Clinical efficacy and tolerability of direct-acting antivirals in elderly patients with chronic hepatitis C

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Background There is a lack of evidence-based data on aged patients with newer direct-acting antivirals (DAAs) and with shorter duration of treatment regimens involving DAAs with or without ribavirin (RBV) and pegylated interferon (Peg IFN).

Patients and methods Medical records of 240 patients treated with DAAs with or without Peg IFN and RBV between January 2013 and July 2015 were retrospectively analyzed. Patients were divided into two groups: patients aged 65 years and older ($N=84$) and patients aged younger than 65 years ($N=156$). Pretreatment baseline patient characteristics, treatment efficacy, factors affecting sustained virologic response at 12 weeks after treatment, and adverse reactions were compared between the groups.

Results No statistically significant difference was observed with end of treatment response (98.8 vs. 98%, $P=0.667$) and sustained virologic response at 12 weeks after treatment (93.1 vs. 94.1%, $P=0.767$) between patients aged 65 and older and those younger than 65 years of age. Fatigue was the most common adverse event recorded (32.5%), followed by anemia (19.6%), leukopenia (11.7%), thrombocytopenia (10%), skin rash (8.3%), and headache (7.9%). The RBV dose was reduced in eight (8%) patients and four patients discontinued the RBV treatment because of severe anemia. RBV dose reduction or discontinuation did not reach statistical significance ($P=0.913$). Increased fibrosis, cirrhosis, aspartate aminotransferase, alanine aminotransferase, hemoglobin, and platelet levels seem to affect the sustained virologic response in the elderly. Twelve (6.28%) patients failed to respond to treatment and the failure rate was not significant ($P=0.767$) between the groups.

Conclusion DAAs with or without IFN and RBV in the standard recommended 12 or 24-week treatment regimens are effective, well tolerated, and may be safely extended to elderly patients infected with chronic hepatitis C. Eur J Gastroenterol Hepatol 29:767–776

Introduction

Globally, chronic hepatitis C virus (HCV) infection has been estimated to affect 2–3% (about 170 million) of the world's population [1]. A National Health and Nutrition Examination Survey 2003–2010 analysis estimated that ~2.7 (1.0%) million USA residents have infection with chronic HCV [2]. Chronic HCV is the leading cause of cirrhosis, hepatocellular carcinoma (HCC), and its related complications, and thus elimination of HCV significantly reduces the risk of HCC, liver failure, and death [3].

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Keywords: adverse drug reactions, chronic hepatitis C, direct-acting antiviral agents, elderly patients, interferon, ribavirin, sustained virologic response

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An increased prevalence of chronic HCV infection is observed with advancing age. These patients are likely to have an advanced liver disease including cirrhosis of the liver and related complications [4,5]. In countries such as Japan, Taiwan, and some European countries, the prevalence of chronic hepatitis C infection is the highest in the aged population [6]. According to the USA Census Bureau, by 2030, more than 20% of USA residents are projected to be aged 65 years and older. The baby boomers (born between 1945 and 1965) began turning 65 in 2011 and currently account for three-fourth of all chronic HCV infections among adults in the USA [7].

Older individuals infected with chronic HCV are historically considered a difficult to treat category with less success and more treatment failures than the younger population. The pegylated interferon (peg IFN) and ribavirin (RBV) combination therapy was associated with a high discontinuation rate in the elderly because of the longer duration of treatment and associated adverse events [8]. With the recent introduction of IFN-free direct-acting antivirals (DAAs), the treatment success for chronic HCV infection has improved markedly, with the overall cure rate reaching above 90%. Even though some of the newer drug trials included aged populations, the numbers of elderly patients enrolled were limited. Although we have achieved considerable advancements in treatment with newer agents, the coadministration of RBV in combination

with newer agents still exists in certain patient groups to achieve an acceptable response rate. A shorter duration of treatment with these regimens and better tolerability are expected in both younger and older populations.

We, therefore, examined the effectiveness and tolerability of newer DAAs in older patients aged older than 65 years compared with younger patients. We also evaluated the factors associated with sustained virologic response (SVR) and the tolerability of DAAs in combination with Peg IFN, RBV, or both with a shorter duration of treatment in an aged population compared with younger patients aged younger than 65 years.

Patients and methods

This retrospective cohort study protocol was approved by the institutional review board of each hospital (New York Presbyterian Brooklyn Methodist Hospital New York and Interfaith Medical Center, New York).

Patients

A total of 279 consecutive patients with chronic HCV treated with either a combination of DAAs or at least one of the newer agents in combination with IFN and RBV between January 2013 and July 2015 at two institutions were retrospectively analyzed. Thirty-nine patients were excluded from the study for various reasons including insufficient documentation of viral load during the treatment and failure to attend follow-up after the end of treatment (Fig. 1).

