RESEARCH

COMPARISON OF THE EFFICACY AND SAFETY OF DIRECT-ACTING ANTIVIRAL AGENTS IN THE TREATMENT OF HEPATITIS C VIRUS GENOTYPE 1 BETWEEN THE TURKISH ELDERLY AND YOUNGER POPULATION

Turkish Journal of Geriatrics
DOI: 10.31086/tjgeri.2022.264
2022; 25(1): 68-78

■ Haydar ADANIR[1]
■ Mete AKIN[1]
■ Erhan ALKAN[2]

CORRESPONDANCE

[1] Mete AKIN

Akdeniz University, Facultyof Medicine, Gastroenterology, Antalya, Turkey

Phone: +905055732010
e-mail: drmeteakin@yahoo.com

Received: Nov 15, 2021
Accepted: Feb 14, 2022

[1] Akdeniz University, Facultyof Medicine, Gastroenterology, Antalya, Turkey

[2] Medical Park Antalya Hospital, Gastroenterology, Antalya, Turkey

Abstract

Introduction: Direct-acting antiviral agents are highly effective and safe treatments for chronic hepatitis C infection; however, the treatment may be more problematic in elderly patients due to accompanying comorbid conditions. This study aimed to assess the efficacy and safety of direct-acting antiviral agents among the hepatitis C virus genotype 1 infected Turkish elderly population (≥65 years).

Materials and Method: Ninety-six patients older than 18 years old treated with direct-acting antiviral regimens (sofosbuvir/ledipasvir ± ribavirin or ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin) were included in the study: 48 patients (50%) constituted Group 1 (<65 years) and 48 (50%) constituted Group 2 (≥65 years). Comorbidities, potential drug–drug interactions, the number of interacting drugs, adverse events, and sustained virologic response rates were evaluated and compared between the groups.

Results: Sustained virologic response rates were 100% for both of the groups, except for the two patients with substance abuse in Group 1 who dropped from the study. Patients in Group 2 had more cirrhosis ($p = 0.005$) and respiratory diseases ($p = 0.037$). There was no significant difference between the two groups in terms of side effects ($p = 0.683$); however, side effects were significantly higher in the elderly group with two or more potential drug interactions ($p = 0.049$). The presence of cardiovascular disease was also found to be associated with more side effects in the elderly ($p = 0.022$).

Conclusion: Direct-acting antiviral regimens are highly effective in elderly patients without a significant increase in the risk of side effects.

Keywords: Geriatrics; Hepatitis C, Chronic; Therapy.

INTRODUCTION

The hepatitis C virus (HCV) is a major global health problem that is estimated to affect 1.6% (about 115 million) of the population worldwide (1). Although approximately 25% of those who have HCV infection develop acute hepatitis with jaundice, chronic disease develops in approximately 70% of infected individuals (2). Globally, genotype 1 (G1) accounted for 46% of all HCV infections among adults, making it the most common (1). The seroprevalence of HCV in Turkey has been reported as 1%, and 29% are 60 years and older. In the same study, age >50 years was found to be a significant predictor for anti-HCV positivity, and the most common genotype was reported as genotype 1 (3).

Chronic hepatitis C infection is the leading cause of cirrhosis and hepatocellular carcinoma (HCC). Twenty seven percent of cirrhosis and 25% of HCC cases were estimated to evolve from HCV infections (4). Older patients are disproportionally affected by HCV infection and are at a higher risk of liver disease progression and its complications than younger patients, as the risk of cirrhosis progression is reported to be proportional to the duration of HCV infection (5).

The treatment of HCV is more challenging among elderly patients because of the increased prevalence of multiple comorbid conditions, leading to an increased risk of side effects. The emergence of highly effective all-oral direct-acting antiviral (DAA) agents with minimal adverse events has provided further data on treatment outcomes in the elderly population. Glecaprevir/pibrentasvir, sofosbuvir (SOF)/ledipasvir (LDV) ± ribavirin (RBV), and ombitasvir/paritaprevir/ritonavir and dasabuvir (OBV/PTV/r and DSV) ± RBV are currently approved treatments in Turkey according to genotype, treatment experience, and presence of cirrhosis. DAA agents have been found to be effective and safe in the elderly population, according to current evidence, with comparable sustained virologic response (SVR) rates (6). Nevertheless, concerns about the higher rates of adverse events and/or drug interactions associated with concurrent medications and the increased prevalence of comorbidity in these patients continue.

