

BioScientific Review (BSR)

Volume 2 Issue 3, 2020

ISSN_(P): 2663-4198 ISSN_(E): 2663-4201

Journal DOI: <https://doi.org/10.32350/BSR>

Issue DOI: <https://doi.org/10.32350/BSR.0203>

Homepage: <https://journals.umt.edu.pk/index.php/BSR>

Journal QR Code:



Article:

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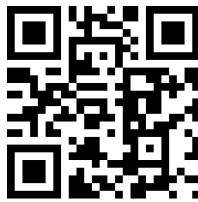
Author(s):

Komal Saleem, Amjad Ali, Shazia Rafique, Noshaba Rani, Braira Wahid

Article DOI:

<https://doi.org/10.32350/BSR.0203.03>

Article QR Code:



Komal Saleem

To cite this article:

Saleem K, Ali A, Rafique S, et al. Successful retreatment of the HCV relapse patients with a 4-Week long therapy using sobuvir, ribavirin, and daclatasvir combination: A case series. *BioSci Rev.* 2020;2(3):17–25.

[Crossref](#)



A publication of the
Department of Life Sciences, School of Science
University of Management and Technology, Lahore, Pakistan

Successful Retreatment of the HCV Relapse Patients with a 4-Week Long Therapy using Sofosbuvir, Ribavirin, and Daclatasvir Combination: A Case Series

Komal Saleem¹, Amjad Ali¹, Shazia Rafique¹, Noshaba Rani¹, Braira Wahid^{2*}

¹Centre of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan

²Centre for Applied Molecular Biology, University of the Punjab, Lahore, Pakistan

*Corresponding author: brairawahid@gmail.com

Abstract

Hepatitis-C virus (HCV) is an enveloped RNA virus that currently infects more than 180 million people, worldwide. Interferon therapy was previously used as a standard therapy for HCV. Now it has been replaced with an interferon-free therapy or the direct acting antiviral (DAA) drug therapy. Although the DAA drug therapy is a potent strategy which has an excellent efficacy against the HCV infection with a majority of patients achieving sustained virological response (SVR), we report here three patients who experienced relapse after a 6-month long DAA drug therapy. The patients experienced relapse after receiving sofosbuvir (400mg) and ribavirin for 6 months. All three patients were later successfully treated with sofosbuvir, ribavirin, and daclatasvir combination. The current study highlights that the retreatment combination of sofosbuvir, ribavirin, and daclatasvir is more efficacious in the Pakistani population where practitioners are still using sofosbuvir and ribavirin.

Keywords: genotype, HCV, HCV relapse, non-responders, therapy

1. Introduction

The annual estimated global bioburden of Hepatitis C virus (HCV) is approximately 130 to 170 million infected people. About 80% of the HCV patients experience chronic hepatitis, cirrhosis, and hepatocellular carcinoma

[1, 2]. Over the past decade, HCV therapeutics have dramatically improved and have significantly reduced the morbidity and mortality rate. Previously, IFN therapy with ribavirin was in common practice but its limited efficacy and other side effects as well as the

Table 1. Clinical Management of HCV with DAA Drug Regimens

Drug Regimen	HCV Genotypes
Sofosbuvir/Ledipasvir +/-Ribavirin	Genotype 1, 4, 5 and 6
Paritaprevir/Ritonavir/Ombitasvir+Dasabuvir+/- Ribavirin	Genotype 1
Sofosbuvir/Simeprevir +/-Ribavirin	Genotype 1 and 4
Sofosbuvir/Daclatasvir +/-Ribavirin	All genotypes
Paritaprevir/Ritonavir/Ombitasvir+/-Ribavirin	Genotype 4
Sofosbuvir + Ribavirin	Genotype 2 and 3

HCV: hepatitis C virus; DDA: direct acting antiviral agent

chances of relapse necessitated the development of new therapeutic approaches [3]. The recent development of the direct acting anti-viral (DAA) drugs has revolutionized the treatment of HCV. This current and standard treatment is efficacious, safe, and well-tolerated in a majority of the patients [4-7]. Table 1 describes the clinical management of HCV with DAA drug regimens (see Table 1). In Table 2, we report the first case series of the non-responsiveness of the HCV patients towards the DAA drugs and further suggest an effective retreatment option.

