Efficacy and Safety of Sofosbuvir-Based Direct Acting Antivirals for Hepatitis C in Septuagenarians and Octogenarians

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Background/aims: Treatment of chronic hepatitis C (HCV) with newer direct acting antiviral (DAA) agents has been highly effective. Unfortunately, patients over 70 years old are underrepresented in studies. Given current recommendations to screen patients born between 1945 and 1965 for HCV, it is essential to determine the efficacy and safety of DAAs within the elderly population. This study aims to evaluate clinical outcomes of patients aged 70 years or older treated for HCV with DAAs at a single tertiary care center. **Methods:** We identified 25 patients aged 70 years or older who were treated for HCV with a sofosbuvir-based regimen. Baseline demographics, prior HCV treatment history, HCV treatment regimen, adverse effects, and interruption or discontinuation of therapy were collected. The primary endpoint was sustained virologic response at 12 weeks after end of treatment (SVR12). Secondary outcomes were self-reported side effects, drug interactions, and changes in medical regimen of treated patients. **Results:** All patients were genotype 1 (13 1a, 9 1b, 3 unspecified). Seventeen (68%) had cirrhosis including 1 Child's Pugh class B. Fifteen patients were treatment-naïve and 10 previously failed treatment with interferon. Seventeen patients were on ledipasvir/sofosbuvir, 4 on simeprevir/sofosbuvir/ribavirin, and 4 on simeprevir/sofosbuvir. Of 25 patients included, 96% (24/25) patients achieved SVR12. Two patients had a greater than 2 g/dL drop in hemoglobin from baseline and both were on ribavirin. Ribavirin was discontinued in 1 patient. One patient required a change in proton pump inhibitor. No patients discontinued therapy due to side effects. **Conclusions:** Patients aged 70 years or older with genotype 1 achieved high rates of sustained virologic response with treatment with newer sofosbuvir-based DAAs without any undue adverse events. (J CLIN EXP HEPATOL 2017;7:93–96)

Chronic hepatitis C virus (HCV) is a global problem with over 185 million people estimated to be infected worldwide.¹ It continues to be associated with significant morbidity and mortality, with increasing frequency of elderly patients now presenting with HCV as compared to the younger population.² In 2012, the Centers for Disease Control and Prevention added a new recommendation for one-time testing for HCV in adults born between 1945 and 1965. This recommendation was based on systematic reviews that found an estimated HCV prevalence of 3.25% within the 1945 to 1965 birth cohort,

which represents approximately 70% of the infected population in the United States.^{3,4}

Historically, older patients have been underrepresented in studies evaluating the efficacy and safety of HCV treatment due to poor tolerability and suboptimal response to interferon-based regimens. However, the availability of interferon-free direct acting antiviral (DAA) agents represents a major paradigm shift in the treatment of HCV infection. These therapies have been shown to achieve higher cure rates with improved side effect profiles in clinical trials. Saab et al. recently conducted a retrospective pooled data analysis of four phase 3 clinical trials comparing the efficacy and safety of ledipasvir/sofosbuvir between HCV genotype 1 infected patients below and above 65 years of age. They reported similar rates of sustained virologic response (SVR) between groups and a similar incidence of adverse effects. However, adverse effects leading to drug modification or interruption were higher among the older group.⁵ Due to the updated HCV screening recommendations for “baby boomers”, it is essential to determine the efficacy, safety, and tolerability of DAAs within the elderly population. We conducted a retrospective case series to evaluate clinical outcomes of sofosbuvir-based DAAs for the treatment of HCV in septuagenarians and octogenarians.

Keywords: direct acting antivirals, elderly, hepatitis C

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Abbreviations: DAA: direct acting antiviral; HCV: hepatitis C virus; SVR: sustained virologic response

