HEP-NET OPINION ABOUT THE MANAGEMENT OF PATIENTS WITH CHRONIC HEPATITIS C IN PAKISTAN IN THE ERA OF AVAILABLE DIRECT ACTING ANTIVIRALS

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ABSTRACT

In Pakistan, we have 4.9% prevalence of HCV in general population, with 79% genotype 3. Recently Sofosbuvir has been made available at compassionate price in Pakistan. Management of chronic hepatitis C includes counseling of HCV patients, their proper assessment to select those who need antiviral therapy, initiation of appropriate antiviral agents & duration of therapy, along-with careful monitoring for safety and efficacy. Hepatic status as well as previous history of HCV therapy needs to be taken in the consideration before starting antiviral therapy. Other factors include co-morbid conditions like obesity, DM, NASH, etc. Treatment of special populations like liver transplant patients, patients with HBV co-infection, chronic kidney disease and hemoglobinopathies need special considerations when initiating HCV therapy.

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INTRODUCTION

Hepatitis C is a global health problem. Around 160 million persons are infected with HCV worldwide. In Pakistan, we have 4.9% prevalence of HCV in general population[1]. Regarding distribution of HCV genotypes, 79% are genotype 3 (GT-3)[2] and most of the rest is genotype 1 (GT-1); genotypes 2, 4, 5 and 6 are less common. The diagnosis of hepatitis C is mostly incidental or related to cirrhosis and its complications.

The treatment of chronic hepatitis C (CHC) has undergone revolutionary change with the availability of first generation earlier and recently the second generation direct acting antiviral agents (DAAs). Therefore need was felt to update all those healthcare professionals who are practically involved in the management of CHC. This "Hep-Net Opinion" is based upon the current recommendations of international and national[3-6] clinical practice guidelines on CHC, focusing on the most prevalent genotypes in our country (GT-3 and GT-1).

American and European authorities (FDA and EMA) have approved following second generations DAAs to be used in clinical practice:

- **Simeprevir**– approved against genotype 1
- **Harvoni** (combo pill containing Sofosbuvir & Ledipsavir)– approved against genotype 1
- **Viekira Pak** (combo pill containing Ombitasvir, Paritaprevir & Ritonavir tablets co-packaged with Dasabuvir tablets)– approved against genotype 1
- **Daclatasvir** – approved against genotype 1, 3 and 4
- **Sofosbuvir**– approved against genotype 1, 2, 3 and 4. It is effective in treatment-naive, treatment-experienced, HIV-coinfected, patients with compensated cirrhosis, and in patients with hepatocellular carcinoma meeting Milan criteria awaiting liver transplantation. Sofosbuvir has been studied in a wide range of populations including persons 65 and older, persons with mild to moderate renal impairment. Recently Sofosbuvir has been made available at compassionate price in Pakistan

Assessment of Patients before initiation of HCV Therapy

This includes confirmation of chronic hepatitis C, looking for hepatitis B co-infection, virological assessment of hepatitis C, assessment of liver disease severity and eligibility for interferon therapy, and looking for comorbid conditions [5,6].

- **Confirmation of chronic hepatitis C:** Anti-HCV antibodies are the first line diagnostic test for HCV infection. In many regions of Pakistan, ICT kits with questionable sensitivity are still in use. It is recommended that anti-HCV by ELISA should be used for the initial screening of HCV infection. In suspected case of acute hepatitis C or in immunocompromised patients, HCV RNA testing should be the part of the initial evaluation.

After anti-HCV antibodies are found to be "Reactive" by ELISA, HCV RNA should be determined by a sensitive molecular assay (lower limit of detection of <15 IU/ml). If HCV-RNA is reported to be "Not-detected", it should be retested after 3 months to confirm "spontaneously recovered case of HCV" status.