In this respect, given the increasing use of DAAs in the elderly population and the high comorbid conditions and multiple drug use in this population, more real-world studies on different subgroups are needed. Thus, this study aimed to assess the efficacy and safety of DAA therapy among the Turkish elderly population (≥65 years) with chronic HCV genotype 1 (GT1) infection and compare them with younger (<65 years) patients.

MATERIALS AND METHOD

HCV genotype 1 infected patients older than 18 years old who were treated with a DAA-based regimen at the Akdeniz University Medical Faculty Gastroenterology Outpatient Clinic were scanned retrospectively. Patients treated with glecaprevir/pibrentasvir were not included due to a relatively new treatment option in Turkey, and most patients were previously treated with SOF/LDV ± RBV or OBV/PTV/r and DSV ± RBV. Patients with HBV and HIV coinfection and patients with solid organ transplantation (kidney, liver, pancreas) were excluded.

Elderly patients were defined as being 65 years and older. Patients under 65 years of age were determined to be the same number as the elderly population. Demographic parameters including age and gender, medical history and previous treatment(s), the number and type of comorbidities (HCC, diabetes mellitus, hypertension, cardiovascular, renal, and respiratory diseases), presence of cirrhosis (if any), and concomitant medications, were retrospectively analyzed from the electronic database of hospital and printed patient files. The groups were named Group 1 (aged <65 years) and Group 2 (aged ≥65 years), and the two groups were compared in terms of variables.

Hemoglobin, thrombocyte, bilirubin, albumin,

natrium, and creatine values and estimated glomerular filtration rates (eGFR) at the beginning of the treatment, every 4 weeks during the treatment, and at the end of the treatment (12 or 24 weeks) were also recorded for each patient. Potential drug–drug interactions (DDIs) were evaluated using the University of Liverpool web interaction-checker (available at *www.hep-druginteractions.org*), and the number of interacting drugs were noted. The patients had received two different treatment protocols: (1) SOF/LDV ± RBV and (2) OBV/PTV/r and DSV ± RBV, and their treatment continued for 12 or 24 weeks, according to the current guidelines of that period (7).

SVR was defined as a viral load below the lower limit of quantification at least 12 weeks after the end of treatment (8). The type, severity, and number of adverse events (AEs) were recorded per person. AEs that did not require treatment discontinuation and/or dose modification were defined as mild side effects, whereas side effects that caused the patient to pause or discontinue the treatment or dose modification were defined as severe. Child-Pugh (CP) scores and models for end-staged liver disease (MELD) scores were calculated and recorded before and after treatment in patients with cirrhosis.

Statistical Analysis

The suitability of the numerical variables included in the study to normal distribution was tested with the Shapiro–Wilk test. Numerical variables were described using mean and standard deviation or median and interquartile difference (NAF) values, and categorical variables were described using frequency and percentage values. The relationship between two categorical variables was investigated using the chi-square test (precision test). Bonferroni correction was used in the post-hoc examination of categorical variables that took more than two values. The non-parametric Mann–Whitney U test was used to compare the two independent means. The study was conducted at a 95% confidence level ($p < 0.05$ statistically significant difference was accepted).

Ethical Approval

Ethical approval was obtained for this study from the Akdeniz University School of Medicine Clinical Research Ethics Committee (Approval no:709). Study was conducted according to the World Medical Association Declaration of Helsinki. Approval of the Akdeniz University Hospital Administration was also obtained for access to patient records.

RESULTS

Baseline characteristics

A total of 96 patients older than 18 years old treated with DAA combination regimens were included in the study: 48 patients (50%) constituted Group 1 (<65 years) and 48 (50%) constituted Group 2 (≥65 years). Among patients in Groups 1 and 2, the mean age was 49.0 ± 13.4 and 69.7 ± 3.7 respectively. Twenty-seven patients were men and 21 patients were women in Group 1, and 18 were men and 30 were women in Group 2; 20.8% and 47.9% had cirrhosis in Groups 1 and 2, respectively.

