Indian National Association for Study of the Liver (INASL) Guidance for Antiviral Therapy Against HCV Infection in 2015

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Overall prevalence of HCV infection in India has been estimated to be approximately 1.3% in the general population. Recent introduction of sofosbuvir in India at a relatively affordable price has led to great optimism about prospects of cure for these patients. This drug is likely to form the backbone of current and future treatment regimes for HCV infection, displacing pegylated interferon. Availability of directly acting antiviral drugs (DAAs) has necessitated revision of INASL guidelines for the treatment of HCV published in 2014, as has happened across the world. Current considerations for the treatment of HCV in India include the poorer response of genotype 3, nonavailability of many of the DAAs recommended by other guidelines and the cost of therapy. Since only one DAA, sofosbuvir, is available in India, only two sofosbuvir-based regimes are possible: either dual drug therapy in combination with ribavirin alone for 6 months or triple drug therapy in combination with ribavirin and pegylated interferon for 3 months. The utility of these regimes in various situations has been discussed. Availability of a few other newer DAAs, expected in 2016, is expected to lead to more widespread use of these agents. Current guidance will be updated once newer DAAs, newer evidence with DAAs and 'real-life experience' with use of DAAs accumulate in India. (J Clin Exp Hepatol 2015;5:221–238)

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Abbreviations: ALT: alanine aminotransferase; ANC: absolute neutrophil count; anti-HCV: antibody to HCV; AST: aspartate aminotransferase; CH-C: chronic hepatitis C; CTP: Child-Turcotte Pugh; DAA: directly acting antiviral agents; EIA: enzyme immunoassay; ESRD: end stage renal disease; EVR: early virological response; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IFN-α: interferon alfa; INASL: Indian National Association for Study of the Liver; PCR: polymerase chain reaction; Peg-IFNα: pegylated interferon alfa; RBV: ribavirin; RVR: rapid virological response; SOC: standard of care; Sof: sofosbuvir; SVR: sustained virological response; ULN: upper limit of normal

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The management of chronic hepatitis C (CH-C) evolved gradually in the 1990s; it had been almost static from 2001 to 2011, when pegylated interferon alfa (Peg-IFNα) with ribavirin (RBV) became the global standard of care for CH-C, but evolution has become a revolution in the last five years. Introduction of triple therapy in 2011, with the addition of protease inhibitors boceprevir or telaprevir to Peg-IFNα/RBV, increased sustained virological response (SVR) rates in genotype 1 infection. However, these advances were eclipsed in 2013 by the arrival of another new directly acting antiviral agent (DAA), sofosbuvir (Sof), the first-in-class pangenotypic NS5B nucleotide polymerase inhibitor.

In consonance with the rapidly accumulating new evidence in the management of CH-C, there have been a spate of new guidelines and guidance in this area. The American

Association for the Study of Liver Diseases (AASLD), in collaboration with the Infectious Diseases Society of America (IDSA), revised their guidelines for testing and treating hepatitis C in December 2014, less than a year after the original guidelines were released, and these were further updated online in June 2015.[1,] In March 2014, the World Health Organization (WHO) released its first ever set of global guidelines for hepatitis C virus (HCV) treatment were updated at the APASL meeting in Istanbul in March 2015.[2,] The European Association for Study of Liver Diseases (EASL) has updated its HCV management guidelines issued in August 2014 at its annual meeting in Vienna in April 2015.[3,] Similarly Canadian (January-February 2015),[4,] Dutch (October 2014),[5,] and NICE (February 2015)[6] guidelines have all been published recently.

However, uncritical implementation of these guidelines in India may neither be appropriate nor possible. Considerations in India include the prevalent genotype and its response to therapy, availability of drugs, and cost of therapy. Many of the DAAs recommended for management of CH-C are either not approved for use in India or not likely to be available in India in the near future or can be imported only at a prohibitive cost.

The Indian National Association for Study of the Liver (INASL) has recently reviewed the epidemiology of HCV infection in India[7,] and has formulated guidelines for treating HCV infection with Peg-IFNα/RBV, the standard-of-care (SOC) till 2014.[8] Anticipating the imminent arrival of DAAs in India, these guidelines had recommended that it would be prudent to consider deferring treatment in patients with no or minimal fibrosis or with poor likelihood of response to Peg-IFNα/RBV therapy.

The arrival of oral DAAs has been eagerly awaited in India. Not only is the efficacy of Sof-based therapy expected to be higher than of Peg-IFNα/RBV therapy, but fewer side effects, better tolerability, shorter duration of therapy, simpler administration, easier monitoring and, importantly, reduction in the cost of therapy anticipated with the newer DAAs, are also advantages likely to significantly increase access to antiviral therapy among Indian patients.[9] It is expected that effective drugs will obviate need for response-guided therapy and will reduce need for repeated blood tests to monitor viral load and adverse effects. However, a word of caution is important. A combination of DAAs has been recommended in most situations and therapy with a single DAA-with-RBV combination may not be successful in all patient groups, especially in difficult-to-treat situations. Full benefits of oral, interferon-free antiviral therapy against hepatitis C are likely to be reaped only after a second potent DAA becomes available in India.

The arrival of Sof in the Indian market in March 2015 has mandated a revision of the INASL 2014 recommendations for the management of CH-C in India, recognizing that further changes are likely in these recommendations, as the fast-paced scenario of changing HCV therapy unfolds in India.

CURRENT CLINICAL PRACTICE IN INDIA

It has been estimated that India has a burden of 8.7 million patients with HCV viremia who are candidates for therapy. About 20% have advanced stages of disease with F3-F4 fibrosis, compensated cirrhosis, decompensation or HCC. Fewer than 5% have ever been diagnosed and less than 0.2% have ever received treatment.[10,11] In 2014, it was estimated that approximately 17,000 received treatment with Peg-IFN/RBV, which was the SOC then, and about 65% of them achieved SVR. With the availability of Sof in India at an affordable price, a dramatic increase in the number of patients being prescribed therapy was anticipated, as several barriers to interferon-based therapy were likely to be breached and a large number of 'warehoused' interferon ineligible patients and relapsers were likely to be offered treatment. That this is indeed happening, and at a pace anticipated by few, is suggested by data from pharmaceutical industry sources for the first three months after Sof became available, ending June 30th, 2015, according to which more than 19,000 patients have been prescribed Sof-based treatment, including ~6600 prescribed triple therapy (personal communication). Results of therapy are likely to be available soon.

LABORATORY TESTING OF HCV IN THE ERA OF DAA

Investigations for patients with HCV include serological assays for antibodies to hepatitis C (anti-HCV) and assays to check for viral nucleic acid and viral genotype besides investigations for status of the infected liver, including evaluation of the stage of hepatic fibrosis.

Viral Kinetics in the Era of DAA

Studying HCV kinetics during treatment with Peg-IFNα/RBV has allowed clinicians to develop response-guided therapy paradigms. A rapid viral decline early during therapy with undetectable HCVRNA by highly sensitive assays after 4 weeks of treatment (rapid virologic response, RVR) and negative HCVRNA at 12 weeks (early virologic response, EVR) are important predictors of sustained virologic response (SVR), that is, cure of HCV infection. These terms should be restricted to responses on therapy with Peg-IFNα/RBV. Traditionally, with Peg-IFNα-based therapy, SVR referred to the absence of detectable virus 24 weeks after the completion of therapy (SVR24). However recent data suggest that absence of detectable virus at 12 weeks after completion of therapy (SVR12) is concordant with SVR24.[12,] Concordance of SVR4 and SVR8 with SVR24 and SVR12 has also been assessed for Sof therapy, however, they have not been found to be adequate.[13]

During therapy with Sof-based combinations, HCVRNA levels decline to undetectable levels in ~70% of patients at week 2 and in over 95% of patients at week 4. The need for repeated HCV RNA testing during DAA therapy for residual viremia remains unclear, given that a response-guided therapy paradigm has not yet been proposed and that, to date, no data have emerged to suggest that those with detectable viral load at 4 weeks will not attain SVR. It is anticipated that the use of highly effective DAA-based regimens will reduce need for frequent pre-treatment and on-treatment viral load testing; detection of HCV-RNA prior to therapy and demonstrating its absence 12 weeks after end of therapy may suffice.

