



Outcomes and Predictors of Non-Responsiveness in Treatment of Naïve and Non-Cirrhotic Patients with HCV Genotype 3 Infection – A Third World Perspective

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2022/v34i39B36242

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/87461>

Original Research Article

Received 13 March 2022

Accepted 26 May 2022

Published 31 May 2022

ABSTRACT

Objective: To assess the clinical outcome in treatment naïve and non-cirrhotic patients with HCV genotype 3 infection after treatment with Sofosbuvir with delectasvir and valpatasvir (in case of non-responsiveness).

Methods: Study included 263 participants. The inclusion criteria were HCV genotype 3 infection confirmed through PCR, age above 18 years, treatment naïve and non-cirrhotic. HCV PCR below the threshold of quantification at 12th week of treatment was defined as SVR12 (sustained virological response). The patients were started on a fixed dose generic combination of delectasvir 60 mg and Sofosbuvir 400 mg and PCR was performed at 12, 24 and 48 weeks. PCR positive patients at 24 weeks were given valpatasvir with Sofosbuvir.

Results: There were 162 males and 101 females. PCR performed at 12 weeks showed that 251 patients (95.4%) became PCR negative and 12 (4.56%) remained positive. Repeat PCR of these 12 patients started on valpatasvir and Sofosbuvir at 48 weeks was negative. The treatment was well

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tolerated by all. Probability of positive HCV PCR at 12 weeks decreases by 0.73 with one unit increase in the hemoglobin, whereas one unit increase in TLC reduces the probability of HCV PCR at 12 weeks, positive by 0.001.

Conclusion: The combination of Sofosbuvir and dechlorasvir is a cheap and effective treatment strategy for treatment naïve and non-cirrhotic HCV genotype 3 infections. Those not responding will achieve PCR negativity with a 6 month therapy of Sofosbuvir and valpatasvir combination. A high hemoglobin level and high total leucocyte count are predictors of good treatment response.

Keywords: Declastasvir; Sofosbuvir; HCV genotype 3; PCR; non responsiveness.

1. INTRODUCTION

Hepatitis C is a leading health problem in Pakistan with a prevalence of 6.7%, Pakistan ranks second in the world [1]. There are six genotypes of this deadly virus and the commonest and most difficult to treat genotype is genotype 3 in Pakistani population [2]. The advent of directly acting antiviral agents (DAA) have revolutionized the management of hepatitis C, but its high cost and troublesome side effects limits the use of these agents in our population [3]. Pakistan has a per capita income of 1260.0 USD [4]. It has a poverty rate of 5% as such for most people the generic locally manufactured DAAs are a cheap and good alternative for their disease.

Declastasvir is an NS 5A inhibitor while Sofosbuvir is an NS5B inhibitor. According to recent trials this combination is safe for genotype 3 [5]. The sustained virological response (SVR) achieved for treatment naïve, a non cirrhotic patient is 92% but it drops to 89% in treatment experienced patients [6]. The Glecaprevir/Pibrentasvir combination however achieves an SVR12 of about 97% as found in some studies [7]. According to the recent AASLD guidelines for treatment naïve, non-cirrhotic genotype 3 infections the recommended drugs are fixed dose combinations of Glecaprevir/Pibrentasvir given for 8 weeks or a 12 week treatment with valpatasvir and Sofosbuvir [8].

However the cost and availability limit the use of these options in our patients. The current cost of generic Glecaprevir/Pibrentasvir combination given for 12 weeks drug is 30,710 USD, which is unbearable for the ordinary citizens of Pakistan [9]. In contrast to this, currently the monthly cost of declastasvir is only 5.51USD and Sofosbuvir is 15.5 USD. The 12 week cost of Sofosbuvir and declastasvir is only 63.0 USD. Similarly valpatasvir costs about 39.8 USD monthly in Pakistan and in combination with Sofosbuvir its

12 weekly cost is 55.3 USD only [10]. This is a substantially low price, and as such it is an attractive option for HCV, which is primarily a disease of the poor. The biggest concern for gastroenterologists is the doubtful efficacy and tolerability of the locally manufactured drugs.

