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ORIGINAL ARTICLE

Acute hepatitis C treatment in advanced renal failure using 8 weeks of pan-genotypic daclatasvir and reduced-dose sofosbuvir

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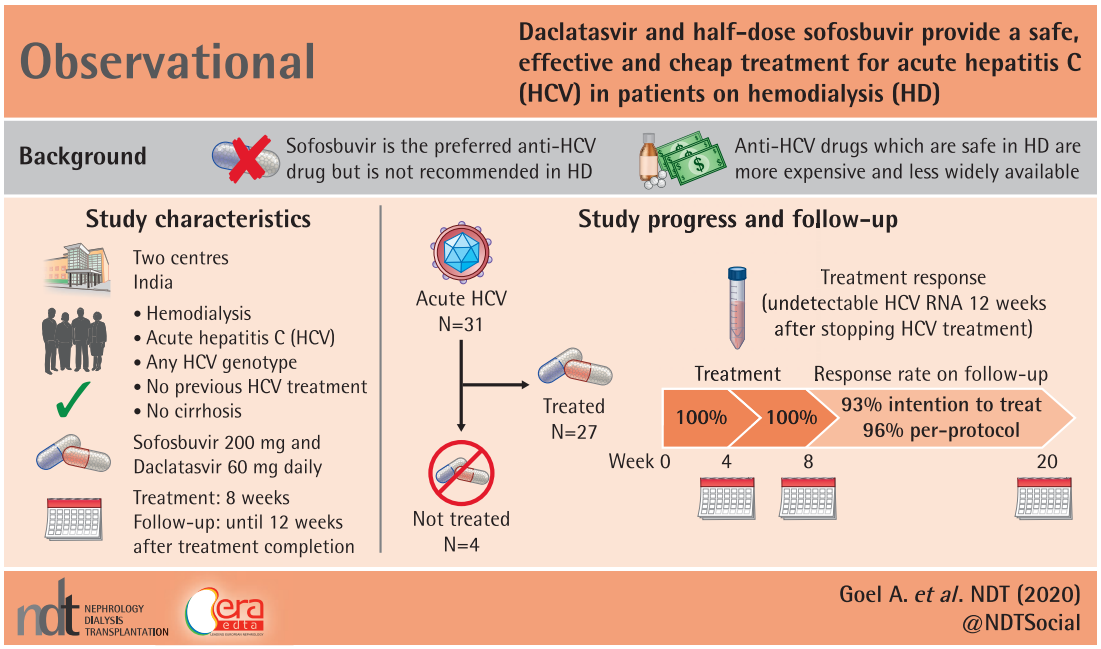
GRAPHICAL ABSTRACT



ABSTRACT

Background. Sofosbuvir is not recommended in persons with estimated glomerular filtration rate (eGFR) <30 mL/min. We report the results of treatment with an off-label 8-week regimen of daclatasvir and half-dose sofosbuvir in patients with acute infection with hepatitis C virus (HCV) and eGFR <30 mL/min.

Methods. Clinic records were searched to identify treatment-naïve, noncirrhotic adults with acute hepatitis C (HCV viremia and a ≥10-fold elevation of serum alanine aminotransferase activity) and eGFR <30 mL/min, who had been treated with a sofosbuvir-based regimen. Treatment response was assessed using serum HCV RNA testing at 4 weeks of treatment, end of the 8-week treatment and 12 weeks after stopping treatment.

Results. Of the 31 patients with acute hepatitis C, 27 [median age (range): 36 (18–74) years; 20 (74%) male] were started on treatment with 200 mg sofosbuvir and 60 mg daclatasvir daily for 8 weeks, irrespective of HCV genotype. All the 27 completed the planned 8-week treatment. One patient died 10 weeks after completing the treatment of an unrelated cause. All the 27 patients had undetectable HCV RNA after 4 weeks of and at the end of treatment. At 12 weeks after completion of treatment, only one tested HCV RNA positive and 25 were negative, with sustained

virological response rate of 25/27 (92.6%) and 25/26 (96.2%) on intention-to-treat and per-protocol basis, respectively.
Conclusion. Eight-week course of daclatasvir and half-dose sofosbuvir is effective for acute hepatitis C in patients with eGFR <30 mL/min and could be a useful alternative to costly, kidney-safe anti-HCV oral drugs in resource-constrained settings.