In Group 1, 6 of the patients were receiving OBV/PTV/r and DSV treatment, 10 patients were receiving OBV/PTV/r and DSV + RBV, 20 patients were receiving SOF/LDV, and 12 patients were receiving SOF/LDV + RBV. In Group 2, OBV/PTV/r and DSV + RBV were used by 4 patients, SOF/LDV by 16 patients, and SOF/LDV + RBV by 10 patients. The number of patients on OBV/PTV/r and DSV therapy was significantly higher (18 patients) in Group 2. Regarding RBV use, 22 patients in Group 1 and 14 patients in Group 2 were using RBV, and there was no statistically significant difference between the two groups in terms of RBV use.

In Group 1, 34 patients received 12 weeks and 14 patients received 24 weeks of treatment; in Group 2, 31 patients received 12 weeks and 17 patients received 24 weeks of treatment, and there was no statistically significant difference between the two groups in terms of treatment duration. Considering the number of drug interactions, 29 and 24 patients

received no potentially interacting drugs, 15 and 16 patients used one potential interacting drug, and 4 and 8 patients used two or more potential interacting drugs in Groups 1 and 2, respectively. There was no statistically significant difference between the groups.

The SVR rates were 100% for both groups, except for the two patients with substance abuse in Group 1, who dropped from the study. When both groups were compared in terms of side effects related to treatment, no significant difference was found between the two groups ($p = 0.683$).

Nearly half of the patients had failed a prior course of IFN-based therapy (50% and 54.2% for Groups 1 and 2, respectively). Baseline characteristics of the study population according to age groups are shown in Table 1.

A comparison of comorbid diseases revealed equal distribution between the groups in terms of the presence of HCC, diabetes mellitus, hypertension, and cardiovascular diseases, whereas Group 2 had more cirrhosis (10 vs. 23, $p = 0.005$) and respiratory diseases (3 vs. 10, $p = 0.037$). Chronic renal diseases were higher in Group 1 (8 vs. 1, $p = 0.014$) (since our center is a transplant center, many HCV patients were also candidates for kidney transplantation). Comorbid diseases in the groups are presented in Table 2.

The most common adverse event was fatigue in both groups. Fatigue was followed by nausea, vomiting, diarrhea, and dyspepsia. The rarest side effects were dizziness, loss of appetite, constipation, and dyspnea. There was no discontinuation of treatment due to adverse events. In both groups, the correlation of the presence of side effects with gender, treatment protocols, use of RBV, duration of treatment, number of potential drug interactions, treatment history, and comorbid diseases were also analyzed. We found that the incidence of side effects was significantly higher in the elderly group with two or more potential drug interactions ($p = 0.049$). The presence of cardiovascular disease was also found to be associated with more side effects in the elderly ($p = 0.022$). The associations between the presence of side effects and other variables are presented in Table 3. RBV-induced anemia (decrease in hemoglobin (Hb) %) was statistically higher in Group 1 (-19.1% vs. -5.9 $p < 0.001$). The baseline Hb levels of this group were also significantly higher (12.5 vs. 13.7, $p = 0.049$) (Table 4).

There was no significant difference between the two groups in terms of decreases in CP and MELD scores with treatment (Table 5).

DISCUSSION

The human lifespan is gradually increasing in most countries, including Turkey (9). Elderly patients represent a significant and rapidly increasing proportion of patients infected with chronic HCV (10). Historically, age has been a major constraint for IFN/RBV-based antiviral therapy due to the large number of treatment-related side effects, especially anemia, which can severely impair the patient's clinical course, particularly in elderly patients with cardiovascular comorbidities. However, there is increasing evidence that IFN-free DAA regimens can successfully treat HCV in these patients (11,12). Antiviral therapy in elderly patients with chronic hepatitis C is still controversial; thus, the benefits expected from DAAs should be weighed against the complex clinic of this population, and the most appropriate decision for the patient should be made. While these patients need urgent treatment due to the higher likelihood of advanced liver disease, liver-related complications (cirrhosis, hepatocarcinoma), hospitalization, and death (13,14), the treatment team also has to deal with the burden of coexisting multiple comorbidities that mutually worsen each other's progression and complicate patient management.

