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Hepatitis C Retreatment With First-Line Direct Acting Antiviral Drugs

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Background and Aims: **Sofosbuvir (S), daclatasvir (D), ledipasvir, or velpatasvir (V) containing first-line hepatitis c virus (HCV) treatment regimens fail to cure viremia in 5–10%. We report our experience of HCV retreatment using these first-line drugs, in a setting where second-line anti-HCV drugs are not available.** ***Methods:*** **Adults, who had relapsed after first complete course of a sofosbuvir-containing first-line, pegylated interferon free, anti-HCV treatment regimen with or without ribavirin (Riba) were included. Retreatment regimen, tailored to the failed anti-HCV regimen, was based on principle of using first-line drugs for 24 weeks with ribavirin and swapping between pangenotypic and genotype-specific regimens. Retreatment outcome was categorized as successful (achieved undetectable HCV RNA at the end of treatment [ETR] and sustained viral response at week 12 [SVR12]), non-responder (failed to achieve ETR), or relapse (achieved ETR but not achieved SVR12).** ***Results:*** **Twelve patients (9 male; 7 cirrhosis; all genotype 3) who had relapsed to prior anti-HCV treatment (4 SD12, 4 SD24, 1 SDRiba12, 1 SDRiba24, 2 SV12) were included. Following retreatment (2 SDRiba24, 10 SVRiba24), all achieved ETR but only 9 (75%) achieved SVR12. Two among three, in whom retreatment failed, achieved SVR12 following another course of sofosbuvir/velpatasvir/ribavirin for 24 weeks. Overall, 11/12 (92%) patients achieved SVR12 following retreatment with the first-line anti-HCV drugs.** ***Conclusion:*** **HCV retreatment could be a treatment option if second-line anti-HCV drugs are not available. Successful retreatment could be achieved, in a large proportion, with the use of first-line drugs for 24 weeks with ribavirin and swapping of pangenotypic/genotype-specific regimens (NCT03483987). (J Clin Exp Hepatol xxxx;xxx:xxx)**

Recently, the treatment of hepatitis C virus (HCV) infection is revolutionized.[1] Now, HCV is treated with oral drugs, collectively named as 'direct acting antiviral agents (DAAs)'. The DAAs belong to three classes, namely NS3/4 protease inhibitors (e.g., voxilaprevir), NS5a inhibitors (e.g., daclatasvir, velpatasvir, ledipasvir), and NS5b inhibitors (e.g., sofosbuvir).[2,3]

Guidelines recommend to combine the DAAs from two or three different classes[3–5] for HCV treatment. Sofosbuvir, the DAA widely available at an affordable price, is used along with a NS5a inhibitor. In India, only first-line DAAs (sofosbuvir, daclatasvir, sofosbuvir/ledipasvir combination, and sofosbuvir/velpatasvir combination) are approved by the drug regulatory authority. The sofosbuvir/velpatasvir combination is a pangenotypic DAA. Initially, sofosbuvir/daclatasvir was considered as a genotype-specific regimen effective against HCV genotype 3. Later on, sofosbuvir/daclatasvir was found to be equally effective against other genotypes and was accepted as a pangenotypic alternative. Sofosbuvir/ledipasvir combination is truly genotype-specific and is effective against HCV genotype 1, 4, and 6.[6]

Data from clinical trials and real-life settings suggest that sofosbuvir-containing regimens successfully clear HCV infection in 90–95% of patients.[7,8] The presence of certain risk factors increase the chances for treatment failure. Factors shown to be associated with treatment failure are cirrhosis, genotype 3 infection, low platelet counts, metabolic syndrome, noncompliance to the drugs, the presence of psychiatric illness, drug-to-drug interaction, immunosuppression, post-transplant status, and HIV or HBV coinfection.[9–11]

