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Review Article

Treatment of chronic hepatitis C: What is new?

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ABSTRACT

Hepatitis C Virus infection is a global problem that leads to development of chronic hepatitis, cirrhosis and hepatocellular carcinoma. So far this infection was being treated with interferon and ribavirin combination which has a large number of adverse effects. Last few years have seen availability of a large number of new molecules that are revolutionising the treatment of hepatitis C. Some of these newer drugs like sofosbuvir have been called game changer because they have changed the way we think of HCV treatment. The cost and availability of these newer drugs in India remains a problem so far. Efforts are on to bring these drugs within the reach of people at an affordable cost, but it is not clear as to how much time it will take. Till then, in our setting, we may continue to recommend the treatment that was standard of care for whole world before these game changers came in. In fact we also explore cheaper options, which are equally effective to make treatment within reach of poorer patients. It may be prudent to withhold treatment for patients with low levels of fibrosis (F1 or F2, with genotype 1 or 4 infection), 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.

1. Introduction

The management of chronic hepatitis C (CH–C) is rapidly evolving and recent introduction of Sofosbuvir in the armamentarium has brightened the prospects for patients' suffering from HCV infection. So far, the standard of care for most genotypes of HCV infection was treatment with a combination of pegylated interferon alpha (Peg-IFNα2) and ribavirin with or without addition of first generation protease inhibitors. This later therapy led to response rates around 50–80% in various genotypes. The therapy though successful to some extend was associated with several undesirable adverse effects making the regimen uncomfortable and even dangerous in some situations. Newer 'directly acting antiviral' (DAA) drugs are safer and highly effective in achieving cure but have brought in different kind of controversies.

There are currently multiple guidelines on the management of CH–C, which have been issued by leading authorities.[1–4] In Indian setting, one needs to consider type of genotype, the stage of disease and cost/affordability of treatment before implementation of any such guideline for the management of CH–C. The most prevalent genotype of HCV in India is genotype 3 unlike in western countries where

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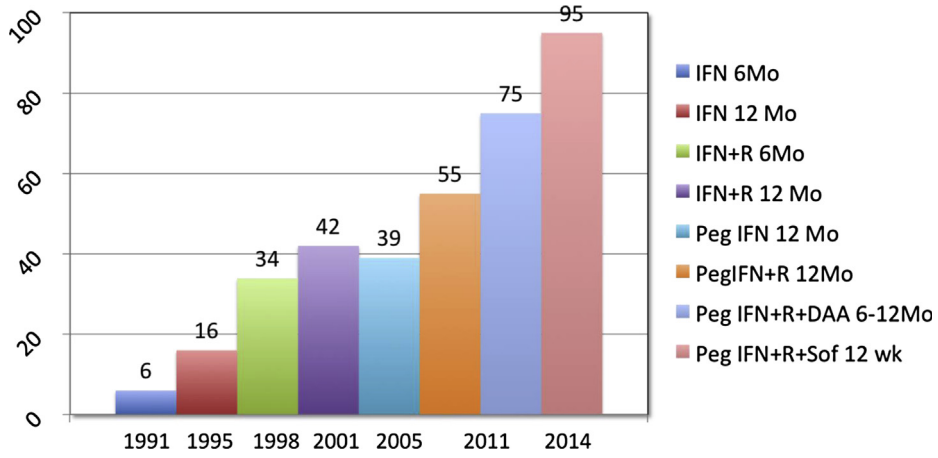

Fig. 1 – Sustained viral response rates for hepatitis C treatment over years, as the treatment has evolved. Figure shows mainly the results related to genotype 1, which is more commonly seen in Western countries. Numbers near the top of bars indicate response rates in percentage, while numbers along the horizontal axis above indicate year of introduction of regimen. Note: IFN = Interferon, PegIFN = Pegylated interferon, Sof = sofosbuvir, Mo = months and wk = weeks.

genotype 1 is more common. Most guidelines have clubbed genotype 2 and 3 together and labeled them easy to treat often for shorter duration and with lower and flat dose of ribavirin (800 mg/day). Our experience shows that genotype 3 is associated with higher steatosis, has a more rapid progression to fibrosis,[5] and has higher incidence of hepatocellular carcinoma.[6] Its treatment responses are poorer as compared to genotype 2 and therefore it needs to be considered separately.