Although most studies have reported similar DAA efficacy in elderly patients as in younger patients, concerns have been raised that treatment success may be adversely affected in subgroups

Table 1. Baseline characteristics of the study population

	Group 1 (n=48)	Group 2 (n=48)	p
Age (mean ± SD)	49.0±13.4	69.7±3.7	<0.001
Gender (n, %)			
Male	27 (56.3)	18 (37.5)	0,066
Female	21 (43.8)	30 (62.5)	
Treatment protocol (n, %)			
OBV/PTV/r /DSV	6 (12.5)	18 (37.5)	0.027[a]
OBV/PTV/r/DSV +RBV	10 (20.8)	4 (8.3)	
SOF/LDV	20 (41.7)	16 (33.3)	
SOF/LDV+RBV	12 (25)	10 (20.8)	
Agent (n, %)			
OBV/PTV/r /DSV	16 (33.3)	22 (45.8)	0,210
SOF/LDV	32 (66.7)	26 (54.2)	
RBV (n, %)			
No	26 (54.2)	34 (70.8)	0,092
Yes	22 (45.8)	14 (29.2)	
Duration of treatment (n, %)			
12 week	34 (70.8)	31 (64.6)	0,513
24 week	14 (29.2)	17 (35.4)	
Potential interacting drug(s) (n, %)			
none	29 (60.4)	24 (50)	0,399
1	15 (31.3)	16 (33.3)	
>1	4 (8.3)	8 (16.7)	
Previous HCV treatment (n, %)			
No	24 (50)	22 (45.8)	0,683
Yes	24 (50)	26 (54.2)	
Side effect(s) (n, %)			
No	36 (75)	30 (62.5)	0,186
Yes	12 (25)	18 (37.5)	

SOF/LDV: Sofosbuvir/ledipasvir, OBV/PTV/r /DSV: Ombitasvir/paritaprevir/ritonavir and dasabuvir RBV: Ribavirin, [a]: OBV/PTV/r /DSV vs OBV/PTV/r /DSV +RBV

Table 2. Comorbid diseases accompanying HCV

Comorbid disease (n, %)	Group 1 (n=48)	Group 2 (n=48)	p
Cirrhosis	10 (20.8)	23 (47.9)	0,005
HCC	1 (2.1)	4 (8.3)	0,168
DM	6 (12.5)	8 (16.7)	0,563
HT	17 (35.4)	22 (45.8)	0,299
Cardiovascular diseases	2 (4.2)	6 (12.5)	0,140
Respiratory diseases	3 (6.3)	10 (20.8)	0,037
Chronic renal diseases	8 (16.7)	1 (2.3)	0,014

HCC: Hepatocellular carcinoma, DM: Diabetes mellitus, HT: Hypertension

Table 3. The associations between the presence of side effects and other variables

Variables (n, %)	Group 1			Group 2		
	SE (-)	SE (+)	p	SE (-)	SE (+)	p
Gender						
Male	21 (58.3)	6 (50)	0,614	10 (33.3)	8 (44.4)	0,441
Female	15 (41.7)	6 (50)		20 (66.7)	10 (55.6)	
Treatment protocol						
OBV/PTV/r/DSV	6 (16.7)	0 (0)	0,297	13 (43.3)	5 (27.8)	0,404
OBV/PTV/r/DSV +RBV	6 (16.7)	4 (33.3)		1 (3.3)	3 (16.7)	
SOF/LDV	16 (44.4)	4 (33.3)		10 (33.3)	6 (33.3)	
SOF/LDV+RBV	8 (22.2)	4 (33.3)		6 (20)	4 (22.2)	
Agent						
OBV/PTV/r /DSV	12 (33.3)	4 (33.3)	>0.999	14 (46.7)	8 (44.4)	0,881
SOF/LDV	24 (66.7)	8 (66.7)		16 (53.3)	10 (55.6)	
RBV						
No	22 (61.1)	4 (33.3)	0,094	23 (76.7)	11 (61.1)	0,251
Yes	14 (38.9)	8 (66.7)		7 (23.3)	7 (38.9)	
Duration of treatment						
12 weeks	25 (69.4)	9 (75)	>0.999	20 (66.7)	11 (61.1)	0,697
24 weeks	11 (30.6)	3 (25)		10 (33.3)	7 (38.9)	
Drug interaction(s)						
none	23 (63.9)	6 (50)	0,186	19 (63.3)	5 (27.8)	0,049
1	9 (25)	6 (50)		8 (26.7)	8 (44.4)	
>1	4 (11.1)	0 (0)		3 (10)	5 (27.8)	

