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Efficacy of sofosbuvir and daclatasvir in compensated chronic hepatitis C infection: A single center, open-label and proof of concept study

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***Abstract*---**Aims and objectives: The advent of directly acting agents for the treatment of Hepatitis C infection has forever transformed our understanding and management of viral infections. With over 95 % patients achieving a sustained viral response at 12 weeks with some of these newly inducted agents, the prospect of eradicating the Hepatitis C virus seems like an achievable target, which makes this one of the most important discoveries in modern medicine. We studied the combination of Sofosbuvir and Daclatasvir in patients with chronic hepatitis C infection (Genotype 3) to assess the rates of sustained virological response at 12 weeks. Methods: We studied 67 treatment naive patients with compensated chronic hepatitis C infection (genotype 3). They were all started on Tab Sofosbuvir 400 mg daily and Tab Daclatasvir 60 mg once daily for 12 weeks and followed

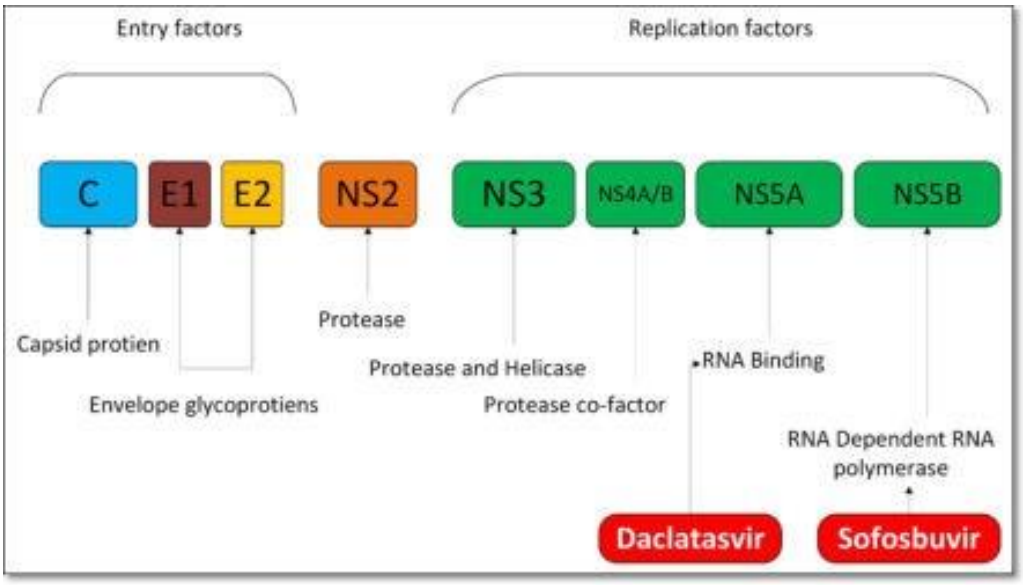
up for a total of 24 weeks, which includes a treatment duration and observation period of 12 weeks each. The patients were monitored with HCV RNA levels at one, three and six months, with as many evaluations of liver function and routine hemogram. Results: Our results show that 70.5% ($p<0.05$) achieved a rapid virological response, 88.5% ($p<0.05$) achieved an end of treatment response and, similarly, an impressive 88.05% ($p<0.05$) showed a sustained virological response at the end of 12 weeks. One patient who developed a psoriasiform rash discontinued the medication and was excluded from the analysis, as duration of treatment had not been completed. No major dose related adverse events were reported. Conclusions: Sofosbuvir and Daclatasvir is an acceptable, well tolerated regimen for treatment naive, compensated patients with genotype 3 infection. Based on our observations and data, we recommend this as the first line DAA for patient with compensated genotype 3 infection until medications with higher SVR 12 are available in the Indian market.