The anti-HCV seroprevalence in India varies between 0.45 and 2.0% and we have an estimated burden of 5.0 million HCV infection among low-risk adult population[12,13] which is primarily transmitted through unsafe injection use.[14] It is known that over 70% of HCV infection in our country is due to genotype 3.[15] Real-life data from Indian studies suggest that a small proportion of those treated with DAA fail to clear virus.[7] Considering the

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Abbreviations: DAAs: Direct acting antiviral agents; ETR: End of treatment response; HCV: Hepatitis C virus; LS: Liver stiffness; RVR4: Rapid virological response at week 4; SVR12: Sustained virological response at 12 weeks

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huge burden of HCV in India, a large number of people are likely to require HCV retreatment.

Data on HCV retreatment with the use of DAAs available in the country are limited. We report our experience of HCV retreatment with first-line DDAs which are currently available in the country.

METHODS

Included adults (age >18 years) with chronic HCV infection, who attended our outpatient services between February 2018 and April 2022, were screened for selection criteria. Those fulfilling the eligibility criteria enrolled after obtaining written informed consent.

Study Participants

Patients who had completed a single course of a sofosbuvir-containing, pegylated-interferon (IFN) free, first-line DAA-based, anti-HCV treatment regimen, and failed to achieve sustained virological response at week 12 (SVR12) were included irrespective of severity of liver disease, HCV genotype, inclusion of ribavirin (Riba) in the failed DAA regimen, and history of prior treatment with pegylated-IFN/ribavirin. The participants who had taken an incomplete course of DAA were excluded. We excluded the participants with chronic kidney disease, prior organ transplantation, congenital or acquired immunocompromised states. We also excluded those who had been treated with DAA-containing regimen on two or more occasions or with DAA which are not marketed in India. We did not include the patients with decompensated cirrhosis because they were less likely to tolerate ribavirin containing treatment. Before inclusion of participant, SVR12 were tested at least twice on specimens collected at different time points to ensure that the prior anti-HCV treatment had really failed.

Retreatment Regimens

The retreatment regimen was selected according to the prior failed DAA regimen. Retreatment regimens were empirically designed to (i) use first-line anti-HCV drugs available in India (sofosbuvir, ledipasvir, daclatasvir, and velpatasvir), (ii) for 24-week duration, (iii) along with ribavirin, and (iv) swap between pangenotypic and genotype-specific regimen, i.e., if a pangenotypic regimen (sofosbuvir plus velpatasvir ± ribavirin) had failed earlier, retreatment was given with a genotype-specific regimen (sofosbuvir plus daclatasvir/ledipasvir ± ribavirin) or vice-versa (Table 1).

Assessment of Response to Anti-HCV Treatment

Relevant clinical, laboratory, and treatment details were recorded in our predefined data collection form. Participants were classified as with or without cirrhosis, defined by liver stiffness (LS) exceeding 12.5 Kilopascal (KPa) on fibroscan (FibroScan®, Echosens, France). All the LS measurements were performed as per our standard protocol as described elsewhere.[16]

Patients were followed at 4 and 12 weeks after the start of retreatment and at the end of 24-weeks treatment. More frequent follow-up was done for those with advanced cirrhosis or if clinically warranted. Virological response was assessed by measuring quantitative HCV RNA after 4 weeks of treatment (rapid virological response [RVR4]), at the end of the 24 weeks treatment (end of treatment response [ETR]) and SVR12.

Participants were grouped as responders (achieved ETR and SVR12), non-responders (not achieved viral suppression as judged on ETR), or relapsers (achieved viral suppression on ETR but failed to achieve SVR12) following retreatment.

Laboratory Methods

HCV RNA was measured using COBAS® AmpliPrep/COBAS® TaqMan® HCV quantitative Test, v2.0 (Roche, Branchburg, NJ, USA) with lower limit of detection of 15 IU/mL. The absence of detectable HCV RNA using this assay at different time points was used to define RVR4, ETR, and SVR12. Any missing data were treated as failure of response.

