

DAA treatment failures in a low-resource setting with a high burden of hepatitis C infections: a case series

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Abstract

Globally, 58 million people are living with hepatitis C virus (HCV) infection and 1.5 million new patients are infected every year. The advent of direct acting antivirals (DAAs) has revolutionized the treatment of HCV, opening the door to the ambitious World Health Organization HCV infection elimination strategy by 2030. However, emerging resistance to DAAs could jeopardize any hope of achieving these targets. We discuss a series of 18 patients within a resource-limited setting, who after failing standard sofosbuvir-daclatasvir-based regimen also failed to respond to advanced pan-genotypic treatment regimens, i.e. sofosbuvir-velpatasvir, sofosbuvir-velpatasvir-ribavirin and sofosbuvir-velpatasvir-voxilaprevir. To avoid the spread of refractory HCV strains within the existing epidemic, we call for increased attention and research regarding patients failing treatment on standard pan-genotypic regimens and the spread of HCV-resistant strains within the communities.

INTRODUCTION

Globally, over 58 million people are estimated to live with a hepatitis C virus (HCV) infection, and annually, ~1.5 million people are getting newly infected [1]. Since 2014, direct acting antivirals (DAAs) have revolutionised HCV treatment, increasing cure rates to over 95% [2]. However, a significant proportion of patients (1–6%) on DAAs fail to achieve the target of sustained virologic response (SVR) at 12 weeks after the end of treatment [3]. DAAs target specific viral proteins (NS5A, NS5B and NS3): genetic mutations in these targets, termed resistance-associated substitutions (RAS), confer resistance to treatment.

Since 2015, Médecins Sans Frontières (MSF) has been operating a Hepatitis C clinic offering free-of-cost DAA-based treatment at Machar Colony, an informal settlement in Karachi. Being a low-resource setting, an aspartate aminotransferase to platelet ratio index (APRI) score is used to determine the stage of the liver disease. If indicated (APRI > 1), a child turcotte pugh (CTP) evaluation is done to differentiate compensated (CTP Class A) and decompensated patients (CTP Classes B and C). Our first-line treatment is sofosbuvir-daclatasvir 12 weeks (APRI < 1), and sofosbuvir-daclatasvir 24 weeks (APRI

> 1) plus ribavirin in case of decompensated cirrhosis (CTP Class B or C). Second-line treatment regimen is sofosbuvir-velpatasvir for 12 weeks +/- ribavirin. From February 2015 to December 2020, 4648 chronic HCV patients were initiated on oral DAA therapy; among them, 3446 reached sustained virological response at 12 weeks after treatment completion (SVR12) and 187 (4.02%) failed to achieve SVR12. Here, we discuss a case series of 18 patients (Table 1) who failed first- and second-line therapies i.e. sofosbuvir-daclatasvir +/- ribavirin and sofosbuvir-velpatasvir +/- ribavirin or voxilaprevir.

CASE SERIES

Cases 1–5 were initiated on a sofosbuvir-velpatasvir 12-week treatment regimen after having failed first-line therapy of sofosbuvir-daclatasvir +/- ribavirin. Case 1 had failed 24 weeks of sofosbuvir-ribavirin therapy prior to sofosbuvir-daclatasvir-ribavirin for 12 weeks. None of the five patients had clinical signs of decompensation and cirrhotic patients all were categorized as CTP Class A. While none achieved SVR12, four out of the five patients had a significant reduction in the viral load. Case 3 was

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Table 1. Specific treatment regimens and their outcomes