All the 240 patients included in this retrospective cohort study received at least eight weeks of treatment with one of the recommended combination regimens in standard doses for chronic HCV infection. Patients were divided into two groups: patients aged younger than 65 years ($N=156$) and those aged 65 years and older ($N=84$). The choice of treatment regimens used was made on the basis of the American Association of Study of Liver Disease guidelines during that period. During early 2013, treatment recommendation was triple therapy with a protease inhibitor, Peg IFN, and RBV. In the years 2014 and 2015, the rest of the regimens were used as they were approved one after the other by the Food and Drug Administration. The combination treatment regimens used were Peg IFN α-2a + RBV + sofosbuvir `(SOF), SOF + RBV, ledipasvir (LDV) + SOF (Harvoni; Gilead Sciences, Foster City, California, USA), LDV + SOF + RBV (Harvoni + RBV), ombitasvir + paritaprevir + ritonavir- + dasabuvir (Viekira Pak; AbbVie Inc, Illinois, North Chicago, USA), ombitasvir + paritaprevir + ritonavir + dasabuvir + RBV (Viekira Pak + RBV), and simeprevir (SPV) + sofosbuvir. Only three patients were treated with Peg IFN + RBV + telaprevir and one patient each received the Peg IFN + RBV + boceprevir, Peg IFN + RBV + Harvoni, and SPV + SOF + RBV combination (Fig. 2). The duration of the treatment period ranged from a minimum of 8 weeks ($N=3$, all with Harvoni) to a standard 12 weeks ($N=201$) or 24 weeks ($N=36$) depending on their status of previous treatment and cirrhosis. All patients who received the IFN-based regimen received Peg IFN at a standard dose of 180 mg subcutaneously once a week. A weight-based RBV dose was used at 1200 mg daily in two divided doses for those weighing 75 kg and 1000 mg for those weighing less than 75 kg.

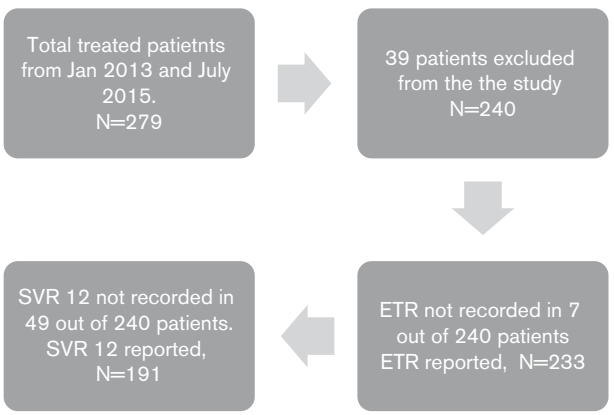

Fig. 1. Patient recruitment. ETR, end of treatment response; SVR, sustained virologic response.

Study assessments

Pretreatment baseline characteristics (Table 1), laboratory studies, baseline HCV viral load, treatment efficacy with the end of treatment response (ETR), and sustained virologic response at 12 weeks after the completion of treatment (SVR12) were compared between the groups. We determined the factors associated with SVR on baseline characteristics by univariate analysis. A separate analysis was carried out in patients aged older than or equal to 65 years to determine the factors associated with SVR in the elderly group. The safety and tolerability of antiviral drug regimens were assessed by reviewing the documented common or serious adverse events, treatment completion rate, and reduction in the medication dosage or discontinuation of medications.

Assessment of liver fibrosis was performed with invasive liver biopsy in some cases and noninvasive testing with a fibrosure test or a fibroscore test and the aspartate aminotransferase (AST)-to-aspartate platelet ratio index (APRI) score. Patients who had clinical, laboratory, and radiologic evidence of cirrhosis were treated without any further assessment of fibrosis.

Treatment response was assessed with HCV RNA viral load (IU/ml) at four weeks after initiation of treatment, at the end of treatment, and 12 weeks after the completion of treatment. The test was performed using Cobas AmpliPrep/Cobas TaqMan HCV Quantitative Test, v2.0 (Roche Molecular Diagnostics, Pleasanton, California, USA) with a lower limit of quantification of HCV RNA 15 IU/ml. ETR was defined as undetectable viral load at the end of completion of treatment. SVR12 was defined as undetectable viral load at 12 weeks after the end of treatment.

Statistical analysis

The SPSS statistics software package (IBM SPSS Statistics, version 21; IBM Corp, Armonk, New York, USA) was used for statistical analysis. Values were expressed as mean ± SD and the mean quantitative values were analyzed using Student's t-test. The χ^2-test was used to analyze differences in qualitative values. All P values were two tailed and a P value of less than 0.05 was considered