HCV Genotyping

All patients underwent HCV genotyping prior to treatment. In brief, RNA was extracted using QIAamp Viral RNA Mini Kits (QIAGEN, Hilden, Germany) from serum/plasma and subjected to reverse-transcription using high-capacity cDNA RT Kit with RNAse inhibitor (Thermo Fisher Scientific, Massachusetts, United States) followed

Table 1 Retreatment Regimens.

Treatment regimen failed	HCV genotype	Regimen for re-treatment
Sof + Ledi ± Riba × 12–24 wks Sof + Dacla ± Riba × 12–24 wks	Any genotype	Sof + Velpa + Riba × 24
Sof + Velpa ± Riba × 12–24 wks	1, 4, 5 or 6 2 or 3	Sof + Ledi + Riba × 24 wk Sof + Dacla + Riba × 24 wk

HCV, hepatitis c virus; Sof, sofosbuvir; Riba, ribavirin; Peg-IFN, pegylated interferon; Ledi, ledipasvir; Dacla, daclatasvir; Velpa, Velpatasvir.

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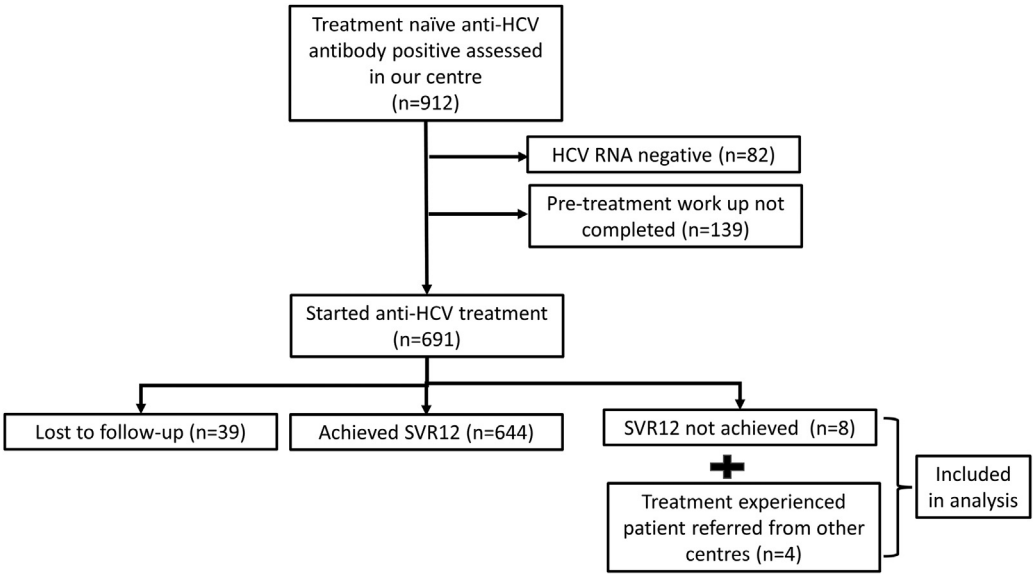

Figure 1 Flow chart showing the cohort of anti-HCV positive patients who were followed in our center.

by amplification of DNA with PCR using primers corresponding to 5′UTR and NS5B regimens. The amplification products were cleaned and subjected to Sanger sequencing using the BigDye Terminator version 3.1 dye chemistry on an ABI 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) in both directions. The merged sequences so obtained were aligned with these of various HCV genotypes retrieved from the GenBank database [http://www.ncbi.nlm.nih.gov/nucleotide], and a phylogenetic tree was generated using MEGA 7 software and UPGMA method.

Considering the flow of HCV patients in our center, we had empirically planned to enroll 50 participants in three years of time; however, the study had to be terminated before complete enrollment due to disruption of routine hepatitis care services secondary to COVID-19 pandemic. The study was approved by our institute's ethics committee (2017-202-IP-100) and registered in clinicaltrails.gov (NCT03483987).