***Keywords*---**sofosbuvir and daclatasvir, hepatitis C, infection.

Introduction

Chronic Hepatitis C infection affects 200 million peopleworldwide (1, 2). In more than 70% of people with an acute infection,Hepatitis C causes a chronic infection, which predisposes to bothcirrhosis and hepatocellular carcinoma (3-5). It forms a majorindication for liver transplantation (6). The single strandedpositive sense RNA; belonging to the family *Flaviviridae*induces a CD8 mediated damage of the hepatocytes,suggesting a central immune mechanism for the liver injury(7, 8). Additionally, the virus is associated with various hepaticmanifestations (9-14) like autoimmune hepatitis, NHL (15-19),lichen planus, mixed cryoglobulinemia (11, 20), monoclonalgammopathies and porphyria cutanea tarda (21, 22) which adds to its already indolent but serious capabilities (23).

The fact that hepatitis C spreads by both percutaneous [IV drug use (24, 25), blood transfusions] and non-percutaneous [sexual contact and perinatal infection (26, 27)] routes makes it a major public health threat for all age groups in our country.



Schematic diagram showing structure of Hepatitis C and targets of Sofosbuvir and Daclatasvir

HCV related mortality increased dramatically after 1995, but has reduced since 2002. In our country, where transplant is often not available, the morbidity and mortality from hepatitis C infection is significant (28). When compounded with the rising trend of alcohol use, the virus poses major health threats to all age groups in our country. Less than 05 years ago, the standard of care was a combination of PEGylated interferon and ribavirin. Subsequently, telaprevir and boceprevir (29-31) were introduced which met their obituary with ever reaching Indian shores. This was the era when the chance of a sustained response at 24 weeks was about 40%. If the IL28 genotype or cirrhosis was present, then these rates were lower (32-34). If LDL was low, then the SVR offered by Telaprevir was low. Furthermore, the adverse effect profile made the situation worse, with up to one quarter discontinuing the medication according to a study in France. The cirrhotic and carcinogenic march of Hepatitis C continued, unabated. However, the past few years have ushered in an era of hope and progress. Chronic viral hepatitis C is the only viral infection that can be cured (35, 36). For genotype 3, the options include Elbasvir + Grazoprevir and Sofosbuvir + Daclatasvir and Sofosbuvir + Velpatasvir(1, 37, 38). Of these, only a few are available in our country. Regardless, these molecules have revolutionized the treatment of Hepatitis C by acting on some key non-structural components of the HCV virion. The structure of the HCV virion consists of core and envelope proteins adjacent to NS2 (cysteine protease), NS3 (Serine protease and RNA helicase), NS4 (NS3 protease co-factor), NS5A (RNA binding site) and NS5B (RNA dependent RNA polymerase), as shown in the schematic diagram (7, 8). The non-structural components have been the main focus of Hepatitis C pharmacotherapy recently (8, 39).

MEAN BASELINE CHARACTERISTICS OF PATIENTS (N=67)		
Age	47	years
HCV RNA at baseline	920587.5	copies/ml
Hemoglobin	12.4	gm/dl
TLC	6398.8	per cumm
Platelets	2.5	lakhs
Bilirubin	1	mg/dl
ALT	42.4	IU/ml
AST	42.2	IU/ml

After Michael Sofia's groundbreaking discovery in 2007, of a new drug and a new approach in the treatment of Chronic Hepatitis C, the concept of management of chronic viral infections would change forever (39). In December 2013, this molecule, targeting the NS5B component, was granted breakthrough status by the FDA. This drug, Sofosbuvir, got the distinction of being the fastest ever launched drug in the US history. As it reached Indian Shores less than six months later, another drug, Daclatasvir, which inhibited the NS5A (RNA binding site) was added to the Hepatitis C armamentarium (40-43).