1.1. *Evolution of HCV treatment so far*

The treatment of hepatitis C virus (HCV) infection was started even before the virus was discovered when it was called a parentrally transmitted non-A, non-B virus.[7] Initial results of treatment were measured as a durable normalization of transaminases and were seen in about 10% of patients without a relapse. In 1991 ribavirin was discovered and was shown to have antiviral effect against Flaviviruses.[8] Around this time, we also learned that virus has six genotypes, which behave in different manner and have different patterns of response to treatment.[4] A combination of ribavirin with interferon alpha increased therapeutic responses to around 40%.[9] Some time later, pegylated forms of interferon were developed and it boosted the sustained virological response (SVR, as the response is now measured after discovery of HCV RNA) to around 55%.[10] Soon thereafter in-vitro models of HCV replication were developed and the full cycle of HCV replication and its enzymes was understood which made it possible to design newer drugs to interfere with RNA replication.[11] In the year 2011, first generation of antiproteases, Boceprevir and Telaprevir were added to Pegylated interferons + ribavirin (PR) regimen and it increased the SVR by additional 25–30%. Latest introduction of Sofosbuvir has taken the response rates to 90% and above.[12] (Fig. 1) The results with newer drugs are so good that it may be worthwhile waiting for them to become available in many situations, rather than starting treatment with available drugs.[13]

The reason for suggesting this strategy is abundance of adverse reactions with existing regimens. Pegylated Interferon and ribavirin (PR) combination therapy for CH–C produces a number of troublesome side effects, which include fatigue, influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms such as depression. Combination therapy with pegylated interferons (peg-interferon alpha-2a and alpha-2b) yields an adverse event profile similar to standard interferon. Some 10–14% patients may discontinue therapy on account of such side effects.[14] Most adverse events however can be safely and effectively managed by dose reduction using predetermined criteria. The most common reason for dose reduction is hematologic abnormalities, such as anemia, thrombocytopenia and neutropenia, with the latter two more frequent with peg-IFNα2 treatment. If one adheres to a prescribed treatment regimen, better antiviral responses are achieved. Strategies to maximize adherence have been developed with selective use of hematopoietic growth factors to ameliorate hematologic abnormalities.[15] First generation protease inhibitors Telaprevir and Boceprevir have added their own side effects to above list. They can enhance fatigue, anemia nausea and add diarrhea, anal itching, change in sense of taste and distressing skin rashes.[16]

However, so far, treatment has been recommended with above drugs despite adverse effects because of benefits it can give to patients. Questions have been raised about usefulness of above regimes. There were two main reasons why usefulness of this therapy was doubted. Firstly, Cochrane database systematic review had shown that SVR as a virological biomarker is universally used to evaluate treatment efficacy in both clinical practice as well as in drug development. Conclusive evidence for the clinical benefit of antiviral therapy or validity of SVR as surrogate marker, as derived from trials randomizing patients to a treatment or control arm, is lacking.[17] Secondly, 'hepatitis C antiviral long-term treatment against cirrhosis' (HALT-C) trial recently showed an increased mortality rate among interferon treated patients compared to untreated controls. Therefore, the recommendation to treat

Table 1 – Newer drugs for treatment of Hepatitis C.

I. Host targeting agents (act on various targets in the host response to the virus)
  a. Immuno-modulators: Newer Interferons, Thymosin
  b. Cyclophilin inhibitors: Alisporivir, NIM-111, SCY-835
  c. Micro-RNA sequestering agents: Miravirsen
II. Directly acting agents (act against the virus at various steps in viral replication)
  a. NS3 Protease inhibitors: Telaprevir, Boceprevir, Simeprevir, Faldaprevir, Asunaprevir, ABT-450, MK 5172, Sovaprevir and ACH-2684
  b. NS5A inhibitors: Daclatasvir, Ledipasvir, ABT-267, GS-5816, ACH-3102, PPI-668, GSK-2336805, samatasvir, MK-8742
  c. RNA Polymerase inhibitors
    i. Nucleosides: Sofosbuvir, vx-135, IDX-20963, 791325, ACH-3422
    ii. Non-nucleoside: ABT-333, Deleobuvir, BMS-, PPI-383, GS-9669, TMC-647055

patients with chronic HCV infection was being challenged by some. Detailed analysis however, showed that the possible harmful effect of long-term low-dose pegylated interferon monotherapy, as was observed in the HALT-C trial cohort, couldn't be extrapolated to potentially curative short-term treatment regimens. Moreover, several studies have shown an association between SVR and improvements in health-related quality of life, hepatic inflammation and fibrosis, and portal pressure as well as a reduced risk for hepatocellular carcinoma (HCC), liver failure and mortality.[18]

1.2. *Development of newer drugs*

As mentioned earlier, once in-vitro models of HCV replication were available and the full cycle of HCV replication and its enzymes was understood, designing newer methods of arresting replication of virus were vigorously pursued and it did pay rich dividends. A large number of drugs have been developed or are in pipeline of which first two have received FDA approval a few months back (Table 1). It has been a practice to use these drugs in various combinations to achieve optimum effect. A brief account of some of these drugs and clinical results of trials using them are presented below.