- **Looking for HBV co-infection:** As hepatitis B and C have same modes of transmission; therefore B & C co-infection is not uncommon in our clinical practice. We have 4.9% prevalence of HCV and 2.5% prevalence of HBV in our general population[1]. Therefore all CHC patients must be screened for hepatitis B virus (HBV) by testing HBsAg by ELISA.

If HBsAg is found to be "Reactive" by ELISA, HBV-DNA quantitative PCR, HBeAg & anti-HBe, along-with anti-HDV should be tested, to determine whether HBV infection is active or not, and to look for concomitant hepatitis D virus (HDV) infection. In high-risk patients, human immune-deficiency virus (HIV) testing should also be performed.

- **Virological assessment of hepatitis C:** It includes:
  - HCV RNA detection and quantification by a sensitive assay (lower limit of detection of <15 IU/ml)
  - HCV genotyping prior to initiation of antiviral treatment to determine the choice and duration of therapy
- **Assessment of liver disease severity:** Chronic hepatitis C is essentially characterized by varying degree of hepatic fibrosis. In the absence of effective treatment, the fibrosis increases in severity from F1 to F4 grade and ultimately results in development of liver cirrhosis. Therefore, liver disease severity should be assessed prior to therapy. Identifying patients with cirrhosis is of particular importance, as their prognosis is altered and their treatment regimen may be adapted. Fibrosis stage should be assessed by non-invasive methods; liver biopsy should be considered only to look for potential additional aetiologies.
  - Based on the abundant literature, liver stiffness measurement (LSM) by FibroScan transient elastography (TE) in chronic hepatitis C has high sensitivity in identifying patients with significant fibrosis (≥F2) and no fibrosis (<F2).
  - If TE by FibroScan is not available, some reasonable idea of advanced liver fibrosis /compensated cirrhosis (F4) can be made by combining coarse parenchyma of liver and splenomegaly on ultrasound with low platelet count, AST to platelet ratio index (APRI), low serum albumin, prolonged PT-INR, evidence of esophageal varices on endoscopy, and of course, clinical peripheral stigmata of chronic liver disease on physical examination.

It is worth mentioning that the absence of significant fibrosis (i.e F0 and F1) may be used a safety parameter

if antiviral needs to be delayed because of pregnancy, lactation, or unaffordability, etc.

Since significant fibrosis may be present in patients with repeatedly normal ALT, evaluation of disease severity should be performed regardless of ALT patterns.

- **Assessment of eligibility for interferon therapy:** Patient must be assessed for the eligibility for interferon-based therapy. Treatment of CHC with IFN+RBV containing regimens is absolutely contra-indicated in:
  - Pregnant and lactating women
  - Uncontrolled depression, psychosis or epilepsy
  - Marked anemia (baseline hemoglobin below 10 g/Dl)
  - Marked neutropenia (baseline neutrophil count below 1500/µL)
  - Marked thrombocytopenia (baseline platelet count below 75,000/µL)
  - Decompensated liver cirrhosis (CTP-class B and C, Tab 1); and
  - Severe concurrent medical disease(s)
- **Looking for comorbid conditions:** There are many co-morbid conditions which aid to the progression of liver disease, therefor it is mandatory to look for these and treat them before starting AVT. These conditions include:
  - Alcohol
  - Nonalcoholic steatohepatitis (NASH)
  - Diabetes mellitus (DM)
  - Drug induced liver injury (DILI)
  - Autoimmune disorders
  - Hemochromatosis, and
  - HIV infection
- **IL28B genotyping:** IL28B (recently known as interferon lambda-3) has three genotypes: CC, CT and TT. Patients with CC genotype respond better to IFN as compared to TT genotype. IL28B genotyping has variable role in making therapeutic decisions related to interferon based therapy in patients with HCV:
  - In GT-1&4, it predicts response in all patients
  - In GT-3, it predicts response in those patients who don't achieve RVR[7]
  - It has no role in IFN-free regimens (including Sofosbuvir)

Counselling of Patients before initiation of HCV Therapy

It is mandatory to educate and counsel all patients on the following aspects, before starting them on AVT:

- **General aspects of HCV:** These include
  - Natural course of HCV

Table 1: Child-Turcotte-Pugh Classification

Scoring: The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement			
Measure	**1 Point**	**2 Points**	**3 Points**
Total Bilirubin, mg/dL (<34µmol/L)	<2 (<34)	2 – 3 (34-50)	>3 (>50)
Serum Albumin, g/dL	>3.5	2.8 – 3.5	<2.8
PT-INR	<1.7	1.71 – 2.3	>2.3
Ascites	None	Mild	Moderate to Severe
Hepatic Encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (Refractory)
Interpretation: Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above			
Points	**Class**	**1-year survival**	**2-years survival**
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

PT-INR = Prothrombin Time and International Normalized Ratio

Table 2: Therapeutic options available for chronic hepatitis C patients in Pakistan

Patients without cirrhosis and with compensated cirrhosis (CTP-Class A)		
HCV Genotype	**IFN eligibility**	**Therapeutic Options**
Genotype 3 as well as Genotype 1	Eligible	PEG-IFN+RBV+SOF (12 weeks)
	Ineligible	SOF+RBV (24 weeks)
Patients with decompensated cirrhosis (CTP-Class B and C)		
Irrespective of HCV genotype, these patients should be referred to highly experienced HCV treatment providers (ideally in a liver transplant center) for treatment with SOF+RBV [with consideration of the patient's creatinine clearance and hemoglobin level] for up to 24 weeks / till liver transplantation, with close monitoring for the safety and efficacy.		

PEG-IFN = Pegylated-Interferon, RBV=Ribavirin, SOF=Sofosbuvir

Table 3: Therapeutic dosages of anti-HCV drugs (For Adults)

Drug	**Dosage**
PEG-IFNα2a	180 mcg, s/c, once a week
PEG-IFNα2b	1.5 mcg/kg body weight, s/c, once a week
Ribavirin	<75 kg: 1000 mg in divided doses
	>75 kg: 1200 mg in divided doses
Sofosbuvir	400 mg daily in a single dose

PEG-IFN = pegylated Interferon

Table 4: Therapeutic dosages of anti-HCV drugs (For Adults)

Patients Population	**Sustained Virological Response at 12 weeks (SVR12)**		
	Valence Study8	**Boson Study9**	
	SOF+RBV x 24weeks	SOF+RBV x 24weeks	SOF+RBV+pIFN x 12wks
IFN-Naïve Non-cirrhotics	95% (87/92)	90% (65/72)	96% (68/71)
IFN-Naïve Cirrhotics	IFN-Exp Non-cirrhotics	82% (18/22)	91% (21/23)
IFN-Exp Non-cirrhotics	87% (85/98)	82% (44/54)	94% (49/52)
IFN-Exp Cirrhotics	62% (29/47)	77% (26/34)	86% (30/35)

IFN=Interferon, Exp=Experienced

Renal Impairment	**CrCl/eGFR Level (mL/min/1.73 m2)**	**Interferon**	**Ribavirin***	**Sofosbuvir**
Normal	≥ 80	PEG-IFNα2a – 180 µg PEG-IFNα2b – 1.5 µg/kg	Standard	Standard
Mild	50-80			
Moderate	30-50	PEG-IFNα2a – 180 µg PEG-IFNα2b – 1 µg/kg	Alternating doses: 200 and 400 mg every other day	
Severe	15-30	PEG-IFNα2a – 135 µg PEG-IFNα2b – 1 µg/kg	200 mg daily	Well-established data not available
ESRD/HD	< 15	PEG-IFNα2a – 135 µg PEG-IFNα2b – 1 µg/kg IFN – 3 MIU 3x/wk		

*In ESRD/HD, Ribavirin dose needs to be carefully monitored. CrCl = Creatinine Clearance eGFR = Estimated Glomerular Filtration rate ESRD = End-Stage Renal Disease HD = Hemodialysis PEG-IFN = Pegylated Interferon IFN = Standard Interferon

- Disease status of the patient
- Alleviation of baseless worries and misbelieves associated with suffering from HCV infection
- Screening of other family members for HCV and HBV
- The measures to prevent spread of HCV to other family members and community
- Emphasis on good nutrition, avoidance of any dietary restrictions. The only avoidance is that of smoking and alcohol.