The combination of these two agents was soon approved for pan-genotypic use and became first line before being recently replaced by Elbasvir and Grazoprevir (1). Daclatasvir was also found to be useful when combined with Asunaprevir for co-infection with HIV (44). It can also be combined with Simeprevir and Ribavirin for patients with HCV recurrence after transplantation (45-47). While the Sofosbuvir- Daclatasvir combination remains quite expensive, experience at our center has shown a rising trend for its use. At present, for patients without cirrhosis, interferon free regimens are preferred.

Trial Design

In this single center, open-label, proof of concept study, we started Tab Sofosbuvir 400 mg and Tab Daclatasvir 60 mg once daily to 67 patients with chronic compensated hepatitis C infection. This was based on several internationally acclaimed recommendations. All patients were diagnosed based on anti-HCV RNA positivity. Baseline RNA levels was measured in all patients, followed by serial measurements at one, three and six months. Hemogram and liver function tests were also undertaken at these intervals. Written consent was waived since the patients were being treated based on the existing standard of care. Patients were also monitored for any known (and unknown) adverse effects of the two medications such as flu-like symptoms, bradyarrhythmia and others.

Exclusions

Patients with evidence of decompensation were excluded from the study. This was achieved by a ultrasonographical evaluation of all patients at baseline. Two patients on concurrent anti-tubercular therapy, 3 patients on anti- convulsant

therapy and one patient on ART were also excluded as these drugs have significant interactions with Sofosbuvir (a substrate of p-glycoprotein, which in the presence of inducers like rifampicin could reduce the serum levels of Sofosbuvir) and Daclatasvir.One patient developed a skin rash after 22 days of commencement of therapy and discontinued the medication. Finally, patients with concurrent chronic kidney disease were also excluded to due to unpredictable drug kinetics.

Results

Of the 67 patients who completed 12 weeks of treatment, 48 (70.5 %, CI 95%, P=<0.04) patients had undetectable levels of HCV RNA at four weeks, and 59 out of 67 (88.05%, CI 95%, p<0.05) attained an end of treatment response and a sustained virological response at 12 weeks. Though neither powered nor intended to assess the progression of liver parameters, there weren't any significant changes over the 24- week period.

Table1: HCVRNA baseline

HCVRNA baseline	Frequency	Percent
Below1L	5	7.2
1L to 5L	16	23.2
5Lto10L	20	29.0
10L to15L	12	17.4
15Lto20L	16	23.2
Total	69	100.0

The frequency distribution of patients according to HCV RNA baseline along with it's bar graph is as given below.

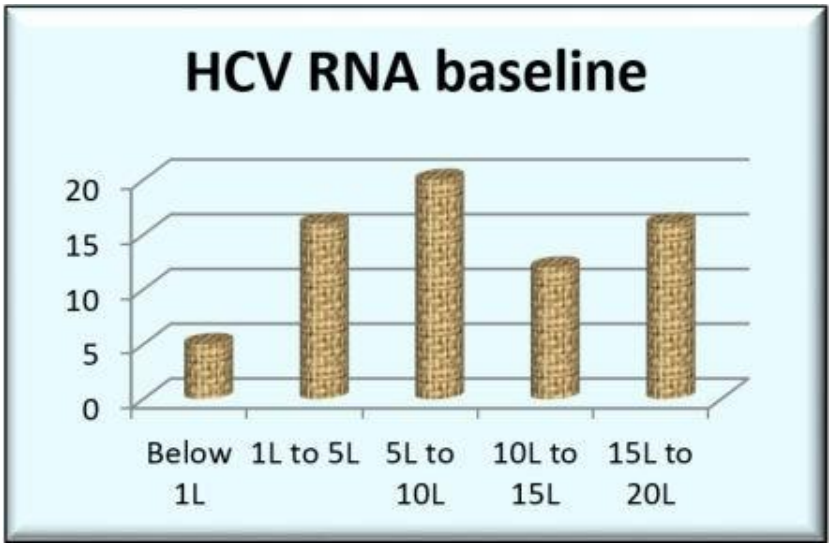


Table2: HCVRNA 4weeks

HCVRNA 4weeks	Frequency	Percent
Undetectable	48	69.6
Detectable	21	30.4
Total	69	100.0

The frequency distribution of patients according to HCVRNA 4weeks along with its bar graph is as given below.

