 17–30%.[88–91] Higher SVR and treatment-related withdrawal rates for conventional IFNα monotherapy in ESRD patients than those in non-uremic patients might be explained by altered IFNα pharmacokinetics, specifically decreased renal clearance and higher IFN serum concentrations.[92] Additionally, recent acquisition of the infection and mild histological disease might also be responsible for better virological response in these patients.

Peg-IFNα Monotherapy

Several studies have investigated Peg-IFNα monotherapy for patients with CH–C in ESRD. Results of few large studies and a meta-analysis showed that the SVR and treatment-related withdrawal rates in patients receiving Peg-IFNα were 31–37% and 23–28%, which are not superior to conventional IFNα.[93–95]

Combination Therapy

RBV is traditionally contraindicated in the treatment of ESRD patients with CHC because of the risk of hemolytic anemia. However, several studies showed that combination of either conventional IFNα or Peg-IFNα with low-dose RBV (200 mg three times per week to 400 mg daily) was feasible keeping the target RBV concentrations of 10–15 mmol/L and by using high-dose erythropoietin (20,000–30 000 IU/week) while treating ESRD patients with CH–C.[96–99] A recent meta-analysis of studies using both conventional IFNα and Peg-IFNα with variable doses of RBV showed the improvement in SVR to 56%, much higher than the monotherapy with IFNα with no increase in dropout rates because of anemia.[100]

Indian Experience

Not all patients with ESRD and CH–C are able to initiate treatment because of the poor affordability and not many patients are able to complete treatment because of the higher complications, poor tolerance of interferon and higher dropout rate in these patients. There is sparse published Indian literature on the treatment of CH–C in patients with ESRD. In a small study from Mumbai, SVR was achieved in 50% ESRD patients who maintained the HCV negative status after renal transplantation.[101] In a retrospective analysis from Chandigarh, 40 (62%) of the 65 patients with ESRD and CH–C were counseled about this therapy but never came back after the initial consultation for CH–C and finally only 17 (26%) patients agreed for treatment. Of 11 patients who achieved EVR, ETR was achieved in 7 patients (44%). Even though the end of treatment response (ETR) rate is less than the non-ESRD patients, it is still acceptable given the fact that majority of treated patients were genotype 1. Even though the number of patients so treated was small, the side effects and dropout rate on treatment was high. Overall 7 patients (44%) had dropped out on treatment. The reasons for drop out were mainly related to the poor affordability in 4 patients (25%) rather than intolerance and side effects of drugs in three patients (13%).[102]

Consensus Statement: Management of Patients with Hepatitis C and ESRD

49. ***All efforts should be made to treat patients with ESRD and CHC before renal transplantation (Strength-1, Level of evidence-A)***.
50. ***Patients can be treated with conventional IFNα or Peg-IFNα without RBV (Strength-1, Level of evidence-A)***.
51. ***But for the convenience of once weekly injection, monotherapy with Peg-IFNα does not have any additional advantage over conventional interferon in terms of SVR rates (Strength-1, Level of evidence-A)***.
52. ***Low dose RBV may be added to interferon in controlled manner to improve the results (Strength-1, Level of evidence-B)***.
53. ***Interferon treatment is not recommended post renal transplantation unless there are compelling situations like FCH or life threatening vasculitis (Strength-1, Level of evidence-A)***.

Management of Hepatitis C in ß Thalassemia Major (ßTM)

Improved survival and quality of life in Thalassemia has made it necessary for protocols to be drawn for effective management of chronic liver disease, as it is a major cause of morbidity and mortality. Virological assessment and viral load and genotyping should be done as in other HCV patients if patients are willing for treatment as in other HCV patients. Liver biopsy gives information about iron overload, a quantitative estimation of hepatic iron as well as changes due to HCV. Noninvasive measurement of hepatic iron can be performed accurately with MRI R2 methodology.[103,104] Liver stiffness measurement by transient elastography can be useful to detect advanced fibrosis and cirrhosis in the setting of ßTM irrespective of iron overload.[105]