RESULTS

We included 12 patients who had relapsed after first course of DAA-based treatment given either in our center (n = 8) or elsewhere (n = 4) (Figure 1). All the 12 patients (9 male; 7 with cirrhosis) had HCV genotype 3 infection. All the participants were fully compliant during their prior failed anti-HCV therapy. Their relevant clinical and laboratory details are summarized in Table 2. All those with cirrhosis (n = 7) had compensated disease (CTP class A) and none had any evidence of decompensation. The details of the prior failed anti-HCV treatment, retreatment details, liver fibrosis status, and the outcome of retreatment for each of the participants are summarized in Table 3.

Table 2 Clinical and Laboratory Parameters of the Study Participants (n = 12).

Characteristics	Value
Age, median (range)	55 (43–62)
Male gender	9 (75)
Associated conditions	
Diabetes mellitus	4 (33)
Hypertension	3 (25)
Laboratory investigations	
Hemoglobin (g/dL)	11.8 (10.6–13.2)
Total leukocyte cell count (×1000/μL)	6.5 (4.7–8.7)
Platelets ($\times 10^6/\mu L$)	115 (86–144)
Creatinine (mg/dL)	0.9 (0.7–1.2)
Total serum bilirubin (mg/dL)	1.0 (0.9–1.3)
Albumin (g/dL)	4.1 (3.5–4.5)
Alanine aminotransferase (IU/L)	71 (51–92)
Aspartate aminotransferase (IU/L)	83 (53–92)
International normalized ratio	1.16 (1.01–1.30)
Log_{10} HCV RNA titer	5.77 (5.77–6.11)
Prior treatment with pegylated interferon	None
Clinical category	
Chronic hepatitis C (no cirrhosis)	5 (42)
HCV cirrhosis	7 (58)
Liver fibrosis indicators	
Liver stiffness (kPa)	16.5 (11.0–29.2)
AST-Platelet ratio (APRI)	1.45 (1.01–2.66)
FIB-4	4.54 (2.36–6.57)

HCV, hepatitis c virus; Categorical variables are expressed as number (percentage) and continuous variables are expressed as median (interquartile range).

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Table 3 Characteristics, Treatment Details, and the Virological Outcome of Study Participants.

Age (y), Gender	Cirrhosis	Liver stiffness (Transient elastography score; KPa)	HCV genotype	Prior anti-HCV treatment	Retreatment details				
					Pre-retreatment HCV RNA log10 (IU/mL)	Anti-HCV retreatment regimen	RVR4 achieved	ETR achieved	SVR12 achieved
55, Male	Yes	27.7	3b	SD24	4.61	SVRiba24	Achieved	Achieved	Not achieved
62, Male	Yes	17	3	SD24	4.87	SVRiba24	Achieved	Achieved	Not achieved
42, Male	Yes	16	3	SDRiba12	6.06	SVRiba24	Achieved	Achieved	Yes
67, Male	Yes	33.8	3b	SD24	5.97	SVRiba24	Achieved	Achieved	Yes
43, Female	No	8.7	3a	SD12	3.65	SVRiba24	Achieved	Achieved	Yes
39, Male	No	11.4	3a	SDRiba24	6.96	SVRiba24	Achieved	Achieved	Yes
43, Female	Yes	66.4	3a	SD24	4.85	SVRiba24	Achieved	Achieved	Yes
60, Male	No	10.4	3a	SD12	6.14	SVRiba24	Achieved	Achieved	Yes
72, Female	Yes	22.0	3a	SV12	5.44	SDRiba24	Achieved	Achieved	Not achieved
39, Male	No	7.8	3	SD12	5.56	SVRiba24	Achieved	Achieved	Yes
62, Male	Yes	75	3	SD12	6.10	SVRiba24	Achieved	Achieved	Yes
55, Male	No	11.2	3b	SV12	6.34	SDRiba24	Achieved	Achieved	Yes

HCV, hepatitis c virus; S, sofosbuvir; R, ribavirin; D, daclatasvir; L, ledipasvir; V, velpatasvir; Numbers written in treatment regimen denotes the treatment duration in weeks; RVR4 rapid virological response at 4 weeks; ETR, end of treatment response; SVR12, sustained virological response after 12 weeks of stopping antiviral drugs.