Keywords: acute hepatitis C, chronic kidney disease, end-stage renal disease, hepatitis C virus, maintenance hemodialysis

KEY LEARNING POINTS

What is already known about this subject?

- hepatitis C virus (HCV) infection is common among those on regular hemodialysis;
- sofosbuvir, the drug of choice for HCV treatment, cannot be used in people on dialysis; and
- the drugs, which can be used in such patients, are very costly and are not available in most of the resource-poor countries.

What this study adds?

- half-dose sofosbuvir and daclatasvir combination for 8 weeks was found safe and effective for the treatment of acute hepatitis C; and
- patients with acute HCV infection may be treated with relatively shorter duration of antiviral drugs than the standard 12 or 24 weeks durations.

What impact this may have on practice or policy?

- daclatasvir and half-dose sofosbuvir combination may be an affordable and available alternative to costly renal safe drugs, to treat HCV infection in those on regular dialysis in low-income countries; and
- a shorter course of 8 weeks may further reduce the cost of therapy.

INTRODUCTION

Infection with hepatitis C virus (HCV) is a major cause of liver-related morbidity and mortality around the world. The infection is transmitted by parenteral routes, including transfusion of contaminated blood or blood products, and transcutaneous exposure following nosocomial or other injuries. The acute phase of HCV infection that follows the pathogen's entry into the human body is usually asymptomatic or associated with only a nonspecific mild illness, and often goes unrecognized. However, a large proportion of those infected fail to clear the virus, resulting in chronic HCV infection, which can, over time, lead to cirrhosis and hepatocellular carcinoma. Therapeutic clearance of such HCV infection is associated with a reduction in the risk of liver-related morbidity and mortality [1].

HCV infection and chronic kidney disease (CKD) have a close relationship, and several issues remain unexplained [2]. Patients with CKD receiving maintenance hemodialysis (MHD) have a higher incidence of HCV infection, particularly in low- and middle-income countries [3], and HCV infection adversely impacts various outcomes in patients with CKD. Thus, many dialysis centers closely monitor patients on hemodialysis for development of new HCV infection using periodic testing. This provides a unique opportunity for identification of acute HCV infection, despite the condition being asymptomatic. Literature supports the treatment of acute HCV infection in such patients, because it reduces the risk of HCV transmission to others in the dialysis unit [4]. Further, treatment of HCV infection when it has not yet become chronic may require drugs to be administered for a shorter duration [5].

Currently, the treatment of HCV infection is based on direct-acting antiviral agents (DAAs), which specifically inhibit one of three HCV proteins [6]. Combination drug regimens that contain two or more of these drugs acting on different viral targets have been shown to have high-efficacy rates in several clinical trials as well as varied real-life settings and very few adverse events. Such treatment permits cure of HCV infection in several patient populations, including those that were earlier considered as difficult-to-treat, such as persons with hemophilia, HIV coinfection and organ transplant recipients. However, the use of DAAs has failed to benefit persons with CKD in several parts of the world, since sofosbuvir, the mainstay of DAA combination therapy, has a predominant renal excretion, which restricts its use to patients with estimated glomerular filtration rate (eGFR) of ≥30 mL/min. Though DAA regimens using drugs with nonrenal excretion (such as grazoprevir/elbasvir, paritaprevir/ritonavir/ombitasvir/dasabuvir and glecaprevir/pibrentasvir) have been approved for use in such patients, these latter drugs are not available in many countries, due either to lack of regulatory approval or marketing, or to high cost [6, 7].

In the interferon era, we treated our patients with low-dose pegylated interferon and ribavirin [8]. Since the introduction of DAAs in our country, our group has treated several patients with chronic HCV infection and CKD with eGFR <30 mL/min using an off-label daclatasvir and half-dose sofosbuvir combination for 12–24 weeks [9]. Successful results in those patients encouraged us to try this drug combination for a shorter 8-week duration for off-label treatment of persons with acute HCV infection and eGFR <30 mL/min.