1.2.1. *Host targeting agents*

This group of drugs act on various targets in the host response to the virus. It includes three subgroups of drugs:

1.2.1.1. *Immuno-modulators*. Interferon is the best known immunomodulator and there has been constant endeavor to improve on its actions. About two decades back, pegylated interferons were made which were definite improvement over then existing conventional interferons in terms of clinical efficacy. Next big step may have been discovery and initial description of the interferon-lambda (IFN-lambda) family in early 2003. There are 3 IFN-lambda genes that encode 3 distinct but highly related proteins denoted IFN-lambda1, -lambda2, and -lambda3. These proteins are also known as interleukin-29 (IL-29), IL-28A, and IL-28B, respectively. Collectively, these 3 cytokines comprise the type III subset of IFNs. They signal through a heterodimeric receptor complex that is different from the receptors used by type I (interferon alpha and beta) or type II IFNs (interferon gamma). Consistent with their antiviral activity, expression of the IFN-lambda genes and their corresponding proteins is inducible by infection with many types of viruses. IFN-lambda receptors are largely restricted to cells of epithelial origin.[19] In combination with ribavirin interferon lambda was used for HCV treatment associated with a comparable SVR 24 (sustained viral response after 24 weeks of stopping treatment) rate in patients with HCV genotype 2, 3 with fewer musculoskeletal and flu-like symptoms, less hematologic toxicity and fewer dose modifications. The primary dose-limiting toxicities associated with Lambda were >5xULN ALT and bilirubin elevations, which were less common with 180mcg dose and resolved with dose modification or discontinuation.[20,21]

1.2.1.2. *Cyclophilin inhibitors*. Several drugs are being developed in this group, which includes Alisporivir (debio 025), NIM-111, SCY-835 and so on. Cyclophilin A is a host cellular protein, which is a cofactor for HCV replication, interacting with NS5A, NS5B, NS2 at various stages. These drugs work by preventing cyclophilin A recruitment into replication complex and by interfering with NS5B polymerase activity. They also neutralizes NS2 and NS5A activities and inhibits assembly and release of viral particles. Initial trials using these agents as adjunct to existing therapy have been very promising.[22–24]

1.2.1.3. *Micro-RNA sequestering agents*. Micro-RNAs (miRNAs) are small, endogenous, noncoding RNAs that direct post-transcriptional regulation of gene expression. One of them, Micro-RNA-122 (miR-122) binds to two closely spaced target sites (S1 and S2) in the 5′ noncoding region of the HCV genome and thereby promotes the propagation of HCV RNA. Miravirsen, a nucleic acid–modified antisense oligonucleotide, sequesters mature miR-122 in a highly stable heteroduplex, which results in the functional inhibition of miR-122. In one study, the use of Miravirsen in patients with chronic HCV genotype 1 infection showed prolonged dose-dependent reductions in HCV RNA levels without evidence of viral resistance. During follow up, HCV RNA was not detectable 1 patient in 5 mg group and in 4 in 7 mg group. There were no major adverse effects.[25] A word of caution, miR-122 is a tumor suppressor gene for HCC, hence, a possibility that it may promote HCC cannot be ruled out.

1.2.2. *Directly acting agents*

Directly acting antiviral (DAA) drugs act against the HCV virus at various steps in viral replication and some exciting developments have been noticed in this group. They have been sub classified according to the HCV RNA product that they interfere with.

1.2.2.1. *NS3/4 protease inhibitors*. NS3/4 proteases act at a crucial stage of HCV life cycle by cleaving the polyprotein transcribed from of HCV RNA, at a site between non-structural

protein 3 and 4. First generation drugs such as Telaprevir and Boceprevir were approved by FDA in mid 2011 and its use enhanced the SVR rates of HCV therapy from around 55% to 75% in genotype 1 infections. These drugs had several drawbacks. It had to be taken multiple times in a day, had several unpleasant side effects, were specific for one genotype and had low genetic barrier to resistance. Second wave of first generation drugs correct most of these shortcomings and include Simeprevir, Faldaprevir, and Asunaprevir. Of these Simeprevir and Faldaprevir have already been approved by FDA and marketed, while other two are nearing completion of phase 3 clinical trials. Danoprevir, Sovaprevir, and ABT-450 are completing phase 2 trials. Second generation protease inhibitors appear even more exciting as they have macrocyclic structure, have broader genotypic coverage and have higher genetic barrier to developing resistance. These drugs include MK 5172, and ACH-2684 and are undergoing phase 2 clinical trials.