HCV Core-antigen

Traditionally HCV RNA testing by PCR has been used to differentiate between active and resolved HCV infection and for following response to antiviral therapy. HCV core-antigen (HCV-Ag) testing appears to be an attractive option for simplifying testing and monitoring of HCV therapy. HCV-Ag is a protein with a highly conserved sequence, which can be detected using enzyme-immunoassays.[14,] The major advantage of HCV-Ag testing is that it is simple to perform, does not require skilled manpower, is cheap, and can be performed at the same time as the anti-HCV test. Automated platforms, such as Abbott Architect®, are able to perform anti-HCV and HCV-Ag together in a short period of time. HCV core-Ag testing has been shown to be valuable in situations such as detection of active HCV infection, detection of HCV infection in seronegative hemodialysis patients, early treatment monitoring and as a cost-effective alternative to nucleic acid technology for the identification of blood donors in the pre-seroconversion window.[15–19] HCV-Ag ELISA is likely to be useful in resource-constrained settings, enabling small laboratories where HCV RNA testing may not be feasible, to detect active HCV infection.[20] Although algorithms incorporating HCV-Ag testing have been proposed for management of patients with CH-C, further evaluation is required to assess whether this test can obviate need for HCV RNA testing.[21,22]

Role of IL 28B Polymorphisms in the Era of DAA

IL28B polymorphisms have been shown to be valuable in predicting spontaneous clearance of acute HCV infection as well as response to treatment with Peg-IFNα-based therapy.[23,] In the era of DAAs, testing for IL28B genotype appears to have lost its relevance, though it may have a role in predicting outcome of therapy when DAAs are used in combination with Peg-IFNα/RBV. In the NEUTRINO trial, among treatment-naive genotype 1, 4, 5, and 6 patients who were treated for 12 weeks with Sof/Peg-IFNα/RBV, multivariate analysis revealed that non-CC IL28B genotype (SVR12 rate 87% vs. 98%) and presence of cirrhosis (SVR12 rate 80% vs. 92%) were significantly associated with reduced response.[24]

Assessment of Hepatic Fibrosis in the Era of DAA Therapy

During the era of Peg-IFNα/RBV therapy, assessment of hepatic fibrosis was important not only for predicting outcome of therapy but also for determining treatment eligibility in difficult-to-treat patients, treatment being started only in those with >F2 fibrosis among patients with genotype 1 infection or HIV-HCV co-infection. In this new era of rapidly improving cure rates for HCV with DAAs, fibrosis assessment may not be important anymore for deciding treatment eligibility in F0-F3 disease, particularly in genotype 1, 2, and 4 disease. However, establishing presence of cirrhosis continues to be important as it predicts response to therapy and may dictate choice of regimens, especially in difficult-to-treat subsets such as treatment-experienced patients with cirrhosis due to genotype 3 infection.

Assessment Prior to Treatment

Prior to starting treatment, the following evaluation should be done:

- A detailed history and physical examination are essential, including detailed history of alcohol consumption and drug abuse. Detailed cardiac, pulmonary and psychiatric evaluation should be done, if indicated.
- *Baseline tests* include complete hemogram and liver biochemistry [alanine aminotransferase (ALT) and aspartate aminotransferase (AST) alkaline phosphatase, bilirubin, gamma-glutamyl transpeptidase (GGT), prothrombin time or INR, albumin], renal function, and thyroid function.
- *Investigations for viral co-infections*: Hepatitis B surface Antigen, anti-HIV.
- *Evaluation for other causes*: The causal relationship between HCV infection and liver disease should be established and additional tests for a second etiology or co-morbidities may be done as indicated e.g., antimitochondrial antibodies, antinuclear antibodies, anti-smooth muscle antibodies, serum ceruloplasmin, serum ferritin, etc.
- Serum HCV RNA (quantitative) and HCV genotyping.
- IL28B genotyping is not recommended for routine use
- *Detection of liver fibrosis and cirrhosis:* Though liver biopsy remains the 'gold standard', liver cirrhosis is usually diagnosed on the basis of a combination of clinical, biochemical, sonographic, and endoscopic criteria. This approach is reliable for detecting compensated cirrhosis with portal hypertension but not in the absence of portal hypertension. The increasing use of liver stiffness measurements using techniques such as Fibroscan™, acoustic radiation force impulse (ARFI) and shear wave elastography (SWE) allows detection of cirrhosis without portal hypertension, a subset which was earlier included in the 'no cirrhosis' group. Transient elastography has been used as a diagnostic method to rule out cirrhosis with a reasonable accuracy. ARFI and batteries of biochemical tests used for detection of fibrosis, such as aspartate transaminase-platelet ratio index (APRI) or FIB-4 are not widely validated or have lower diagnostic accuracy.[25,26]

- Cardiac and pulmonary evaluation, if indicated.
- Psychiatric evaluation, if indicated.
- In women of child-bearing age, urine pregnancy test is required.

ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS C IN 2015

Rating Response to Antiviral Drug Regimens

Antiviral regimens for CH-C are evolving rapidly and many drugs continue to gush out of a briskly flowing pipeline. It is important to rate efficacy of various regimens objectively, particularly for genotype 1 infection where the clinician is spoilt for choice between highly effective regimens. Though choices are limited in genotype 3 CH-C, rating their efficacy is just as important. An antiviral regimen may be rated as '**ideal**' if it achieves cure in all categories of patients with negligible side effects and no treatment emergent resistance associated variants (RAVs). Such a 'perfectovir' regimen, the Holy Grail of antiviral therapy for CHC, still remains elusive. A regimen which achieves SVR in ~90–95% of treated patients, with minimal or acceptable side effects, is '**optimal**' for that particular category of patients. An '**alternate**' regimen is one which has efficacy equivalent to, or marginally lower than, an 'optimal' regimen but has some drawbacks or limitations, such as side-effects, treatment emergent variants or cost that do not allow it to be considered the therapy of choice. An '**acceptable**' regimen is one with <90% SVR when no better regimen is available for that population. There is urgent need to develop better regimens in this subset of patients. Regimens achieving SVR rates below 90% are '**suboptimal**' for patient populations where **optimal** regimens are available.

Today, only three drugs are approved and available for treatment of CH-C in India and, until newer DAAs are approved, these can be used only in one of two regimens. The drugs are interferon (IFNα), standard and pegylated, RBV, and sofosbuvir (Sof), a pangenotypic nucleotide polymerase inhibitor (NPI) acting on viral RNA polymerase coded by the NS5B gene of the HCV genome. All patients with CHC are candidates for either the dual drug regimen of Sof and RBV (Sof/RBV) or the triple drug regimen of Sof, RBV and peg-IFN (Sof/RBV/Peg-IFN). The dual regimen of Peg-IFN/RBV is now obsolete. Patients on this regimen should complete their originally planned therapy, if they are responding satisfactorily; if they are facing problems, they need to be dealt with on a case-by-case basis. Recommendations for HCV therapy will need to be revisited as and when other drugs, such as pangenotyic NS5A replication complex inhibitors ledipasvir (LDV) and daclatasvir (DCV), are licensed and become freely available in India.

Peglylated Interferon Alfa

Peg-IFNα is available as Peg-IFNα2a, which is used at a dose of 180 μg/week; and Peg-IFNα2b, which is used at a dose of 1.5 μg/kg/week. Peg-IFNα related side effects, which need frequent dose adjustments and use of growth factors, are anemia and low blood counts. The other side effects are flu-like symptoms, fatigue, depression, sleep disorder, irritability, dyspnea, headache, injection-site reaction, autoimmune reactions, hearing and visual disturbances, and interstitial lung disease. Peg-IFNα should be used with caution in patients with advanced cirrhosis as hepatic decompensation may occur.

Ribavirin

RBV is available as 200 mg tablet and the recommended dosage is weight based, being 1000 mg/day in patients with body weight of <75 kg, and 1200 mg/day in patients with body weight of >75 kg. It might be preferable to use the optimum weight-based dose for RBV (15 mg/kg). The significant side effect of RBV is anemia.

Sofosbuvir

Sof, an analog of the pyrimidine nucleotide uridine, inhibits viral NS5B RNA-dependent RNA polymerase (RdRp). It is a prodrug that undergoes intracellular metabolism in the hepatocytes to its active form, GS-461203, which acts as a chain terminator. It is available as a 400 mg capsule and is given once per day. The major route of excretion of the drug is renal and it is therefore not recommended in patients with severe renal impairment (estimated glomerular filtration rate <30 ml/min). Common adverse effects of Sofin combination with RBV are fatigue, headache, nausea, insomnia and anemia. Sof is transported by P-glycoprotein (P-gp) and P-gp inducers decrease the plasma levels of Sof. Co-administration of Sof with amiodarone is contraindicated due to serious risk of symptomatic bradycardia. The drug interactions of Sof are given in Table 1.