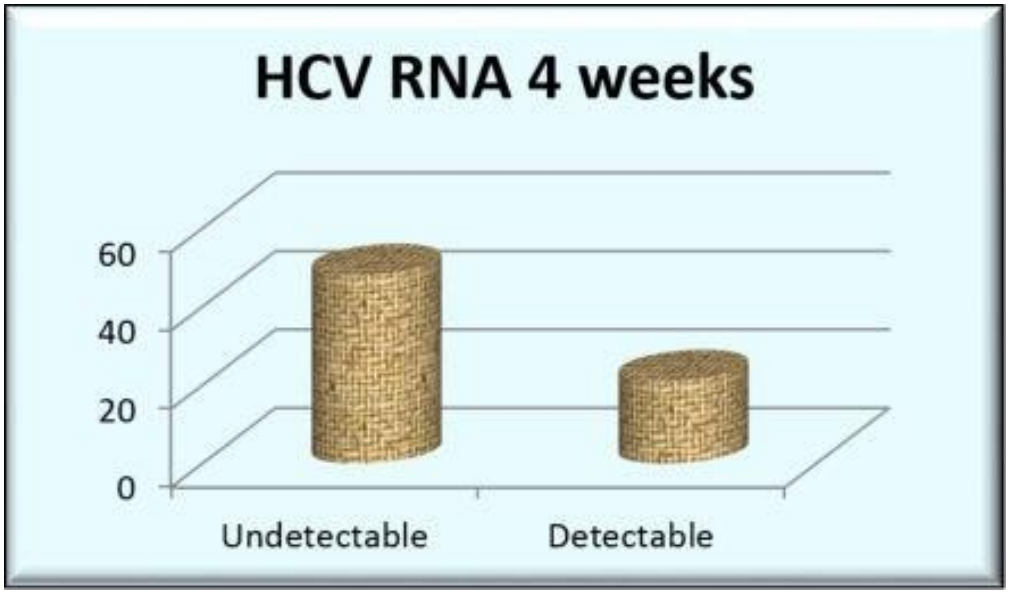


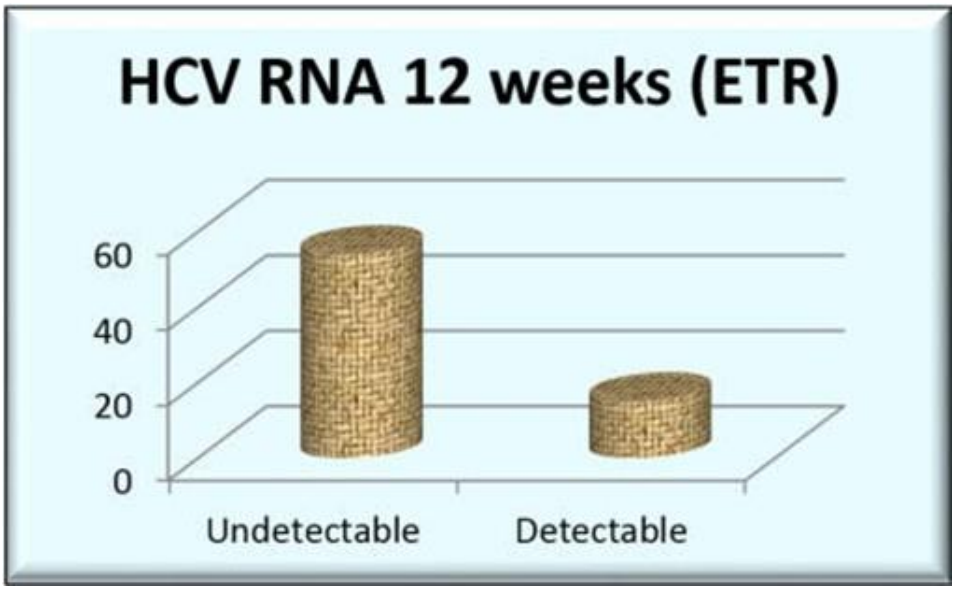
Table3: HCVRNA 12weeks (ETR)