The evidence that led to approval of Simeprevir and Faldaprevir will be briefly mentioned here. Simeprevir has been tried in naive genotype 1 patients in two phase III randomized, double-blind, placebo-controlled clinical trials (named as QUEST 1 and QUEST 2). Patients in the treatment groups were given Simeprevir 150 mg daily for 12 weeks plus peg-interferon and ribavirin (PR) for 12 weeks, followed by PR only for either 12 or 36 weeks based on the individual's virological response to therapy. Patients in the control groups were given placebo for 12 weeks combined with PR for 48 weeks. Pooled results showed an SVR12 (sustained viral response for 12 weeks after stopping treatment) rate of 80% in the treatment group and 50% in the control group. SVR12 rates were significantly higher in the Simeprevir arm compared with the placebo arm in all other subgroup analyses. SVR rates were lower in patients with bridging fibrosis and cirrhosis.[26] In another paper treating HCV genotype 1 who were relapsers to prior PR therapy (PROMISE study) the SVR12 rate was 79% in the treatment group and 36% in the control group. Serious or major adverse reactions were observed with equal frequency in treatment and placebo arm.

Faldaprevir (FDV) was also evaluated amongst genotype 1 naive patients with hepatitis C in two multicenter, randomized, double-blind, placebo-controlled phase III studies ($N = 1314$ STARTVerso1 and 2 trials), which had a similar design. In treatment arms, patients achieving early treatment success (ETS) stopped all treatment at week 24. FDV plus PR increased SVR12 compared with PR alone from 50 to 72%. For some reason, SVR12 rates were lower in patients from North America (63%) than in patients from Europe (78%) and Asia (88%). In another trial (START-Verso3), efficacy and safety of FDV (240 mg QD) plus PR was tested in treatment-experienced patients with chronic HCV genotype 1 infection. This was also a multicenter, randomized, double-blind, placebo-controlled phase III trial ($N = 678$) and showed that FDV 240 mg plus PR was effective in treatment-experienced patients with HCV genotype 1 infection. The majority (87%) of prior relapsers receiving FDV achieved ETS and were eligible to stop treatment at week 24. The SVR12 rates in the placebo groups were very poor (14% prior relapsers; 3% prior partial responders). FDV 240 mg for 12 weeks was found to be as good as for 24 weeks. In yet another trial using Faldaprevir in HIV-HCV co-infected patients (STARTVerso 4), this drug was found to be highly efficacious and well tolerated. FDV resulted in a total SVR4 (sustained viral response at 4 weeks after stopping treatment) rate of 74% in all patients. The safety profile of FDV in all these trials was satisfactory. All these studies are available as abstracts and hence a recent review paper has been quoted.[26]

1.2.2.2. NS5A inhibitors. Nonstructural protein 5A (NS5A) of RNA genome product is comprised of 3 distinct domains (i) Domain I (aa 37–213) is essential for viral RNA replication; (ii) Domain II binds to cyclophilin A and has a role in antagonizing the innate immune response to HCV; and finally (iii) Domain III which plays an important role in viral assembly. There are several dugs being developed which can interfere with NS5A functioning and they include Daclatasvir, Ledipasvir, ABT-267, GS-5816, ACH-3102, PPI-668, GSK-2336805, Samatasvir, MK-8742. Some of these are being described below where interferon free regimens are being discussed. The strong points of some of these drugs are that they are pan-genotypic but they still have low genetic barrier to resistance against HCV genotype 1a.

1.2.2.3. RNA polymerase inhibitors. Inhibitors of nonstructural domain 5B (NS5B) which codes for RNA polymerase, are available in two classes: nucleoside polymerase inhibitors and non-nucleoside inhibitors. Nucleoside polymerase inhibitors include drugs like Mericitabine, vx-135, IDX-20963, 791325, ACH-3422 and Sofosbuvir. These can be regarded as close to natural substrates that bind the active site of NS5B and terminate viral RNA chain generation. They are pan-genotypic and have high genetic barrier of resistance. Non-nucleoside polymerase inhibitors (NNI) include drugs such as ABT-333, Deleobuvir, BMS-, PPI-383, GS-9669 and TMC-647055. These drugs act by binding to various allosteric sites, inducing conformational changes in the polymerase enzyme. They have low to medium antiviral efficacy and low genetic barrier of resistance. They are also genotype-dependent and subset-dependent and its efficacy is influenced by IL-28B polymorphisms.