The aim of the study is to establish the efficacy of the low cost easily available locally manufactured drug combinations against HCV genotype 3 in treatment naïve, non-cirrhotic patients and to find out the likely reasons behind the treatment non-responsiveness.

2. MATERIALS AND METHODS

The study was conducted at Bilal Medical Trust, district Buner, Peshawar. After approval from the hospital administration the study was conducted on 263 participants recruited through non probability consecutive sampling. A written and informed consent was obtained in all cases. The inclusion criterion was HCV (hepatitis C virus) genotype 3 infection confirmed through PCR (polymerase chain reaction).

The patients included in the study were older than 18 years of age, treatment naïve and non-cirrhotic. After performing detailed history and physical examination, PCR analysis was done using TagMan Probe Real Time PCR and using Sa Cyler-96 instrument sequence specific primers were identified. A minimal threshold of 50 IU/mL was assigned for reporting negatives. HCV PCR below the threshold of quantification at 12th week of treatment was termed as SVR12 (sustained virological response).

Ultrasound of the liver was performed to exclude cirrhosis. Pregnant and breast feeding women and those with eGFR less than 30ml/min/day, patients with liver cirrhosis and with HCV genotypes other than genotype 3 were excluded from the study. The patients were then started on a generic combination of declastasvir 60 mg and

Sofosbuvir 400 mg and PCR was performed at 12 weeks, 24 weeks and one year (48 weeks).

Those patients remaining PCR positive at 12 weeks were offered an additional 12 week therapy with the same drugs. Valpatasvir in combination with Sofosbuvir was given to patients remaining PCR positive at 24 weeks and the response was assessed again at 48 weeks.

The findings were recorded on a structured proforma and the results were analyzed using SPSS version 23. Percentages and frequencies were calculated for the categorical variables and the cause of treatment non-responsiveness was correlated with the variables under consideration. The P value of < 0.05 was taken as significant.

3. RESULTS

Out of the total 263 patients, minimum age was 22 and maximum age was 57 years, mean age was 39.9 years. Mean ALT was 102 U/L whereas the mean total leukocyte count (TLC) found was 6400/mm³. Out of the 263 patients, 162 (61.6%) were males and 101 (38.4%) were females, as shown in Table 1.

PCR performed at 12 weeks showed that out of the total 263 patients about 251 (95.4%) became PCR negative and 12 (4.56%) remained positive at 12 weeks of treatment with dectasvir and Sofosbuvir combination, as shown in Table 2.

These patients were given an additional 12 week therapy with the same drugs but they remained non-responsive. The patients were then shifted to valpatasvir and Sofosbuvir combination as per the WHO guidelines and PCR done again at 48 weeks showed all of them to become PCR

negative. The treatment was well tolerated by all patients and no serious side effects were noted. The cause of the treatment non-responsiveness was then assessed taking into consideration the age, gender, TLC, hemoglobin (hb), and baseline ALT and it was observed that only TLC ($p < 0.025$) and hemoglobin ($p < 0.023$) had a significant relationship with SVR (sustained virological response, PCR negative at 12 weeks). Results of the model shows that the probability of positive HCV PCR at 12 weeks decreases by 0.73 with one unit increase in the hemoglobin, whereas one unit increase in TLC reduces the probability of HCV PCR at 12 weeks, positive by 0.001. The rest of the independent variables did not have any significant relationship with treatment non-responsiveness, as shown in Table 3.

4. DISCUSSION

Since the advent of DAA for the treatment of HCV infection, the management of the disease has had a significant improvement, however in third world countries the price and the availability of this costly medication is a big concern [10]. There are numerous generic formulations available but there is very little data regarding the safety and efficacy of these drugs. Genotype 3 is the most difficult type to treat and unfortunately in Pakistan this is the commonest type encountered [11].

The recent guidelines published by AASLD (American Association for the study of Liver diseases) puts emphasis on using newer agents like Glecaprevir/Pibrentasvir which are safe and highly efficacious but as HCV in our country HCV is primarily a disease of the poor so, the total cost of 30.710 USD makes this combination out of reach of the majority of the patients.