- **Important aspects of AVT:** These include
  - The aims of AVT
  - Common side-effects of AVT and general measures to cope with these
  - Proper schedule of AVT
  - Adherence to AVT
  - Regular follow-ups and monitoring for safety and efficacy of AVT
  - Use of double contraceptive methods including condoms

Basics of HCV Therapy

After CHC is confirmed, CHB co-infection is excluded, virological status of CHC, liver disease severity and eligibility for interferon therapy is properly assessed, and other comorbid conditions are looked for, antiviral therapy should be initiated, keeping in view the following important aspects in mind:

- **Goal of therapy** is to eradicate HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, and death. In patients with cirrhosis, HCV eradication reduces the rate of decompensation and will reduce the risk of HCC. In these patients surveillance for HCC should be continued.
- **Endpoint of therapy** is undetectable HCV RNA in a sensitive assay (<15 IU/ml) 12 and 24 weeks after the end of treatment (i.e. SVR).
- **General principle of therapy** is that all treatment-naïve and -experienced patients should be considered for therapy. Severity of liver disease has pivotal role in selecting patients for therapy, as explained below:
  - In patient with no or mild disease (<F2), antiviral therapy may safely be delayed, if there is some genuine reason.
  - In patient with significant fibrosis (≥F2), antiviral therapy needs to be initiated in the absence of absolute contraindication(s).
  - In patient with decompensated cirrhosis (CTP class B and C), antiviral therapy should not be withheld until there is absolute contraindication. Such patient must be referred to highly experienced HCV treatment provider (ideally in a liver transplant center) at earliest. AVT for such patient should be:
    - IFN-free therapy i.e Sofosbuvir and Ribavirin (SOF+RBV)
    - Given for up to 24 weeks/till liver transplantation
    - Close monitoring for the safety and efficacy of AVT is mandatory

Therapeutic Options for HCV in Pakistan

As Sofosbuvir is the only DAA available in Pakistan at present; therefore rest of the DAAs will not be discussed in this "Hep-Net Opinion". On the basis of latest recommendations of international clinical practice guidelines on CHC[5,6], two treatment options are available for chronic HCV patients in Pakistan (Table 2). Dosages of different drugs are given in Table 3.

- **HCV Genotype 3:** Daclatasvir and Sofosbuvir are the approved DAAs against genotype 3; as Daclatasvir is still not available in Pakistan, therefore the only option left for these patients is Sofosbuvir. Therapeutic options depend upon eligibility of interferon, as shown below:
  - Combination of Sofosbuvir, Ribavirin and Pegylated-Interferon (SOF+RBV+ PEG-IFN) for 12 weeks for interferon-eligible patients
  - Combination of Sofosbuvir and Ribavirin (SOF+RBV) for 24 weeks for interferon-ineligible patients

Dual therapy (SOF+RBV for 24 weeks) was evaluated in Valence study[8] in 2014 (Table 4). Triple therapy (SOF+RBV+PEG-IFN for 12 weeks) is better than dual therapy (SOF+RBV for 24 weeks) in all categories of genotype 3 patients as shown by Boson study[9], presented in EASL 2015 (Table 4); and therefore remains the preferred therapeutic option. Dual therapy (SOF+RBV for 24 weeks) should be given only to those patients who are ineligible or intolerable to interferon, or not willing for interferon.