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METHODS

We conducted a retrospective review of patients treated for HCV at the Methodist University Hospital Center for Advanced Liver Disease between January 2012 and December 2015. The study protocol was approved by the Institutional Review Board of University of Tennessee Health Sciences Center. Patients were included if they received treatment with a sofosbuvir-based regimen and were at least 70 years old at the initiation of therapy. Baseline demographics, prior HCV treatment history, HCV treatment regimen, adverse effects, interruption or discontinuation of therapy, and SVR at 12 weeks after treatment completion were collected. Underlying comorbid conditions, total number of concomitant medications, use of commonly prescribed medications in the elderly, and the identification of potential drug-drug interactions requiring a change in medication regimen was recorded. The index date of treatment was defined as the first day patient initiated DAA regimen and end of treatment (EOT) was defined as the last day of DAA treatment. SVR was determined by quantitative testing for HCV RNA: <15 IU/mL (undetectable) and ≥ 15 IU/mL (detectable). For this report, SVR rates were collected at 12 weeks post-treatment. Patients were classified as having cirrhosis if liver biopsy demonstrated a METAVIR score of 4 or Ishak score >5 , a FibroScan value >12.5 kPa, or laboratory biomarkers indicating cirrhosis (FibroTest score >0.75).

Descriptive statistics were calculated for all of the key variables. Continuous variables were expressed as mean with standard deviation and categorical variables as total number with percentages. All analyses were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY), with cases with missing data excluded on a per-analysis basis.

RESULTS

Baseline Characteristics

A total of 25 patients were included in the study. The cohort of subjects had a mean age of 73.2 years (range 70–81 years, Table 1). A majority of patients (76%) were females and 56% were African American. All patients had HCV genotype 1 infection including 13 with 1a, 9 with 1b and 3 did not have a subtype specified. Mean estimated glomerular filtration rate (eGFR) was 68.44 mL/min/ 1.73 m^2 and mean hemoglobin was 11.48 g/dL prior to initiation of therapy. 17 patients (68%) were cirrhotic at time of treatment. All but one of these patients had compensated disease. 10 patients (40%) previously failed treatment with an interferon-based regimen. Hypertension (84%), diabetes mellitus (36%), and chronic kidney disease stage 3 (32%) were the most common comorbid conditions (Table 2). There were 4 patients who were treated post liver

Table 1 Baseline Characteristics.

Characteristic	Patients N = 25
Mean age $\pm$ standard deviation, yrs	73.2 $\pm$ 2.5
Male, n (%)	6 (24%)
African American, n (%)	14 (56%)
Genotype, n (%)	
1a	13 (52%)
1b	9 (36%)
1 subtype unspecified	3 (12%)
Stage of fibrosis, n (%)	
1	1 (4%)
2	3 (12%)
3	4 (16%)
4	17 (68%)
Baseline HCV RNA <6 million, n (%)	22 (88%)
Prior treatment, n (%)	
Naïve	15 (60%)
Interferon-based therapy	10 (40%)

transplant. Three HCV treatment regimens were utilized in this study cohort (Table 3): 17 patients received ledipasvir/sofosbuvir (LDV/SOF), 4 received simeprevir/sofosbuvir (SIM/SOF), and 4 received SIM/SOF plus ribavirin. Of the LDV/SOF group, 8 patients were treated for 24 weeks, while the remaining completed 12 weeks of treatment.

Table 2 Comorbid Conditions and Prescribed Medications.

Variable	Patients N = 25
Comorbid condition, n (%)	
Hypertension	21 (84%)
Diabetes mellitus	9 (36%)
Chronic kidney disease stage 3	8 (32%)
Hyperlipidemia	4 (16%)
Coronary artery disease	1 (4%)
Post liver transplant	4 (16%)
Hepatocellular carcinoma	1 (4%)
Prescribed medication, n (%)	
Beta blocker	15 (60%)
Statin	7 (28%)
Proton pump inhibitor	6 (24%)
Calcineurin inhibitor	4 (16%)
Calcium channel blocker	3 (12%)
Selective serotonin reuptake inhibitor	2 (8%)
H2 receptor antagonist	2 (8%)

Table 3 HCV Treatment Regimen.

Treatment regimen	Patients N = 25
Ledipasvir/sofosbuvir for 12 weeks	9 (36%)
Ledipasvir/sofosbuvir for 24 weeks	8 (32%)
Simeprevir/sofosbuvir + Ribavirin for 12 weeks	4 (16%)
Simeprevir/sofosbuvir for 12 weeks	3 (12%)
Simeprevir/sofosbuvir for 16 weeks	1 (4%)

Efficacy

Twenty-four patients (96%) achieved SVR12. The patient who did not achieve SVR12 was treated post liver transplant; he had recurrent genotype 1a infection with allo-graft cirrhosis and had previously been treated with interferon-based therapies. This patient had baseline chronic kidney disease stage 3 with an eGFR of 50.1 ml/min/1.73 m² and a baseline hemoglobin of 9.2 g/dL. He received 12 weeks of SIM/SOF. Of the remaining treatment-experienced patients, 7 achieved SVR12 with LDV/SOF and 2 with SIM/SOF + ribavirin. Of these patients, 7 had cirrhosis as well.