As sofosbuvir has already been marketed, a brief description of evidence leading to its approval by FDA is presented. A series of trials named Neutrino, Electron, Proton, Neutron, Positron etc have been carried out and presented in various fora. The NEUTRINO trial was a phase III study of sofosbuvir plus PR in 327 naive patients infected with HCV genotypes 1, 4, 5 or 6.[27] Most of the patients who were included in the study had HCV genotype 1 (89%); 9% had genotype 4 and 2% had genotypes 5 or 6. All patients received sofosbuvir + PR for 12 weeks. Sofosbuvir was given orally at a dose of 400 mg, once a day. A total of 295 of the 327 patients (90%) had an SVR12. According to the HCV genotype: 89% for patients with HCV genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% (27/28) for those with genotype 4 had SVR. The single patient with genotype 5 and all six patients with genotype 6 in this trial had an SVR. Treatment discontinuation because of adverse events was uncommon among patients receiving sofosbuvir regimens, with rates of 2%. The most common adverse events in all study groups were fatigue, headache, nausea and insomnia.

Table 2 – Interferon free regimens for genotype 1and non genotype 1 patients with HCV infection in various groups such as naive patients, null responders, and cirrhotic patients. There are atleast 1500 drug trials on treatment of chronic hepatitis C in progress and only some have been outlined in this table (Note: SVR = sustained viral response; Geno = genotype).

Drugs regimens used	Trial name	HCV subgroup	Response rates (SVR)
ABT-450 + ABT-267	PEARL-1	Geno 1b-naive subjects and null responders all without cirrhosis	95.2% 90%
Faldaprevir + Deleobuvir	SOUND-C2	Naive Geno-1 (Including cirrhosis)	85% (67%)
ABT-450 + ABT-267 + ABT-333	AVIATOR	Naive Geno-1 (Including cirrhosis)	97.5% 93.3%
Sofosbuvir + Ledipasvir + Ribavirin	ELECTRON	Genotype 1	100%
Daclatasvir + Sofosbuvir		Genotype 1, 2, 3	86–100%
Daclatasvir + Asunaprevir + BMS-791325		Genotype 1	94%
Daclatasvir + Asunaprevir		HCV genotype 1 null responders, ineligible, intolerant to interferon	81–87%
Simeprevir + Sofosbuvir	COSMOS	Genotype 1-naive subjects which included cirrhotics, non-cirrhotic and prior null responders	94–96%
Sofosbuvir + Ledipasvir	LONESTAR	Genotype 1 Naive and previously treated	93–100%
Sofosbuvir + Ribavirin	FISSION	Genotype 2 and 3	56–97%
Sofosbuvir + Ribavirin	POSITRON	Genotype 2 and 3 Interferon intolerant or ineligible	78%
Sofosbuvir + Ribavirin	FUSION	Genotype 2 and 3 null responders	50–73%
Sofosbuvir + Ribavirin	VALENCE	Genotype 2 and 3: Naive or experience with or without cirrhosis	85–100%

1.2.3. *Interferon free regimens*

Most spectacular innovation in the treatment of HCV infection has been to use combinations of directly acting antivirals (DAA) in interferon free regimens.[28] A large number of trials have been held to show efficacy of DAA in various subgroups of patients. A summary of some of these trials is presented below.

1.2.3.1. *IFN-free regimen for genotype 1-naive and PR experienced subjects*. Proof of concept that interferon free regimens can work was provided by INFORM-1 trial.[29] Danoprevir (NS3/4A protease inhibitor) and Mericitabine (nucleoside analog NS5a inhibitor of HCV RNA-dependent RNA polymerase) were tried for two weeks followed by regular P + R regimen among HCV genotype 1 infection. There was 5 log reduction in HCV RNA level during first two weeks treatment and 44% patients became negative for HCV RNA. Results of some other IFN-free DAA regimens[30] in treatment-naive genotype 1 individuals are presented in Table 2 for naive and treatment-experienced patients of genotype 1, 2 and 3 infection.