Results of Antiviral Therapy for CH-C

Results of therapy with both regimens will be reviewed for each HCV genotype, beginning with genotype 3, which is responsible for ~65% of CH-C, followed by genotype 1, which is responsible for ~30% of CH-C and then the other genotypes, which, collectively, account for ~5% of all CH-C in India.

Table 1 Drug Interactions of Sofosbuvir.

Sofosbuvir is not recommended for co-administration with:
• Anticonvulsants—Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
• Antimycobacterials—Rifabutin, Rifampin, Rifapentine
• Herbal supplements—St. John's wort
• HIV protease inhibitors—Tipranavir/Ritonavir
• Amiodarone[a]

[a]Co-administration with amiodarone may lead to serious symptomatic bradycardia, while that with other drugs may lead to decrease in sofosbuvir levels.

Treatment of Genotype 3 CH-C in India

Genotype 3 is the second commonest HCV genotype known to infect humans, accounting for an estimated total of 54.3 million (30.1%) of all HCV infected individuals in the world.[27] It is the commonest genotype in India, which probably harbors the largest number of genotype 3 patients (~5.4 million) in the world.[10]

Results of Sof/RBV regimens in genotype 3 CH-C: Given the experience from the interferon-era of genotypes 2 and 3 being easy-to-treat viruses, initial studies with DAAs have lumped them together and used DAAs for short, 12-week periods. Evidence in support of Sof and RBV therapy in genotype 2 and 3 has come from the FISSION[22] (treatment-naïve, interferon-eligible patients), POSITRON[28] (treatment-naive and treatment-experienced patients, ineligible, intolerant or unwilling for interferon), FUSION[28] (treatment-experienced patients), an arm in the ELECTRON trial,[29] and the VALENCE[30] (treatment-naive and treatment-experienced patients) trials.

Recently these data have been supplemented by the BOSON trial.[31]

Results of the ELECTRON trial, the first trial with Sof/RBV in genotype 2 and 3 patients, were reported in January 2013. 100% SVR was reported in 10 treatment-naïve patients receiving Sof/RBV for 12 weeks as well as in 30 patients receiving Sof/RBV for 12 weeks with Peg-IFNα for 4, 8 or 12 weeks.[29]

The FISSION trial[22] was a phase 3, randomized, open-label, non-inferiority trial in 499 treatment-naïve genotype 2 and 3 patients, in which 72% patients were genotype 3 and 20% were cirrhotics. They were randomized to 12 weeks therapy with Sof/RBV versus 24 weeks with Peg-IFN/RBV. There was no difference in SVR 12 rates between the two groups, being 63% (110/176) in the Peg-IFN/RBV group compared with 56% (102/183) in Sof/RBV group. The low SVR 12 rate in treatment-naive cirrhotics (34%) compared with treatment-naïve non-cirrhotics (61%) highlighted the inadequacy of the 12-week oral regimen among cirrhotics. SVR 12 rates were even worse in treatment-experienced patients, being 37% in non-cirrhotics and 19% in cirrhotics. This study made it clear that genotype 3 was the new difficult-to-treat virus and that the 12-week regimen was inadequate for treating genotype 3 cirrhotic and treatment-experienced patients.

The POSITRON trial[28] recruited 277 treatment-naïve or treatment-experienced patients with genotype 2 or 3 HCV, who were ineligible, intolerant or unwilling for Peg-IFNα. SVR rate after 12 weeks of Sof/RBV therapy in genotype 3 was 61% (101/109), being 68% in those without cirrhosis and a meager 21% in those with cirrhosis. This study reinforced the observation in the FISSION study that 12 weeks of Sof/RBV is inadequate therapy for genotype 3 patients.

The FUSION trial[28] was designed to assess the benefit of extending duration of treatment in patients who had failed previous therapy. This phase-3 trial compared Sof/RBV for 12 weeks with Sof/RBV for 16 weeks in treatment-experienced patients with genotype 2 or 3 HCV infection. Only 19 of 64 (30%) genotype 3 patients achieved an SVR12 with Sof/RBV for 12 weeks, which improved to 39/63 (62%) in the 16-week group. The benefit was especially pronounced in 47 genotype 3 patients with cirrhosis, the SVR12 rates being significantly higher with the 16-week regimen (61%) than with the 12-week regimen (19%). However, even the 16-week regimen was suboptimal for treatment-experienced genotype 3 patients.

The phase-3 VALENCE trial[30] included 419 patients (261 with genotype 3) explored results of extending treatment with Sof/RBV to 24 weeks in genotype 3 patients, including treatment experienced and cirrhotic patients. While improvement in SVR 12 rates was gratifying in treatment-naïve patients (93% in non-cirrhotic and 90% in cirrhotic patients) as well as in treatment experienced non-cirrhotic patients (87%), it was a disappointing 62% in treatment-experienced patients with liver cirrhosis. On multivariate logistic regression analysis, SVR rates were lower with age >50 (OR 2.8), male gender (OR 3.18), presence of liver cirrhosis (OR 3.46), and baseline HCV RNA above $6\log_{10}$ (OR 4.2). This study has established the paradigm that genotype 3 patients need 24 weeks of Sof/RBV and that even this regimen is suboptimal for treatment-experienced patients with liver cirrhosis.

Although, more genotype 3 patients ($n = 363$) were included in the two Sof/RBV arms of the BOSON trial than in the VALENCE trial ($n = 261$), more patients (250) received Sof/RBV for 24 weeks in the VALENCE trial due to change in design of the VALENCE study, with only 11 patients being treated for 16 weeks. In the BOSON study 182 received Sof/RBV for 16 weeks, 181 received it for 24 weeks. However, while SVR rates were slightly lower in the BOSON study in the treatment-naïve no cirrhosis (90% vs. 93%), treatment-naïve with cirrhosis (82% vs. 90%) and treatment-experienced no cirrhosis (82% vs. 87%) groups, they were slightly better in the treatment-experienced with cirrhosis group (77% vs. 62%).

Results of trials using Sof/RBV combination for various durations and different categories of patients are summarized in Table 2.

Results of Sof/RBV/Peg-IFN in genotype 3 CH-C: Evidence from pivotal trials for standard categories of genotype 3 patients is briefly reviewed below.

The triple regimen of Sof/Peg-IFNα/RBV has been shown to have a response rate of 90–100% for treatment-naïve patients with genotype 3 CH-C in ELECTRON[29] and PROTON[32] trials.

The open-label ELECTRON study,[29] reported in January 2013, was the first Sof trial to be published and included a total of 95 patients in two genotype 1 and six genotype 2 or 3 cohorts. It recorded 100% SVR in 30

Table 2 Trials of Sofosbuvir and Ribavirin Therapy in Genotype 3.

Trial (Ref.)	Treatment Regimen (weeks)		n	SVR
Weeks	0 4 8 12 16 24			
Treatment Naive				
FISSION[22]	Sof + RBV (12 wks)		183	56%
	Peg + RBV (800 mg)		176	63%
POSITRON[28]	Sof + RBV (12 wks)		98	61%
ELECTRON[29]	Sof + RBV (12 wks)		10	100%
	Sof		10	60%
VALENCE [30]	Sof + RBV (12 wks)		11	27%
	Sof + RBV (24 wks)		105	94%
BOSON [31]	Sof/RBV (16 weeks)		272*	77%
	Sof/RBV (24 weeks)			88%
Treatment Experienced				
FUSION[28]	Sof + RBV (12 wks)		64	30%
	Sof + RBV (16 wks)		63	62%
VALENCE [30]	Sof + RBV (24 wks)		145	79%
POSITRON [28]	Sof + RBV (12 wks)		17	77%
BOSON [31]	Sof + RBV (16 weeks)		272*	64%
	Sof/RBV (24 weeks)			80%
Cirrhotics				
FISSION[22]	Sof + RBV (12 wks)	Rx Naive	49	47%
	Peg + RBV (800 mg)	Rx Naive	50	38%
POSITRON[28]	Sof + RBV (12 wks)	Rx Naive	14	21%
VALENCE [30]	Sof + RBV (24 wks)	Rx Naive	13	92%
		Rx Experienced	47	62%
FUSION [28]	Sof + RBV (12 wks)	Rx Experienced	26	61%
	Sof + RBV (16 wks)	Rx Experienced	23	85%
BOSON[31]	Sof/RBV (16 weeks)	Rx Naive	21	57%
		Rx Experienced	36	47%
	Sof/RBV (24 weeks)	Rx Naive	22	82%
		Rx Experienced	34	77%

treatment-naïve patients with genotype 2 or 3 infection (19 patients with genotype 3) who received Sof/RBV for 12 weeks with Peg-IFNα for 4, 8 or 12 weeks as well as in another group of ten patients with genotype 3 CH-C receiving Sof/RBV/Peg-IFNα for 8 weeks.