- **HCV Genotype 1:** Harvoni, Viekira Pak, Daclatasvir and Simeprevir are the approved DAAs against genotype 1; as these agents are still not available in Pakistan, therefore the only option left for these patients is SOF+RBV+ PEG-IFN for 12 weeks. The dual therapy (SOF+RBV- 24 WK) should not be used, except in patients not eligible for interferon, till the other DAAs become available.

- **Treatment Failure Patients:** patients who fail on SOF-based therapy should wait for better drug combination to become available in future; but if they have advanced liver disease, alternate SOF-based therapy may be tried, as shown below:
  - SOF+RBV for 24 weeks in case of triple therapy failure cases
  - SOF+RBV+ PEG-IFN for 12 weeks in case of dual therapy failure (provided IFN-eligible)
- **Various Government & Non Governmental Support programs should prioritize allocation of resources for patients with significant fibrosis.**
- **Patients with decompensated cirrhosis (CTP-Class B & C):** Irrespective of HCV genotype, these patients should be referred to highly experienced HCV treatment providers (ideally in a liver transplant center) for treatment with SOF+RBV [with consideration of the patient's creatinine clearance and hemoglobin level] for up to 24 weeks / till liver transplantation, with close monitoring for the safety and efficacy. AASLD guidelines recommend up to 48 weeks treatment but the evidence and recommendation is weak and the cost may become prohibitive for our population.

Monitoring during and after HCV Therapy

- **For Safety of HCV Therapy:**
  - The patients receiving IFN+RBV should be assessed for clinical side effects at each visit, while the hematological side effects should be assessed at weeks 2 and 4 of therapy and at 4 to 8 week intervals thereafter.
  - Renal function should be checked regularly in patients receiving sofosbuvir.
  - The efficacy and toxicity of concurrent drugs given for comorbidities and potential drug-drug interactions should be monitored during treatment.
  - Amiodarone should not be co-administrated with any Sofosbuvir containing regimen.
  - Help may be taken from online (http://www.hep-druginteractions.org/) and mobile applications (Liverpool HEP iChart) to look for interaction of DAAs with other drugs.
- **For Efficacy of HCV Therapy:**
  - A real-time PCR-based assay with a lower limit of detection of <15 IU/ml should be used to monitor HCV RNA levels during and after therapy.
  - In patients treated with triple therapy (SOF+RBV+ PEG-IFN) for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12 (end of treatment), and 12 or 24 weeks after the end of therapy.
  - In patients treated with dual therapy (SOF+RBV) for 24 weeks, HCV RNA should be measured at baseline, week 4, 12, 24 (end of treatment), and 12 or 24 weeks after the end of therapy.
  - After achieving SVR:
    - In non-cirrhotic patients, ALT and HCV RNA should be retested at 24 and then 48 weeks, with no further monitoring, if ALT is normal and HCV RNA is negative.
    - In cirrhotic patients, ultrasound should be done every 6 months as surveillance for HCC. Guidelines for management of portal hypertension and varices should be implemented.

Management of hematological side effects

Management of Anemia: - If patient's hemoglobin drops below 11 g/dL, the appropriate management depends upon the level of hemoglobin:

- Hemoglobin level (10-11 g/dL): Good nutrition should be reemphasized along-with careful monitoring of hemoglobin.
- Hemoglobin level (8.5-10 g/dL):
  - Within 8 weeks of initiation of AVT – Erythropoietin, followed by RBV dose reduction, if needed.
  - After 8 weeks of initiation of AVT – RBV dose reduction, followed by Erythropoietin, if needed.
- Hemoglobin level (below 8.5 g/dL): RBV should be discontinued and patient should be started on Erythropoietin therapy.

Management of Neutropenia: - If patient's absolute neutrophil count (ANC) drops below 1000/ mm^3 appropriate management depends upon the level of ANC:

- ANC level (500-1000/mm^3): Good nutrition and avoidance of exposure to source of infection should be reemphasized along-with careful monitoring of CBC.
- ANC level (250-500/mm^3):
  - Within 8 weeks of initiation of AVT – Filgrastim, followed by IFN dose reduction, if needed.
  - After 8 weeks of initiation of AVT – IFN dose reduction, followed by Filgrastim, if needed.

