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ORIGINAL ARTICLE

Hepatitis C direct-acting antiviral outcomes in patients 75 years and older

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Abstract

Background and Aim: Elderly patients with hepatitis C virus (HCV) infection have worse interferon-based treatment outcomes than young patients. Direct-acting antiviral (DAA) regimens have enabled the treatment of previously difficult-to-cure populations. There are few studies that specifically assess DAA treatment outcomes in patients over 75 years of age.

Methods: Design: This was a cohort study. Setting: The setting was three Canadian HCV specialty sites. Participants: Patients aged 75 years and older and treated with DAA without interferon were enrolled. Measurements: Patient demographics, liver fibrosis by transient elastography, treatment regimen, and treatment outcome data were collected.

Results: The mean age of 78 patients in our analysis was 78.6 years (SD 3.5; range: 75–88 years). The most common genotype was 1b (35%). The most frequently utilized regimens included sofosbuvir-velpatasvir (33%) and ledipasvir-sofosbuvir (32%). Ribavirin was included for 17% of recipients. Sustained virological response (SVR) was achieved in 94% of patients (69% of those receiving ribavirin and 98% of patients on ribavirin-free regimens). Ribavirin toxicity contributed to the lower SVR rates in ribavirin-exposed patients. Ribavirin dosage was decreased in three patients and ultimately discontinued in two of these patients. All treatment was discontinued in another two patients.

Conclusion: Ribavirin-free DAA therapy is safe and achieves SVR rates in older adults comparable to those described in the general population. RBV inclusion frequently results in complications, often leads to treatment modification or interruption, and does not improve SVR rates in those with advanced age.

Introduction

Hepatitis C virus (HCV) infection disproportionately affects older adults.[1,2] Older adults are burdened by higher rates of liver disease, cirrhosis, fibrosis, and hepatocellular carcinoma (HCC) as a result of being infected longer than younger patients.[1–7] It has been speculated that increased vulnerability to oxidative stress, decreased hepatic blood flow, and reduced mitochondrial capacity could explain why older adults experience accelerated rates of liver fibrosis with HCV infection.[3,7–9]

Treating older adults with HCV in the interferon era was fraught with complications.[2,3,10,11] The elderly discontinued interferon (IFN)-based treatment more frequently due to side effects and achieved lower sustained virologic response (SVR) rates than younger patients.[2,5,7–9,12,13] As a result of comorbid medical conditions and poorer treatment outcomes, older adults were often precluded from interferon-based HCV treatment.[2,5,6,14,15]

The advent of direct-acting antivirals (DAAs) has opened up treatment to previously difficult-to-treat groups, including the elderly.[7] Adults aged 65 years and older were underrepresented in the original phase III licensing studies for most DAA regimens, but data are emerging that DAAs are safe and produce equivalent SVR rates in older adults as younger patients.[2,10,11,13,15–17]

Ribavirin is sometimes added to DAA regimens to bolster SVR rates in patients with cirrhosis and those who have failed prior treatment.[18,19] Ribavirin use is complicated by adverse effects, including hemolytic anemia, with older patients being especially vulnerable to toxicities.[2,18–20]

There is currently no consistent upper age cutoff for HCV treatment outlined in the literature, but even among studies of older adults, patients aged 75 years and older remain underrepresented.[6,8,16,20] We describe HCV treatment outcomes with DAAs, with and without ribavirin in patients aged over 75 years treated in three Canadian HCV specialty treatment centers.

Methods

Patients aged 75 years and older who were treated with DAA without interferon were included in these analyses. Information on patient demographics, liver fibrosis (by transient elastography), treatment regimen, and treatment outcomes were collected from three Canadian, urban, specialty treatment sites. Study sites included two tertiary care academic sites—one in Ottawa, Ontario and the other in Edmonton, Alberta—and a community teaching hospital in Brampton, Ontario.

Secondary outcomes included completion of treatment and premature interruption of therapy due to side effects, serious adverse events, failed virologic response, or loss to follow-up. In cases where multiple contributing factors to patients abandoning HCV therapy were identified, only the primary reason for abandoning therapy was included. In patients who received ribavirin, baseline characteristics, ribavirin dosage, baseline hemoglobin, ribavirin dose reductions, need for red blood cell transfusions, and SVR rate were analyzed.