Cirrhosis						
No	27 (75)	11 (91.7)	0,414	17 (56.7)	8 (44.4)	0,412
Yes	9 (25)	1 (8.3)		13 (43.3)	10 (55.6)	
Treatment history						
No	20 (55.6)	4 (33.3)	0,182	14 (46.7)	8 (44.4)	0,881
Yes	16 (44.4)	8 (66.7)		16 (53.3)	10 (55.6)	
HCC						
No	35 (97.2)	12 (100)	>0.999	28 (93.3)	16 (88.9)	0,624
Yes	1 (2.8)	0 (0)		2 (6.7)	2 (11.1)	
DM						
No	32 (88.9)	10 (83.3)	0,631	25 (83.3)	15 (83.3)	>0.999
Yes	4 (11.1)	2 (16.7)		5 (16.7)	3 (16.7)	
HT						
No	25 (69.4)	6 (50)	0,300	17 (56.7)	9 (50)	0,654
Yes	11 (30.6)	6 (50)		13 (43.3)	9 (50)	
Cardiovasculer diseases						
No	34 (94.4)	12 (100)	>0.999	29 (96.7)	13 (72.2)	0,022
Yes	2 (5.6)	0 (0)		1 (3.3)	5 (27.8)	
Respiratory diseases						
No	34 (94.4)	11 (91.7)	>0.999	25 (83.3)	13 (72.2)	0,468
Yes	2 (5.6)	1 (8.3)		5 (16.7)	5 (27.8)	
Chronic renal diseases						
No	31 (86.1)	9 (75)	0,394	30 (100)	17 (94.4)	0,375
Yes	5 (13.9)	3 (25)		0 (0)	1 (5.6)	

SE: Side effect, SOF/LDV: Sofosbuvir/ledipasvir, OBV/PTV/r /DSV: Ombitasvir/paritaprevir/ritonavir and dasabuvir, RBV: Ribavirin, HCC: Hepatocellular carcinoma, DM: Diabetes mellitus, HT: Hypertension

Table 4. Comparison of two groups in terms of Ribavirin-induced hemoglobin change

	Group 1			Group 2		
	RBV (-) (n=26)	**RBV (+) (n=22)**	**p**	**RBV (-) (n=34)**	**RBV (+) (n=14)**	**p**
Hb first (mean ± SD)	12.5±2.0	13.7±1.4	0,049	12.4±2.0	12.8±1.2	0,715
Hb last (mean ± SD)	12.2±1.8	11.3±1.7	0,090	12.2±2.2	12.0±1.5	0,460
dHb (median, IQR)	-1.6 (12)	-19.1 (18.1)	<0.001	-1.7 (10.6)	-5.9 (14.1)	0,149

HB: Hemoglobin, RBV: Ribavirin, SD: Standart deviation, IQR: Interquartile difference

Table 5. Comparison of two groups in terms of decrease in CP and MELD- scores with treatment in cirrhotic patients

	Group 1 (n=10)	Group 2 (n=23)	p
CP first (median, IQR)	6 (3)	6 (2)	0,804
CP last (median, IQR)	5.5 (2.3)	5 (2)	0,882
dCP (n, %)			
increase	0 (0)	2 (8.7)	0,859
no change	7 (70)	14 (60.9)	
decrease	3 (30)	7 (30.4)	
MELD first (median, IQR)	10.5 (9.5)	10 (6)	0,767
MELD last (median, IQR)	10.5 (8.5)	8 (4)	0,220
dMELD (n, %)			
increase	2 (20)	1 (4.3)	0,281
no change	5 (50)	10 (43.5)	
decrease	3 (30)	12 (52.2)	

CP: Child-Pugh, MELD: Model for end-staged liver disease, IQR: Interquartile difference

with other negative predictive factors, including the presence of cirrhosis and some HCV genotypes (15-18). There are also studies reporting higher rates of SAEs and discontinuation of treatment in the elderly population (19-23). Therefore, studies in subgroups of this sensitive population are needed.