SOUND-C2 trial used Faldaprevir (protease inhibitor) + Deleobuvir (polymerase inhibitor), with or without RBV in a Phase IIb study ($n = 362$) among treatment-naive HCV genotype 1 subjects (including patients with cirrhosis). There was SVR in up to 85% of HCV individuals infected with genotype 1b after 28 weeks of treatment. Patients with cirrhosis achieved SVR rates of up to 67%.[31] AVIATOR study used a combination of three Abbott molecules ABT-450 (a ritonavir-boosted protease inhibitor), ABT-267 (NS5A inhibitor), ABT-333 (NS5B polymerase NNI) with or without ribavirin.[32] Treatment was tried in non-cirrhotic treatment-naive subjects with genotype 1 infection and in prior PR null responders. SVR12 in treatment-naive subjects and null responders was 97.5% and 93.3% respectively. Response in genotype 1b was better than in those with genotype 1a infection and the treatment was well tolerated.

PEARL I trial used ABT-450/r and ABT-267 regimen in genotype 1b-naive subjects ($n = 42$) and null responders ($n = 40$) all without cirrhosis. SVR of 95.2% for treatment-naive subjects, and 90% for null responders was reported. The triple-DAA combination is currently being studied in Phase III clinical trials.[33] ELECTRON study is examining a 12-week therapy with sofosbuvir (NS5B nucleotide inhibitor) plus GS-5885 (NS5A inhibitor) and ribavirin in subjects with genotype 1 chronic HCV infection and has released it interim results. All patients (100%) achieved SVR 4. The combination was well tolerated in this study. The most common AEs were headache, fatigue, upper respiratory tract infection and nausea.

A phase II study was carried out using Daclatasvir (NS5A inhibitor) and sofosbuvir in HCV genotype 1, 2 and 3, with or without RBV, for 12 or 24 weeks of therapy, and with or without a week-long run-in period with sofosbuvir. Eighty-eight to 100% subjects achieved SVR12. Daclatasvir (NS5A replication complex inhibitor), Asunaprevir (NS3 protease inhibitor) and BMS-791325 (NS5B polymerase NNI) were given for 12 or 24 weeks in treatment-naive persons with genotype 1 chronic HCV infection. In the 24-week group, 94% achieved SVR4 while in the 12-week treatment group, SVR12 was achieved in 94% of patients.[33]

A phase III trial of Daclatasvir plus Asunaprevir evaluated IFN ineligible naive/intolerant and non-responders to prior IFN-based therapy in Japanese subjects with genotype 1b infection. The study reported SVR (24 weeks) rate of 81–87%.[34] In LONESTAR trial, patient with naive as well as previously treated genotype 1 patients were treated with Sofosbuvir plus Ledipasvir and showed 83–100% response rates in terms of SVR, and results were better in those without cirrhosis than in those with cirrhosis.[35] In COSMOS study Simeprevir plus sofosbuvir with or without ribavirin were tried for 12 or 24 weeks in genotype 1-naive subjects which included cirrhotics, non-cirrhotic and prior null responders. SVRs with 94–96% response was noted in different groups.[33]

Table 3 – Summary of recommendations for treatment of hepatitis C as issued by American Association for the Study of Liver (AASLD) and Infectious Disease Society of America (IDSA) in 2014. Treatment recommended is for treatment-naive patients and of special groups have not been included in the table (Note: CHC = chronic hepatitis C).

Type of infection in the patient	Treatment	Duration
Genotype 1 or 4 CHC	Sofosbuvir + peg-interferon alpha + Ribavirin	12 weeks
Genotype 2 CHC	Sofosbuvir + Ribavirin	12 weeks
Genotype 3 CHC	Sofosbuvir + Ribavirin	24 weeks

1.2.3.2. *IFN-free regimen for genotype non-1 subjects*. The FISSION study tried sofosbuvir plus RBV in naive subjects with genotype 2 and 3 HCV infection. Sofosbuvir–RBV has been shown to be non-inferior to PEG-IFN/RBV. An SVR occurred in 97% of subjects with genotype 2 and in 56% of those with genotype 3 in the group receiving sofosbuvir/RBV, as compared with response rates of 78 and 63%, respectively, in the group receiving PEG-IFN/RBV. A similar POSITRON trial was done in genotype 2 and 3 HCV-infected subjects who were interferon intolerant or ineligible. The rate of SVR at 12 weeks after treatment was 78% among subjects receiving sofosbuvir/RBV compared with 0% among those receiving placebo ($P < 0.001$).[33]