Case number	Sex	Age	Tx initiation	Pre-Tx APRI	Pre-treatment VL	Post-treatment VL
Case 1	Female	45	SOF-RIB 24 W	2.00	1 606 881	179 536
			SOF-DAC-RIB 12 W	1.76	179 536	74 489
			SOF-VEL 12 W	1.67	74 489	41 800
			SOF-VEL-VOX 12 W	2.80	41 800	Not detected
Case 2	Male	51	SOF-DAC 12 W	0.83	568 628	1 230 000
			SOF-VEL 12 W	1.06	123 000	57 100
			SOF-VEL-VOX 12 W	0.43	57 100	Not detected
Case 3	Female	36	SOF-DAC 12 W	0.60	1 624 920	29 705
			SOF-VEL 12 W	0.71	29 705	1 450 000
			SOF-VEL-VOX 12 W	0.74	145 000	Not detected
Case 4	Female	50	SOF-DAC-RIB 12 W	3.36	56 016	503 000
			SOF-VEL-RIB 12 W	1.21	589 000	236 000
			SOF-VEL-VOX 12 W	0.75	236 000	Not detected
Case 5	Male	60	SOF-DAC-RIB 24 W	1.28	235 000	100 000
			SOF-VEL 12 W	1.41	100 000	15 600
			SOF-VEL-VOX 12 W	1.50	15 600	Not detected
Case 6	Male	60	SOF-DAC 12 W	0.21	3 620 000	1 350 000
			SOF-VEL-RIB 12 W	0.52	1 350 000	7 680 000
			SOF-VEL-RIB 12 W	0.52	7 680 000	Not detected
Case 7	Female	50	SOF-DAC 24 W	3.66	26 900	18 800
			SOF-DAC 24 W	3.66	26 900	18 800
			SOF-VEL 4 W	1.10	18 800	473 000
Case 8	Male	50	SOF-DAC 12 W	0.35	112 000	472 000
			SOF-VEL 12 W	0.36	472 000	316 000
Case 9	Female	28	SOF-DAC 24 W	5.68	9560	41 900
			SOF-VEL 12 W	–	41 900	203 000
Case 10	Female	52	SOF-DAC 24 W	4.00	68 600	96 600
			SOF-VEL 12 W	3.07	96 600	134 000
Case 11	Male	55	SOF-DAC 24 W	1.92	6 300 000	1 060 000
			SOF-VEL 12 W	1.35	1 060 000	289 000
Case 12	Male	58	SOF-DAC 12 W	0.75	Qualitative	444 000
			SOF-VEL 12 W	–	444 000	77 000
Case 13	Male	46	SOF-DAC 12 W	0.68	772 000	2 350 000
			SOF-VEL 12 W	0.75	2 350 000	1 170 000
Case 14	Male	46	SOF-DAC 12 W	0.67	1 860 000	10
			SOF-VEL 12 W	–	10	823 000
Case 15	Male	36	SOF-DCV 12 W	0.92	2 100 000	164 000
			SOF-VEL-VOX 12 W	0.77	3 290 000	3 290 000
Case 16	Male	50	SOF-DAC 12 W	0.57	158 000	50 500
			SOF-VEL-RIB 12 W	0.15	50 500	10 900 000
			SOF-VEL-VOX 12 W	–	10 900 000	1 990 000
Case 17	Male	57	SOF-RIB 24 W	2.59	103 581	58
			SOF-DAC-RIB 24 W	1.33	9379	142 000
			SOF-VEL-RIB 12 W	–	142 000	135 000
Case 18	Female	45	SOF-DAC 12 W	0.99	517 232	139 000
			SOF-VEL 12 W	–	139 000	98 800

Tx, Treatment; SOF, Sofosbuvir; RIB, Ribavirin; DAC, Daclatasvir; VEL, Velpatasvir; VOX, Voxilaprevir.

the only patient whose viral load increased while being on treatment. None of the five patients had any documented adherence issues and all completed the entire duration of treatment. No risk factors for reinfection were identified. All five patients were retreated with 12 weeks of sofosbuvir-velpatasvir-voxilaprevir and were successfully able to achieve SVR12.

Case 6 was initiated on sofosbuvir-velpatasvir 12-week treatment after failing first-line therapy and

again failed to achieve SVR12. Case 6 had completed 12 weeks of sofosbuvir-velpatasvir treatment; whereas Case 7 interrupted sofosbuvir-velpatasvir treatment after just 1 month. The reasons provided for interruption were social in nature. Both patients had a significant increase in viral load on reassessment. Case 6 was retreated with sofosbuvir-velpatasvir with the addition of weight-based ribavirin for 12 weeks on the advice of a tertiary care referral centre (Sindh Institute of Urology

and Transplantation (SIUT), Pakistan) and successfully achieved SVR12. Case 7 received sub-optimal treatment, and an elevated APRI score suggested advanced liver disease. This patient is planned to be re-initiated on treatment with sofosbuvir-velpatasvir-ribavirin after being traced and re-counselled.

Cases 8–14 were started on sofosbuvir-velpatasvir 12-week regimen. None of the patients had any clinical signs of decompensation and all cirrhotic patients were categorized as CTP Class A. All except two patients (Cases 9 and 11) had a significant reduction in viral load. Cases 9 and 11 had an increase in viral load on re-analysis at 12 weeks after the completion of treatment. None of the patients had any adherence issues. All seven patients are awaiting re-initiation of treatment with sofosbuvir-velpatasvir-voxilaprevir.