The PROTON trial[32] was another early randomized, two-cohort, phase-2 trial, which enrolled treatment-naïve non-cirrhotic patients with genotypes 1, 2, and 3 and treated them with the Sof/RBV/Peg-IFN regimen for 12 weeks. Although 23/25 (92%) patients achieved SVR24, there were only 10 genotype 3 patients in this cohort.

The LONESTAR-2 trial[33] was an open-label, single-arm, phase-2 trial with Sof/RBV/Peg-IFN for 12 weeks used in treatment-experienced genotype 2 and 3 patients, including those with compensated cirrhosis. SVR12 rates of 83% (10/12) were noted in both non-cirrhotic as well as in cirrhotic genotype 3 patients, with no major side effects in either arm. Along with previous small studies, this trial

suggested that the 12-week triple regimen was a promising option for the difficult-to-treat group of treatment-experienced genotype 3 patients with cirrhosis.

The BOSON trial[31] is a randomized phase-3 study that enrolled 592 patients, including 544 with genotype 3. It compared safety and efficacy of Sof/RBV for 16 or 24 weeks with Sof/RBV and Peg-IFN for 12 weeks among treatment-naïve or treatment-experienced genotype 3 patients, including 37% with cirrhosis. SVR12 rates were higher among those receiving the triple regimen (93%; 168/181), compared with those receiving either the 24 weeks (84%; 153/182) or 16 weeks regimen (71%; 128/181). For all subgroups of patients, there was a 6–12% SVR advantage in the triple therapy cohort compared with the 24-week dual therapy cohort (88 vs. 79% in those with and 95% vs. 87% in those without cirrhosis; 95% vs. 88% in the treatment-naïve and 91% vs. 80% in the treatment-experienced groups). In the treatment-experienced cirrhotics, SVR12 rates were 86 percent (30/35) in the triple therapy vs. 77% (26/34) in the 24-week dual therapy group. Treatment was well tolerated in all patients; grade 3–4 adverse events (AEs; 4% vs. 8%), serious AEs (SAEs; 5% vs. 6%) and treatment discontinuation due to SAEs (1% vs. 0.5%) were similar in the 24-week Sof/RBV and the 12-week Sof/Peg IFN-α/RBV groups. However virological failure, noted in 85 (14.6%) patients, was uncommon after Sof/Peg IFN-α/RBV (5%; 9/195) and occurred mainly in the Sof/RBV treated groups (19.5%; 76/390), more so in those treated for 16 weeks (52/195; 26.7%). A disturbing observation was that resistance analysis, done by deep sequencing in 78 of these patients, revealed that 12% (9/78) had treatment-emergent variants (TEVs), something that had not been reported in previous studies with Sof. Though S282T was not detected, 7 patients had the L159F variant and 2 had the V321A variant.

Reinforcing the findings of the LONESTAR-2 trial, this study has reaffirmed that the triple combination continues to be valuable in treating various subsets of patients with HCV genotype 3 infection.

Esteban et al.[34] showed that patients who had not achieved SVR, relapsing after Sof/RBV therapy, achieved SVR in 91% (20/22) of cases after triple therapy with Sof/Peg IFN-α/RBV.

Table 3 Trials of Sofosbuvir and RBV with Peg-IFNα for 12 Weeks in Genotype 3 HCV Infection.

Name of Trial	Treatment Regimen (weeks)			n	SVR (%)
Weeks	*0 4 8 12 16 24 48*				
Treatment-Naïve					
PROTON[32]	Sof/RBV/Peg-IFNα			10	90
ELECTRON[29]	Sof/RBV+ Peg-IFNα (wk 1-4)			9	100
	Sof/RBV+ Peg-IFNα (wk 1-8)			10	100
BOSON[31]	Sof/Peg-IFNα+ RBV 12 weeks			94	95
Treatment Experienced *(Previous Peg +RBV)*					
LONESTAR-2[33]	Sof/RBV/Peg-IFNα 12 wks			24	83
BOSON[31]	Sof/RBV/Peg-IFNα			87	91
Treatment Experienced *(Previous Sofosbuvir+ RBV)*					
Esteban et al[34]	Sof/RBV/Peg-IFNα			22	91
Cirrhotics					
LONESTAR-2[33]	Sof/RBV/Peg-IFNα			12	83
BOSON[31]	Sof/RBV/Peg-IFNα		Treatment-naïve	23	91
			Treatment-experienced	35	86

Results of trials using the Sof/RBV/Peg-IFN regimen for 12 weeks in patients with genotype 3 CH-C are summarized in Table 3.

Treatment of Genotype 1 CH-C in India

Globally, genotype 1 is the commonest HCV genotype known to infect humans, accounting for an estimated total of 83.4 million (46.2%) of all HCV infected individuals in the world.[27] It is the second most common genotype in India, with ~2.6 million patients suffering from genotype 1 CH-C.[10]

Though at least six different treatment options have been proposed, by AASLD 2015,[1] EASL 2015,[3] NICE 2015[6] and others, for patients with HCV genotype 1 infection, in India only one of these options is available in 2015, i.e. Sof/Peg IFN-α/RBV. Drugs that are part of other IFN-α-containing and IFN-α-free options recommended by these guidelines [Peg IFN-α, RBV and simeprevir; Sof and ledipasvir; paritaprevir, ritonavir, ombitasvir and dasabuvir; Sof, and simeprevir with or without RBV; Sof and daclatasvir with or without RBV] are not available in India. Though the combination of Sof and RBV has been used, it is not recommended in patients infected with HCV genotype 1, as discussed below.

Results of Sof/RBV in genotype 1 CH-C: Six trials have addressed the issue of Sof and RBV therapy in the management of HCV Genotype 1. These include the NEUTRINO,[24] ELECTRON,[29] PROTON,[32] ATOMIC,[35] NIH SPARE,[36] and QUANTUM[37] trials. All the trials enrolled treatment-naïve patients of genotype 1, except for the one arm of treatment-experienced genotype 1 patients in the ELECTRON trial (n = 10). Data for the use of Sof and RBV used alone without Peg-IFNα are available from the NIH SPARE, ELECTRON and the QUANTUM trials.

Treatment-naïve genotype 1: The NIH SPARE[36] trial exclusively studied the role of Sof and RBV in genotype 1 patients. In the NIH SPARE trial, Osinusi et al. evaluated the role of Sof and RBV in 60 treatment-naïve patients with HCV genotype 1 and unfavorable characteristics (e.g. African-American race and advanced fibrosis). In the proof-of-concept part of the study, 9/10 (90%) patients with early to moderate liver fibrosis treated with Sof (400 mg daily) plus weight-based RBV for 24 weeks achieved SVR. In part 2 of the trial, 50 patients with all stages of liver fibrosis were randomized to receive 400 mg Sof with either weight-based RBV or low dose RBV (600 mg daily) for 24 weeks. However, results of the study were dismal. SVR24 was seen in only 68% (17/25) in the weight-based RBV group and 48% (12/25) in the low-dose RBV group.

The ELECTRON study included both treatment-naïve (n = 25) and treatment-experienced (n = 10) patients with chronic HCV genotype 1 who were treated with Sof and RBV for 12 weeks. SVR was achieved in 84% (21/25) of treatment-naïve patients.[29]

However, in the QUANTUM study, which included 38 treatment-naïve HCV genotype 1 patients randomized into 12 or 24 weeks of treatment with Sof and RBV, the response rate was only 50%, with 53% (10/19) in the 12-week arm and 47% (9/19) in the 24-week arm achieving SVR.[37]

Table 4 Trials of Sofosbuvir and Ribavirin Therapy in Genotype 1.