Demographic characteristics and SVR rates were analyzed descriptively and reported as frequencies, percentages, mean ± SD, or medians and interquartile range as appropriate.

SVR was defined as an HCV viral load below the lower limit of detection of our laboratory assay a minimum of 12 weeks after the completion of therapy.

Table 1 Baseline patient characteristics

Demographics (n = 78)	n	%
Gender		
Female	41	52.6
Male	37	47.4
Race		
White	44	56.4
Asian	10	12.8
Black	10	12.8
Southeast Asian	6	7.7
Middle Eastern	4	5.1
Latino	2	2.6
Indigenous	1	1.3
Other	1	1.3
Treatment experienced	8	10.3
Treatment naïve	70	89.7
Genotype		
1a	14	17.9
1b	27	34.6
1ab	1	1.3
1 (subtype unknown)	5	6.4
2	17	21.8
3	5	6.4
4	7	9.0
6	1	1.3
Mixed	1	1.3
Fibrosis stage by transient elastography	n = 77	
F0-1	16	20.8
F2	19	24.7
F3	10	13.0
F4	32	41.5

Results

There were 78 patients identified and included in the analysis. The mean age of patients was 78.6 (SD 3.5; range: 75–88 years). Of patients, 36% were 80 years of age or older, and 53% were female (Table 1). The largest proportion of infections were with genotype 1b (35%). The mean fibrosis stage calculated by transient elastography measurement in kilopascals converted to METAVIR score was 2.8. Of patients, 78% were identified as having fibrosis scores of F2 or higher, and 41% had cirrhosis. The primary treatment regimens in our cohort included sofosbuvir-velpatasvir (33.3%) and ledipasvir-sofosbuvir (32.1%). Of 78 patients, 13 (17%) received ribavirin as part of their regimen (Table 2).

Of 78 patients, 73 (93.6%) achieved an SVR. The prescribed treatment was not completed by 3.8% of patients, one patient completed treatment but was not SVR tested, and another patient was lost to follow-up. No patients experienced virologic failure or relapse. Unsuccessful treatments occurred in individuals with genotypes 1b (n = 1), 2 (n = 1), 3 (n = 2) and 4e (n = 1). Three of five unsuccessful treatments occurred in those with advanced fibrosis (n = 3/42; defined as F3/4- all F4). Two of five unsuccessful treatments occurred in those with minimal fibrosis (n = 2/35; defined as F0-2- both F2). Four of five unsuccessful treatments occurred with the sofosbuvir-ribavirin regimen. The other treatment failure occurred in a ledipasvir-sofosbuvir recipient. These findings were not determined to be statistically significant. However, the analysis is limited by small sample size. Of note, only 9 of 13 (69.2%) patients who received ribavirin achieved SVR compared to 64 of 65 (98.5%) who achieved SVR with ribavirin-free regimens (Fisher's exact test, P = 0.002).

Two deaths occurred in patients receiving ribavirin. One death occurred from end-stage liver disease and the other from HCC. One ribavirin recipient was lost to follow-up, and another

Table 2 Direct-acting antiviral treatment regimens

Regimens (n = 78)	n	%
Sofosbuvir-Velpatasvir	26	33.3
Ledipasvir-Sofosbuvir	25	32.1
Elbasvir-Grazoprevir	13	16.7
Sofosbuvir-Ribavirin	10	12.8
Paritaprevir/ritonavir–Ombitasvir–Dasabuvir–Ribavirin	3	3.8
Sofosbuvir-Velpatasvir-Voxilaprevir	1	1.3

Table 3 Baseline characteristics and treatment outcomes for patients who received ribavirin

	Age	Gender	Race	GT	Fibrosis score	RBV dose (mg)	Hb Nadir	RBV dose change	PRBC	Outcome
1	76	M	White	3	4	1000	95	None	N	Death[†]
2	75	F	White	1b	4	1000	103	↓, then D/C	N	SVR
3	76	F	Asian	1b	4	1000	94	↓,then D/C	N	SVR
4	75	M	Other	1a	4	1000	120	None	N	SVR
5	75	M	White	2 ac	4	1000	117	None	N	SVR
6	75	F	Asian	2	4	1000	97	None	N	SVR
7	75	M	SE Asian	3	4	1000	UNK	UNK	N	LTFU
8	84	F	Asian	2	2	800	78	D/C All Tx at 2/52	Y	No
9	76	M	White	2	1	1000	128	↓	N	SVR
10	76	F	White	2	2	800	106	None	N	SVR
11	80	F	Asian	2	3	800	71	None	Y	SVR
12	79	F	Black	4e	4	600	57	All Tx D/C	Y	Death[‡]
13	77	F	White	2	4	400	69	None	N	SVR

[†]Died of hepatocellular carcinoma 6 months post-treatment.