RBV induced hemolysis and subsequent worsening of the preexisting anemia and iron overload due to transfusions are major deterrents to combination therapy. Despite transfusion related siderosis, studies have shown a promising response to IFN therapy in thalassemic patients unaffected by iron overload, provided chelation is continued. The benefit of combination therapy with IFNα and RBV in polytransfused thalassemic patients with hepatitis C was reinforced by a recent meta-analysis. Pooled odds ratios of SVR for genotype 1 versus non-genotype 1 infected thalassemic patients were 0.46 in IFNα monotherapy and 1.7 in RBV combination therapy. Addition of RBV did not increase the adverse events or require discontinuation of therapy, though there was a higher need for transfusions.[106] Continuation of iron chelation therapy while on RBV was shown to offset the adverse effect of iron overload caused by increase in blood transfusions. Sood et al[83] from India reinforced the benefit of combination therapy with Peg-IFNα and RBV over monotherapy with Peg-IFNα in their prospective randomized trial. As is expected in India, this study had predominantly genotype 3 patients. In addition, this study also showed that biochemical remission does not correlate with SVR in ßTM patients unlike other chronic HCV patients, probably due to the effect of iron overload.

Adverse effects of IFNα and RBV combination therapy that warrant special mention are anemia and neutropenia. Patients may be more prone for sepsis after splenectomy. Patients with severe cardiomyopathy secondary to iron overload need to be monitored carefully. On the whole, antiviral therapy is likely to benefit a significant proportion of CH–C patients with ßTM, but needs a careful multidisciplinary approach and frequent monitoring of hematological parameters. Frequent blood transfusions need to be given so that Hb is kept above a cut off of 8–9 g/dL and continuation of chelation are crucial. Neutropenia may be managed with growth factors but use of erythropoietin is not recommended.[107] Tabatabaei et al[108] have described that combination therapy with RBV when tailored according to Hb (800 mg when Hb-10 g, 600 mg when Hb < 10 g) to have significantly higher SVR rates when compared to monotherapy.

It is important to remember that patients in whom antiviral therapy cannot be offered for various reasons also need regular monitoring of their liver status to look for progression to cirrhosis and subsequently surveillance for HCC.

Consensus Statement: Management of Hepatitis C in β Thalassemia Major

54. ***Chronic HCV infection should be treated in patients with β thalassemia under close monitoring in consultation with a hematologist (Strength-1, Level of evidence-B).***
55. ***Combination therapy with Peg-IFNα and RBV should be used. (Strength-1, Level of evidence-B)***
56. ***Hemoglobin should be maintained between 8 and 9 g/dL with frequent blood transfusions (Strength-2, Level of evidence-B).***
57. ***Iron chelation should be continued (Strength-2, Level of evidence-B).***
58. ***Patients with cirrhosis and advanced fibrosis should undergo 6 monthly ultrasonogram abdomen for surveillance for HCC (Strength-1, Level of evidence-B).***

Management of Hepatitis C in Hematopoietic Stem Cell Transplantation

Bone marrow and peripheral hematopoietic stem cell transplant recipients are at high risk of contracting HCV infection due to transfusion of blood products either during pre-transplant management of malignancy, aplastic anemia, βTM and or following transplantation. The prevalence of HCV infection among long-term survivors ranges from 5% to 70%, depending on the background sero-prevalence of the country studied.[109] The concerns regarding HCV infected patients undergoing HSCT include increased risk of veno-occlusive disease (VOD), graft versus host disease (GVHD), fulminant HCV hepatitis, cirrhosis and HCC in the long term. With more HSCT patients becoming long-term survivors, it becomes very important to treat the frequently accompanying chronic HCV.[110]

Peffault de Latour et al[111] reported the efficacy of antiviral therapy in a selected group of 22 patients with HSCT. Therapy was initiated only when there was no cytopenia, 2 years after HSCTS, with donor-type chimerism, no chronic GVHD, no immunosuppressive therapy, no hyper gammaglobulinemia or autoantibodies, no psychiatric disease, alcohol or drug consumption. Combination therapy with IFNα and RBV was associated with a better SVR 20% compared to 10% with monotherapy.

The largest prospective cohort study conducted by the Infectious Diseases Working Party of the European Group

of Blood and Marrow Transplantation (EBMT) recruited patients between 1993 and 1996 to study liver related morbidity and mortality in HCV positive HSCT patients and responses to antiviral therapy. A total of 195 patients were included from 12 centers. The median follow-up from HSCT was 16.8 years and the maximum 27.2 years. Liver disease was directly implicated as a cause of death in 6/195 patients resulting in a cumulative incidence of 4.1% at 15 years and 6.1% at 20 years after HSCT. In this cohort, 85 patients (45.6%) received antiviral therapy with IFNα/Peg-IFNα with or without RBV with an SVR of 40%. Combination therapy showed a higher SVR compared to monotherapy. Antiviral therapy reduced the risk of development of severe liver complications. Therapy could also be given safely because the number of serious side effects was quite low and similar to what could be expected in an otherwise healthy population. In addition, there were no signs indicating a risk for worsened chronic GVHD in patients having undergone allogeneic HSCT.[112]

In conclusion, antiviral therapy might reduce the risk for severe liver complications and can be given safely with similar rates of side effects and antiviral response as in non-HSCT patients.