2. Case 1

On 28 October 2015, a 45-year-old female patient was referred to a hepatologist with elevated liver enzymes aspartate aminotransferase (AST) 102 U/L (reference range <37 U/L), alanine aminotransferase (ALT) 125 U/L (reference range <42 U/L), alkaline phosphatase (ALP) 148 IU/ml (reference range <115 IU/ml) and bilirubin 0.3 mg/dL (reference range <0.2 mg/dL). The risk factor identified was the blood transfusion she received after an inguinal hernia surgery in 2010. The patient was diagnosed with the HCV infection. Her initial viral load was determined to be 4, 05,600 U/ml and the genotype was 3a. No changes in the size and appearance of the liver were noticed in the abdominal ultrasound. The treatment was administered with sofosbuvir and ribavirin from November 2015 to April 2016. The virus was completely eradicated after six months of treatment. During the follow-up care, her PCR came negative for HCV in August 2016 (4 months after the end of the treatment). In November 2016, the patient once again paid a visit to the hospital for routine tests. Her HCV PCR testing showed a significant viral load of

7, 93,754 U/ml and 3a genotype, seven months after the completion of the treatment. Endoscopy showed mild ascites and an abdominal ultrasound revealed an enlarged spleen and a fatty liver. A significant elevation in the liver enzymes, a weight loss of 5kg, and a mild decline in the platelet count and hemoglobin (Hb) was also observed. It was a confirmed case of relapse because the patient's detailed history revealed no risk factors responsible for a reinfection. HCV relapse was later cured after receiving daclatasvir, ribavirin, and sofosbuvir combination for 4 weeks.

3. Case 2

A 55-year-old female patient without a medical history complained about the loss of appetite, fatigue, lethargy, and a progressive weight loss for 3 months. In July 2015, she visited a medical centre for her detailed clinical assessment. Her liver function enzymes were mildly elevated. The patient was infected with the 3a genotype of HCV. Her initial viral load analyzed through an HCV PCR was 18, 63,723 U/ml. The patient received a 6-month long sofosbuvir + ribavirin treatment. By the end of her HCV treatment, the PCR showed a significant decline in the viral load but the virus was not entirely eliminated. The treatment continued for another two months till the virus was eliminated. During a follow-up routine test in May 2016 (2 months after the completion of the treatment), HCV was detected and once again the 3a genotype was identified. The PCR analysis showed that the viral load was 1, 68,080 U/ml. The liver function enzymes were in the normal range. The liver and spleen size were also normal. A second treatment with sofosbuvir was administered for a further four months (from May 10, 2016 to October 17, 2016) which showed a ten-fold increase

Table 2. Medical History of Patients

Parameter	Case 1	Case 2	Case 3
Age	45	55	60
Gender	Female	Female	Male
HCV genotype	3a	3a	3a
BMI (kg/m ²)	9.7	13.5	8.5
Possible cause of exposure	Surgery	Manner of acquisition unknown	Manner of acquisition unknown
Regimen	Sofosbuvir (400 mg) + Ribavirin (1000 mg)	Sofosbuvir (400 mg) + Ribavirin (1000 mg)	Sofosbuvir (400 mg) + ribavirin (1000 mg)
Relapse	7 months after the completion of treatment	2 months after the completion of treatment	8 months after the completion of treatment

HCV: Hepatitis C virus; BMI: Body mass

indein the viral load (1,110,597 U/ml) and non-responsiveness towards the sofosbuvir treatment. The patient was later successfully treated with sofosbuvir, ribavirin, and daclatasvir combination.

4. Case 3

From December 2015 to May 2016, a 60-year-old male patient with a confirmed diagnosis of HCV (3a genotype, viral load 106,104 U/ml) was treated with a 6-month-long regimen comprising ribazole and sofosbuvir. The patient received regular treatment for six months and the viral load was reduced to an undetectable level. A mild change in ALP, ALT, ASP, bilirubin, Hb, and platelets during the course of the treatment was also observed. The patient achieved sustained virological response (SVR) and visited the hospital on November 8, 2016 for a follow-up. A relapse was observed and the HCV RNA viral load analyzed through PCR was 77,110 U/ml. Afterwards, the viral load declined below the detection limit after administering sofsobuvir, ribavirin, and daclatasvir combination for 4 weeks.