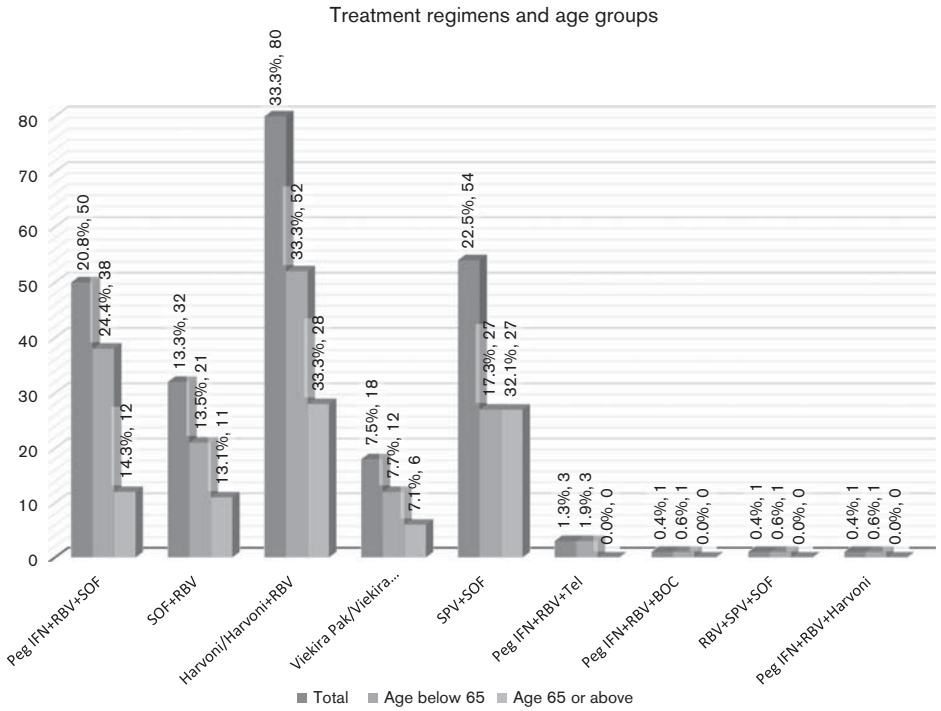

Fig. 2. Treatment regimens used and the number of patients in both patient groups. Peg IFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; SPV, simeprevir; Tel, telaprevir.

significant. One-way analysis of variance was used to determine whether there were differences among the group means. Univariate analysis was used to identify the factors related to SVR.

Results

Patients

Sixty-five percent ($N=156$) of the total of 240 patients were younger than 65 years and patients aged 65 years or older comprised 35% ($N=84$) of treated patients, with the range being 22–94 years (59.96 ± 10.89). Ninety-nine patients were men and 57 patients were women in the group younger than 65 years of age and 46 were men and 38 were women in the group 65 years of age and older, respectively. Most of the patients were Black (51%, 123/240), followed by White (23%, 56/240), Hispanic (11%, 27/240), and Asians (1%, 2/240). The 32 (13%) patients categorized as others were genotype (GT) 4 and were of Middle-Eastern or Egyptian origin. Also, 32 patients were coinfected with HIV and were receiving their antiretroviral therapy for HIV infection during HCV treatment; no dose adjustment was required. The basic clinical characteristics of all treated patients are summarized in Table 1.

GTs 1a and 1b was present in 78.3% of the treated patients. The next most common genotype was GT 4, found in 11.7% of patients. GTs 2 and 3 were present in 6.7 and 3.3% of all treated patients, respectively. Seventy-five patients were treatment experienced, 50 of whom were <65 years old and 25 patients who were ≥ 65 years. These treatment experienced patients had either previously failed treatment with the IFN and RBV combination or IFN and RBV in combination with newer DAAs. Model for end-stage liver disease (MELD) score was high in patients aged 65 years and older and was statistically significant ($P=0.048$). A significant difference was observed between the groups with baseline medical comorbidities HTN ($P=0.004$), coronary artery disease ($P=0.041$), and chronic kidney disease ($P=0.008$) in patients aged 65 years and older, and tended to have more comorbidities than younger age groups. Except for baseline hemoglobin ($P=0.004$) and alanine aminotransferase (ALT) ($P=0.018$), no difference was noted between the initial laboratory studies within the groups. The mean viral load remained similar in both groups ($P=0.624$). No statistical significance was observed with sex ($P=0.189$), BMI ($P=0.713$), APRI score ($P=0.619$), or status of previous treatment ($P=0.715$).

Response to therapy

In seven out of the total 240 patients, no end of treatment response was recorded; however, viral load was recorded as undetectable at 4 or 8 weeks on treatment, except one patient, who had a quantifiable viral load at 2 weeks. SVR12 was not reported in 49 patients, either because of pending follow-up or because it was not determined and recorded. With all the treatment regimens combined, the overall ETR rate was 98.2% ($N=233$) and SVR12 was 94% ($N=191$) (Figs 3 and 4). No statistically significant difference was observed with ETR (98.8 vs. 98%, $P=0.667$) and SVR12 (93.1 vs. 94.1%, $P=0.767$) between patients aged 65 years and older and those younger than 65 years of age. SVR12 for DAA with IFN

Table 1. Baseline characteristics of all 240 patients

	Total ($N=240$)	Age <65 years ($N=156$)	Age ≥ 65 years ($N=84$)	P Value
Sex				
Male	145	99	46	0.189
Female	95	57	38	
Race				
White	56	38	18	0.034
Black	123	70	53	
Asian	2	2	0	
Hispanic	27	19	8	
Others	32	27	5	
BMI (mean ± SD)	28.492 ± 5.5501	28.589 ± 5.7451	28.312 ± 5.1971	0.713
Prior treatment				
TN	165	106	59	0.715
TE	75	50	25	
Genotypes				
1a	132	91	41	0.014
1b	56	27	29	
2	16	9	7	
3	8	7	1	
4	28	22	6	
Initial viral load (mean ± SD)	3575178.82 ± 6308947.686	3722094.12 ± 5262996.040	3302336.11 ± 7922736.168	0.624
APRI score				
<1	163	104	59	0.664
≥ 1	76	51	25	
Cirrhosis				
No	170	112	58	0.655
Yes	70	44	26	
MELD score				
MELD <10	178	124	54	0.012
MELD ≥ 10	61	31	30	
CTP class				
A	211	142	69	0.094
B	26	12	14	
C	2	1	1	
DM	62	38	24	0.477
HTN	115	64	51	0.004
CAD	11	4	7	0.041
CKD	17	6	11	0.008
ESRD	1	1	0	0.462
Chronic anemia	5	2	3	0.236

APRI, aspartate aminotransferase-to-platelet ratio index; CAD, coronary artery disease; CKD, chronic kidney disease; CTP, Child–Turcotte–Pugh class; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; MELD, model for end-stage liver disease; TE, treatment experienced; TN, treatment naive.