[‡]Died of end-stage renal disease while on treatment.

GT, genotype; Hb, hemoglobin; LTFU, lost to follow-up; PRBC, packed red blood cells; RBV, Ribavirin; SVR, sustained virologic response; UNK, unknown.

discontinued all HCV therapy at week 2 (Table 3). The mean on-treatment nadir hemoglobin in ribavirin recipients was 95 g/L (SD 22; range: 57–128). The ribavirin dose was reduced in 3 of 13 patients and later discontinued in 2 of these 3 cases. Of 13 patients, 3 received packed red blood cell transfusions while on ribavirin therapy.

Discussion

Our analysis focused on elderly adults aged 75 years and older. Patients had a median age of 79 years, and roughly one-third of patients were aged 80 years or older. The focus on older adults is highly relevant given the paucity of existing data. The original phase III studies for ledipasvir/sofosbuvir and sofosbuvir/velpatasvir included only approximately 1% of patients aged over 75 years.[2,8,20]

A large proportion of our patients had advanced fibrosis or cirrhosis. Despite this, we observed a high SVR rate, suggesting that DAAs are similarly effective in elderly adults with liver disease as younger HCV-infected populations. Therefore, older patients with HCV should not be excluded from therapy on the basis of age alone. However, treatment decisions still require individualization. Up to 40% of patients treated for HCV might be affected by drug–drug interactions.[19] Special attention must be paid to drug–drug interactions with certain DAA regimens, especially in the elderly who are at particularly increased risk of drug interactions due to the increased number of concurrent medications.[2,21] For example, the concurrent use of amiodarone with sofosbuvir-containing regimens is contraindicated due to the risk of symptomatic bradycardia.[19] In addition to adverse drug effects, drug interactions can also reduce the effectiveness of HCV therapy. Proton pump inhibitors increase gastric pH, which in turn decreases the solubility and bioavailability of velpatasvir, glecaprevir, and ledipasvir,[19] although the effect on SVR is less clear. Smolders *et al*. report that elbasvir/grazoprevir and sofosbuvir/velpatasvir had the lowest risk of drug–drug interactions, while sofosbuvir plus simeprevir had the highest.[21]

No patients in our cohort experienced virologic failure or relapse on DAA therapy. Our findings are consistent with a recent metanalysis by Villani *et al*., who found a pooled SVR rate of 92.4% among adults aged 65 years or older with DAA therapy.[17] Ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, elbasvir/grazoprevir, and sofosbuvir plus simeprevir regimens were included in the analysis.[17] In studies from Su *et al*. and Trifan *et al*., paritaprevir/ritonavir, ombitasvir, and dasabuvir were found to produce SVR rates approaching 100% in patients over 70 years.[14,15]

Ribavirin was added to HCV treatment to augment SVR rates and decrease relapses in the interferon era.[18,19] The addition of ribavirin to DAA regimens may allow for shortened treatment duration and is sometimes used as part of salvage regimens in those with prior treatment failure[18,19] and recommended in patients with decompensated cirrhosis. Ribavirin is associated with potential toxicities, including hemolytic anemia, fatigue, pruritus, and upper respiratory symptoms.[18,19] Elderly patients are known to be more vulnerable to the risk of hemolytic anemia with ribavirin than younger patients.[2,20] We found that the inclusion of ribavirin in treatment regimens did not result in improved SVR rates. In fact, we found that patients receiving ribavirin had lower SVR rates than patients on ribavirin-free regimens. We acknowledge that the lower SVR rates observed in the ribavirin group could be explained by selection bias. Patients who receive ribavirin tend to have more difficult-to-cure disease, and they are also the most likely to experience drug toxicities and have a diminished likelihood of cure. Other studies investigating treatment outcomes with DAA that included ribavirin in elderly patients found that dose reductions of ribavirin had no effect on treatment failure.[2,22]