HCVRNA 12weeks (ETR)	Frequency	Percent
Undetectable	54	78.3
Detectable	15	21.7
Total	69	100.0

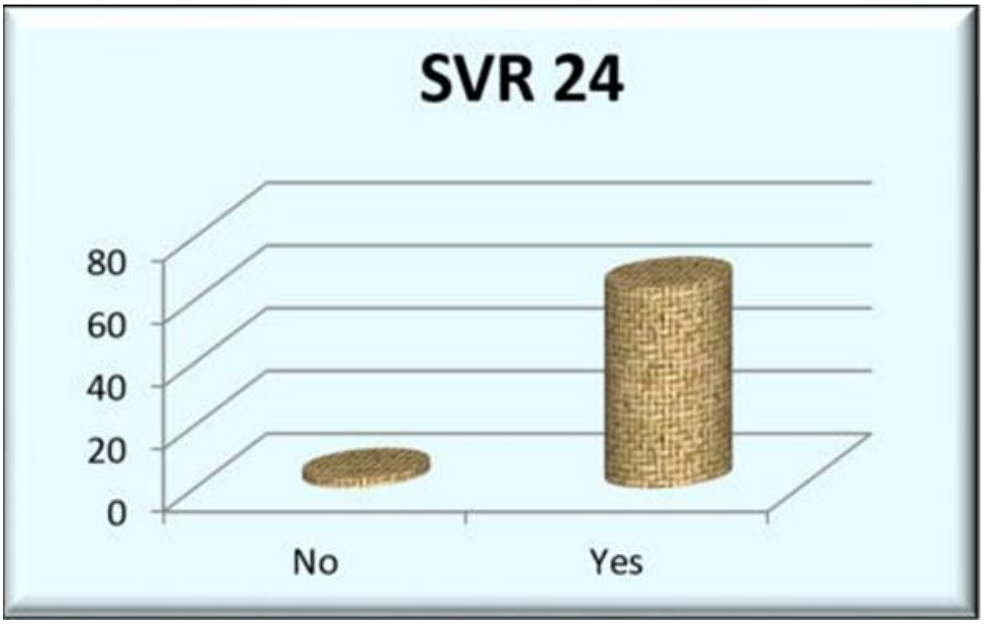
Table4: SVR24

SVR24	Frequency	Percent
No	3	4.5
Yes	64	95.5
Total	67	100.0

The frequency distribution of patients according to HCVRNA 12weeks (ETR) along with it's bar graph is as given below.



The frequency distribution of patients according to SVR 24 along with it's bar graph is as given below.



Aim 1: To decide whether difference in HCV RNA baseline is significant with respect to HCVRNA 4weeks.

The test used is t test for two independent samples.

Calculation Table

Group Statistics					
HCVRNA4weeks		N	Mean	Std. Deviation	Std. Error Mean
HCVRNA baseline	undetectable	48	890743.69	656603.51	94772.55
	detectable	21	951499.62	589071.76	128546.00

Independent Samples Test						
		Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	Pvalue (2-tailed)
HCVRNA baseline	Equal variances assumed	.680	.413	-.364	67	.717
	Equal variances not assumed			-.380	42.330	.706

Since p value>0.05, the level of significance, the difference in HCV RNA baseline is not significant with respect to HCV RNA 4weeks. The absolute values of HCVRNA have been analysed.

Aim 2: To decide whether difference in HCV RNA baseline is significant with respect to HCVRNA 12weeks (ETR).

