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Hepatitis C: Paradigm Shift in the Management

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INTRODUCTION

Hepatitis C virus (HCV) has affected over 150 million people around the world with global prevalence of 2-3%. Prevalence of HCV infection in India is 0.9 to 1.9%, which varies across the different regions of the country. Genotype 3 is the most common genotype in India, followed by genotype 1. Initially only interferon based treatments were available which were not well tolerated, especially in patients with cirrhosis. Since 2015, with the availability of generic directly acting antivirals (DAA), there has been a paradigm shift in the treatment of HCV in India.

EVALUATION OF THE PATIENT WITH HEPATITIS C

Most patients would be unaware of their infection. Screening if undertaken should be targeted to those at high risk of the infection. In India, common risk factors for transmission are unsafe injections and past history of blood transfusions prior to the year 2002, when testing for Hepatitis C became mandatory for all blood banks in India. Positive HCV antibody test needs to be followed by a HCV RNA test to confirm presence of the virus. HCV Antibody may be negative very early after the infection upto few weeks and in immune compromised states like patients on hemodialysis and those with HIV infection. HCV RNA test then is required for diagnosis of the infection.

Genotyping and subtyping is done prior to treatment as certain treatment regimes are less effective in certain subtypes (e.g. Geno1a v/s. 1b) or ineffective in some (eg Sofosbuvir + Ledepasvir in Geno 3). With effective pan genotypic combinations like Sofosbuvir + Velpatsvir and Sofosbuvir + Daclatasvir this requirement should become irrelevant. Genotype (GT) 3 accounts for 54- 80% of cases in India. Initially Geno 3 was grouped with Geno 2 and considered it "easy to treat". With the advent of D.A.A.s it was realized that Geno 3 patients especially those with cirrhosis who have failed treatment in past are now a difficult to treat population with lower response rates in this genotype.

Role of IL28B polymorphism has become less important in the era of new DAA as response rates are more than 90% in most situations. Assessment of clinical status and noninvasive assessment of fibrosis by imaging is important as presence of cirrhosis and decompensation and prior treatment failure may affect sustained virological response (SVR).

TREATMENT OF CHRONIC HEPATITIS C

Who should be treated?

In the ideal world all those having a hepatitis C virus infection needs treatment. Earlier when treatment was limited in safety and efficacy only patients with significant liver disease were identified for treatment. With safe and effective oral therapy now, only the cost of treatment remains the limiting factor. Treatment may be prioritized in certain patients who have high risk of progression like those with significant fibrosis or cirrhosis especially, ones with decompensated cirrhosis, HBV or HIV co-infection, HCV recurrence after liver transplantation, presence of clinically significant extra-hepatic manifestations and individuals who are at the risk of transmitting HCV. Counselling to stop alcohol consumption needs to be emphasized.

Goal of the treatment

The goal of therapy is to cure HCV infection in order to prevent the complications of HCV-related liver fibrosis and cirrhosis which can result in decompensation, HCC and death. The endpoint of therapy is a SVR, defined by undetectable HCV RNA 12-24 weeks after end of treatment. Once the virus is undetectable 12-24 weeks after end of treatment (SVR 12/24) the chances of recurrence are <1% and can be termed a cure in more than 99% of cases.

In patients with advanced fibrosis and cirrhosis, HCV eradication reduces the rate of decompensation and may reduce however not abolish the risk of HCC surveillance for HCC by six monthly ultrasound will need to be continued even after viral clearance. Anti HCV tests remains positive in the majority despite successful viral clearance and should not raise concern of persistent or recurrent infection.

How to treat

Superior safety, efficacy and broader eligibility make oral DAA the preferred regime. No single DAA is known to be efficacious by itself. Combination of two or more DAAs for 12-24 weeks, with/without Ribavirin are currently recommended. Currently available combinations are tabulated in Table 1. Drug-Drug interactions need to be looked into before prescribing. All currently accepted combinations have response rates > 90%. The efficacy is lower in presence of decompensated cirrhosis especially in Genotype 3. Extending treatment duration to 24 weeks and addition of Ribavirin will then be needed to be considered to optimize response (Figure 1). Resistance is not known to Sofosbuvir but clinically relevant resistant

Table1: Currently available DAA combinations

Combination	Protease Inhibitors	Polymerase Inhibitors		NS5A Inhibitors	Geno	Availability In India
		Nucleotide	Non-nucleotide			
1		Sofosbuvir		Ledipasvir	1,4,5,6	YES
2		Sofosbuvir		Velpatasvir	All	NO (likely in 2017)
3		Sofosbuvir		Daclatasvir	All	YES
4	Paritaprevir/Ritonavir		Dasabuvir	Ombitasvir	1,4,5,6	NO
5	Grazoprevir			Elbasvir	1,4,5,6	NO