In FUSION study same regimen was used against previous null responders. The rates of SVR achieved were superior to the historical control rate of 25%, with rates of 50% in the 12-week group and 73% in the 16-week group ($P < 0.001$ for each comparison). Among subjects with cirrhosis who received 16 weeks of treatment, the rate of SVR was 66% (78% with genotype 2 HCV infection and 61% with genotype 3 HCV infection) as compared with 76% among subjects without cirrhosis (100% with genotype 2 HCV infection and 63% with GT3 HCV infection). On basis of these findings, American Association for the Study of Liver (AASLD) and Infectious Disease Society of America (IDSA) have revised their recommendations for treatment of hepatitis C and a summary their recommendations is presented in Table 3. Treatment of special groups has not been included in this discussion.[1]

1.3. *Prevalence and profile in India*

Approximately 150 million persons have HCV infection worldwide.[36–42] The prevalence of HCV infection in different areas of the world has been categorized as "high" (>3.5%), "moderate" (1.5%–3.5%), or "low" (<1.5%). India has been estimated to have a low to moderate prevalence of HCV ranging from 0.9 to 1.9%.[43,44] In one of the most systematically performed epidemiological study from India, Chowdhury et al[45] studied the prevalence of HCV in the rural Birbhum district of the state of West Bengal and found a prevalence of 0.87%. Another study from Mullanpur in the north Indian state of Punjab, India, mixed urban and rural population, Sood et al[46] screened 5258 subjects and found an HCV prevalence of 5.2%. The highest prevalence was noticed in the 40–60 years age group and there was significant clustering within families. A study from western India in rural Maharashtra by Chadha et al[47] also showed a low prevalence rate of 0.09%. Prevalence of HCV was 1.4% in patients attending gastroenterology camps in Hyderabad.[48] HCV prevalence was found to be higher in several tribal populations for example it is 7.89% of Lisu tribe,[49] 2.02% in Lambada tribe[50] and a variable prevalence of 1–14.4% in the seven central Indian tribes of Chhattisgarh.[51]

Transmission of HCV occurs due to transfusion of blood or blood products, intravenous drug use, unsafe therapeutic injections, occupational injuries by needle prick exposure or conjunctival transmission and surgical/health care related procedures including hemodialysis and organ transplantation. A community based surveillance study of IVDUs of Kolkata showed an increase of HCV infection from 17 to 80% over seven years despite an ongoing needle exchange programme.[52] Unsafe injection practices are a common cause of HCV spread in India. Among patients receiving multiple injections to treat Kala Azar, 31.1% had been found to have HCV infection.[53] The median fraction of HCV infections attributed to unsafe medical injections in India is 38%.[54]

While blood transfusion was a common source of HCV infection in past, the situation has changed today. The Govt of India has made screening for HCV mandatory only from 01 June 2001. Patients receiving dialysis have been found to have a high risk of HCV infection. The prevalence of anti-HCV antibodies in dialysis patients has been reported to vary from 4.3 to 46%.[55–61] Occult infection, of HCV has been reported to range from 79.16 to 90%.[62,63] The prevalence of HCV infection in renal transplant recipients in India has been reported in 26.2–55.9%.

Commonest genotype in India is genotype 3 ranging from 54 to 80% in North, West and Eastern parts of India,[64–73] while in South India, a higher prevalence of genotype 1 alongside genotype 3 has been reported.[74] genotype 4 has been reported in some cases from Southern and Western India[75] and genotype 6 infection was initially reported in two cases from Eastern India.[75]

1.4. *Recommended regimens for India*

Ideally the recommendations made by AASLD for American patients on basis of available evidence should also apply to Indian patients. However, in real life the situation is different. Firstly the new drug has been marketed in USA at a price approximately 1000 US dollars for one day treatment[76] and total cost of treatment for 12 weeks will work out to 84000 US dollars or approximately, or in our context, 16,80,000 for 24 weeks for genotype 3, which is the dominant genotype in India. In terms of Indian rupees, it comes to approximately Rs. 1,00,80,000 only. While from scientific standpoint, we are steadily moving towards a pill a day for cure of HCV infection, the prohibitive cost of drugs makes it out of reach of most patients, atleast in developing countries like India. Second and most important point is that this drug is still not available in India. It may be recalled that earlier two protease inhibitor drugs, Boceprevir and Telaprevir, have become obsolete without being marketed in India. Although, efforts are on to bring Sofosbuvir, the game changer in HCV treatment to India, it is not certain when will it become available and at what cost.