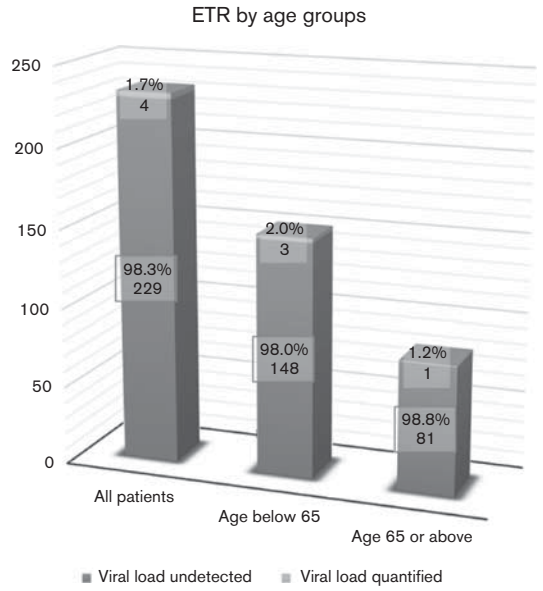

Fig. 3. Overall end of treatment response (ETR) rate in all patients.

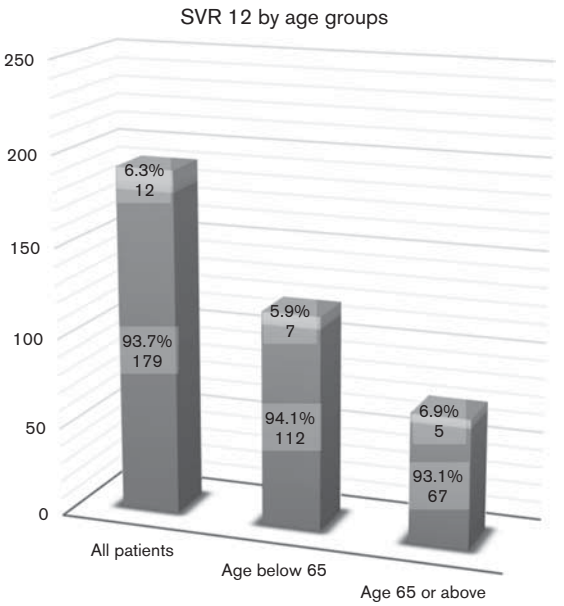

Fig. 4. Sustained virologic response at 12 weeks after treatment (SVR12) in all patients and in patients aged 65 years and older and younger than 65 years.

Table 2. Factors associated with a SVR12 by univariate analysis

	Total patients ($N=191$)	Achieved SVR12 ($N=179$)	Did not achieve SVR12 ($N=12$)	P value
Sex (male/female)	113/78	103/76	10/2	0.079
Age (mean ± SD)	60.39 ± 10.95	60.26 ± 10.72	62.33 ± 14.36	0.448
Race (W/B/A/H/O)	46/94/2/23/26	43/89/2/22/23	3/5/0/1/3	0.804
BMI (mean ± SD)	28.3 ± 5.46	28.32 ± 5.25	27.83 ± 8.19	0.000
TN/TE	129/62	121/58	8/4	0.947
GT (1a, 1b, 2, 3, 4)	100/47/14/ 6/24	92/47/13/ 5/22	8/0/1/1/2	0.298
HCV RNA (IU/ml)	3127912.62 ± 4185696.82	3072746.63 ± 4207845.41	3950805.33 ± 3913601.07	0.125
APRI score (< 1/ ≥ 1)	131/59	128/50	3/9	0.001
MELD score (< 10/ ≥ 10)	141/49	136/42	5/7	0.008
CTP class (A/B/C)	167/22/1	159/18/1	8/4/0	0.051
Cirrhosis (no/yes)	136/55	133/46	3/9	0.000
Baseline ALT (μ/l)	63.42 ± 42.78	61.92 ± 40.12	85.58 ± 70.49	0.016
Baseline AST (μ/l)	56.34 ± 36.1	54.35 ± 34.02	85.83 ± 52.463	0.000
Hemoglobin (g/dl)	13.5 ± 3.11	13.49 ± 3.19	13.62 ± 1.46	0.001
Platelets (K/μl)	183.58 ± 76.45	188.81 ± 75.21	105.50 ± 47.91	0.023

A, Asian; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; B, Black; CTP, Child–Turcotte–Pugh class; GT, genotype; HCV, hepatitis C virus; H, Hispanic; MELD, model for end-stage liver disease score; O, others; SVR12, sustained virologic response at 12 weeks after treatment; TE, treatment experienced; TN, treatment naive; W; White.