Safety and Tolerability

All patients completed the prescribed treatment duration and there were no reported interruptions in therapy. Two patients on ribavirin experienced a drop in hemoglobin of greater than 2 g/dL from baseline and ribavirin was discontinued in 1 patient. A total of 7 patients experienced at least one adverse effect (AE) during treatment. The most commonly reported AEs were mild headache and mild fatigue. There were no serious adverse events reported and there were no deaths during treatment.

Drug Interactions

The study group was on an average of 7.5 ± 4.7 prescribed medicines. Beta blockers (60%), statins (28%), and proton pump inhibitors (24%) were the most commonly prescribed medicines (Table 2). Only one patient was on warfarin and no patients were on amiodarone. Drug interaction concerns led to a medication change in only one patient. In this case, dexlansoprazole was changed to omeprazole for the treatment period. No other interactions or medication changes were reported. All 4 patients who were treated post liver transplant were on tacrolimus monotherapy. No change in immunosuppressive regimen was required during the treatment of HCV.

DISCUSSION

The prevalence of HCV-related cirrhosis is expected to significantly increase to more than 879,000 patients by

2030 in an untreated population.⁶ A longer duration of HCV infection and an increased rate of fibrosis progression places older patients at risk for advanced liver disease and liver-related complications.⁷ Achievement of SVR decreases the incidence of complications and overall mortality in patients with advanced fibrosis.⁸ Due to the increasing risks of cirrhosis and hepatocellular carcinoma with advanced age, it is essential to identify an effective antiviral treatment regimen for this patient population. Most of the newer DAAs have a low pill burden and minimal side effects making these treatment regimens more tolerable compared to previous therapies. They can also be utilized in various special populations including those with renal dysfunction.

Our study suggests that age is no longer a barrier or predictor to achieving SVR12. 96% of patients over age 70 years old in our study achieved SVR12, which is comparable to the rates of SVR12 reported by industry funded phase 3 studies. A significant number of these patients had cirrhosis and a history of treatment failure. In addition, a significant number of patients had other comorbid conditions requiring treatment with a number of prescribed agents. The DAA regimens were well tolerated among this elderly population, with no patients requiring interruptions or discontinuation due to AE. Only mild, non-serious AEs were reported. There were no serious drug interactions reported.

The treatment of geriatric patients for HCV with DAA regimens has been found to be a cost effective therapy. Based on various models, researchers have concluded that treating “baby boomers” decreases mortality and increases quality-adjusted life years.^{9–11} However, a careful assessment of an elderly patient's condition should still be considered when evaluating candidacy for treatment.

Our study is limited by its retrospective design, small sample size, and lack of control arm. Adverse event profile reported in the current study is solely based on data abstraction from medical record review and such few minor adverse events may have been under reported. The retrospective data set also limits our ability to capture any refusal or exclusion of patients based on age or comorbid conditions for DAA therapy, and this needs to be addressed in prospective follow up studies. We included only HCV genotype 1 patients in this study due to the lack of elderly patients with non-genotype 1 infections at our center during this time frame. However, efficacy of sofosbuvir-based regimens in other genotypes has been confirmed by recent studies. Ogawa et al. conducted a large, multicenter study consisting of 446 Japanese HCV genotype 2 patients (303 treatment-naïve and 143 treatment-experienced), including 190 (42.6%) aged ≥ 65 and 90 (20.2%) with compensated cirrhosis. The SVR12 rate of patients aged ≥ 65 was 95.3% (181/190).¹²

In conclusion, our study found that sofosbuvir-based DAA regimens are highly effective, safe, and tolerable for

the treatment of HCV in septuagenarians and octogenarians. Although age was historically considered a negative predictor of cure with interferon-based therapies, it should no longer be viewed as a barrier to treatment with the newer DAAs.

CONFLICTS OF INTEREST

The authors have none to declare.

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