MATERIALS AND METHODS

Study subjects

This retrospective observational study was carried out in outpatient clinics of two hospitals, with prospective databases

of patients with HCV infection. From these databases, we extracted records of all adult (>18 years) patients who (i) had detectable HCV RNA in serum, (ii) had CKD with eGFR <30 mL/min calculated using Chronic Kidney Disease Epidemiology Collaboration equation [10] and (iii) had received treatment with a combination of sofosbuvir and daclatasvir, but without pegylated interferon or ribavirin, for at least 1 week between 1 April 2017 and 31 March 2019. Patients with prior exposure to a DAA (irrespective of duration), portal vein thrombosis, hepatocellular carcinoma, liver cirrhosis, coinfections with hepatitis B virus or prior organ transplantation were excluded.

From the above patients, patients with acute hepatitis C were identified and their records were reviewed. To be diagnosed as having acute hepatitis C, a person needed to have evidence of recent HCV infection and a 10-fold or higher elevation (from baseline) of serum alanine aminotransferase (ALT) activity and exclusion of other common causes of liver enzymes elevation [11]. The diagnosis of recent HCV infection was based on the finding of seroconversion from a negative test result for anti-HCV antibody or HCV RNA in the previous 26 weeks to a recent positive test result.

Patients were included irrespective of whether they completed the treatment or discontinued it prematurely, and of the treatment outcome. The end-points of follow-up were (i) 12 weeks after treatment completion, (ii) early discontinuation of anti-HCV treatment or (iii) death or loss to follow-up either during treatment or within the first 12 weeks after completion of treatment.

Patients with liver cirrhosis were excluded. Liver cirrhosis was diagnosed if a person had gastroesophageal varices at endoscopy or ascites with serum-ascites albumin gradient >1.1 g/dL [12], with additional supporting clinical and/or biochemical features.

Treatment protocol

All the patients had been treated with half the usual dose of sofosbuvir (i.e. 200 mg/day) and the usual dose of daclatasvir (60 mg/day), orally in a single dose for 8 weeks, irrespective of the HCV genotype. This dose had been based on the available pharmacokinetic data [13], and the previously published clinical experience in patients with renal disease and chronic hepatitis C of our group [9] as well as others [14].

Assessment of efficacy and safety of HCV treatment

The patients were followed up clinically every 2 weeks during treatment, and every 4 weeks thereafter, until 12 weeks after completion of treatment. More frequent follow-up was done if the treating physician considered this necessary for any reason. At each visit, any major adverse events were recorded. However, minor adverse events were not monitored, because of the frequent occurrence of minor symptoms in such patients.

Treatment response was assessed by measuring serum HCV RNA concentration at three time points during follow-up, namely after the initial 4 weeks of treatment (rapid virological response), at the end of the planned 8 weeks of treatment (end-of-treatment response) and 12 weeks after stopping treatment [sustained virological response (SVR12)]. This was done using COBAS® AmpliPrep/COBAS® TaqMan® HCV quantitative test, v2.0 (Roche, Branchburg, NJ, USA), with the lower limit of detection of 15 IU/mL. An intention-to-treat analysis was done, with any missing data being treated as failure.

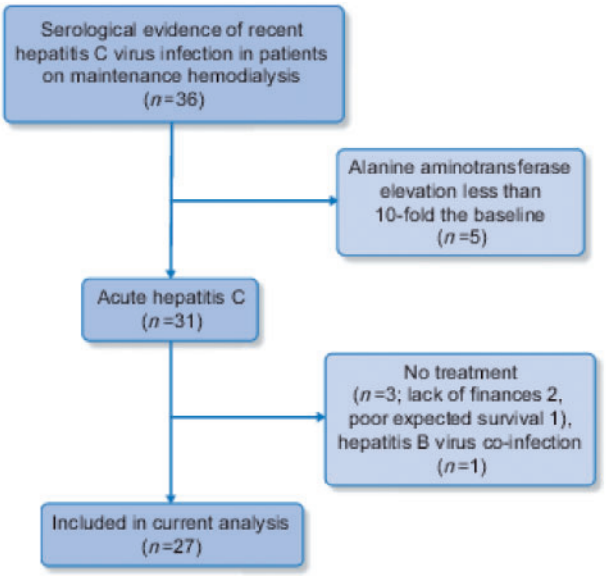


FIGURE 1: Flow chart showing selection of study subjects.