and RBV treatment was 98% (49/50), higher than 91.4% (118/129) achieved with IFN-free DAA regimens, but was not statistically significant. A similar response rate was observed in patients older than or equal to 65 years, with 100% of the patients on the IFN-based regimen achieving an SVR compared with only 91.07% SVR with the IFN-free treatment regimen. ETR and SVR12 for GTs 1a, 1b, 2, 3, and GT 4 were 97.7, 100, 93.8, 100, and 100% and 92, 100, 92.9, 83.3, and 91.7%, respectively (Fig. 6). Patients with GT 3 were the lowest responders, highlighting the fact that GT 3 is the most difficult to treat with DAA agents. The ETR rate and SVR12 rates for subgroups Peg IFN + RBV + SOF, SOF + RBV, Harvoni, Viekira Pak/ Viekira Pak + RBV, and SPV + SOF were 100, 96.7, 97.4, 100, 98.1%, and 97.8, 88, 94.1, 100, and 90.6%, respectively. For patients who had previous treatment failure or were naïve to treatment, no significant difference in ETR ($P=0.783$) or SVR12 ($P=0.947$) was observed between the younger and the older age groups. The univariate analysis determined the factors associated with an SVR (Table 2). The SVR12 was significantly lower in patients with high APRI and a high MELD score, indicating that advanced fibrosis is a major factor in determining the response to treatment ($P=0.001$ and 0.008, respectively). Baseline ALT and AST were significantly higher in patients who failed to achieve an SVR than in patients who did achieve SVR12 ($P=0.016$ and 0.000, respectively). BMI was significantly higher in patients who achieved SVR12 ($P=0.000$) Table 2. Factors associated with SVR12 were analyzed separately for patients aged older than or equal to 65 years (Table 4). The ratio of GT 1 patients who achieved an SVR12 was significantly lower compare to other genotypes ($P=0.001$). Cirrhosis and MELD score of more than ten were associated with a low SVR ($P=0.001$ and 0.042, respectively). Baseline ALT and AST tended to be higher in those who did not achieve an SVR ($P=0.020$ and 0.000, respectively) and BMI tended to be lower in patients who failed to respond to treatment. Only seven patients had the IL28B GT tested and hence were not included in the evaluation of factors predicting the SVR.

There were 12 (6.28%) patients ($5 \geq 65$ and $7 < 65$ years) who failed to respond to treatment. Eight patients developed relapse after treatment, three responded partially, and one achieved a virologic breakthrough during the treatment period (Table 3). Nine out of 12 patients who did not respond to treatment were cirrhotic. The difference in the failure rate between the two groups was not significant statistically ($P=0.767$).

Safety and tolerability

None of the adverse reactions reported were severe, except severe anemia in two patients. Fatigue was the most common adverse event recorded (32.5%), followed by

Table 3. Characteristics of patients who failed to respond to treatment

Patient nos	Regimen	Duration (weeks)	Failure type	Age (years)	Sex	GT	TN/TE	Cirrhosis	HIV status
1	SOF + RBV	12	Partial response	65	Male	2	TN	Yes	Negative
2	Harvoni	12	Partial response	49	Male	1a	TN	No	Positive
3	Harvoni	12	Partial response	60	Female	1a	TN	Yes	Positive
4	SPV + SOF	12	Breakthrough	60	Male	1a	TE	Yes	Positive
5	IFN + RBV + SOF	24	Relapse	58	Male	1a	TE	No	Negative
6	SOF + RBV	12	Relapse	58	Male	1a	TN	Yes	Negative
7	SPV + SOF	12	Relapse	67	Male	1a	TN	Yes	Negative
8	SPV + SOF	12	Relapse	66	Male	1a	TE	Yes	Negative
9	SOF + RBV	24	Relapse	94	Female	3	TN	Yes	Negative
10	Harvoni	12	Relapse	33	Male	1a	TN	No	Negative
11	SOF + RBV	24	Relapse	64	Male	4	TN	Yes	Positive
12	SPV + RBV	12	Relapse	74	Male	4	TE	Yes	Positive

GT, genotype; IFN, interferon; RBV, ribavirin; SOF, sofosbuvir; SPV, simeprevir; TE, treatment experienced; TN, treatment naive.

Table 4. Univariate analysis of factors associated with an SVR12 in patients aged ≥65 years

	Total patients (*N* = 72)	Achieved SVR12 (*N* = 67)	Did not achieve SVR12 (*N* = 5)	*P* value
Sex (male/female)	40/32	36/31	4/1	0.260
Age (mean ± SD)	70.24 ± 5.85	70.01 ± 5.22	73.20/12.15	0.451
Race (W/B/A/H/O)	16/44/0/8/4	15/42/0/7/3	1/2/0/1/1	0.437
BMI (mean ± SD)	28.44 ± 5.45	28.49 ± 5.51	27.80 ± 5.17	0.020
TN/TE	51/21	48/19	3/2	0.587
GT (1a, 1b, 2, 3, 4)	35/25/7/1/4	33/25/6/0/3	2/0/1/1/1	0.001
HCV RNA (IU/ml)	2427008.67 ± 2551516.96	2375698.61 ± 2392219.92	3114563.40 ± 4527351.28	0.536
APRI score (< 1/≥ 1)	67/5	47/20	2/3	0.168
MELD score (< 10/≥ 10)	45/27	44/23	1/4	0.042
CTP class (A/B/C)	58/13/1	55/11/1	3/2/0	0.420
Cirrhosis (no/yes)	48/24	48/19	0/5	0.001
Baseline ALT (μ/l)	56.44 ± 39.64	54.61 ± 39.30	81.00 ± 39.95	0.020
Baseline AST (μ/l)	56.49 ± 33.86	54.61 ± 33.12	81.60 ± 37.40	0.000
Hemoglobin (g/dl)	12.71 ± 1.51	12.67 ± 1.53	13.28 ± 1.17	0.013
Platelets (K/μl)	171.11 ± 88.53	185.42 ± 87.68	94.60 ± 51.77	0.311

A, Asian; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate aminotransferase; B, Black; CTP, Child–Turcotte–Pugh class; GT, genotype; HCV, hepatitis C virus; H, Hispanic; MELD, model for end-stage liver disease score; O, others; SVR12, sustained virologic response at 12 weeks after treatment; TE, treatment experienced; TN, treatment naive; W; White.