The main strength of this analysis is the focus on patients aged 75 years and older, a group that has been largely ignored in previous studies. With an aging global population, the elderly will continue to represent a growing reservoir of infection that will need to be considered for eradication strategies.[1] From an individual patient perspective, treatment of HCV infection may

improve subjective quality-of-life scores in elderly patients.[9] Patients with HCV achieve poor health-related quality-of-life index scores secondary to fatigue and neuropsychiatric symptoms, social stigma, and anxiety related to deteriorating health.[23] Patient-reported outcomes (PROs) have been shown to improve during DAA therapy and are sustained once treatment is completed in those who achieve SVR.[24,25] HCV treatment increases survival, decreases the risk of HCC, and can stabilize and reduce varices and cirrhosis.[26] It seems reasonable to assume that the elderly would also reap these physical and psychological benefits of DAA treatment.

A limitation shared with other studies is that we did not capture any long-term liver outcomes (progression to fibrosis and/or development of HCC). New findings from Ide *et al* suggest that the development of HCC does not decrease in older adults treated with DAA in up to a 3-year follow-up period.[27] We also did not capture any PROs in our analysis. PROs could provide valuable insight into barriers and challenges patients encounter while completing therapy and assist in developing interventions aimed at maximizing treatment uptake. Although it was beyond the scope of our study, another limitation to our analysis was that we did not specifically look at the relative resource requirements that are required to assist older patients with treatment initiation and completion and, by extension, whether treating older adults with HCV is an effective public health strategy. Further work looking at long-term liver outcomes in patients cured of HCV with DAA are required, as well as analyses evaluating the health economics and feasibility of HCV treatment in the elderly.

Conclusion

There is similar safety and efficacy of DAA therapy free of RBV in the elderly population as in younger patients. Complications of RBV are frequent, and the addition of RBV did not improve SVR proportions in elderly patients. Toxicity precludes the widespread use of ribavirin in the elderly, and it should only be used with great caution in older patients.

References

1 Alvarez K, Smaldone A, Larson E. Burden of hepatitis C virus infection among older adults in long-term care settings: a systematic review of the literature and meta-analysis. *Curr. Infect. Dis. Rep.* 2016; **18**: 13.

2 Huang C, Yu M. Treating hepatitis C in the elderly: pharmacotherapeutic considerations and developments. *Expert Opin. Pharmacother.* 2017; **18**: 1867–74.

3 Cainelli F. Hepatitis C virus infection in the elderly: epidemiology, natural history and management. *Drugs Aging*. 2008; **25**: 9–18.

4 Foster G, Asselah T, Kopecky-Bromberg S *et al*. Safety and efficacy of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C in patients aged 65 years or older. *PLoS One*. 2019; **14**: e0208506.

5 Huang C, Chuang W, Yu M. Chronic hepatitis C infection in the elderly. *Kaohsiung J. Med. Sci.* 2011; **27**: 533–7.

6 Ippolito A, Iacobellis A, Milella M *et al*. Hepatitis C Virus clearance in older adults. *J. Am. Geriatr. Soc.* 2018; **66**: 85–91.

7 Reid M, Price J, Tien P. Hepatitis C virus infection in the older patient. *Infect. Dis. Clin. North Am.* 2017; **31**: 827–38.

8 Conti F, Vitale G, Andreone P. Treating hepatitis C in the elderly: the future is near? *Expert Opin. Pharmacother.* 2014; **15**: 2019–28.

9 Vespasiani-Gentilucci U, Galati G, Gallo P, de Vincentis A, Riva E, Picardi A. Hepatitis C treatment in the elderly: new possibilities and controversies towards interferon-free regimens. *World J. Gastroenterol.* 2015; **21**: 7412–26.

10 Dultz G, Muller T, Petersen J *et al*. Effectiveness and safety of direct-acting antiviral combination therapies for treatment of hepatitis C virus in elderly patients: results from the German Hepatitis C Registry. *Drugs Aging*. 2018; **35**: 843–57.

