Efficacy of Directly Acting Antiviral Drugs for HCV in Real Life: Experience from a Tertiary Care Centre of North India

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ABSTRACT

BACKGROUND
Since its discovery, treatment of hepatitis C virus (HCV) has undergone extensive changes. Antiviral treatments and sustained virological responses (SVR) have also improved from the early interferon monotherapy to the current all-oral regimens using direct acting antiviral (DAAs). We aimed to analyse our experience for last 4 years in treatment of hepatitis C with the currently available antivirals in terms of SVR at various time-points, new onset decompensation, hepatocellular carcinoma (HCC), mortality and side effects.

METHODS
Data of all patients with anti-HCV were collected prospectively and analysed. This included history taking, examination findings, routine blood investigations, viral markers, HCV RNA before initiating antivirals and at the end of giving antivirals and every 3 months thereafter among all HCV positive patients, HCV genotype, and ultrasonography of whole abdomen, upper gastrointestinal endoscopy and alpha fetoprotein (AFP).

RESULTS
A total of 520 patients was found positive for anti HCV, from 2014 to 2018, of which 276 (53%) were male and 244 (47%) were female patients. Among all 520 patients, 353 (68%) had detectable HCV RNA, of which 43 (12%) patients had cirrhosis and 310 (88%) had chronic infection. 29 (8%) received Sofosbuvir plus Ledipasvir, 73 (20%) Sofosbuvir plus Ribavirin, 115 (33%) Sofosbuvir plus Daclatasvir, and 70 (20%) received Sofosbuvir plus Velpatasvir. All except one achieved SVR. No any new onset HCC was detected while 7 (2%) patients developed new onset decompensation. Total 3 (7%) cirrhotic patients expired. One patient developed self-limiting erythematous rash.

CONCLUSIONS
Directly acting antivirals (DAAs) are highly effective and safer drugs for the treatment of chronic hepatitis C infection even in real life scenario as evident from our study most of the patients receiving antivirals survived.

KEYWORDS
Direct Acting Antiviral (DAA), Hepatitis C Virus (HCV), Hepatocellular Carcinoma (HCC), Sustained Virological Response (SVR).


BACKGROUND
Chronic hepatitis C (CHC) infection is a major cause for liver failure and liver cancer. Global prevalence of HCV is estimated to range from 0.09% to 2.02%⁵,⁶ and can be treated with highly effective all oral directly acting antiviral (DAA) drugs. Since its discovery, treatment of hepatitis C virus (HCV) has undergone extensive changes. Antiviral treatments and sustained virological responses (SVR) have also improved from the early interferon monotherapy to the current all-oral regimens using direct acting antiviral (DAAs). Sofosbuvir, Velpatasvir, Daclatasvir, Ledipasvir and Ribavirin are the currently available oral drugs in India. Chronic hepatitis C (CHC) treatment has continuously evolved. An oral treatment with direct-acting antiviral (DAA) agents is the current standard of care with and without interferon. Recently, a combination of two direct-acting antiviral agents, sofosbuvir 400 mg (anti-NS5B) with any one amongst,
ledipasvir 90 mg (anti-NS5A), daclatasvir 60 mg (NS5A inhibitor) or velpatasvir 100 mg (NS5A inhibitor) has been approved in the US and the European Union for the treatment of chronic hepatitis C viral infection. A fixed-dose combination of sofosbuvir and velpatasvir for 12 weeks was compared with standard treatment with sofosbuvir plus ribavirin for 12 or 24 weeks in patients who had received prior treatment for HCV genotype 2 or 3 infection was done and sustained virological response rates (SVR) was >90%. In Phase 3 trials (ASTRAL-2 and ASTRAL-3) of HCV genotype 2 patients, SVR rate in the sofosbuvir–velpatasvir group was 99%, which was higher to the rate of 94% in the sofosbuvir–ribavirin group (P=0.02) and this was significant. Among patients with HCV genotype 3, the rate of sustained virologic response in the sofosbuvir–velpatasvir group was 95%, which was superior to the rate of 80% in the sofosbuvir–ribavirin group (p<0.001). The SOLAR-2 study was another open-label Phase II, multicenter, randomized trial that evaluated the efficacy and safety of a fixed-dose combination of LDV/SOF for the treatment of chronic HCV genotype-1 or genotype-4 infection in patients with compensated cirrhosis and patients in trial achieved comparably high efficacy with the LDV/SOF combination (SVR rates 87-96%). Studies have produced conflicting results of the incidence of hepatocellular carcinoma (HCC) in patients with in hepatitis C virus (HCV)-associated cirrhosis treated with direct-acting antivirals (DAAs). In a prospective observational study confirms that the early benefit of viral eradication in HCV associated cirrhosis persists throughout all stages of cirrhosis. The occurrence of HCC is significantly decreased in patients with compensated cirrhosis without signs of portal hypertension and normal liver function. In patients with advanced disease, eradication of HCV infection lowers the risk of developing HCC.

Aims and Objectives

Analysis of HCV treatment from 2014 to 2018 with the currently available directly acting antivirals in terms of SVR at various time intervals, new onset decompensation, development of hepatocellular carcinoma (HCC), prognosis and side effects.

METHODS

We prospectively collected and analysed data from 2014 to 2018 of all anti-HCV positive patients from outdoor clinics of our department in the form of history and examination, routine blood tests, HCV RNA at the time of start of antivirals, at end of treatment and every 3 months thereafter, HCV genotype, ultrasound abdomen, upper GI endoscopy and alpha fetoprotein (AFP).