Consensus Statement: Management of Hepatitis C in Hematopoietic Stem Cell Transplantation

59. ***Antiviral therapy might reduce the risk for severe liver complications and can be given safely to patients with hematopoietic stem cell transplantation (Strength-1, Level of evidence-B)***.
60. ***Combination therapy with Peg-IFNt and RBV should be used (Strength-1, Level of evidence-B)***.

Treatment of Hepatitis C in the Presence of Hepatic Steatosis and Metabolic Syndrome

Hepatic steatosis is commonly observed in CH–C[113] and can affect the hepatic fibrosis and response to treatment. In genotype 3 infection, this is clearly a cytopathic effect of the virus (viral steatosis) because it is present in approximately two thirds of infected individuals and resolves completely in patients who achieve sustained virologic response to therapy.[114] A second pathogenic mechanism of hepatic steatosis predominantly is the 'metabolic steatosis' associated with the metabolic syndrome and its components similar to what is seen in patients with nonalcoholic fatty liver disease (NAFLD). Of the various Indian studies, variable degree of histological steatosis has been reported in 20–68% of patients with higher frequency and more severe steatosis in patients with genotype 3.[54,115–117]

In addition to hepatic steatosis, patients with CH–C have been shown to have higher prevalence of insulin resistance (IR) in comparison to controls.[118] Indian data also suggests a higher prevalence of IR in patients with CH–C with prevalence of metabolic syndrome almost similar to healthy controls.[115] In contrast to hepatic steatosis, which is more common in genotype 3, IR has been reported to be more common in patients with genotype 1 in comparison to other genotypes. However, Indian data suggests that IR is equally common in patients with genotype 3 as in genotype 1 (57% vs 66%).[115]

Data also suggests that it is IR and not the hepatic steatosis which is responsible for fibrosis progression in patients with CH–C. In a study involving 263 non-diabetic CH–C patients from Asian-region involving both Genotype 2 (171) and Genotype 3 (92) patients, HOMA–IR (OR- 8.42) was found to be one of the factors associated with significant fibrosis in addition to necro-inflammatory grade (OR = 3.17) and age (OR = 1.07) of the patients.[119]

Hepatic Steatosis and Metabolic Factors as Predictors of Response

The value of steatosis as a negative predictor of response to anti-HCV therapy was confirmed in large clinical trials.[120,121] Recent data also suggests hepatic steatosis to be an independent predictor of relapse in patients with genotype 3 patients with CH–C. A global multicentre study including an Indian center, and involving patients with CH–C (HCV genotype 2–427, genotype 3–505) found age, sex, weight, BMI, insulin resistance, hepatic steatosis, levels of GGT, ALT, liver fibrosis and baseline HCV RNA to be important predictors of SVR on multivariate logistic regression. RVR, SVR, and relapse rates among patients with HCV genotype 3 were 79.6%, 79.2%, and 15.6%, respectively. Independent predictors of relapse included hepatic steatosis (odds ratio 3.0; P = 0.003) and HCV RNA $\geq$400,000 IU/mL (odds ratio 2.5; P = 0 0.04).[122]

Of the various metabolic risk factors, overweight or obesity is probably the most important factor in determining the response to treatment in patients with CH–C. In addition to causing IR, obesity decreases the bioavailability of IFNα and by causing altered cytokine function leads on to oxidative stress and inflammation and thereby reducing the response to IFNα.[123] Indian data on 97 treatment-naive patients with CHC genotype 3 (mean age 41.46 $\pm$ 11.51 years, M:F 79:18) also revealed age and BMI to be the important predictors (P < 0.05) of SVR while hepatic steatosis was not found to be significant in determining the treatment response.[115]

Effect of Weight Reduction and Insulin Sensitizing Drugs in the Treatment of Hepatitis C