The dominant HCV genotype worldwide was found to be genotype 1 with a rate of 46% (1). Similarly, the dominant HCV genotype was also genotype 1 in our country (90%–93.3%) followed by genotype 3 (3.7–4.9%), genotype 2 (1.5–2.2%) and genotype 4 (1.1–2.5%) (3,24,25). Therefore, we were interested in investigating genotype 1 in our population.

In a retrospective cohort study by Qureshi et al. (26), SVR12 rates and predictors of treatment failure were evaluated in elderly (≥70 years) and noelderly (<70 years) HCV patients (mostly genotype 1) treated with different DAA regimens. SVR12 rates were reported as 81% in elderly group and 95% in nonelderly group. In this study, age >70 years, presence of cirrhosis, HCC and the prior treatment experience were reported as independent predictors for HCV treatment failure in univariate analysis, however, in multivariate analysis only age >70 years and cirrhosis were found as statistically significant predictors. Moreover, in this study, when age of ≥ 65 years was used only the presence of cirrhosis achieved statistical significance to predict treatment failure. In our study age ≥65 years were defined as the elderly group. Elderly group had also more cirrhosis in our study, however, this situation didn't affect the SVR12 rates. History of treatment experience and HCC were similar in both groups. Our results showed that SOF/LDV±RBV and OBV/PTV/r/DSV ± RBV-based regimens resulted in high SVR rates in patients of advanced age. Among difficult-to-treat subgroups, including patients with cirrhosis, elderly patients had similar SVRs compared with younger patients.

Actually, SVR rates were 100% for both groups, except for the two patients with substance abuse who dropped from the study. Another study investigated SVR rates of 17487 HCV-infected patients treated with SOF/LDV and OBV/PTV/r/DSV-based regimens reported high SVR12 rates without differences among the 5 age categories (SVR rates were 91.2%, 89.8%, 90.8%, 91.1%, 90.0%, and 93.8% in patients aged below 55, 55–59, 60–64, 65–69, 70–74, and 75 years or older. age was not found a predictive of SVR (27).

Consistent with our study, another retrospective post hoc analysis conducted by Saab et al. (12), who examined the efficacy of SOF/LDV in an elderly population (aged 65 years and older) with HCV genotype-1, the SVR12 rates were 97% in patients <65 years and 98% in patients ≥65 years. At the subgroup level, the SVR rate was found to be 100% in patients who were 75 years old and older, whereas the SVR12 rate was 97% and 99% in treatment-naive and treatment-experienced elderly patients, respectively. Similarly, results from the German Hepatitis C Registry reported that SVR12 rates in the elderly patient group (>70 years) were similar to the younger population (≤70 years) (92.6% vs 90.7%, respectively) (28).