1 Sof + Ledipasvir 2 Sof+ Velpatasvir 3 Sof + Daclatasvir

4 Partiprevir/Ritonavir + Dasabuvir + Ombitasvir 5 Grazoprevir + Elbasvir

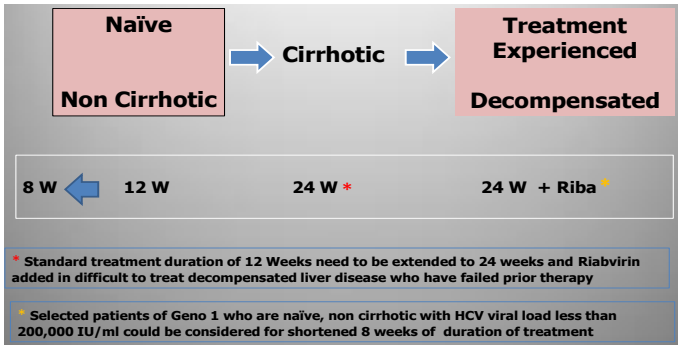

Fig. 1: Choice of Regimes in Different Clinical Situations

variants are noted with other groups of DAAs. Pegylated Interferon based regime are not known to have any resistance. PegIFN and Ribavirin in combination with Sofosburvir for 12 weeks is recommended for difficult to treat patients who are prior non responders to current DAAs.

Those not responding to currently available regimes will have the opportunity for treatment with the next generation of DAAs.

SPECIAL SUBGROUPS

HBV Coinfections

In patients with HBV- HCV co-infection, C virus is usually the predominant virus. HBVDNA may be low or undetectable. HCV should then be treated with same regimes as discussed previously. HBV replication should be monitored during and following the therapy as anti HBV treatment will need to be started to prevent reactivation of Hepatitis B after clearance of HCV.

HIV Coinfections

In HIV/HCV coinfection, there is higher rate of HCV persistence, faster progression to cirrhosis and end stage liver disease. Lower responses to Peginterferon and Ribavirin were noted but with DAA, the response in HCV mono infected and HIV/HCV coinfected patients are similar but drug to drug interactions will need to be kept in mind.

Pateints with Chronic Kidney Disease with/without hemodialysis

Standard Sofosbuvir based regimes are safe to be used in CKD with EGFR >30 ml/min and no dose adjustments are needed. Simeprevir, Daclatasvir, combination of Grazoprevir with Elbasvir and the triple combination of Ritonavir boosted Paritaprevir, Ombitasvir and Dasabuvir are all cleared by hepatic metabolism and can be used in patients with severe renal disease. Sofosbuvir is eliminated only by renal route and Sofosbuvir based regimes are not licensed for use in patients with end stage renal disease on dialysis and EGFR <30 ml/min. as concerns have been raised about higher concentrations of Sofosbuvir and its renally excreted metabolite. Although use of Sofosbuvir based regimes in advanced renal disease

have been reported in literature (despite it not being licensed for use) no dose adjustments are recommended for its use in this setting. Progressive deterioration of renal function has been noted in this setting.

Non sofosbuvir based regime may be given in patients on dialysis but are effective only in Genotype 1 and as yet unavailable in India.

Decision needs to be taken whether treatment for HCV can be postponed till after the renal transplant when it can be safe and efficacious.

Unless strict infection control practices are followed in the hemodialysis units reinfection of the HCV patient who is not a transplant candidate and continued non hemodialysis is always a possibility.

Treatment of Acute HCV

Icteric illness following an acute HCV infection usually results in spontaneous clearance of the virus. However, acute HCV infections are usually asymptomatic, and may have high rate (50-90%) of chronicity. Hence, antiviral treatment should be considered in all acute HCV infections if HCV viremia persists beyond12 weeks. High SVR rates were reported with Peginterferon therapy in this situation which are being replicated in early studies with the oral DAAs.

There is no indication of antiviral therapy as post exposure prophylaxis in the absence of documented HCV transmission.

Hemoglobinopathy and bleeding disorders

Interferon and Ribavirin free regimen with DAAs are now possible for HCV patients with hemoglobinopathy and bleeding disorders.

CONCLUSIONS

With the advent of DAAs, treatment of HCV now can result in a cure in more than 90% of patients. Strategies for screening and early detection with access to care are now the challenges to be faced. Prevention of end stage liver disease and HCC with early recognition and treatment of HCV may still take decades to achieve but is a goal towards which we need to persevere.

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