5. Discussion

Six months of DAA therapy is effective and well-tolerated in about 95% of the patients with a chronic HCV infection. A recent study suggested that 8 to 12 weeks of therapy is more cost-effective and efficacious, although it is not sufficient to eliminate the virus completely in 90% of the patients [8]. In this study, we examined the non-responsiveness of three HCV patients after receiving 6 months of DAA therapy (Table 2).

A significant rise in the viral load was observed after the treatment was completed. Platelet count and Hb declined in all of these patients. The body mass index (BMI) of all the three patients was also below the normal range. A moderate elevation in the liver function enzymes before and after the treatment was also observed. One of these non-responders also experienced mild ascites and an enlargement of the spleen. Two of the patients were female while all of them belonged to different age groups. All the three patients were infected with genotype 3 and denied exposure to HCV after the treatment was

Table 3. Detailed Account of Patients Profile Before and after Treatment

Parameter	Case 1		Case 2		Case 3	
	Before treatment	After relapse	Before treatment	After relapse	Before treatment	After relapse
Viral load IU/ml	4,05,600	7,93,754	1,68,060	18,63,723	1,06,104	77,110
Bilirubin mg/dL	0.5	0.3	0.5	0.5	0.5	1
Platelet per μ l	96,000	82,000	1,30,000	1,16,000	3,98,000	271,000
Hb g/dL	13	9	10.9	9.3	12	10
ALT U/L	125	125	185	179	53	18
AST U/L	111	102	48	50	16	44
ALP U/L	156	148	185	179	114	115
Liver size	Normal	Normal	Normal	Normal	Normal	Normal
Spleen size	Normal	Enlarged	Normal	Normal	Normal	Normal
		Mild Ascites				

Hb: Hemoglobin; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase

withdrawn. Moreover, their detailed medical history showed a no-risk factor for reinfection. Hence, all patients were confirmed relapse cases (Table 3).

All patients received a combination therapy consisting of polymerase inhibitors sofosbuvir and ribavirin. Two patients experienced relapse after attaining SVR, whereas in one patient relapse occurred after 2 months of achieving SVR. Factors such as individual DAA metabolism, fibrosis and cirrhosis of liver, genetic background and immune status of patient, adherence to therapy, drug resistant viral populations, transient suppression of viral replication, lifestyle of patients, drug abuse and nutritional habits, co-infection with other viruses, and substandard quality of drugs lead to the failure of the treatment [9].

Donaleson *et al.* reported sofosbuvir resistance even when this drug was used with pegylated IFN or with ribavirin in the HCV chronic patients [10, 11]. Novel NS5B gene mutations such as L159F, L320F and V321A as well as N316 polymorphism were detected in the Sofosbuvir non-responders [10-12]. According to JM Pawlotsky, the viruses resistant to the NS3-5A inhibitor persist in the blood for years, whereas NS3-4A protease inhibitor resistant viruses are eliminated from the blood within a few weeks or months. After the completion of the treatment, the resistant variants of the HCV undergo mutations and become fit to propagate in the liver [11].

SVR is difficult to achieve in the patients with HCV associated hepatic impairments. In fact, cirrhosis itself is an important reason behind treatment failure [13, 14]. The administration of

DAAs in patients with advanced fibrosis or cirrhosis increases the treatment's side effects and potency [15].

Asma *et al.* reported resistance associated mutations and HCV resistant variants in patients who did not achieve SVR. Some common resistance associated variants include V55A, Q80K, R155K, T54S/A, V36M, L159F, S282R, V321A, C316N, Y93H, L31V, Q30, and M28 that decrease the viral susceptibility towards NS3/4A inhibitor, NS5B NP1, NS5B NNP1, and NS5A inhibitors.

Another possible cause of relapse is the suppression of viral replication because the virus reaches an undetectable level during the therapeutic period. Yet, during the post-treatment period this residual virus become active, starts replicating and causes relapse.