Since insulin resistance is an important determinant of disease progression and hepatic steatosis and obesity are important determinants of treatment response, it is rational to improve the insulin sensitivity and hepatic steatosis by either lifestyle modifications or insulin sensitizing

drugs in addition to antiviral treatment in patients with CH–C. Weight reduction with lifestyle modifications has been shown to improve ALT and reduce steatosis and fibrosis.[124]Adding metformin or Pioglitazone to antiviral drugs has been shown some improvement in response in patients with CH–C, though more data is required on this intervention.[125,126]

Consensus Statement: Treatment of CH–C in the Presence of Hepatic Steatosis and Metabolic Syndrome

61. ***Hepatic steatosis is more common in genotype 3 CH–C in comparison to non-3 genotypes (Strength-1, Level of evidence-A)***.
62. ***In comparison to general population, IR is more common and metabolic syndrome is as common in CH–C (Strength-1, Level of evidence-A)***.
63. ***IR is as common in genotype 3 as in genotype 1 patients with CH–C (Strength-2, Level of evidence-B)***.
64. ***IR and not hepatic steatosis affects the hepatic fibrosis in patients with CH–C (Strength-1, Level of evidence-A)***.
65. ***Hepatic steatosis and obesity may adversely affect the treatment response in patients with CH–C (Strength-1, Level of evidence-A)***.
66. ***More data is required regarding the effect of lifestyle interventions and insulin sensitizing drugs on SVR in patients with CH–C (Strength-1, Level of evidence-A)***.

Management of Hepatitis B and Hepatitis C Co-infection

The incidence of co-infection in a chronic liver disease population in India has been variously reported between 3 and 16%.[127–129] However, data are sparse and not representative of the whole country, expert opinion says that the incidence of co-infection in our country is around 5%.

Co-infection of Hepatitis B and Hepatitis C–Pathogenesis & Interactions

Most of the published clinical trials have reported a reciprocal inhibition of HBV and HCV virus replication in co-infection. It was believed that these viruses inhibit each other at the cellular level, which has been lately challenged by two important experimental studies.[130,131] Both these studies, conducted in HuH-7 cell lines, have shown that both viruses can replicate in the same cell without overt interference. So reciprocal inhibition seen in clinical studies is primarily due to host factors rather than direct interaction between HBV and HCV.

Hepatitis B and Hepatitis C Co-infection – Host Factors

The clinical studies published on co-infection have reported variable observations on disease outcomes and progression. Reports of reciprocal replicative suppression in HBV–HCV co-infection[132,133] have now been attributed to host factors modulating the viral replication. The clinical profile depends on the pattern of infection. Four patterns of infection have been described, namely 1) acute co-infection; 2) super infection of HBV over chronic HCV; 3) super infection of HCV over chronic HBV and 4) chronic co-infection. First three categories have been reported to have higher incidence of acute liver failure as well as higher rate of clearance of one or both viruses.[134] However in all these scenarios, the commonest outcome is chronic co-infection. HBV DNA is usually low in co-infected patients; the disease activity is predominantly described due to HCV infection. There is a higher probability of advanced liver damage, fibrosis/cirrhosis as well as a higher prevalence of hepatocellular carcinoma in co-infection as compared to either infection alone.[134–137]

Treatment of Hepatitis B and Hepatitis C Co-infection

As previously discussed, HBV DNA level is often low or undetectable and HCV is responsible for the activity of chronic hepatitis in most patients, although this maybe vary from patient to patient. Co-infection patients should receive standard treatment for HCV, which includes Peg-IFNα, is active against HBV also.[134,138,139] SVR for HCV is comparable in co-infection with HCV mono-infected patients.[135,138–141]There is a potential risk of HBV reactivation during treatment or after clearance of HCV.[135,138] Therefore, it is mandatory to monitor HBV DNA levels during and after therapy. Any HBV reactivation must then be treated with nucleoside/tide analogs.

Consensus Statement: Management of Hepatitis B and Hepatitis C Co-infection

67. ***The incidence of co-infection of HBV and HCV in our country is around 5% (Strength-2, Level of evidence-C)***.
68. ***The reciprocal inhibition seen in clinical studies between HBV and HCV is likely to be due to host factors rather than direct interaction between HBV and HCV (Strength-1, Level of evidence-B)***.
69. ***There is a higher probability of advanced liver damage, fibrosis/cirrhosis as well as a higher prevalence of hepatocellular carcinoma in co-infection as compared to either infection alone (Strength-1, Level of evidence-B)***.
70. ***Co-infection patients should receive standard treatment for HCV, which includes Peg-IFNα is active against HBV also (Strength-1, Level of evidence-B)***.
71. ***HBV DNA levels should be monitored during and after therapy, as there is a potential risk of HBV reactivation during treatment or after clearance of HCV. Any HBV reactivation must then be treated with nucleoside/tide analogs (Strength-1, Level of evidence-B)***.