Name of Trial	Treatment Regimen (weeks)				n	SVR
Weeks	0 4 8 12		24	48		
Treatment Naive						
NIH SPARE[36]	Part 1: Sof + RBV (wt based)- 24 wks				10	90%
	Part 2: Sof + RBV (wt based)- 24 wks				25	68%
	Part 2: Sof + RBV (600 mg)- 24 wks				25	48%
ELECTRON[29]	Sof + RBV -12 wks				25	84%
QUANTUM[37]	Sof + RBV -24 wks				19	53%
	Sof + RBV -12 wks				19	47%
Treatment Experienced						
ELECTRON[29]	Sof + RBV (12 wks)				10	10%
Advanced Fibrosis and Cirrhosis						
NIH SPARE[36]	Sof + RBV (wt based)- 24 wks				6	46%
	Sof + RBV (600 mg)- 24 wks				7	

Treatment-experienced genotype 1: In the ELECTRON trial, unlike in treatment-naïve patients, results of Sof and RBV therapy were dismal in treatment-experienced patients, with only 10% (1/10) achieving SVR.[29]

Genotype 1 with advanced fibrosis and cirrhosis: In the NIH SPARE trial, 7 of 13 participants (54%) with advanced liver fibrosis treated in this study relapsed, including all 4 patients with cirrhosis.[36]

Available data for Sof/RBV in genotype 1CH-C are scanty and are summarized in Table 4. In summary, Sof used as a single DAA along with RBV has poor results for genotype 1 HCV infection. The results of Sof and RBV therapy in prior treatment failures and in cirrhotics are even worse. Considering the excellent treatment response of regimens combining DAAs, it is no surprise that the current AASLD and EASL guidelines do not recommend use of the Sof/RBV combination in the treatment of genotype 1 CH-C.

Results of Sof/RBV/Peg-IFN α in genotype 1 CH-C

Treatment-naïve patients: The PROTON,[32] ATOMIC,[35] and NEUTRINO[24] trials showed that adding Sof to standard Peg-IFNα and RBV therapy in treatment-naïve patients improved SVR rates in genotype 1 CH-C.

One of the early Sof trials, the PROTON trial[32] is noteworthy for its design. It is the only trial in which two doses of Sof (200 or 400 mg) were compared with placebo and in which the duration of therapy was guided by patient response. It included 122 patients with HCV genotype 1 who were randomized to receive Sof 400 mg or 200 mg for 12 weeks plus Peg-IFNα/RBV for 24 or 48 weeks (response-guided) or placebo for 12 weeks plus Peg-IFNα/RBV for 48 weeks. The SVR rates were 91% and 90% respectively in the Sof cohorts.

In the ATOMIC[35] trial, 316 patients with genotype 1 CH-C were randomized to receive Sof 400 mg plus Peg-IFNα/RBV for 12 weeks or 24 weeks or for 12 weeks followed by 12 weeks of either Sof mono-therapy or Sof plus RBV. The SVR rates in all three cohorts ranged from 87 to 89%.

In the NEUTRINO trial,[24] treatment-naive genotype 1, 4, 5 and 6 patients were treated for 12 weeks with Sof/Peg-IFNα/RBV. Among genotype 1 patients, the overall SVR12 was 89% (259/291); it was 92% (207/225) for subtype 1a and 82% (54/66) for subtype 1b.

Treatment naïve cirrhosis: In the NEUTRINO study, presence of cirrhosis was associated with significantly reduced SVR rates (80% vs. 92%).[24]

In another recent study, Pearlman et al.[38] found Sof and simeprevir therapy for 12 weeks in genotype 1a HCV related Child A cirrhosis to be superior to the results of 12 weeks of Sof plus Peg-IFNα/RBV. Though lower than the results in the Sof/simeprevir cohort, SVR rate was a respectable 75% with Sof/Peg-IFNα/RBV in this difficult to treat group.

Treatment experienced patients: Though none of the trials looked at this group, based on historical studies and NEUTRINO results, the US Food and Drug Administration predicted that 78% of those who had failed previous therapy with Peg-IFNα/RBV would achieve an SVR with the triple combination of Peg-IFNα/RBV and Sof.[39] Some information on the treatment-experienced subset of genotype 1 CH-C patients is available from the initial results of this regimen reported in two large US real-life cohorts, the HCV TARGET 2.0[40] and the TRIO study.[41] In HCV TARGET 2.0, SVR4 was 85% (140/164; 55% treatment-naïve, 45% treatment-experienced) and was higher among non-cirrhotics (90%; 114/127) than in patients with cirrhosis (70%; 26/37).[40] In the TRIO real-life study, SVR12 was 81% among treatment-naive patients and was similar among non-cirrhotics (81%; 112/138) and cirrhotics (81%; 25/31). However, among treatment-experienced patients SVR12 was achieved in 77% (30/39) without cirrhosis but in only 62% (53/85) with cirrhosis.[41]

The results of triple therapy with Sof and Peg-IFNα/RBV in genotype 1 are shown in Table 5.

Treatment of Genotype 2 CH-C in India

Genotypes 2, 4, 5, 6 together constitute fewer than 5% of patients with CH-C in India.

Results with Sof/RBV in genotype 2 CH-C: In all four published trials, Sof and RBV therapy for 12 weeks has resulted in excellent SVR rates in genotype 2 CH-C. In the FISSION trial, SVR rate was 97% in among treatment-naïve genotype 2 patients, being similar in those with [91% (10/11)] and without cirrhosis [98% (58/59)].[22] In the POSITRON trial, SVR rate was 93% (101/109) among IFN-unwilling, ineligible, or intolerant genotype 2 patients.[28] In the FUSION trial, among treatment-experienced genotype 2 patients, SVR rates were better, with 16 weeks of therapy (94%) than after 12 weeks (86%). This was also the case in genotype 2 patients with cirrhosis; SVR rates were better after 16 weeks of therapy (78%; 7/9) than after 12 weeks (60%; 6/10). Though numbers were small, this observation indicated that cirrhotic patients might need therapy for more than 12 weeks.[28] In the VALENCE trial, among patients with genotype 2 HCV treated for 12 weeks with Sof and RBV, SVR rate was 93% (68/73), being 94% (59/63) without and 82% (9/11) with cirrhosis.[30] According to treatment experience, SVR rate was 97% (29/30) in treatment-naïve non-cirrhotic patients, 100% (2/2) in treatment-naïve cirrhotic patients, 91% (30/33) in treatment-experienced non-cirrhotic patients, and 88% (7/8) in treatment-experienced cirrhotic patients. The combination was well tolerated, no virological breakthroughs were observed in treatment-adherent patients and no resistance-associated variants (RAVs) were reported. The recently reported BOSON study has reinforced these results. In a cohort of

Table 5 Trials of Sofosbuvir and RBV Along with Peg-IFNα in Genotype 1.

Name of Trial	Treatment Regimen (weeks)			n	SVR
Weeks	0 4 8 12 24 48				
Treatment Naive					
NEUTRINO [24]	Sof + Peg-IFNα/RBV			292	89%
ATOMIC[35]	Sof + Peg-IFNα/RBV			52	90%
	Sof + Peg-IFNα/RBV			109	93%
	Sof + Peg-IFNα/RBV	Sof or Sof/RBV		155	91%
PROTON[32]	Sof (200)+ Peg-IFNα/RBV	Peg-IFNα/RBV	-RVR	48	90%
			+ RVR: Peg-IFNα/RBV		
	Sof (400)+ Peg-IFNα/RBV	Peg-IFNα/RBV	-RVR	47	91%
			+ RVR: Peg-IFNα/RBV		
	Placebo + Peg-IFNα/RBV	Peg-IFNα/RBV		26	58%
HCV TARGET2.0[41]	Sof + Peg-IFNα/RBV			164	85%*
TRIO[41]	Sof + Peg-IFNα/RBV			169	81%
Cirrhotics					
Neutrino[24]	Sof + Peg-IFNα/RBV			54	80%
Pearlman[38]	Sof + Peg-IFNα/RBV			24	75%
	Sof + Simeprevir(12)			58	93%
TRIO[40]	Sof + Peg-IFNα/RBV		Rx naive	31	81%
			Rx experienced	85	62%
HCV TARGET 2.0 [41]	Sof + Peg-IFNα/RBV			37	70%*

*SVR4 results; Sof, sofosbuvir; RBV, ribavirin; Peg-IFN, pegylated interferon.