As mentioned above comorbidity and multidrug use may be higher in elderly patients. So, it is necessary to be more careful about side effects and DDIs. There are many studies in the literature, evaluating side effects and DDIs during the treatment of hepatitis C in elderly patients. In Saab's study, considering the rates of treatment modification or interruption because of the side effects, was 6% in patients under 65 years of age, and 13% in patients aged ≥65 years. The rate of treatment discontinuation was similar in both groups at 1% (12). Lens et al. (29) reported higher significant side effects in patients ≥75 years comparing to the patients 65-74 years (13% and 8.8% respectively, p=0.04). Qureshi et al. (26) reported that approximately 50% of the elderly patients had side effects (most commonly fatigue and weakness), but there were no patients discontinued the treatment. They also stated that the use of additional drugs and DDIs are more common in the elderly population. Vermehren et al. (22) also reported that, in patients with chronic HCV treated with DAAs, the predicted clinically significant DDIs was higher in patients >65 years old (54% vs 28%; P < 0.0001) however, this situation was not effect the SVR rates. In our study, no severe adverse events related to DAAs were noted. Severity and the number of adverse events did not differ between the two age groups. The most common side effect was fatigue in both groups. There was no treatment discontinuation due to adverse events. This may be attributable to the fact that there was no statistically significant difference in terms of the number of drug interactions between the two groups and the equal distribution of most of the comorbid diseases, including HCC, diabetes mellitus, hypertension, and cardiovascular diseases, except for more cirrhosis and respiratory diseases in Group 2 and more chronic renal diseases in Group 1. In both groups, the correlation of the presence of side effects with gender, treatment protocols, use of RBV, duration of treatment, number of potential drug interactions, treatment history, and comorbid diseases were also analyzed. The incidence of side effects was significantly higher in the elderly group with two or more potential drug interactions. The presence of cardiovascular disease was also found to be associated with more side effects in the elderly (p = 0.022). However, RBV-induced anemia (decrease in Hb%) was statistically higher in the Group 1.

In a recent study by Krassenburg et al (30), SVR after DAA therapy was found the associated with reduced risk of disease progression in CP A cirrhosis, but not in CP B-C cirrhosis. Altough, ≥2-point decrease in MELD scores was observed after therapy in 19% of CP B-C patients, it was found that this did not affect the event-free survival in these group. In our study, 47.9% of elderly patients (≥65 years) and 20.8% of younger patiens had cirrhosis (p=0,005).

There was no significant difference between the cirrhotic patients in two groups in terms of decreases in CP and MELD scores after SVR12. Most of our cirrhotic patients had CP A cirrhosis, therefore, good clinical outcomes can be predicted for our patients achieved SVR.

The strengths of the study are, the fact that it was conducted in the Turkish population with the dominant genotype and with real-life data, availability of SVR 12 datas of all patients in the elderly group, assesment of drug-drug interactions and comparison of results with younger population. However, it also has several limitations, including the study's retrospective design and heterogeneous treatment regimens.

In conclusion, DAA regimens were highly effective in the treatment of elderly HCV population, without a significant increase in the risk of adverse effects. With proper evaluation about comorbidities and DDIs (Using an internet database about drug interactions can be helpful in this respect) adverse events and treatment failures can be effectively prevented.

REFERENCES:

1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014;61(1 Suppl): 45-57. (PMID: 25086286).
2. Barut HS, Günal O. Global and national epidemiology of hepatitis C. Klimik Journal 2009; 22(2): 38-43. (in Turkish)
3. Tozun N, Ozdogan O, Cakaloglu Y, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect 2015;21(11): 1020-6. (PMID: 26163105).
4. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45(4): 529–38. (PMID: 16879891).
5. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV) infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138(2): 513-21. (PMID: 19861128).
6. Jhaveri MA, Manne V, Kowdley KV. Chronic Hepatitis C in Elderly Patients: Current Evidence with Direct-Acting Antivirals. Drugs Aging 2018;35(2): 117–22. (PMID: 29417462).
7. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C. J Hepatol 2017;66(1): 153–94. (PMID: 27667367).
8. Zeuzem S, Heathcote EJ, Shiffman ML, et al. Twelve weeks of follow-up is sufficient for the determination of sustained virologic response in patients treated with interferon alpha for chronic hepatitis C. J Hepatol 2003;39(1): 106–11. (PMID: 12821051).
9. Turkish Statistical Institute. The Results of Address Based Population Registration System 2020. [Internet]. Available from: https://data.tuik.gov.tr/Bulten/Index p= The-Results-of-Address-Based-Population-Registration-System-2020-37210. Accessed: 04.02.2021.
10. Su F, Beste LA, Green PK, Berry K, Ioannou GN. 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(6): 686-93. (PMID: 28195877).
11. Mücke MM, Mücke VT, Lange CM, Zeuzem S. Special populations: treating hepatitis C in patients with decompensated cirrhosis and/or advanced renal impairment. Liver Int 2017;37(Suppl 1): 19-25. (PMID: 28052635).
12. Saab S, Park SH, 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(4): 1112-9. (PMID: 26704693).
13. Golabi P, Otgonsuren M, Suen W, Koenig AB, Noor B, Younossi ZM. Predictors of inpatient mortality and resource utilization for the elderly patients with chronic hepatitis C (CH-C) in the United States. Medicine (Baltimore) 2016;95: e2482. (PMID: 26817883).
14. Asahina Y, Tsuchiya K, Tamaki N, et al. Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. Hepatology 2010;52(2): 518-27. (PMID: 20683951).