Table 5. Adverse events associated with treatment regimens

Adverse events	Total	Age < 65 years	Age ≥ 65 years	*P* value
Fatigue	78	46	32	0.174
Anemia	47	25	22	0.058
Leukopenia	28	16	12	0.354
Thrombocytopenia	24	13	11	0.241
Skin rash	20	12	8	0.624
Headache	19	15	4	0.184
Arthralgia	11	9	2	0.231
Nausea	11	8	3	0.582
Abdominal pain	10	10	0	0.018
Insomnia	8	7	1	0.175
Itching	7	3	4	0.213
Dizziness	5	2	3	0.236
Depression	4	3	1	0.672
Diarrhea	4	4	0	0.139
Vomiting	2	2	0	0.297
Photosensitivity rash	2	2	0	0.297
Constipation	1	1	0	0.462

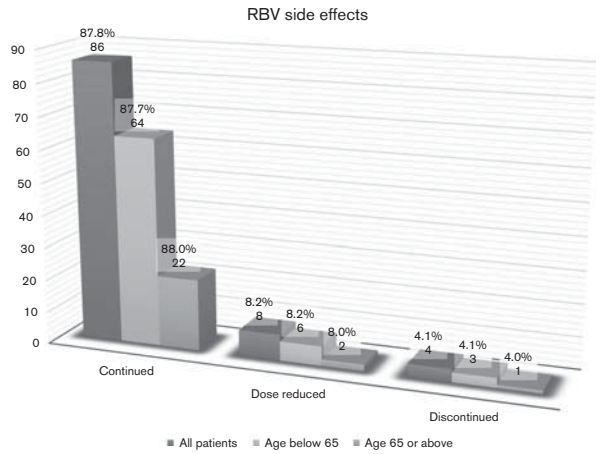

Fig. 5. Ribavirin (RBV) dose reduction and discontinuation.

anemia (19.6%), leukopenia (11.7%), thrombocytopenia (10%), skin rash (8.3%), and headache (7.9%) (Tables 5,6 and 7). Nearly half of the patients who received IFN and RBV developed anemia, leucopenia, or thrombocytopenia (Table 2). The RBV dose was reduced in eight (6 < 65 and 2 ≥ 65 years) patients (Fig. 5). Four (3 < 65 and 1 ≥ 65 years) patients discontinued the RBV treatment because of severe anemia (decrease in hematocrit > 25% from baseline); however, they all achieved SVR12. RBV dose reduction or discontinuation did not reach statistical significance between the two groups ($P = 0.913$) (Fig. 5).

Discussion

Eradication of HCV reduces the risk of progression to cirrhosis, HCC, and liver-related mortality, and thus leads to an improvement in overall survival and quality of life [9]. Historically, the standard longer duration of IFN and RBV treatment produced significant adverse events in elderly patients, necessitating dose reduction or discontinuation of medications [10,11]. The overall SVR rate was less than 50% with standard dual therapy with Peg IFN and RBV regimens. With the introduction of first DAAs in 2011, the triple therapy (boceprevir or telaprevir with Peg IFN and RBV) increased the SVR12 to 65–70% in GT 1 patients. Subsequent, substantial progress with further trials including combination NS5A and NS5B inhibitors, SVR12 approached more than 90%.

Current guidelines do not specify the age limit for treating elderly patients. The American Association of Study of Liver Disease recommends one of the six- DAA combination regimens for GT 1, the most common type of chronic HCV infection in the United States [12]. RBV is still an integral part of the treatment regimen and utilized in combination with DAAs in GT 4 and as an alternative treatment regimen in GTs 1 and 3 patients with compensated cirrhosis.

A recent meta-analysis by Yang *et al.* [8] concluded that the overall SVR in patients aged older than or equal to 65 years treated with a prolonged course of IFN/RBV regimens was significantly lower and had a significantly higher risk of relapse than in patients younger than 65 years of age. IFN and RBV discontinuation rate were also significantly higher in older patients than in younger patients. We did not find any significant difference in RBV dose reduction or discontinuation rate ($P = 0.913$) in patients aged 65 years and older compared with younger patients. These findings indicate that elderly patients are tolerating equally the shorter course of treatment involving