32 treatment-experienced genotype 2 cirrhotics, SVR rates were 87% (13/15) after 16 weeks of Sof/RBV therapy and 100% (17/17) after 24 weeks.[31]

Sofosbuvir with Peg IFN-α/RBV for genotype 2 CH-C: In the LONESTAR-2 study,[33,] following 12 weeks of Sof/Peg IFN-α/RBV therapy, SVR rate was 96% (22/23) in treatment-experienced patients with genotype 2 CH-C, including 14 with cirrhosis. In the BOSON study, this triple combination yielded an SVR rate of 94% (15/16) among treatment-experienced genotype 2 cirrhotics.[31,] In another study, Esteban et al. reported 100% SVR in 4 patients retreated for 12 weeks with this triple combination after having relapsed following treatment with Sof and RBV.[34]

Treatment of genotype 4 CH-C

Genotype 4 infection is seen in fewer than 2–3% of CH-C patients in India. Recently, there have been reports of some pockets in Kerala. Though data for therapy are scanty, both Sof with RBV and Sof with peg IFN-α/RBV have been used successfully to treat CH-C due to genotype 4.

Results with Sof/RBV in genotype 4CH-C: In the Egyptian ancestry trial, Ruane et al.[42,] enrolled 30 treatment-naïve and 30 previously treated genotype 4 patients who were treated for 12 weeks (n = 31) or 24 weeks (n = 29) with Sof and RBV. SVR12 was achieved in 68% of patients in the 12-week group and in 93% of patients in the 24-week group. Doss et al.[43] treated 103 treatment-naïve or experienced HCV genotype 4 Egyptian patients and reported SVR12 rates of 90% (46/51) with 24 weeks and 77% (40/52) with 12 weeks of Sof and RBV therapy. Patients with cirrhosis at baseline had lower rates of SVR12 (63% after 12 weeks, 78% after 24 weeks therapy) than those without cirrhosis (80% after 12 weeks, 93% after 24 weeks).

Sofosbuvir with Peg IFN-α/RBV for genotype 4 CHC: This combination has been evaluated in the NEUTRINO trial in treatment-naïve patients.[24] The SVR rate in genotype 4 patients was 96% (27/28). Patients who failed on this regimen did not select HCV variants resistant to Sof. No data with this regimen are available in treatment-experienced patients or in HIV co-infected patients. Whether treatment duration should be prolonged in the most difficult-to-treat populations is unknown.

Treatment of HCV Genotype 5 or 6 Infection

Sofosbuvir with Peg IFN-α/RBV for genotype 5 or 6 CHC: Genotypes 5 and 6 are extremely rare in India. Very scanty data are available for these rare genotypes. Only a single treatment-naïve patient with genotype 5, and 6 patients with genotype 6 were included in the phase III NEUTRINO trial.[24] All these patients achieved an SVR. No data with this regimen have been presented in treatment-experienced patients.

Only one treatment option, the triple combination of Sof with Peg IFN-α and RBV is available presently in India for patients infected with HCV genotypes 5 or 6. IFN-free combinations of Sof and ledipasvir and of Sof and daclatasvir are expected soon in India and are likely to replace triple therapy.

TREATMENT RECOMMENDATIONS FOR CHRONIC HEPATITIS C IN INDIA IN 2015

Except for Sof, the other DAA recommended by the AASLD[1,] and EASL[3] guidelines are not available in India. Hence such guidelines cannot be applicable to the Indian scenario. Till such time as oral combination therapy with DAA is available, along with Sof and RBV, Peg-IFNα therapy will continue to play a role in the management of HCV in India.

Indications for Therapy

All patients with active HCV infection who have evidence of viral replication and no contraindications to therapy should be considered for treatment. Patients in urgent need of treatment are those with advanced fibrosis (fibrosis score F3 or F4) or significant extra-hepatic manifestations (symptomatic cryoglobulinemia or HCV immune complexes nephropathy). Antiviral treatment decision for patients with HCV infection should not be based only on alanine aminotransferase (ALT) values, as significant liver disease may exist even in patients with persistently normal ALT.[44]

Whom to Treat?

Patients with CHC fall into **standard categories**, based on presence or absence of cirrhosis and previous treatment status, or into **special categories,** which need separate discussion (Table 6).

Standard categories include treatment-naïve patients with no cirrhosis **(TN-NC),** treatment-naïve patients with compensated liver cirrhosis **(TN-LC),** treatment-experienced patients with no cirrhosis **(TE-NC)** and treatment-experienced patients with compensated liver cirrhosis **(TE-LC)**. Since the efficacy of DAA regimens differs in these different categories, assessment for presence or absence of liver cirrhosis plays a major role in predicting outcome of therapy for CHC.

Ineligible, Intolerant, or Unwilling for Interferon Therapy

An important consideration is dealing with the patient ineligible for, intolerant to or unwilling for interferon therapy. A patient with absolute or relative contra-indications will be ineligible for interferon therapy.

Contraindication to Peg-IFNα/RBV or Sofosbuvir Therapy

Absolute contraindications to Peg-IFNα therapy include decompensated liver disease [Child-Turcotte Pugh (CTP) score ≥7], uncontrolled depression, psychosis, epilepsy; uncontrolled autoimmune disease including retinal disease and autoimmune thyroid disease; pregnancy or planning pregnancy; severe concurrent medical disease like poorly controlled hypertension, diabetes mellitus, heart failure, chronic obstructive pulmonary disease.

Relative contraindications to Peg-IFNα therapy include abnormal hematological parameters (Hb <10.0 gm/dl, baseline neutrophil count <1500/μL, or a baseline platelet count <90,000/μL); 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 case-to-case basis in elderly patients.

Table 6 Categories of Patients with Chronic Hepatitis C.

Standard category	Treatment-naïve, no cirrhosis (TN-NC)
	Treatment-experienced, no cirrhosis (TE-NC)
	Treatment-naïve, compensated liver cirrhosis (TN-LC)
	Treatment-experienced, compensated liver cirrhosis (TE-LC)
Special category	Decompensated liver cirrhosis
	Post-liver transplantation (post-LT)
	Post-renal transplantation (post-RT)
	Post-bone marrow/hemopoeitic stem cell transplantation (post-BMT/HSCT)
	Multi-transfused patients (thallassemics, hemophiliacs)
Co-infection/HCV with another etiology	HIV
	HBV
	Obesity
	Alcohol

Sof therapy is contraindicated in patients with severe renal impairment [estimated glomerular filtration rate (eGFR) <30].

Intolerance to Interferon

Patients developing severe flu-like symptoms, psychiatric symptoms, local or systemic adverse reactions, thrombocytopenia, neutropenia, neurologic complications or GI toxicity while on Peg-IFNα therapy are considered to be intolerant to therapy.

Unwillingness for Therapy with Interferon

Patients may be unwilling for further courses of interferon therapy if they have experienced severe side effects during previous rounds of therapy. With shortening of therapy to 12 weeks, side effects are usually mild and well tolerated. Other patients may be unwilling due to misapprehensions based on hearsay or browsing on the net and need appropriate counseling and reassurance. Despite unpleasant side effects, at present interferon continues to be an important component of regimens for patients with genotype 3 HCV infection and should not be given up without a sound reason.

Monitoring during Treatment

Monitoring during treatment is aimed at monitoring for adverse effects of treatment and monitoring for treatment efficacy. Patients on Sof/Peg-IFNα/RBV therapy are followed at 2 weeks and subsequently every 4 weeks till completion of therapy. At each visit patients should be assessed for assessment of side effects such as flu-like symptoms, fatigue, depression, sleep disorder, irritability, dyspnea, headache, and injection site reaction. Patients should be assessed for infections, autoimmune reactions, hearing and visual disturbances, and interstitial lung disease. Need for contraception should be re-emphasized. Complete blood count at weeks 1, 2, and 4 after start of therapy and every 4 weekly thereafter while liver biochemistry and renal function should be monitored once in every 4 weeks. Thyroid function (TSH level) should be checked every 12 weekly. HCV RNA testing should be done at baseline, at 4 weeks, at 12/24 weeks (end of treatment), and at 12 weeks after the end of therapy.

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.

Recommendations for Choice of Available Therapy

Recommendations for Treating Genotype 3 CH-C

In India, INASL recommends the use of a triple combination of daily Sof (400 mg) with weight-based RBV (1000 mg in patients <75 kg and 1200 mg in patients ≥75 kg) and weekly Peg IFN-α (Sof/Peg-IFNα/RBV) for 12 weeks as an optimal regimen for interferon-eligible genotype 3 patients without cirrhosis, including treatment-naïve (TN-NC) and treatment-experienced (TE-NC) patients, as also for treatment-naïve patients with cirrhosis (TN-LC). It is an acceptable regimen for interferon-eligible genotype 3 patients with treatment-experienced cirrhosis (TE-LC).