- ANC level (below 250/mm^3): IFN should be discontinued and patient should be started on Filgrastim therapy.

Management of Thrombocytopenia: - If patient's platelets count drops below 75,000/mm^3, the appropriate management depends upon the level of platelets count:

- Platelets count (50,000-75,000/mm^3): Good nutrition should be reemphasized along-with careful monitoring of platelets count.
- Platelets count (25,000-50,000/mm^3):
  - Within 8 weeks of initiation of AVT – Eltrombopag, followed by IFN dose reduction, if needed.
  - After 8 weeks of initiation of AVT – IFN dose reduction, followed by Eltrombopag, if needed.
- Platelets count (below 25,000/mm^3): IFN should be discontinued and patient should be started on Eltrombopag therapy.

Chronic Hepatitis C and Liver Transplantation

This includes two types of scenarios: Pre-Transplant and Post-Transplant

- Patients with an indication for liver transplantation: Anti-viral therapy must be given to all patients awaiting liver transplantation to make them HCV-RNA PCR negative at least 30 days prior to transplantation to prevent graft infection:
  - Patients with conserved liver function (Child-Pugh Class A), in whom the indication for transplantation is HCC, should be treated with SOF+RBV until liver transplantation or SOF+RBV+ PEG-IFN for 12 weeks.
  - Patients with decompensated cirrhosis awaiting liver transplantation (Child-Pugh Class B & C) should be treated with SOF+RBV in experienced centers under close monitoring, with consideration of the patient's creatinine clearance and hemoglobin level, until liver transplantation. IFN is contra-indicated in these patients.
  - Patients with decompensated cirrhosis not on a transplant list should only be treated with SOF+RBV within experienced centers, because the efficacy, safety and outcomes have not yet been established for this group.
- **Post-liver transplantation recurrence:** Hepatitis C recurs invariably after the liver transplant. These patients should be evaluated at 6-12 months post-transplant and considered for therapy if significant fibrosis (≥F2) is found:
  - Daily Sofosbuvir (400 mg) and RBV (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [>75 kg] 1200 mg) with consideration of the patient's CrCl value and hemoglobin level for 24 weeks.
  - In the absence of contraindication, PEG-IFN should be added to the regimen in genotype 1.
  - No dose adjustment is required for Tacrolimus or Cyclosporine with any of these combinations. Careful monitoring is however important in the absence of safety data in this population.

CHC Patients who have HBV Co-infection

In patients with HCV-HBV co-infection, the HBV DNA level is often low or undetectable, although it may fluctuate widely, and HCV is usually the main driver of chronic hepatitis activity. Patients should be carefully characterized for the replicative status of both HBV and HCV, and hepatitis delta virus infection should be sought. When HCV is replicating and causes liver disease, it should be treated following the same rules as applied to HCV mono-infected patients. There is a potential risk of HBV reactivation during or after HCV clearance. In that case, or if HBV replication is detectable at a significant level, concurrent HBV nucleoside/nucleotide analogue therapy is indicated.

CHC Patients with Chronic Kidney Disease (CKD)

The kidney is important for the catabolism and/or filtration of interferon, ribavirin and sofosbuvir, and therefore, reduced doses are warranted in patients with reduced kidney functioning. Whether to use IFN vs PEG-IFN for patients with kidney failure is an important question. There is reduced excretion of PEG-IFN in these patients, and the literature actually suggests that there may be a higher rate of adverse events with IFN / PEG-IFN. In addition, the management of adverse events may be more difficult with IFN / PEG-IFN for these patients. Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. Almost 80% of the drug is eliminated by the kidneys.

Patients with CKD can be divided into two main categories: 1) Pre-renal transplant patients and 2) Post-renal transplant patients.