Management of Acute Hepatitis C

The prevalence of acute hepatitis C is very low, mainly because most patients are asymptomatic and it is difficult to diagnose unless strongly suspected. The factors associated with spontaneous viral clearance include symptomatic disease, young age, female gender and favorable IL-28B genotype. Viremia may resolve spontaneously in 10–50% patients by 12 weeks. If the infection persists beyond 12 weeks, the risk of chronicity is high, therefore should be treated immediately. The response rates are more than 85–90% if treatment is initiated timely.

IL-28B gene testing be incorporated in decision making to decide upon the initiation of therapy and patients with acute HCV and an unfavorable IL-28B genotype could be considered for early therapeutic intervention, given their low likelihood of spontaneous clearance. Treatment should be at least monotherapy with Peg-IFNα for 24 weeks. For genotype 3 patients with favorable response factors the treatment duration may be shortened to 12 weeks.

Consensus Statement: Management of Acute Hepatitis C

72. ***Acute HCV is asymptomatic and uncommonly diagnosed unless strongly suspected (Strength-1, Level of evidence-A)***.
73. ***Acute HCV is likely to resolve spontaneously in 10–50% by 12 weeks (Strength-1, Level of evidence-B)***.
74. ***If viremia persists beyond 12 weeks, early treatment is likely to result in 85–95% response rates (Strength-1, Level of evidence-B)***.
75. ***Patients with favorable IL-28B genotypes should be considered for early treatment given their lower likelihood of spontaneous clearance (Strength-2, Level of evidence-B)***.
76. ***Treatment of acute HCV should be with monotherapy with Peg-IFNα for 24 weeks (Strength-2, Level of evidence-B)***.
77. ***Shortened therapy for 12 weeks may be considered for genotype 3 patients with favorable risk factors (Strength-2, Level of evidence-C)***.

Management of Hepatitis C in Cirrhosis

Treatment of HCV in cirrhosis should be started if tolerated as it may halt the disease progression and possibly prevent the need for liver transplantation in patients who achieve SVR. Besides, treatment may prevent HCV recurrence post transplant and prevent the development of HCC. Patients with compensated cirrhosis should be treated to prevent complications.

However these patients are likely to develop adverse effects of therapy and require close monitoring. Growth factors may be beneficial in cytopenias. Sood et al[142] have shown that combination therapy with Peg-IFNα2b at a dose 1 μ/kg along with oral RBV results in 53% SVR in cirrhotics. Hypersplenism may be a deterrent to therapy with Peg-IFNα2B and RBV. An option that has been tried has been splenectomy to improve cytopenias allowing institution of specific therapy for HCV.[143] Patients with HCV related cirrhosis should undergo regular monitoring for HCC.

Consensus Statement: Management of Hepatitis C in Cirrhosis

78. ***Treatment of HCV should be considered in patients with cirrhosis to prevent complications and recurrence after transplantation (Strength-2, Level of evidence-B)***.
79. ***However, patients with cirrhosis are likely to tolerate Peg-IFNα2B/RBV therapy poorly and may benefit from growth factors in case of cytopenias (Strength-2, Level of evidence-C)***.
80. ***Patients with decompensated liver disease not being considered for early liver transplantation may wait for availability of DAA (Strength-2, Level of evidence-C)***.
81. ***Patients with HCV related cirrhosis should undergo regular monitoring for HCC (Strength-1, Level of evidence-A)***.

Management of Non-responders

Twenty to fifty percent of patients treated with Peg-IFNα and RBV will not achieve an SVR. The approach to patients who fail therapy depends on the nature of the initial response, on the potency of initial treatment and on host–viral factors. Options for non-responders to Peg-IFNα and RBV are limited. Retreatment with the same regimen with same duration of therapy leads to an SVR in fewer than 5% of patients and therefore cannot be recommended. Newer DAAs have been developed to improve the virological response rates to current standard of treatment and may shorten the duration of therapy.

These patients can broadly be divided into three groups according to the pattern of response and virological failure during dual therapy.