Statistical analysis

Categorical and numeric data were summarized using proportions/ratios and median (range), respectively, and compared between groups using chi-square and Mann–Whitney U tests, respectively. P-values <0.05 were considered significant. The study was approved by our institution's Ethics Committee, with a waiver of need for consent.

RESULTS

Of the 36 patients with acute hepatitis C and eGFR of <30 mL/min who were identified, 27 had been started on sofosbuvir–daclatasvir combination for treatment of HCV infection (Figure 1) and had their data analyzed. Clinical, biochemical and virological characteristics of these patients are summarized in Table 1. All the patients had detectable anti-HCV antibody and were negative for HIV infection. A large majority of patients had Genotype 3 or Genotype 1 HCV infection. Of the 27 patients, 24 were on MHD and the other three had received intermittent hemodialysis for temporary worsening of renal function in the recent past but were not dialysis-dependent when the treatment for HCV infection was begun. A comparison of paired biochemical data before and after the onset of HCV infection showed that the patients had recent elevation of serum aminotransferase levels, as mandated by inclusion criteria, but had serum bilirubin level within the normal range.

All the 27 patients tolerated the daclatasvir and half-dose sofosbuvir treatment well without any major adverse event, and

Table 1. Clinical and laboratory characteristics of patients with acute hepatitis C and renal disease with eGFR <30 mL/min, treated with a combination of daclatasvir and low-dose sofosbuvir for 8 weeks

Characteristic	Value
Age, years	36 (18–74)
Male, *n* (%)	20 (74)
Nature of kidney disease, *n* (%)	
Chronic glomerulonephritis	10 (37)
Chronic interstitial nephritis	10 (37)
Diabetic kidney disease	7 (26)
eGFR, mL/min	8 (4–23)
Hemoglobin, g/dL	10 (6.6–15.4)
Leukocyte count, ×1000/μL	7.6 (4.1–10.8)
Platelet count, ×1000/μL	182 (105–388)
Serum creatinine, mg/dL	7.4 (4.4–13.3)
Serum bilirubin, mg/dL	
Before HCV infection	0.5 (0.3–1.2)
After HCV infection	0.5 (0.3–5.0)
Serum albumin, g/dL	3.8 (2.6–4.5)
Serum alanine aminotransferase, IU/L	
Before HCV infection	16 (7–39)
After HCV infection	302 (145–1501)
Fold elevation after HCV infection	16.2 (10.5–84.7)
Serum aspartate aminotransferase, IU/L	
Before HCV infection	19 (8–47)
After HCV infection	222 (100–973)
Fold elevation after HCV infection	11.8 (2.9–59.3)
Prothrombin time, international normalized ratio	1.1 (0.9–1.7)
HCV genotype, *n* (%)	
1	6 (22)
3	10 (37)
4	2 (7)
Not tested	9 (33)
HCV RNA concentration, $\log_{10}$ IU/mL	5.51 (4.52–6.53)

Data are shown as *n* (%) or as median (range), as appropriate.

completed the scheduled 8-week regimen. One patient died at home 10 weeks after completion of the treatment. The most likely cause of death, as ascertained by interviewing the family members, was acute pneumonia.

All the 27 patients tested negative for HCV RNA at 4 weeks after the start of antiviral treatment and at the end of the 8-week treatment period. At the end of the 12 weeks follow-up after stopping treatment, 25 (92.6%) of the 27 patients tested negative for HCV RNA; of the remaining 2 patients, 1 had died before he could complete the 12-week follow-up and 1 patient had had a relapse after stopping the treatment. Thus, the SVR12 rate was 25/27 (92.6%) and 25/26 (96.2%) on intention-to-treat basis and per-protocol bases, respectively.

DISCUSSION

This study reports the results of a real-life experience of treating acute hepatitis C in patients with advanced renal failure using a short-course DAA combination regimen based on low-dose sofosbuvir. To our knowledge, this is the largest such experience reported to date. It revealed that acute HCV infection can be cured in a large majority of such patients with a short-duration DAA regimen that contains low-dose sofosbuvir, regardless of the HCV genotype.

Acute HCV infection is mostly detected in patients on MHD because of their monitoring for HCV infection. In people on MHD, early institution of anti-HCV treatment is believed to be useful since it reduces the risk of transmission of infection to others [4]. Also, it is felt that if the treatment is begun before the infection has become chronic, a shorter duration of drug administration may suffice [5], thereby reducing the cost of treatment. In mathematical modeling, early treatment of acute HCV has been found to be cost-effective and cost-saving [15].