The genetic background of patients acts as a predictor of the treatment response, for example, SNPs near the *IL 28B* gene on chromosome 19 are frequently found in the responders as compared to the non-responders. Likewise, another study showed a strong association of rs12979860 with EVR and SVR.

The immune status of patients and metabolic alterations such as old age, high waist circumference, oxidative stress, high serum uric acid level, LDL-cholesterol, low hemoglobin level, increased bilirubin, hypolipidemia, vitamin D and vitamin B12 deficiencies, diabetes, obesity, and changes in adipocytokines also result in treatment failure.

Likewise, co-infection with other viruses such as HIV and HBV alters the treatment response. Several studies show that the rates of SVR are significantly lower in co-infected patients as

compared to the patients with HCV mono-infection.

A comparative analysis of hypothyroidism between two different groups of patients (one group was treated with sofosbuvir, pegylated-IFN- α , ribavirin, while the other group received sofosbuvir, daclatasvir, ribavirin) was recently published. The findings confirmed the high prevalence of hypothyroidism among patients treated with sofosbuvir, pegylated-IFN- α , and ribavirin. The study suggested the need of the regular monitoring of the thyroid stimulating hormone in the HCV patients during treatment. There is another study that reported the abrupt onset of diabetes and poor glycemic control following the DAA drug treatment. The evidence of the DAA drug induced hepatotoxicity is also available in the literature [16, 17, 18]. This case series also confirmed that the combination of sofosbuvir and ribavirin is not too effective due to which most of the clinicians in Pakistan prescribe sofosbuvir, ribavirin, and daclatasvir combination to the HCV patients.

In Pakistan, local companies have obtained the license to manufacture an authorized version of Sovaldi. Patient 1 used Sofohil manufactured by Hilton Pharma Limited, whereas the rest of the two non-responding patients were treated with Sovaldi manufactured by Ferozsons Laboratories Limited who have an exclusive agreement with Gilead Sciences, USA. The rampant counterfeiting of drugs is a major public health issue in the country. According to the Pakistani Pharmacist Association, there are about 100,000 illegal merchants selling fake medications and not a single pharmaceutical company of Pakistan has either FDA or WHO approval. In March

2015, the Drug Regulatory Authority of Pakistan (DRAP) reported the illegal production of Sovaldi in Kahuta Industrial Area, Pakistan.

Clinicians need to reconsider the response of DAA by evaluating the patients' metabolism, immune status, as well as the quality of drugs to assess the efficacy of treatment for the benefit of the infected individuals and the population at large. Moreover, most clinicians do not adhere to the internationally recommended guidelines since sofosbuvir is the only available drug in Pakistan. Therefore, health officials must ensure the adequate provision of all anti-viral drugs.

5.1. Future Prospects

As of January 2021, a series of published studies have highlighted the clinical complications associated with DAA drug treated patients. Therefore, it's quite obvious that the researchers working in the area of personalized medicine should be developing other treatment options to cater the special needs of the HCV infected DAA drug non-responders.

6. Conclusion

Although the newly developed DAA drugs have a high SVR rate worldwide, yet their efficacy has not been properly analyzed in the low-income countries. Therefore, this case series highlights the need to conduct efficacy trials with a large sample size to precisely monitor the treatment response of the DAA drugs and their associated adverse effects. During the early years of the DAA drugs' introduction, many clinicians used to prescribe the DAA drug combination of sofosbuvir and ribavirin. The findings of this case series have also

confirmed that this combination is not effective at all.

Funding: None

Conflict of interest: The authors declare nothing to disclose regarding the conflict of interest with respect to this manuscript.

Acknowledgement: Special thanks to the diagnostic wing of the Centre for Applied Molecular Biology, University of the Punjab, Lahore, Pakistan.

Ethical Consent: Obtained from all patients.