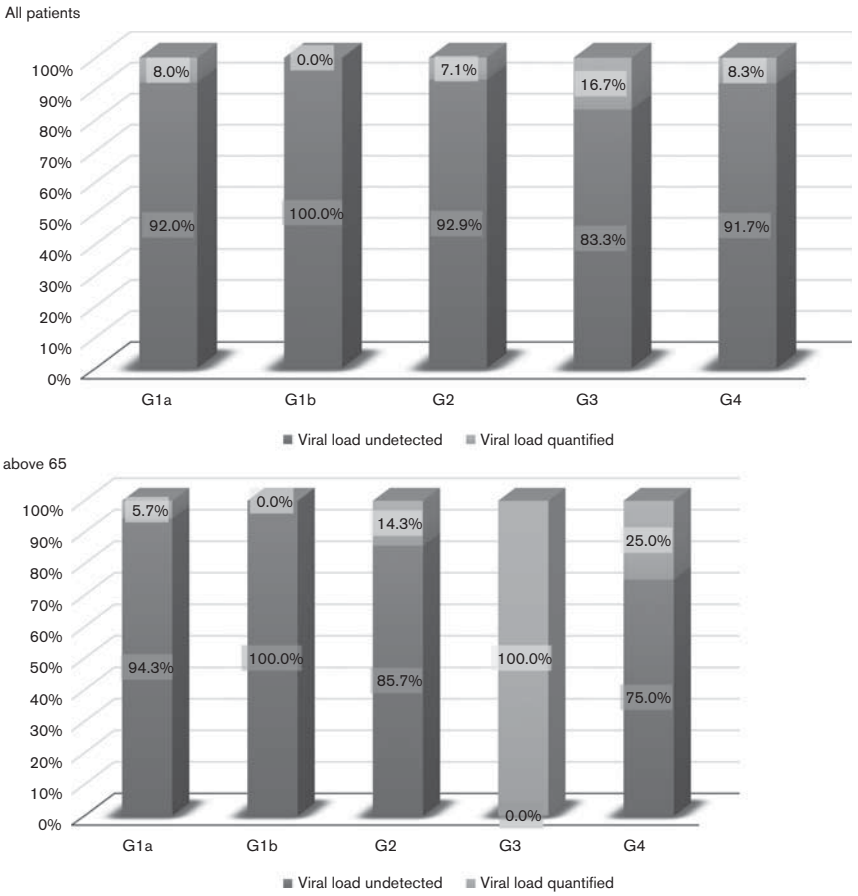

Fig. 6. Sustained virologic response at 12 weeks after treatment with different genotypes.

Table 6. Adverse events associated with interferon-based treatment regimens

Adverse events	Interferon-based ($N=55$)	Age <65 years ($N=43$)	Age ≥ 65 years ($N=12$)	*P* value
Fatigue	27	18	9	0.055
Anemia	25	16	9	0.026
Leukopenia	22	14	8	0.047
Thrombocytopenia	14	9	5	0.259
Skin rash	9	6	3	0.392
Headache	4	3	1	1.000
Arthralgia	5	5	0	0.574
Nausea	5	3	2	0.298
Abdominal pain	6	6	0	0.321
Insomnia	2	2	0	1.000
Itching	2	1	1	0.392
Dizziness	1	1	0	1.000
Depression	3	2	1	0.530
Diarrhea	1	1	0	1.000
Vomiting	1	1	0	1.000
Photosensitivity rash	0	0	0	
Constipation	0	0	0	

Table 7. Adverse events associated with interferon-free treatment regimens

Adverse events	Interferon-free regimens ($N=185$)	Age <65 years ($N=113$)	Age ≥ 65 years ($N=72$)	*P* value
Fatigue	51	28	23	0.314
Anemia	22	9	13	0.060
Leukopenia	6	2	4	0.210
Thrombocytopenia	10	4	6	0.191
Skin rash	11	6	5	0.753
Headache	15	12	3	0.168
Arthralgia	6	4	2	1.000
Nausea	5	3	2	0.298
Abdominal pain	4	4	0	0.158
Insomnia	6	5	1	0.407
Itching	5	2	3	0.379
Dizziness	4	1	3	0.301
Depression	1	1	0	1.000
Diarrhea	3	3	0	0.283
Vomiting	1	1	0	1.000
Photosensitivity rash	2	2	0	0.522
Constipation	1	1	0	1.000

IFN-based and RBV-based regimens as younger patients. ETR and SVR12 for elderly patients were similar to those of younger patients (93.06 vs. 94.12%), supporting previous observations, but with the improved virologic response rate in combination with DAAs [13]. Fatigue is the most common adverse event observed in both IFN-based and IFN-free treatment regimens (Tables 6 and 7). Most of the incidences of anemia and leukopenia noted in IFN-free regimens were because of RBV in combination with newer agents. None of the patients discontinued the treatment because of adverse events, supporting the fact that a shorter duration of IFN/RBV-based treatment is

better tolerated and can be administered to any age group safely with close monitoring during the treatment.

In most initial trials on protease inhibitors, a small number of patients older than 65 years of age were included. Although there was no upper age limit in NS5B nucleotide polymerase inhibitor SOF and NS3/4A second-generation protease inhibitor simeprevir trials, the number of elderly patients included was too small to draw any conclusion [14,15]. In most of the trials involving SOF, most of the patients treated were in their 50s [16–21]. In our study, 54 (27 in each group) patients treated with SPV and the SOF regimen showed similar SVR12 rates ($P = 0.607$) and adverse events profile. Overall, SVR12 treated with an SOF-based regimen was 91–98%, in agreement with the results observed from the major trials involving SOF [18–22]. In trials involving Viekira Pak, the study group involved were younger than 71 years, with a mean age in the 50s, and the SVR rate was well above 88% [22–26]. Overall, the response rate with Viekira Pak in our study was 100% ($12 < 65$ and $6 > 65$ years), with good tolerance to medication in elderly patients.