Case 15 was a patient who had previously failed sofosbuvir-daclatasvir 12-week therapy. Due to the unavailability of sofosbuvir-velpatasvir drug combination, the patient was initiated on sofosbuvir-velpatasvir-voxilaprevir at the time. The patient was unable to achieve SVR12 after the completion of therapy. Case 16 was a patient who failed treatment with sofosbuvir-daclatasvir 12 weeks and later with sofosbuvir-velpatasvir 12 weeks. The patient started sofosbuvir-velpatasvir-voxilaprevir for 12 weeks and was unable to achieve SVR12 at completion. This unique case failed three separate treatment protocols. Neither of the two patients had any adherence issues nor any identified risk factors of reinfection. The failure of these patients on sofosbuvir-velpatasvir-voxilaprevir presents a unique challenge. There is an intention to treat these patients with glecaprevir-pibrentasvir; however, the drug is yet to be available in the country.

Case 17 was a patient who failed sofosbuvir-ribavirin after 24 weeks and sofosbuvir-daclatasvir-ribavirin after 24 weeks at the MSF treatment centre. The patient was referred for a specialist hepatologist consultation at SIUT, and on their advice, was treated with sofosbuvir-velpatasvir-ribavirin for 24 weeks. However, the patient subsequently failed the treatment regimen, and on advanced investigations at SIUT, the patient was diagnosed with hepatocellular carcinoma. Hence, the patient was transferred out of the cohort for further workup and treatment. Uniquely, this patient was HCV genotype 2, whereas all other patients in this case series were HCV Genotype 3, the most prevalent genotype in Pakistan. Case 18 was a patient who failed 12 weeks of sofosbuvir-velpatasvir treatment therapy. The patient did complete the treatment but complained of an inability to tolerate the sofosbuvir-velpatasvir regimen. As a result, the patient refused to be initiated on sofosbuvir-velpatasvir-voxilaprevir.

DISCUSSION

Although there may be many reasons for treatment failures, one of these may be resistance associated substitutions (RAS). A previous study has suggested

that Y93H RAS, conferring resistance to daclatasvir and velpatasvir, is present in 5–10% of individuals with HCV Genotype 3 infection with no prior exposure to NS5A inhibitors [4]. Considering that Genotype 3 is the most prevalent genotype [5] in Pakistan (69.1%), it is imperative to incorporate second- and third-line treatment regimens with higher barriers of resistance [6, 7] in HCV programmes. Particularly, as the country scales up the HCV elimination programme [8]. Sofosbuvir-velpatasvir-voxilaprevir continues to be an effective rescue therapy with no specific RAS mutations within NS3, NS5A or NS5B in Genotype 3 non-cirrhotic patients [9]. However, at the current price, this regimen remains out of reach of many who could benefit from such therapy.

A continuous advocacy effort is needed to broaden access to new generations of pan-genotypic DAAs as well as reduce price of rescue therapies to an affordable level for both patients who will need to pay out of pocket as well as for governments who need to build robust national elimination plans. Furthermore, advocacy efforts are needed to broaden surveillance for genomic sequencing of RAS mutations, which would inform public health strategies to mitigate the increasing risk of resistant strains. Treatment regimens comprising an HCV protease inhibitor, such as grazoprevir, glecaprevir or voxilaprevir, are contraindicated in patients with decompensated (CTP B or C) cirrhosis and in patients with previous episodes of decompensation [3]. This requires a particular consideration for differentiated care when scaling up treatment to meet the goals of a countrywide elimination plan.

We urge the pharmaceutical industry to ensure affordable and timely access to retreatment options in all low- and middle-income countries (LMICs)—especially those LMICs with a high burden of HCV—to ensure timely treatment of refractory HCV infection. Otherwise, DAA-resistant strains may potentially become widespread in the communities, which may lead to higher failure rates in the future, thereby decreasing the likelihood of achieving the World Health Organization 2030 HCV elimination targets through treatment alone.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

This study has received an exemption from the National Bioethics committee, Pakistan Ref: No.4-87/NBC-625/

Exempt/21/1522 and Médecins Sans Frontières Ethics review board for a posteriori analysis of routinely collected clinical data.

CONSENT

All patients provided an informed, written consent for the use of clinical data for research purposes.

GUARANTOR

Dr Hassaan Zahid.

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