Dual therapy with Sof/RBV for 24 weeks is an alternate regimen for interferon-eligible TN-NC, TN-LC and TE-NC patients but is suboptimal for interferon-eligible patients with TE-LC. For interferon-ineligible patients, Sof/RBV for 24 weeks is an optimal regimen for TN-NC while it is an acceptable regimen for TN-LC, TE-NC and TE-LC patients.

As has been highlighted earlier, unlike genotype 2, genotype 3 is not really an ''easy to treat'' genotype. The data from India also show that the response rates to Peg-IFNα/RBV therapy in genotype 3 are lower than those reported for genotype 2/3 from the west.[45,46]

In the only head-to-head comparison of the two regimens, the BOSON trial[31,] found that triple therapy yielded ~6–12% SVR advantage in all categories of patients over dual therapy. There was no difference between the two regimens with regard to grade 3–4 AEs, SAEs or treatment discontinuation due to SAEs. Virologic failure, particularly the frequency of treatment-emergent variants, was greater with the Sof/RBV regimens. Triple therapy has also been found to be effective in patients who relapse after dual therapy.[34] However, the advantages of an oral regimen with few side-effects, simple administration, easy monitoring, marginally lower cost of therapy and an acceptable SVR rate will attract widespread use of the 24-week Sof/RBV dual regimen. It is likely that physicians who are familiar with the use of interferon will favor the use of the 12-week triple regimen while those who have not used interferon much will favor the 24-week dual regimen until sufficient real-life data are generated.

Recommendations for Treating Genotype 1 CH-C

In India, INASL recommends the use of a triple combination of daily Sof (400 mg) with weight-based RBV (1000 mg in patients <75 kg and 1200 mg in patients ≥75 kg) and weekly Peg IFN-α (Sof/Peg-IFNα/RBV) for 12 weeks in interferon-eligible patients with genotype 1 infection. While this is a close-to-optimal regimen for treatment-naïve patients without cirrhosis (TN-NC), it is acceptable for treatment-naïve patients with cirrhosis (TN-LC) and for treatment-experienced patients with and without cirrhosis (TE-NC, TE-LC) since it is the only effective treatment option available for patients infected with HCV genotype 1 in India in 2015.

Globally, many combinations superior to this regimen are available and this recommendation is likely to be superseded once ledipasvir and/or daclatasvir become

available in India. The combination of Sof-RBV is suboptimal and should not be used in interferon-eligible patients infected with HCV genotype 1 in view of its poor efficacy in all subsets of patients, as shown by the limited available data. This combination is specifically prohibited by AASLD 2015[1], and EASL 2015[3], and is also not recommended by WHO 2015[2], or NICE 2015.[6] Dual therapy with Peg-IFNα and RBV for 48 weeks is obsolete and cannot be recommended.

Based on the high likelihood of availability of the fixed dose combination of Sof with ledipasvir (Sof/LDV) and, possibly daclatasvir (DCV), within the next 6 months in India, it may be prudent to defer treatment in all patients with genotype 1 CH-C patients who can wait for 6 months. Those who cannot wait for treatment and are interferon-eligible, such as patients with compensated liver cirrhosis, should be treated with the triple regimen of Sof/Peg-IFNα/RBV. Sof with RBV may be used only for those patients who cannot wait and are ineligible for or intolerant to Peg-IFNα, such as those with decompensated hepatitis C-related liver cirrhosis, recurrent hepatitis C after liver or renal transplantation or after other solid organ or hemopoeitic stem cell transplantation.

Recommendations for Treating Genotype 2 CH-C

Patients infected with HCV genotype 2 must be treated with daily Sof (400 mg) and weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 12 weeks. Therapy should be prolonged to 16 or 24 weeks in patients with cirrhosis, especially if they are treatment-experienced. Sof with Peg IFNα-RBV (Sof/Peg-IFNα/RBV) for 12 weeks should be reserved for treatment-experienced cirrhotics i.e. those who have relapsed after Peg-IFNα/RBV therapy or for those who relapse after 12 weeks of Sof-RBV therapy.

Management of Other Genotypes

There are recent reports of genotype 4 from India.

Recommendation. Patients infected with HCV genotype 4 can be treated with a combination of daily Sof (400 mg), weekly Peg-IFNα and daily weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively) for 12 weeks.

The dual regimen of Sof/RBV for 24 weeks is an alternate/acceptable option for these patients.

Genotypes 5 and 6 are rare in India and should be managed like genotype 1. Patients with genotypes 5 and 6 should be treated with triple therapy with Sof plus Peg-IFNα/RBV.

Recommendation. Patients infected with HCV genotype 5 or 6 can be treated with a combination of weekly Peg-IFNα, daily weight-based RBV (1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively), and daily Sof (400 mg) 12 weeks.

Genotype wise recommendations for management of CH-C in India are given in Table 7.

Table 7 INASL Recommendations for Management of CH-C in India.

	Treatment-naive no cirrhosis	Treatment-naive compensated liver cirrhosis	Treatment-experienced no cirrhosis	Treatment-experienced compensated liver cirrhosis
Genotype 1				
Triple drug therapy[a]	Optimal regimen	Acceptable regimen	Acceptable regimen	Acceptable regimen
Dual drug therapy[b]	Suboptimal regimen[c]	Suboptimal regimen[c]	Suboptimal regimen[c]	Suboptimal regimen[c]
Genotype 2				
Triple drug therapy[a]	–	–	–	For 12 weeks
Dual drug therapy[b]	For 12 weeks	Extend to 16/24 weeks	For 12 weeks	Extend to 16/24 weeks
Genotype 3				
Triple drug therapy[a]	Optimal regimen	Optimal regimen	Optimal regimen	Acceptable regimen
Dual drug therapy[b]	Alternate regimen[d]	Alternate regimen[d]	Alternate regimen[d]	Suboptimal regimen[d]
Genotype 4				
Triple drug therapy[a]	Optimal regimen	Optimal regimen	Optimal regimen	Optimal regimen
Dual drug therapy[b]	Alternate regimen[d]	Alternate regimen[d]	Alternate regimen[d]	Alternate regimen[d]
Genotype 5 & 6				
Triple drug therapy	Optimal regimen	Optimal regimen	Acceptable regimen	Acceptable regimen

[a]*Triple drug therapy*: Sof/Peg IFN-α/RBV for 12 weeks for interferon eligible patients.
[b]*Dual drug therapy*: Sof/RBV for 24 weeks.
[c]Suboptimal except for interferon-ineligible patients who cannot wait.
[d]Optimal/acceptable for interferon-ineligible patients.

Management of HCV in Special Situations

Some common special situations are listed in Table 6. A common strand that runs through their management protocols is the need for IFNα-free regimens, due to difficulty in using Peg IFN-α in almost all special groups, except in those with HBV-HCV co-infection. With currently available options in India, dual drug therapy with Sof-RBV remains the only option in most of these patients.

Decompensated Cirrhosis

The main aims of treating patients with decompensated liver disease are to cure HCV infection, thus preventing graft infection after liver transplantation (LT) and to stabilize or improve liver function, reversing decompensation sufficiently to defer LT or even to delist patients listed for LT.

Peg-IFNα/RBV treatment had limited efficacy and was poorly tolerated in patients with decompensated liver disease. SVR rates, even with a low accelerating dose regimen (LADR) for IFNα therapy, were around 25%.[47] Importantly, only a small minority of HCV-related decompensated cirrhotics was eligible for Peg-IFNα/RBV, which can be given only to patients with reasonable liver function [Child-Turcotte Pugh (CTP) score ≤7, Model for End-Stage Liver Disease (MELD) score ≤18), such as patients with hepatocellular carcinoma(HCC) and good liver function awaiting LT. In patients with more advanced disease, IFNα-based therapy can result in serious adverse events such as bacterial infections, cytopenias, and worsening decompensation.

The arrival of DAA has made it possible to treat patients with decompensated cirrhosis using interferon-free regimens before and after LT.