(1) Virological relapse: Patients who have undetectable HCV RNA at the end of treatment, but do not achieve an SVR.
(2) Virological partial response: Patients who have >2 log10 IU/ml drop in HCV RNA by 12 weeks of treatment, but do not achieve undetectable HCV RNA.
(3) Virological null response: Patients who have <2 log10 IU/ml drop in HCV RNA by 12 weeks of treatment

Decisions on therapy depend on the extent of liver fibrosis and patient preferences concerning treatment duration and likelihood of response. If a patient has early stage liver fibrosis (none to portal or periportal fibrosis that is F1 and F2) and has no indications that there is rapidly progressive disease, then waiting to treat with

interferon-free options, which are likely to become available in near future, is a reasonable strategy. It is unlikely that they will progress to clinically significant liver fibrosis by the time such options are available. If the patient has bridging fibrosis or compensated cirrhosis (F3 and F4), HCV retreatment should be discussed with the patient.

Genotype 2/3 Non-responders

Boceprevir and Telaprevir are not licensed for genotypes other than 1 and are currently not available in India. Similarly Sofosbuvir and Simeprevir regimen in combination with Peg-IFNα and RBV is not feasible in India at present as these therapies are also not available at present. Longer retreatment durations (48 weeks for genotypes 2 and 3, 72 weeks for genotype 4 patients) can be considered, especially for patients with Late Viral Response (LVR) in the first cycle of treatment. Maintenance therapy with a low dose of Peg-IFNα and RBV is not recommended, as it has not shown any efficacy in preventing chronic hepatitis C complications in the long-term.

Consensus Statement: Management of Hepatitis C Genotype 2/3 Non-responders

82. ***Patients infected with HCV genotypes 2 and 3 and are relapsers should be treated with prolonged therapy for 48 weeks (Strength-2, Level of evidence-B)***.
83. ***Patients with <F2 fibrosis who relapse after Peg-IFNα and RBV may wait for newer therapies (Strength-1, Level of evidence-D)***.
84. ***Patients who had partial response can be treated with prolonged therapy of 36–48 weeks (Strength-2, Level of evidence-B)***.
85. ***Null responder patients should wait for newer DAA-based antiviral therapies (Strength-1, Level of evidence-A)***.

Genotype 1/4 Non-responders

There is a significant benefit in SVR rates among patients who have previously had virological failure with Peg-IFNα and RBV therapy who are retreated with PI containing triple therapy. Benefits of triple therapy over dual therapy are observed best among patients with prior relapse, partial response and null response patterns of failure. Retreatment options in these patients are very limited at present, since these drugs are currently not available in India.

Consensus Statement: Management of Hepatitis C Genotype 1/4 Non-responders

86. ***Previous response to IFNα-based therapy is an important predictor of success in future therapy, with relapsers having higher cure rates than partial responders, who in turn have higher cure rates than null responders (Strength-1, Level of evidence-A)***.
87. ***Patients who are prior null responders should wait for future directly acting antivirals (Strength-1, Level of evidence-A)***
88. ***Patients who are relapsers and have F3 and F4 fibrosis should receive prolonged therapy for 72 weeks. Relapsers who have F1 or F2 fibrosis can wait for DAAs (Strength-2, Level of evidence-C)***.
89. ***Patients who have partial response can be treated with prolonged therapy for 72 weeks. This therapy can be shortened to 48 weeks if complete EVR is achieved (Strength-1, Level of evidence-C)***.
90. ***Patients with null responder status should wait for future directly acting antivirals (Strength-1, Level of evidence-A)***.

Which Patients Can Wait for DAAs?

Patients who can wait for newer DAAs to become available, are those with mild fibrosis (F1, F2) in non genotype 2/3 infection, non-responders, those who are intolerant to IFNα, patients with decompensated liver disease and patients in special groups as has been enumerated above.

CONCLUSIONS

There is a large burden of HCV in India. The current status report summarizes the available data of HCV in India and the INASL recommendations for prevention and management of HCV in India. Considerations for the treatment of HCV in India should include the cost of therapy, the poorer response of genotype 3 as compared to genotype 2 and the non-availability of drugs recommended by some of the other guidelines. The DAAs are on the horizon and the news of their licensing and pricing in India is eagerly awaited by the physicians treating patients with CH–C. The current recommendations will be revised once the newer DAA are available in India.

CONFLICTS OF INTEREST

All authors have none to declare.

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