Apart from above facts that recommended drugs are just not available in India, there are several other reasons why

Western treatment guidelines such as AASLD recommendations cannot be used in India. Most Western guidelines are genotype 1 centric because that is the genotype most prevalent in those countries. We presume our patients will respond the way Americans or Japanese respond but it has been shown to be otherwise, because people are different and the virus is not the same. In Western guidelines genotype 2 and 3 are always clubbed together as easy to treat genotypes. The facts are actually different. genotype 3 has shown consistently poorer response than genotype 2. Moreover, genotype 3 infection is characterized by more rapid progression to fibrosis, higher occurrence of steatosis and higher progresión to HCC. Unlike genotype 1, the role of the IL-28B genotype testing in genotype 3 remains to be defined.

Since all Indian reports especially those from North India have shown predominantly genotype 3 infection; a strong need was felt to have Indian Guidelines for treatment of hepatitis C, which were appropriate for our situations.

2. Indian guidelines

To develop Indian Guidelines, a taskforce was constituted by Indian National Association for the study of Liver (INASL), which met on 02 March 2014 to develop consensus on management of HCV in Indian settings.[77] It was clear that newer drugs will become available in India sooner and later, but India needed clear guidelines to treat patients till the time these new drug combinations became available and were affordable by our patients. Some highlights of these guidelines are summarised below.

Firstly, Indian guidelines were genotype 3 centric and took into account the results of treatment from Indian subcontinent. Asians patients seem to have poorer response to interferon possibly due to an older age at presentation and having more advanced liver disease at presentation.[78] One study found that SVR was highest amongst Asians (Non-South) (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.[79] However, another study, found no difference in treatment response for Asian versus white European patients.[80]

Therapy with Peg-IFNα/RBV therapy in naive CH–C genotype 3 patients from North India[81] showed an SVR of 78.9% in low-dose Peg-IFNα and 92.6% in the standard high-dose Peg-IFNα group. Another study[82] showed SVR rate of 67% in treatment-naive patients with CH–C genotype 3 with standard for 24 weeks. Virological monitoring can identify optimal duration of treatment in genotype 3. Rapid virological response (HCV RNA negative at 4 weeks) can be used to decide the duration of therapy. Patients with RVR without any poor risk factors, can have their therapy shortened to 12–16 weeks, though response rates may be marginally lower than SOC. In a large multinational study, Manns et al[80] compared Peg-IFNα2b (1.5 μg/kg/wk) for 24 weeks (group A); Peg-IFNα2b (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. Since the cost of this treatment is also beyond the means of many patients, cheaper treatment options for Indian patients with CH–C were also explored. A multicentric, prospective, randomized controlled trial[83] compared 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 IFNα2b 3 MU OD + RBV 1000 mg/day was nearly identical to results reported in genotype 3 patients treated with Peg-IFNα (2a or 2b) + RBV for 24 weeks (SVR 67%) from a North Indian center.[82] Hence conventional interferon in place of Pegylated interferons in standard therapy is an economical and viable alternative.

As the whole world is talking about DAA, and AASLD 2014 guidelines[1] consider Peg-IFNα/RBV therapy as "Not Recommended"; Local compulsions dictate that we continue to use standard treatment regimes and even consider conventional IFN in the management of CH–C. It must be clearly understood that when 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.[84]

Another major deviation in Indian guidelines has been recommendation to consider defering treatment for certain groups. It was found that urgency to treat with currently available regimens is not there in certain group of patients such as those with low levels of fibrosis (F1 or F2) (especially those with genotype 1 or 4 infection). Similarly patients who are non-responders, IFN intolerant, decompensated liver disease, and those in special populations such as stable patients after liver and kidney transplantation, HIV co-infected patients and those with cirrhosis od liver, will be much better off if they wait for much safer therapies to be launched in India.

3. Conclusions

Treatment of hepatitis C virus infection has undergone a sea change over past few months. Several highly effective drugs have been introduced in treatment of HCV over past year and many more are in the pipeline. Some of these drugs like sofosbuvir have been called game changer because they have changed the way we think of HCV treatment. However, at the time of going to press, the cost of these drugs appeared prohibitive. Moreover, these drugs have not yet been marketed in India. Although efforts are on to bring these drugs within the reach of people at an affordable cost, it is not clear as to how much time it will take. Till then we may continue to recommend the treatment that was standard of care for whole world before these game changers came in. It may be prudent to withhold treatment for certain group of patients in the hope that newer drugs will soon become available in our country at an affordable cost. This group includes patients with low levels of fibrosis (F1 or F2, especially those with genotype 1 or 4 infection), 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 od liver.

Conflicts of interest

The author has none to declare.

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