References

- [1] Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect.* 2011; 17(2):107-115. <https://doi.org/10.1111/j.14690691.2010.03432.x>
- [2] Hajarizadeh BJ, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nature Rev Gastroenterol Hepatol.* 2013;10(9): 553-562. <https://www.nature.com/articles/nrgastro.2013.107.pdf?origin=ppub>
- [3] Manns M, Wedemeyer H, Cornberg M. Treating viral hepatitis C: Efficacy, side effects, and complications. *Gut.* 2006;55(9):1350-1359. <http://dx.doi.org/10.1136/gut.2005.076646>
- [4] Pockros PJ, et al. Efficacy of direct-acting antiviral combination for patients with hepatitis C virus genotype 1 infection and severe renal impairment or end-stage renal disease. *Gastroenterol.* 2016;150(7): 1590-1598. <https://doi.org/10.1053/j.gastro.2016.02.078>
- [5] Suwanthawornkul T, Anothaisintawee T, Sobhonslidsuk A, et al. Efficacy of

- second generation direct-acting antiviral agents for treatment naïve hepatitis C genotype 1: A systematic review and network meta-analysis. *PloS one*. 2015 Dec 31;10(12):e0145953. <https://doi.org/10.1371/journal.pone.0145953>
- [6] Toyoda H, et al. Safety and efficacy of dual direct-acting antiviral therapy (daclatasvir and asunaprevir) for chronic hepatitis C virus genotype 1 infection in patients on hemodialysis. *J Gastroenterol*. 2016;51(7):141-147.
- [7] Johnson TM, et al. Clinical experience with dolutegravir /abacavir/lamivudine in HIV–HCV co-infected patients treated with a sofosbuvir-based regimen—safety and efficacy. *HIV Clin Trials*. 2016;17(6):242-245. <https://doi.org/10.1080/15284336.2016.1248625>
- [8] Martinello M, et al. Sofosbuvir and ribavirin for six weeks is not effective among people with acute and recently acquired HCV infection: The DARE-C II study. *Hepatol*. 2015;62(1):741-742.
- [9] Pawlotsky JM. Hepatitis C Virus Resistance to Direct-Acting Antiviral Drugs in Interferon-Free Regimens. *Gastroenterol*. 2016; 151(1):70-86. <https://doi.org/10.1053/j.gastro.2016.04.003>
- [10] Donaldson EF, et al. Clinical evidence and bioinformatics characterization of potential hepatitis C virus resistance pathways for sofosbuvir. *Hepatol*. 2015;61(1):56-65. <https://doi.org/10.1002/hep.27375>
- [11] Pawlotsky JM. Treatment failure and resistance with direct-acting antiviral drugs against hepatitis C virus. *Hepatology*. 2011;53(5):1742-1751. <https://doi.org/10.1002/hep.24262>
- [12] Costantino A, et al. Naturally occurring mutations associated with resistance to HCV NS5B polymerase and NS3 protease inhibitors in treatment-naïve patients with chronic hepatitis C. *Virol*. 2015;12(1):186-172.
- [13] Afdhal N, et al. The Effect of Liver Fibrosis and Cirrhosis on SVR in 4913 Patients With Hepatitis C: Results From The WIN-R Trial. *Gastroenterol*. 2006;130(4):212-265
- [14] Abergel A, et al., Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: A multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. *J Viral Hep*. 2006;13(12):811-820. <https://doi.org/10.1111/j.1365-2893.2006.00768.x>
- [15] Im GY, Dieterich DT. Direct-acting antiviral agents in patients with hepatitis C cirrhosis. *Gastroenterol Hepatol*. 2012;8(11):727-765.
- [16] Wahid B, Wasim M, Saleem K, Waqar M, Wahid K, Hussain M, Idrees M. Poor glycemic control and abrupt onset of diabetes in HCV patients receiving direct-acting antiviral drugs: case series. *Future Virol*. 2018;13(08):525-8. <https://doi.org/10.2217/fvl-2017-0147>
- [17] Wahid B. Hepatotoxicity and virological breakthrough of HCV following treatment with sofosbuvir, daclatasvir, and ribavirin in patients previously treated for tuberculosis. *J Med Virol*. 2019;91(12):2195-7. <https://doi.org/10.1002/jmv.25557>

- [18] Wahid B, Shami K, Joiya SA, et al. Comparing the risk of hypothyroidism in HCV patients treated with different DAA drugs combinations (sofosbuvir+ interferon + ribavirin and sofosbuvir+ daclatasvir + ribavirin). *J Med Virol.* 2020;92(12):3868-70. <https://doi.org/10.1002/jmv.25931>