Treatment Protocol

In India, sofosbuvir was marketed in early 2015, and daclatasvir in late 2015, and when both drugs became available, we began treatment to our patients with DAA regimen containing daclatasvir and sofosbuvir, without pegylated interferon and, ribavirin, regardless of HCV genotype. Though ledipasvir is favoured over daclatasvir for the treatment of HCV genotypes 1 and 4, this drug is marketed only as a fixed-dose combination with sofosbuvir. Hence, we decided to use sofosbuvir for all the HCV genotypes and ledipasvir and daclatasvir according to genotype. However, its use is supported by clinical and pharmacokinetic data that have subsequently become available. The treatment was planned for 12 weeks, and also for those with clinical evidence of cirrhosis.

RESULTS

From 2014 to 2018, a total 519 patients were detected to be anti HCV positive. The percentage of male and female is 53:47 and 353 (68%) had detectable HCV RNA. Among these, 43 (12%) patients had cirrhosis and 310 (88%) had chronic infection. Among these 353 patients 29 (8%) received Sofosbuvir plus Ledipasvir, 73 (20%) Sofosbuvir plus Ribavirin, 115 (33%) Sofosbuvir plus Daclatasvir, and 70 (20%) received Sofosbuvir plus Velpatasvir. All except one achieved SVR. No new onset HCC was detected. 7 (2%) patients developed new onset decompensation. None of the chronic hepatitis C had mortality while 3 (7%) cirrhotics died. One patient developed self-limiting erythematous rash.

Demographic and Baseline Characteristics

Total 519 patients were detected to be anti HCV positive and the ratio of male and female was 53:47. Mean age was 39.7±12.5 years. In the group of chronic hepatitis C without cirrhosis, there were 477 patients, in chronic hepatitis C with cirrhosis (Compensated) groups, and in chronic hepatitis C with cirrhosis (Decompensated) 37 patients were there. The mean age of all the patients is 39.7±12.5 year. At the baseline there is no HCC as described in table 1.

Virological Parameters

Genotype 3 was the most common genotype followed by genotype 1 and 4. We could not find any genotype 2 patient in our study. The mean viral load was 5×10^6 ± 1×10^7 in chronic hepatitis C with cirrhosis (Compensated) group in comparison to mean viral load of 1.1×10^6 ± 2.6×10^6 in chronic hepatitis C with cirrhosis (Decompensated) group.
### Treatment

Overall as well as in chronic hepatitis C without cirrhosis, chronic hepatitis C with cirrhosis (Compensated) and in chronic hepatitis C with cirrhosis (Decompensated) groups, we use SOF+VELPA most commonly among all the drug combinations as described in the figure 1. All patients achieved SVR12.

### Change in CTP Score

There were significant changes in CTP score in all the groups of patients at the end of treatment (EOT), and at 12 weeks post-treatment as compared to baseline, ranging from 1.0 to 1.8 with the p value >0.05 in each drug combinations.

![Figure 1. Treatment of all Groups](image1)

### New Onset HCC

None of the patient developed new onset space occupying lesion on USG. Alpha fetoprotein was within normal range at baseline and at the EOT and at 12-week post treatment. So, these results showed that none of the patients developed HCC with any drug combination.

### Mortality and Adverse Effects

Overall three patients died within the 12-week post treatment among these two were in SOF+VELPA groups and one was in SOF+DCV groups. None of the patients develops significant Adverse Effects (AE) but overall eight patients developed minor AE like body ache, fatigue and headache. Among these three were in SOF+VELPA groups and five were in SOF+DCV groups, one patient develops erythematous rashes with subsided spontaneously.

![Figure 2. None of the Patients Developed New Onset Space Occupying Lesion on USG](image2)

### DISCUSSION

Over 170 million patients, chronically infected with HCV worldwide, approximately half have HCV genotypes other than genotype 1, including about one third of patients with HCV in the United States. Currently approved regimens of direct-acting antiviral agents are not equally effective across all genotypes, which means that testing to determine genotype is required before treatment can be initiated. A single combination regimen that is effective in all patients regardless of HCV genotype would obviate the need for pre-treatment testing, which is an obstacle to treatment in resource-limited areas and may limit treatment uptake outside of specialty clinics. In a randomized, double-blind,
placebo-controlled phase 3 study, treatment with sofosbuvir-velpatasvir for 12 weeks resulted in high rates of sustained virologic response in patients with HCV genotype 1, 2, 4, 5, or 6, including those with cirrhosis and those who had received previous treatment and those who had not been treated. In compassionate use program, treatment with the fixed-dose combination tablet of sofosbuvir–velpatasvir with or without ribavirin for 12 weeks and with sofosbuvir–velpatasvir for 24 weeks resulted in a high rate of sustained virologic response and early improvements in hepatic function in patients with decompensated cirrhosis caused by HCV of all genotypes. Our results are similar with those of other recent trials of direct-acting antiviral regimens. In the SOLAR-1 and SOLAR-2 trials, patients with genotype 1 or 4 and CPT class B or C cirrhosis who received ledipasvir-sofosbuvir plus ribavirin for 12 or 24 weeks had rates of sustained virologic response of 86 to 89% at 12 weeks after the end of treatment. In our study we also had cirrhotics who had 100% sustained virological response. Our study showed that none of the patient in any group developed hepatocellular carcinoma. Manns M et al., 2015 study also had similar results.

CONCLUSIONS
DAA drugs against HCV infection have 100% SVR with negligible side effects. 12 weeks regimen is 100% effective even in decompensated cirrhosis, that’s why 12 weeks of treatment should become the standard of care. They are equally efficacious in all stages of HCV infection. They don’t have any favorable or adverse effect on CTP score. There is no evidence of new onset HCC. DAAs are highly efficacious and safe for the treatment of chronic hepatitis C even in real life scenario. DAA treatment must be guaranteed to all patients with cirrhosis at any functional stage, considering the residual and unavoidable risk of HCC after viral eradication.

REFERENCES