11 Saab S, Park S, Mizokami M *et al*. Safety and efficacy of ledipasvir/sofosbuvir for the treatment of genotype 1 hepatitis C in subjects aged 65 years or older. *Hepatology*. 2016; **63**: 1112–9.

12 Honda T, Ishigami M, Masuda H *et al*. Effect of peginterferon alfa-2b and ribavirin on hepatocellular carcinoma prevention in older patients with chronic hepatitis C. *J. Gastroenterol. Hepatol.* 2015; **30**: 321–8.

13 Jhaveri M, Manne V, Kowdley K. Chronic hepatitis C in elderly patients: current evidence with direct-acting antivirals. *Drugs Aging*. 2018; **35**: 117–22.

14 Su F, Beste L, Green P, Berry K, Ioannou G. Direct-acting antivirals are effective for chronic hepatitis C treatment in elderly patients: a real-world study of 17 487 patients. *Eur. J. Gastroenterol. Hepatol.* 2017; **29**: 686–93.

15 Trifan A, Stanciu C, Gheorghe L *et al*. Efficacy and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir with ribavirin for the treatment of HCV genotype 1b compensated cirrhosis in patients aged 70 years or older. *Medicine (Baltimore)*. 2017; **96**: e9271.

16 Snyder H, Ali B, Gonzalez H, Nair S, Satapathy S. Efficacy and safety of sofosbuvir-based direct acting antivirals for hepatitis C in septuagenarians and octogenarians. *J. Clin. Exp. Hepatol.* 2017; **7**: 93–6.

17 Villani R, Monami M, Di Cosimo F *et al*. Direct-acting antivirals for HCV treatment in older patients: a systematic review and meta-analysis. *J. Viral Hepat.* 2019; **26**: 1249–56.

18 Mathur P, Kottilil S, Wilson E. Use of ribavirin for hepatitis C treatment in the modern direct-acting antiviral era. *J. Clin. Transl. Hepatol.* 2018; **6**: 431–7.

19 Sandmann L, Schulte B, Manns M, Maasoumy B. Treatment of chronic hepatitis C: efficacy, side effects and complications. *Visc. Med.* 2019; **35**: 161–70.

20 Conti F, Brillanti S, Buonfiglioli F *et al*. Safety and efficacy of direct-acting antivirals for the treatment of chronic hepatitis C in a real-world population aged 65 years and older. *J. Viral Hepat.* 2017; **24**: 454–63.

21 Smolders E, Smit C, de Kanter C *et al*. Brief report: high need to switch cART or comedication with the initiation of DAAs in elderly HIV/HCV-coinfected patients. *J. Acquir. Immune Defic. Syndr.* 2017; **76**: 193–9.

22 Ogawa E, Furusyo N, Nomura H *et al*. Effectiveness and safety of sofosbuvir plus ribavirin for HCV genotype 2 patients 65 and over with or without cirrhosis. *Antiviral Res.* 2016; **136**: 37–44.

23 Evon D, Golin C, Stewart P *et al*. Patient engagement and study design of PROP UP: a multi-site patient-centered prospective observational study of patients undergoing hepatitis C treatment. *Contemp. Clin. Trials*. 2017; **57**: 58–68.

24 Younossi Z, Stepanova M, Gordon S *et al*. Patient-reported outcomes following treatment of chronic hepatitis C virus infection with sofosbuvir and velpatasvir, with or without voxilaprevir. *Clin. Gastroenterol. Hepatol.* 2018; **16**: 567–74 e6.

25 Younossi Z, Stepanova M, Henry L, Nader F, Hunt S. An in-depth analysis of patient-reported outcomes in patients with chronic hepatitis C treated with different anti-viral regimens. *Am. J. Gastroenterol.* 2016; **111**: 808–16.

26 Marinho R, Vitor S, Velosa J. Benefits of curing hepatitis C infection. *J. Gastrointestin. Liver Dis.* 2014; **23**: 85–90.
27 Ide T, Eguchi Y, Harada M *et al.* Elderly hepatitis C patients who achieved sustained virologic response by direct acting antivirals do not have significant benefits for hepatocellular carcinoma compared with the patients who did not achieve sustained virologic response (1540). In: *America Association for the Study of LIver Diseases. The Liver Meeting (AASLD)*, Vol. **70**. Boston, MA: Hepatology, 2019; 927A.