All the participants completed the planned 24 weeks of treatment. None of the participants, during retreatment, developed any major adverse effects which required an additional hospital visit or hospitalization. All achieved RVR4 and ETR but only nine (75%) could achieve SVR12 on retreatment. Three participants with cirrhosis failed to achieve SVR12. Among those who failed to retreatment (n = 3), SVR12 was achieved following an additional course of either sofosbuvir/velpatasvir/voxilaprevir combination for 12 weeks (n = 1) or sofosbuvir/velpatasvir/ribavirin for 24 weeks (n = 2). Two of the relapsed patients were started on sofosbuvir/velpatasvir/ribavirin for 24 weeks because they could not afford sofosbuvir/velpatasvir/voxilaprevir; further pegylated-IFN-based therapy was not given because of its non-availability, high cost of therapy, and uncertainty about the continuous supply of the drug after start of treatment.

Overall, 11/12 (92%) patients achieved SVR12 following retreatment with the first-line DAAs available in the country.

DISCUSSION

We reported our short experience of 12 HCV patients who relapsed after their first course of DAAs containing treatment. The participants were retreated for 24 weeks with first-line DAAs plus ribavirin and treatment regimen was swapped between pangenotypic and genotype-specific regimens. All the participants achieved RVR4 and ETR. Overall, 75% and 92% could achieve SVR12 after first and second retreatment regimens, respectively.

Globally, sofosbuvir is the backbone of HCV treatment in the present era. Real-life experiences suggest that almost 90% of patients achieve SVR12 with sofosbuvir-containing regimen but 10% people need retreatment.[8] Considering a burden of >5 million HCV infection among adults in India, even 10% failure rate will culminate into a large number who will require retreatment. Sofosbuvir in combination with daclatasvir, ledipasvir, or velpatasvir are the only treatment available for HCV in India. The HCV management guideline recommended the use of either sofosbuvir/velpatasvir/voxilaprevir or glecaprevir/pibrentasvir or dasabuvir/ombitasvir/paritaprevir/ritonavir combinations for HCV retreatment in those who had failed to respond with sofosbuvir-containing regimens.[3,5,17] Among all the retreatment options, sofosbuvir/velpatasvir/voxilaprevir combination has consistently shown its efficacy among different group of population such as cirrhosis,[18,19] across the genotype,[20] and regardless of the presence of resistance-associated variants (RAVs).[21] Unfortunately, these drugs are not available in most of the countries, including India. So far, we have a single case report from India on sofosbuvir/velpatasvir/voxilaprevir use for treatment failure.[22]

Retreatment regimen for DAA failure patients may be selected either empirically or may be guided by the sequencing of the viral genome to identify the RAVs. The data are controversial on the beneficial effect of resistance analysis guided retreatment on achieving SVR12.[21,23] The use of RAVs-guided retreatment is not in vogue at present because of lack of facilities to test for RAVs. Further, the data suggest that RAVs are present in a large proportion

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of treatment naive population,[21] the presence of RAV are unlikely to affect the treatment response,[24] and retreatment outcome is not affected by the use of RAV-guided selection of regimen.[21]

We based our retreatment strategy on the fact that prolongation of treatment duration, from 12 to 24 week, may clear the viruses in those who may be the slow responders to DAA. Addition of ribavirin is known to improve the SVR12 rates, particularly in those with cirrhosis.[5] Use of a drug to which the patient was not exposed earlier in pangenotypic or genotype-specific regimen, may be effective against the virus which failed to clear with the first treatment.