- **Pre-renal transplant patients:** Dose reductions of anti-HCV drugs (IFN, RBV and SOF) depend upon eGFR of these patients (Table 5). Accordingly, these patients can be broadly categorized into two:
  - Patients with CrCl>30 mL/min.1.73m^2 – should be treated with SOF+RBV+ PEG-IFN for 12

weeks (IFN-eligible) or SOF+RBV for 24 weeks (IFN-ineligible). Dose adjustments should be done as detailed out in Tab 4.

- Patients with CrCl<30 mL/min.1.73m^2 and on hemodialysis (HD) should not be treated with Sofosbuvir, because of little data is available for this patient population at present. In a recent study (Saxena V, et al. EASL 2015. Abstract LP08), SVR12 was achieved in 88% patients with a eGFR < 30ml/min using sosfosbuvir based regimen. As the use of sofosbuvir in this population is still "off-label", these patients should be treated with IFN+RBV for 24 weeks in genotype 3 and 48 weeks in genotype 1. Dose adjustments needs to be done as detailed out in Table 5. Other DAAs used in this population are not currently available In Pakistan.
- If there is no significant liver fibrosis on elastography or liver biopsy, these patients should be encouraged to undergo kidney transplant and hepatitis C may be taken care of after renal transplant with Sofosbuvir and ribavirin.

- **Post-renal transplant patients:** Patients acquiring HCV after renal transplant fare better than those acquiring HCV while on hemodialysis. Patient infected with HCV (before renal transplant) have worse patient and allograft survival as compared to uninfected patients. Post-renal transplant IFN based treatment is not recommended due to risk of graft rejection, unless the patient develops fibrosing cholestatic hepatitis (FCH) and cryoglobulinemia. Daily SOF (400 mg) plus RBV (with consideration of the patient's creatinine clearance and hemoglobin level) for 24 weeks for both genotypes 1 & 3.

CHC Patients with Hemoglobinopathies

The indications for HCV therapy are the same in patients with and without hemoglobinopathies. Given that both drugs cause anemia, the use of PEG-IFN plus RBV should be avoided in patients with hemoglobinopathies, when possible. When the use of RBV is needed, careful monitoring is recommended, and blood transfusions may be required. Patients with hemoglobinopathies with HCV infection should be treated with daily weight-based RBV and daily SOF for 24 weeks in both genotypes.

HCV in Children

- **Not enough data is available on use of DAAs in children.**
- **Approved therapy of children is PEG-IFN+RBV as detailed out below[10]:**
  - PRG-IFNα-2b (1.5 µg/Kg per week) in combination with RBV (15mg/kg per day) for age 3 years and older
  - PEG-IFNα-2a (100 µg/m2 per week) in combination with RBV (15mg/kg per day) for children aged 5 years and older
  - Genotypes 1 and 4 should be treated for 48 weeks. Patients with genotypes 2 and 3 should be treated for 24 weeks

AREAS FOR FUTURE RESEARCH

- We need to analyze and document our data of Sofosbuvir regarding its safety and efficacy, appropriate duration of therapy as well as different predictors of response.
- We have significant proportion of patients with advanced cirrhosis, it will be very vital to analyze data of these patients and see the impact of HCV therapy on the course of disease.

SUMMARY

Rational management of chronic hepatitis C includes proper assessment of HCV patients to select patients in need of antiviral therapy, counseling of patients, and selection of appropriate antiviral agents & duration of therapy. After therapy is started, it needs careful monitoring for safety and efficacy. Hematological side-effects are the most significant ones during therapy with interferon and ribavirin, and need appropriate management. Economic status of the patient needs to be taken into the consideration in addition to hepatic status as well as previous history of HCV therapy. Other factors include co-morbid conditions like obesity, DM, NASH, etc. Treatment of special populations like liver transplant patients, patients with HBV co-infection, chronic kidney disease and hemoglobinopathies need special considerations when initiating HCV therapy. We need to document our experience with Sofosbuvir in different populations of patients.

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