Clinical trials involving IFN and RBV-free regimens also did not include enough patients aged 65 years and older to determine whether they respond differently from a younger population. Trials involving the NS5A inhibitor LDV and SOF in ION1, 2, and 3 trials included only 117 patients aged 65 years and older, and the patient population included in LONESTAR Study involving the LDV and the SOF combination was younger than 70 years [27–30]. No overall difference in tolerability and effectiveness was observed with elderly patients, but the data available for the treatment of the aged population with newly approved therapies are still limited not only in registration trials but also in real-world treatments and community-based HCV regimens. Results of evaluation of 80 ($52 < 65$ and $28 > 65$ years) patients treated with Harvoni in our study yielded an ETR of 97% and an SVR12 of 94%, consistent with the results observed in clinical trials. No statistically significant difference was noted in our study with ETR ($P = 0.209$) or SVR12 ($P = 0.120$) between the two age groups, consistent with the recently published study by Saab *et al.* [31]. They analyzed the data from four open-label phase 3 clinical trials that evaluated the safety and efficacy of LDV + SOF and concluded that the combination of LDV and SOF is safe, effective, and well tolerated in patients older than 65 years of age who have GT 1 hepatitis C infection [31]. Of the 2293 patients enrolled in four phase 3 trials, 264 (12%) were older than or equal to 65 years of age, of whom 24 were aged older than or equal to 75 years. 97% of patients aged younger than 65 years achieved SVR12 (1965/2029) and 98% (258/264) of patients aged older than or equal to 65 years achieved SVR12. The most common adverse events in both age groups that occurred in 10% or more patients were headache and fatigue. Most adverse events noted in our study were minor and did not require any intervention, comparable with the study reports from major trials involving similar treatment regimens (Table 5). Adverse events did not differ significantly between the groups, except abdominal pain ($P = 0.018$). Ten (6.4%) patients, all younger than 65 years of age, complained of nonspecific abdominal pain on treatment. Considering that the population involved had significant pain issues at baseline, it appears that this symptom may not be entirely related to the medication agent used. There were two serious adverse reactions during treatment with the regimen involving RBV with severe anemia requiring a blood transfusion and two patients received darbepoietin infusion for correction of anemia. None of the patients discontinued the complete treatment regimen in our study because of adverse reactions, although four patients discontinued the RBV during the treatment; they all achieved SVR12. In 12% of the patients, the RBV dose was reduced during treatment. A recent study by Pernas [32] raised a concern about possible drug interactions and RBV dose reduction because of adverse reactions in a significant number of patients after following 125 patients 65 years and older who were treated for hepatitis C with newer DAA agents. Of the 61.2% of patients who received RBV, in almost half, the dose was reduced during treatment [32]. Clinical trials involving a recently approved IFN-free regimen for GTs 1 and 4, elbasvir, and grazoprevir (Zepatier; Merck & Co Inc, Kenilworth, New Jersey, USA) with or without RBV included 187 patients aged 65 years or older [33]. The higher rate of late ALT elevation was observed in elderly patients; however, no dosage adjustment was required and the ALT level of most patients normalized after the completion of treatment.

SVR differs with GTs. We found a statistically significant low SVR rate with GT 1 in an elderly age group. There are no data identifying which patients will achieve an SVR among older patients with a DDA-based treatment. Our analysis indicates that cirrhosis and increased MELD score are important factors for low SVR in general and in elderly patients. Univariate analysis showed that baseline BMI, ALT, AST, and hemoglobin are factors that are associated significantly with an SVR ($P = 0.020$, 0.020, 0.000, and 0.013, respectively).

In our study, 12 (6.28%) patients failed to respond to treatment ($7 < 65$ and $5 \geq 65$ years). Age was not a factor for the poor virologic response and the failure rate between the groups was not significant ($P = 0.767$). All patients reported adherence to the medication regimen, and there was no clinical evidence of any reinfection in relapsed patients. None of these patients had any pretreatment-resistant or post-treatment-resistant associated variants and are awaiting further treatment. Seventy-five (nine out of 12) percent of the patients who failed to respond to treatment were cirrhotic and 41% (five out of 12) were coinfected with HIV. Further studies are required to evaluate these significant numbers of relapses in HIV-coinfected patients. Nine patients who failed to treatment received one or the other SOF-based regimen.

Some of the limitations of this study are the retrospective nature of our study, the fact that documentation of the common adverse events may not be complete, and that elderly patients involved are still a small number compared with registration trials. However, to our knowledge, our study is the first study involving a real-world community-based treatment comparing HCV patients younger than 65 years of age and 65 years of age and older. Going forward, the IFN-free regimens seem to be the standard of care in both age groups. RBV in combination with other DAAs may still be useful in treating some of the difficult to treat patient groups and in less developed countries, where the cost of newer antiviral medicines is a major hurdle. Shortened treatment course may reduce the drug-related adverse events in general including elderly patients. There is a pressing need to include older patients in

future trials involving IFN-free agents. They require more complex decision-making because of their age and comorbid conditions with multiple medications.

Conclusion

The age of the patient does not seem to have a major impact on the virologic response rate when treating chronic HCV infection. Older patients (age 65 years and older) do not appear to have a higher frequency of adverse events compared with younger patients. Increased fibrosis, cirrhosis, some of the baseline laboratory studies including AST, ALT, Hemoglobin, and platelet levels seem to affect the SVR in the elderly and require further studies. More studies should be carried out in an older population of patients to assess the safety, efficacy, and adverse reactions of newer DAAs regimens. Treatment should not be withheld purely on the grounds of advanced age.

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Conflicts of interest

Dr Mohanty is on the Speakers Bureau for Gilead Science, BMS, and Abbvie Pharmaceuticals. For the remaining authors, there are no conflicts of interest.

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