Our literature search could reveal only a single study in which HCV retreatment was accomplished with the use of first-line DAAs[25] in patients who had relapsed to first-line DAAs. They found 100% SVR12 on per protocol analysis which is close to our results. These results suggest that in the absence of newer DAAs recommended for retreatment, we can consider to use the first-line DAAs available in the country. We need to generate larger experience from multicentric studies so that a more reliable conclusion can be drawn. Successful retreatment with the repeated course of first-line DAA may obviate the need for second-line DAA which are extremely costly.

As of now, several questions remain unanswered before we could choose the optimal retreatment strategy such as what proportion of HCV patients, treated in real-life setting under national viral hepatitis control program (NVHCP), fail to achieve SVR12?; what are the predictors of treatment failure with first-line DAA?; could addition of ribavirin alone may improve the outcome?; whether pangenotypic or genotype-specific first-line DAA regimens are equally effective against genotype 3? Which retreatment regimen will be most cost effective, if widely used in NVHCP? In lack of data from studies to answer these questions, we could ponder to adopt this approach for HCV retreatment in our NVHCP.

Repeated use of first-line DAA, as suggested in our protocol, raises the issue of increasingly selection of sofosbuvir-resistant variants. Such a RAVs may be non-sensitive or less sensitive to voxilaprevir or other second-line DAAs which can jeopardize the response to rescue therapy. Probably the molecular studies of the viral genome, using next generation sequencing, may help us in alleviating our concerns.

Our study is the first prospective study in which all the HCV relapse were treated with a predefined protocol. The results of our data have limitations of small sample size and failure to conduct sequencing of viral genome to identify the RAV responsible for treatment failure. Further, we had not included the patients with decompensated cirrhosis because these patients were less likely to tolerate ribavirin containing treatment, hence our results can not be extrapolated for those with advanced cirrhosis.

In conclusion, HCV retreatment may be successful with first-line DAA if they are given for 24 weeks with ribavirin along with the swap of pangenotypic regimen to genotype-specific regimen or vise-versa.

GUARANTOR OF THE ARTICLE

Dr Amit Goel.

ETHICS APPROVAL

Ethic approval number 2017-202-IP-100.

AVAILABILITY OF DATA/MATERIAL

All the data that support the findings of this study are available from the corresponding author, upon reasonable request.

AUTHORS DECLARATION

All the authors had full access to all the data in the study and approve the final version of the manuscript.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

AG: Concept, Recruitment of the participants, Analysis, Critical editing.

M: Recruitment of the participants, Data extraction, First draft.

HK: Recruitment of the participants, Data extraction, Analysis.

PT: Recruitment of the participants, Data extraction, Analysis, First draft.

SR: Concept, Recruitment of the participants, Data extraction, First draft.

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AS: Recruitment of the participants, Data extraction, First draft.

PR: Concept, Recruitment of the participants, Critical editing.

RA: Concept, Analysis, Critical editing.

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CONFLICTS OF INTEREST

The authors have none to declare.