The test used is t test for two independent samples.

Calculation Table

Group Statistics					
HCVRNA12weeks(ETR)		N	Mean	Std. Deviation	Std. Error Mean
HCVRNA baseline	undetectable	54	843237.56	648687.74	88275.22
	detectable	15	1146824.07	525965.03	135803.59

Independent Samples Test						
		Levene's Test for Equality of Variances		t-test for Equality of Means		
		F	Sig.	t	df	Pvalue(2-tailed)
HCVRNA baseline	Equal variances assumed	1.951	.167	-1.664	67	.101
	Equal variances not assumed			-1.874	27.04	.072

Since p value < 0.05, the level of significance, the difference in HCV RNA baseline is significant with respect to SVR 24.
Since pvalue>0.05, the level of significance, the difference in HCVRNA baseline is not significant with respect to HCVRNA12 weeks (ETR). The absolute values of HCV RNA have been analyzed.

Aim 3: To decide whether difference in HCV RNA baseline is significant with respect to SVR24.

The test used is t test for two independent samples.

Calculation Table:

Group Statistics					
SVR24		N	Mean	Std. Deviation	Std. ErrorMean
HCVRNA baseline	No	3	1225460.33	478662.41	276355.87
	Yes	64	906296.56	641032.72	80129.09

Independent Samples Test						
		Levene's Test for Equality of Variances		t-testfor Equality of Means		
		F	Sig.	t	df	Pvalue(2-tailed)
HCVRNA baseline	Equal variances assumed	1.604	.210	.849	65	.03
	Equal variances not assumed			1.109	2.350	.0.036

Since pvalue<0.05, the level of significance, the difference in HCVRNA baseline is significant with respect t to SVR24.

Results after 12 weeks of Sofosbuvir and Daclatasvir (n=67) (p<0.05)	
Duration	Percentage of patients with undetectable HCV RNA Levels
04 weeks	70.50%
12 weeks	88.50%
SVR 12	88.50%

Discussion

The INASL consensus statement suggested a 0.5 – 1 % prevalence of Hepatitis C infection in India, with hotspots in the northeast and in certain areas of Punjab (48, 49). This prevalence underscores the need for early diagnosis and treatment of this treatment. The ALLY III study was the basis for the approval of Sofosbuvir and Daclatasvir. This study (n=101) demonstrated a SVR 12 of 97% in treatment naïve patients with no evidence of cirrhosis. This is significantly higher than our findings (88.5%). We attribute this difference, in part to the NS5A Y93H polymorphism(50-54) which was associated with significantly lower SVRas demonstrated in the ALLY III study. In patients with no cirrhosis, only 67% patients with this polymorphism attained SVR12. This data has its limitations since only 9 patients had this polymorphism. Analysis of Y93H is not available in our country at this time, and the assumption that it is causing lower SVRs is

purely conjecture. The European compassionate-use program which reported SVR12 rates of 70% in patients with cirrhosis. They also demonstrated a higher SVR12 (86%) when the treatment duration was 24 weeks. Furthermore, SVR12 was higher (86%) in patients with Child A cirrhosis, when compared to Child B/C (70.6%).

At present, the only other recommended regime for genotype 3 without cirrhosis is a 12-week course of Sofosbuvir and Velpatasvir. In presence of cirrhosis, however, daclatasvir and sofosbuvir can be given, with or without weight-based ribavirin for a period of 24 weeks. Also, emerging at the horizon is the combination of Elbasvir and Grazoprevir with sofosbuvir which has shown promising results (37, 38).

The management of Hepatitis C has seen a paradigm shift in the past few years. We have a come a long way from the 40- 50% SVRs found in interferon-based therapies. The ever- expanding armamentarium against hepatitis C may result in the eradication of this virus in the near future.

Abbreviations

SVR 12 – sustained virological response at 12 weeks, IV – Intravenous, ART – anti-retroviral therapy

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