Currently, DAA-based regimens are the standard of care for the treatment of HCV infection and sofosbuvir, an HCV NS5B protein inhibitor, forms the backbone of these regimens. Sofosbuvir is metabolized in the human body into an inactive metabolite GS-331007, with a predominantly renal excretion. This drug is safe in its usual dose of 400 mg/day in patients with CKD and eGFR of ≥30 mL/min. However, since persons with GFR <30 mL/min have shown an >4-fold increase in the serum level of GS-331007 [16], sofosbuvir is currently not labeled for use in persons with such advanced renal dysfunction.

In view of the above concern with the use of sofosbuvir, several DAA combinations, such as grazoprevir/elbasvir, dasabuvir/ombitasvir/paritaprevir/ritonavir and glecaprevir/pibrentasvir, based on drugs that do not need dose modification, have been developed for use in persons with severe renal impairment [6, 7]. However, in several resource-constrained Asian countries, the use of these 'renal-safe' combinations is limited by the lack of availability or high cost of these drugs [17]. We have tried to circumvent this problem with an empiric off-label use of half-daily dose of sofosbuvir in combination with daclatasvir as a pan-genotype regimen for treating chronic HCV infection in persons with advanced renal failure, and found it to be safe and highly effective [9].

Our excellent experience with the combination of low-dose sofosbuvir and usual-dose daclatasvir in patients with advanced renal failure has encouraged us to try this regimen, albeit for a shorter duration, in persons with acute HCV infection. The SVR12 achieved with low-dose sofosbuvir and daclatasvir in this study were comparable to those observed in those with chronic HCV infection in patients with renal disease [9]. The only other study that has previously tried a treatment regimen based on low-dose sofosbuvir for treating acute HCV in MHD population had an SVR12 of 100%, with no treatment failure. This somewhat better response rate in that study could reflect either a random variation or be related to the longer duration of treatment (24 weeks) in that study [14]. Overall, the response rate observed by us is in keeping with those observed in other large cohorts of acute hepatitis C with [14] or without [18, 19] CKD, or of those with chronic HCV infection in persons on MHD [9, 20–22]. Early successful treatment of acute HCV infection may reduce the need for isolation and the use of a dedicated machine for dialysis in such patients, reducing the overall cost of treatment.

Our study had a few limitations. First, our cohort was admittedly small, primarily because of the difficulty of identifying appropriate patients. Second, we limited our study

to those with ≥10-fold ALT elevation; we did this to ensure that the patients had a recent HCV infection, though we are aware that many persons with acute HCV do not have such ALT elevation. And, finally, our study lacked a control arm and hence fails to take into account the possibility of natural clearance of HCV; however, it is well known that the high rate of clearance achieved in our study cannot occur spontaneously. Finally, at least one patient in our study had a relapse, and it remains unclear whether a longer treatment regimen, e.g. for 12 weeks, would have prevented this unsatisfactory outcome in this patient.

In conclusion, our data show that an 8-week course of daclatasvir and half-daily dose of sofosbuvir was highly effective in clearing Genotype 3 or Genotype 1 HCV infection in a real-life cohort of patients with acute HCV infection and renal disease with GFR <30 mL/min. Thus, in resource-constrained settings, where kidney-safe DAAs against HCV are not available, this regimen may be useful for treating such patients, benefitting the patients themselves and potentially reducing the risk of HCV transmission from them to others.

AUTHORS' CONTRIBUTIONS

R.A. is the guarantor of the article. A.Goel, D.S.B., A.Gupta, R.A., P.R. and S.R. contributed to conception of idea. A.Goel, D.S.B., R.A. and A.V. contributed to study design. A.Goel, D.S.B., P.T., A.Gupta, S.R., P.R. and A.V. contributed to data collection. A.Goel, P.T. and A.V. contributed to data analysis. A.Goel, D.S.B., P.T. and P.R. prepared the first draft. R.A. and A.Gupta contributed to critical editing of the manuscript. All the authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented here have not been presented or published as a whole or part or abstract anywhere.

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