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REFERENCES

1. Sadler MD, Lee SS. Revolution in hepatitis C antiviral therapy. *Br Med Bull*. 2015;113:31–44.
2. Ghany MG, Morgan TR, Panel A-IHCG. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. *Hepatology*. 2020;71:686–721.
3. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol*. 2020;73:1170–1218.
4. *Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection*. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
5. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.
6. Puri P, Saraswat VA, Dhiman RK, et al. Indian national association for study of the liver (INASL) guidance for antiviral therapy against HCV infection: update 2016. *J Clin Exp Hepatol*. 2016;6:119–145.
7. Goel A, Bhargava R, Rai P, Aggarwal R. Treatment of chronic genotype-3 hepatitis C virus infection using direct-acting antiviral agents: an Indian experience. *Indian J Gastroenterol*. 2017;36:227–234.
8. Dhiman RK, Grover GS, Premkumar M, et al. Decentralized care with generic direct-acting antivirals in the management of chronic hepatitis C in a public health care setting. *J Hepatol*. 2019;71:1076–1085.
9. Majumdar A, Kitson MT, Roberts SK. Systematic review: current concepts and challenges for the direct-acting antiviral era in hepatitis C cirrhosis. *Aliment Pharmacol Ther*. 2016;43:1276–1292.
10. Lim SG, Phyo WW, Shah SR, et al. Findings from a large Asian chronic hepatitis C real-life study. *J Viral Hepat*. 2018;25:1533–1542.
11. Ampuero J, Romero-Gomez M, Reddy KR. Review article: HCV genotype 3 - the new treatment challenge. *Aliment Pharmacol Ther*. 2014;39:686–698.
12. Goel A, Seguy N, Aggarwal R. Burden of hepatitis C virus infection in India: a systematic review and meta-analysis. *J Gastroenterol Hepatol*. 2019;34:321–329.
13. Goel A, Rewari BB, Sharma M, Konath NM, Aggarwal R. Seroprevalence and burden of hepatitis C virus infection in WHO South-East Asia Region: a systematic review. *J Gastroenterol Hepatol*. 2022;37:964–972.
14. Shalimar, Priya S, Gupta H, et al. A systematic review of risk factors for hepatitis C virus infection among low-risk population in India. *J Clin Exp Hepatol*. 2022;12:1438–1444.
15. Narahari S, Juwle A, Basak S, Saranath D. Prevalence and geographic distribution of Hepatitis C Virus genotypes in Indian patient cohort. *Infect Genet Evol*. 2009;9:643–645.
16. Bhadauria DS, Kumar P, Tiwari P, et al. Liver stiffness is reduced to normal after successful renal transplantation: a prospective cohort study. *J Clin Exp Hepatol*. 2022;12:669–671.
17. Zuckerman A, Chastain CA, Naggie S. Retreatment options following HCV direct acting antiviral failure. *Curr Treat Options Infect Dis*. 2017;9:389–402.
18. Papaluca T, Roberts SK, Strasser SI, et al. Efficacy and safety of sofosbuvir/velpatasvir/voxilaprevir for hepatitis C virus (HCV) NS5A-inhibitor experienced patients with difficult to cure characteristics. *Clin Infect Dis*. 2021;73:e3288–e3295.
19. Patel S, Martin MT, Flamm SL. Sofosbuvir/velpatasvir/voxilaprevir for hepatitis C virus retreatment in decompensated cirrhosis. *Liver Int*. 2021;41:3024–3027.
20. Belperio PS, Shahoumian TA, Loomis TP, Backus LI. Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir in 573 direct-acting antiviral experienced hepatitis C patients. *J Viral Hepat*. 2019;26:980–990.
21. Sarrazin C, Cooper CL, Manns MP, et al. No impact of resistance-associated substitutions on the efficacy of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks in HCV DAA-experienced patients. *J Hepatol*. 2018;69:1221–1230.
22. Tiwari P, Katiyar H, Rai P, Goel A. Use of sofosbuvir/velpatasvir/voxilaprevir for sofosbuvir nonresponder genotype 3 HCV infection in India. *J Clin Exp Hepatol*. 2022;12:669–671.
23. Perez AB, Chueca N, Garcia-Deltoro M, et al. High efficacy of resistance-guided retreatment of HCV patients failing NS5A inhibitors in the real world. *J Hepatol*. 2019;71:876–888.
24. Cabral BCA, Ramos JA, Silveira ALM, et al. Frequency distribution of HCV resistance-associated variants in infected patients treated with direct-acting antivirals. *Int J Infect Dis*. 2022;115:171–177.
25. Elhence A, Singh A, Anand A, et al. Real-world re-treatment outcomes of direct-acting antiviral therapy failure in patients with chronic hepatitis C. *J Med Virol*. 2021;93:4982–4991.

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