15. Sood A, Midha V, Mahajan R, et al. Results of sofosbuvir-based combination therapy for chronic hepatitis C cohort of Indian patients in real-life clinical practice. J Gastroenterol Hepatol 2017;32(4): 894-900. (PMID: 27787910).

16. Abd-Elsalam S, Sharaf-Eldin M, Soliman S, Elfert A, Badawi R, Ahmad YK. Efficacy and safety of sofosbuvir plus ribavirin for treatment of cirrhotic patients with genotype 4 hepatitis C virus in real-life clinical practice. Arch Virol 2018;163(1): 51-6. (PMID: 28983675).

17. Mehta V, Mahajan R, Midha V, et al. Impact of direct acting antiviral therapy for treatment of hepatitis C genotypes 1, 3 and 4: a real life experience from India. J Clin Exp Hepatol 2018;8(1): 7-14. (PMID: 29743791).

18. Kondili LA, Gaeta GB, Brunetto MR, et al. Incidence of DAA failure and the clinical impact of retreatment in real-life patients treated in the advanced stage of liver disease: interim evaluations from the PITER network. PLoS One 2017;12(10): e0185728. (PMID: 28977040).

19. 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. (PMID: 27789224).

20. Calleja JL, Crespo J, Rincón D, et al. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish real-world cohort. J Hepatol 2017;66(6): 1138-48. (PMID: 28189751).

21. Kumada H, Chayama K, Rodrigues L Jr, et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology 2015;62(4): 1037-46. (PMID: 26147154).

22. Vermehren J, Peiffer K-H, Welsch C, et al. The efficacy and safety of direct acting antiviral treatment and clinical significance of drug-drug interactions in elderly patients with chronic hepatitis C virus infection. Aliment Pharmacol Ther 2016;44(8): 856-65. (PMID: 27549000).

23. Mücke MM, Herrmann E, Mücke VT, Graf C, Zeuzem S, Vermehren J. Efficacy and safety of direct-acting antivirals for hepatitis C in the elderly: A systematic review and meta-analysis. Liver Int 2019;39(9): 1652-60. (PMID: 31033122).

24. Altuğlu I, Sertöz R, Aksoy A, Gürsel D, Tüzüner U, Günşar F. Possible transmission risks and genotype distribution of hepatitis C virus infection in Western Turkey. Turk J Gastroenterol 2013;24(4): 349-55. (PMID: 24254268).

25. Gürbüz Y, Tülek NE, Tütüncü EE, et al. Evaluation of Dual Therapy in Real Life Setting in Treatment-Naïve Turkish Patients with HCV Infection: A Multicenter, Retrospective Study. Balkan Med J 2016;33(1): 18-26. (PMID: 26966614).

26. Qureshi K, Petersen T, Andres J. Hepatits C treatment differences in elderly patients: Single-center retrospective study. Ann Pharmacother 2020;54(2): 113-21. (PMID: 31452381).

27. Su F, Beste LA, Green PK, 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(6): 686-96. (PMID: 28195877).

28. Dultz G, Müller T, Petersen J, et al. Efectiveness 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(9): 843-57. (PMID: 30084012).

29. Lens S, Fernández I, Rodríguez-Tajes S, et al. Spanish Group for the Study of the Use of Direct-acting Drugs Hepatitis C Collaborating Group. Interferon-free therapy in elderly patients with advanced liver disease. Am J Gastroenterol 2017;112(9): 1400-9. (PMID: 28585554).

30. Krassenburg LAP, Maan R, Ramji A, et al. Clinical outcomes following DAA therapy in patients with HCV-related cirrhosis depend on disease severity. J Hepatol 2021;74(5): 1053-63. (PMID: 33242501)