Table 1. Demographic characteristics of participants. (n=263)

Variables	Mean±SD n (%)
Mean Age (years)	39.9 years
Gender	Male 162 (61.6%) Female 101 (38.4%)
Mean alanine transaminase (U/L)	102 U/L
Meant total leukocyte count (TLC) (/mm ³)	6400/mm ³

Table 2. PCR Result at 12 weeks

PCR Result	Frequency	Percentage
Negative	251	95.4%
Positive	12	4.6%

Table 3. Correlation between the variables and treatment outcome

Variable 1	Variable 2	Response at 12 weeks	Response at 24 weeks	Response at 48 weeks
Sustained virological response (SVR)	Sex	0.739	0.934	0.994
	Age	0.319	0.791	0.931
	TLC	0.025*	0.437	0.305
	Platelets	0.587	0.303	0.430
	ALT	0.740	0.913	0.305
	Hb	0.023*	0.107	0.189

*P value computed using Pearson Chi Sq Test, taking p value <0.05 as significant

In our study the subjects recruited were given treatment with Sofosbuvir and dectastvir initially for a period of 12 weeks and the total cost of the treatment with locally manufactured generic formulation was only 63.0 USD. The treatment was extended to 24 weeks in case of non-responsiveness and the cost of treatment as well as the drugs was well tolerated by all of the patients.

The SVR12 achieved in our study was 95.4%. Those patients not achieving a response were given a six months' trial of valpatasvir and Sofosbuvir making the total cost of treatment about 181.4 USD. All of the patients became PCR negative at the end of one year treatment. This is a significantly good achievement as compared to some other locally published studies.

According to study by Umar M. etal, an SVR of 83.3% was achieved in their cirrhotic subjects which is significantly lower than our finding of 95.4% [6]. A major reason could be the fact that our study recruited only treatment naïve and non-cirrhotic patients so the subjects were responsive and tolerated the drug better and drug resistance was also not a contributing factor for poor response.

However another study done by Mushtaq.S etal recruited patients with characteristics similar to ours and they produced results similar to our study. According to their study the overall SVR12 was 95.5% [12]. Similarly another study done by Balperio P. etal, suggests an SVR of 90% in patients with similar characteristics, again strengthening the rationale for using these cheap and easily available drugs [13].

As far as other international studies are concerned, ALLY 3+ a leading study on Sofosbuvir and dectastvir showed an SVR of 90%, compared to our findings of 95.4%. The results are very encouraging [14]. A study by

Welzel TM etal shows an SVR of 88% in treatment naïve patients, which is lower as compared to our findings [15]. This may be due to the difference in genetic makeup of our study population or viral characteristics. Further studies are needed in this regard to assess the actual causes behind this discrepancy. It is however interesting to note that Iran, a country with much geological, cultural, health, social and economic similarities as Pakistan has a reported SVR of 98% with these treatment regimens [16].

Our study has probed in to the likely causes behind the treatment non-responsiveness. After considering the age, gender, TLC, baseline ALT and platelet count, we found that a high hemoglobin and high total leucocyte count had a significant relationship with the SVR. They were associated with a good outcome. This is a new feature found in our study. In contrast to this the commonest causes of non-responsiveness have been poor educational status, high ALT, and a high viral load [6,12,13].

A major limitation of our study is the fact that it was performed only on treatment naïve and non-cirrhotic patients. The achieved SVR could be lower and the drug tolerability could be worse if other patients' types were also included in the study. Similarly because of financial constraints important risk factor for poor response like diabetes, obesity and drug resistance could not be assessed.

Despite these limitations our study provides new insights in to the financial aspects of the management of this deadly virus which unfortunately is primarily a disease of the poor.

5. CONCLUSION

The generic fixed dose combinations of Sofosbuvir and dectastvir are a cheap and effective treatment strategy with more than 95.4% of the patients achieving SVR12 in HCV

genotype 3 infections. Those not responding achieved PCR negativity with a trial of six months' therapy with Sofosbuvir and velpatasvir combination. A high hemoglobin ($p < 0.023$) level and high total leucocyte count ($p < 0.025$) were predictors of good treatment response.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

CONSENT

All patients included in the study signed an informed consent form.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:

The peer review history for this paper can be accessed here:
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