Curry et al.[48] demonstrated that Sof and RBV given before LT resulted in good post-transplant virological response (PTVR) and prevented HCV recurrence. They evaluated 61 patients with genotype 1 or 4 HCV related cirrhosis and HCC who received Sof/RBV for up to 48 weeks before LT. 75% of the patients were CTP grade A and in all cases MELD score was <15. 43 of 46 (90%) undergoing LT had undetectable HCV-RNA (<25 IU/mL) at the time of LT. HCV RNA remained undetectable at 12 weeks after liver transplantation (PTVR12), in 70% (30/43) cases, indicating an absence of hepatitis C recurrence. Recurrence related inversely to period for which HCV RNA had remained undetectable before LT. Patients in whom HCV RNA had been undetectable for >30 days before LT had 95% chance of achieving PTVR12.

While there are data on the use of DAA in cirrhotic patients with compensated liver disease,[49–52] there are limited data on safety and efficacy of DAAs in patients with decompensated liver disease and those on the waiting list for LT. Afdhal et al.[53] randomized 50 HCV-related cirrhotic patients with portal hypertension and compensated cirrhosis (Child A or B) into immediate treatment (SOF plus RBV for 48 weeks) or observation period cohorts (treatment after 24 weeks of observation). After 24 weeks, patients in the treatment arm had improvement in platelet count, albumin levels and resolution of ascites and hepatic encephalopathy, and MELD scores.

While regression of advanced F4 fibrosis and even histological cirrhosis has been documented in CH-C after SVR, reversal of advanced cirrhosis with distortion of microvasculature and portal hypertension has not been documented so far and appears unlikely.[54,] Delisting from the LT list has been reported in only one patient.[55] Patients with decompensated cirrhosis may not tolerate DAAs, especially in the presence of impaired renal function. The possibility of deterioration of liver function on therapy, either due to a progressive disease or due to unforeseen complications of therapy, is very real.

Ongoing trials are examining the effectiveness of DAA prior to and after liver transplantation. The SOLAR-1 trial showed improvement in Child and MELD score in 108 patients with genotype 1 HCV related cirrhosis (Child B and C) treated with Sof and ledipasvir.[56] Results of studies with combinations of DAAs, as also availability of the newer DAAs, are eagerly awaited.

Management of HCV after Liver Transplant

Post-transplantation HCV recurrence is universal. Graft reinfection can lead to graft fibrosis, cirrhosis, and decompensation. After LT, progression of recurrent HCV disease is accelerated, response to Peg-IFNα-based antiviral therapy poorer, side effects more frequent, and therapy poorly tolerated compared with the non-transplant population.[57–59] However, successful therapy has been shown to have a positive impact on both graft and patient survival.[60]

The arrival of DAA allows IFNα-free treatment regimen in HCV-infected liver transplant patients. Charlton et al.[61] treated 40 patients with recurrent hepatitis C post-liver transplant due to genotype 1 in 85% with bridging fibrosis/cirrhosis in 63%. SVR12 rate was 70% with Sof and RBV for 24 weeks, showing that Sof/RBV for 24 weeks was an effective and well-tolerated interferon-free treatment for post-transplantation HCV infection.

The beneficial effect of Sof and RBV therapy after LT has also been demonstrated in other studies.[40,62]

Management of HCV in HIV co-infection

HIV infection is associated with advanced liver fibrosis and cirrhosis in patients with HCV 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.[63,] Eradication of HCV with therapy is associated with a regression of liver fibrosis and improved survival in HIV/HCV co-infected patients.[64]

The indications for HCV treatment in co-infected patients are identical to those in patients with HCV

mono-infection. Early in the course of HIV infection, patients are not on anti-retroviral therapy (ART) and drug interactions are not a consideration. Patients with a CD4 relative percentage >25% are more likely to achieve SVR than those with a lower CD4 percentage with IFNα-based therapy.[65] In patients with CD4 cell count <350 cells/μl, ART should be initiated first, beginning anti-HCV treatment only after improving CD4 cell count to >500/μl. However, with DAA therapy, strong immune system is less important and treatment is less likely to be affected by the CD4 count.

In patients on anti-retroviral drugs, drug interactions between DAA and HIV antiviral drugs need to be looked at critically when initiating therapy in HIV/HCV co-infected drugs. Simeprevir has significant drug interactions with efavirenz and darunaprevir/ritonavir. The concomitant administration of RBV and didanosine may result in mitochondrial toxicity leading to hepatomegaly/steatosis, pancreatitis, and lactic acidosis. Concomitant zidovudine use enhances the risk of RBV-associated anemia and should be avoided. Sof is an ideal drug as there are very few significant drug interactions. Sof is not recommended with tipranavir as this drug induces P-gp.[66]

The choice of Sof and RBV with or without Peg-IFNα is based on the same principles as in HCV mono-infected patients, keeping drug interactions in mind. The PHOTON-2 trial evaluated efficacy and safety of Sof plus RBV in patients with HIV and HCV co-infection. The trial enrolled 275 stable HIV and chronic HCV genotypes 1, 2, 3, and 4, including those with compensated cirrhosis. All patients received 24 weeks of Sof and RBV except treatment-naive patients with genotype-2 HCV, who received a 12-week regimen. Overall rates of SVR12 were 85% in patients with genotype-1 HCV, 88% genotype-2 HCV, 89% in genotype-3 HCV, and 84% in genotype-4 HCV. Response rates in treatment-naive patients with HCV genotypes 2 or 3 (89% and 91%, respectively) were similar to those in treatment-experienced patients infected with those genotypes (83% and 86%, respectively).[67]

Although liver fibrosis generally improves following HCV cure in patients with HIV/HCV co-infection, fibrosis progression may occur in association with uncontrolled HIV replication and prolonged exposure to protease inhibitors. Hence, periodic assessment of liver fibrosis is warranted after SVR and screening for hepatocellular carcinoma should continue in co-infected patients with advanced liver fibrosis.[68]

Management of Hepatitis B Virus (HBV) and HCV co-infection

The incidence of co-infection in a chronic liver disease population in India has been variously reported between 3 and 16%.[69–71] However, data are sparse and non-representative. Expert opinion says that the incidence of co-infection in India is around 5%.

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.[72–74] There is a potential risk of HBV reactivation during treatment or after clearance of HCV.[74,75] Therefore, it is mandatory to monitor HBV DNA levels during and after therapy for HCV. Any HBV reactivation must then be treated with nucleos(t)ide analogs.

Management of HCV in End Stage Renal Failure (ESRD) and Renal Transplant Recipients

Treatment is difficult in patients with CHC and ESRD due to altered drug pharmacokinetics, increased susceptibility to drug-related toxicity, the requirement for renal transplantation, and a modified course of disease. Sof is contraindicated in ESRD. RBV is also avoided in the treatment of ESRD patients with CH-C, though several studies have shown that combination of either conventional IFNα or Peg-IFNα with low-dose RBV (200 mg three times per week to 200 mg daily) was feasible while treating ESRD patients with CH-C.[76–79] However, IFNα-based therapies are poorly tolerated and have limited efficacy. DAA that are safe in patients with severe renal disease (simeprevir, daclatasvir, the combinations of paritaprevir, ritonavir, ombitasvir and dasabuvir or grazoprevir and elbasvir) are not available in India. Currently, the only treatment option available in India for these patients is Peg-IFNα as monotherapy or with very low dose of RBV.[80,81] IFNα-based therapy cannot be given after renal transplantation as it may lead to graft rejection.

Increasingly, patients with ESRD and CH-C without cirrhosis are being counseled to proceed to renal transplantation while still viremic, with or without prior treatment of HCV infection for 12 weeks , in the expectation that therapy with Sof/RBV or other Sof-based regimens can be started after renal functions improve following successful renal transplantation. However, results with this approach have not yet been reported in any large case series. Many centers continue to adhere to their policy of not transplanting patients with ESRD and CH-C until they are aviremic.

CONCLUSIONS

There is a large burden of HCV infection in India. The current consensus on guidance for treatment of CH-C summarizes the INASL recommendations for management of HCV in India with currently approved, available drugs. 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 many of the DAA recommended by other

guidelines. Some other DAAs (ledipasvir, daclatasvir) are likely to be approved and become available in 2016. Once they are available, cost of the newer DAA will be a significant factor in their widespread use. The current guidance will be updated once other newer drugs are licensed, more data on treatment of genotype 3 HCV with newer combinations become available and as 'real-life experience' with use of DAAs accumulates in India.

CONFLICTS OF INTEREST

The authors have none to declare.

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