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EFFECTIVENESS OF ORAL DIRECT ACTING ANTIVIRALS IN ELDERLY CHRONIC HEPATITIS C PATIENTS: REAL-WORLD DATA

ABSTRACT

Introduction: Objectives: Elderly cases have not been adequately represented in clinical trials with respect to chronic hepatitis C treatment. Extremely limited real-world data is available on new direct-acting antivirals in elderly patients. Herein, we aim to evaluate real-world data on new direct-acting antivirals used in the treatment of chronic hepatitis C virus.

Materials and Method: Medical records of 122 patients who started treatment with new direct-acting antivirals between January 2018 and December 2019 owing to chronic hepatitis C virus infection were analyzed retrospectively. Patients were divided into two age groups: those younger than 65 years and those aged 65 and older. Sustained virological response at 12 week rates were compared between the two groups. Sustained virological response at 12 week treatment efficacy analyses were performed with both modified intention to tract and per protocol.

Results: Sustained virological response in the 12th week post treatment was similar in both elderly patients and younger patients. Per protocol analysis was 97.6% (42/43) vs. 100% (56/56) and modified intention to tract analysis was 91.3% (43/45) vs. 91.8% (56/61), respectively. The most common genotype of patients aged 65 years and older were 1b 80%, and the most common genotype of patients younger than 65 years was 1b 57%.

Conclusion: In the present study, Sustained virological response rates were similar in elderly patients compared to younger patients; however, very limited information is available on the effectiveness and safety of new, recently approved direct-acting antivirals in the elderly population.

Key words: Hepatitis C, Chronic; Antiviral Agents; Sustained Virologic Response; Turkey

INTRODUCTION

Hepatitis C infection (HCV) is a major global outbreak, and an estimated 71 million people worldwide are considered to be chronically infected with HCV. Approximately 399,000 people die annually because of HCV-related hepatic insufficiency and cancer (1,2). The estimated prevalence of HCV is 0.2%–0.5% in the United States of America (USA) and Western Europe and 1%–3% in Japan (3,4). The prevalence of HCV in the normal population of Turkey is 1% (5). In some European countries and in countries such as Japan and Taiwan, the prevalence of HCV is high in the elderly population (6). In Europe and Japan, the prevalence of HCV can reach up to 12% in people aged between 61 and 70 years. A study conducted in Egypt found that the prevalence of HCV significantly increased with age; it was 60% between 50 and 60 years of age, and about 40% cases occurred over 60 years of age (7).

Efficacy and safety data are very limited in the treatment of HCV in elderly patients, primarily in clinical trials, owing to incomplete reporting and exclusion (8,9). Historically, there have been significant age restrictions in interferon-based antiviral treatments. This is because compliance with treatment is low in elderly patients, side effects are more common, and the response to treatment is low (10).

Very limited information is available in the literature on the effectiveness of newly used direct-acting antiviral (DAA) drugs in Turkey. This study aims to compare the effectiveness of chronic hepatitis C treatment DAAs in patients aged 65 years and older as well as in patients aged younger than 65 years

MATERIALS AND METHOD

Medical records of 122 patients who started treatment with new DAAs between January 2018 and December 2019 because of chronic HCV infection were retrospectively analyzed. Sixteen cases were removed from the study for various reasons (Figure 1).

DAA drug selection and treatment decisions were made according to current guideline recommendations and according to the decision of the treating physician. The drugs used in the treatment were sofosbuvir (SOF) ± ledipasvir (LED) ± ribavirin (RBV), ombitasvir (OBV) + paritaprevir/ritonavir (PTV/r) ± dasabuvir (DSV) ± ribavirin (RBV), and glecapravir (GLE) + pibrentasvir (PIB). The RBV dose was started according to the weight of the patients. The duration of treatment was set as 8, 12, or 24 weeks based on previous treatment experience and the patients' cirrhosis status. In some cases, liver fibrosis was evaluated via invasive liver biopsy or clinically, radiologically, or through laboratory findings in others.

For viral load determination, HCV–RNA levels were studied via real-time PCR (COBAS AmpliPrep/COBAS Tagman, Roche Diagnostics, Germany) and HCV genotypes were studied using real-time HCV Genotype II (Anatolia geneworks, Turkey) system.

Sustained virological response (SVR-12) was described as the inability to detect HCV viral load 12 weeks after treatment completion. Efficiency assessments other than SVR-12 were defined as follows. Early virological response (EVR): absence of serum HCV RNA after 4 weeks of treatment. Virological breakthrough: detection of previously undetected HCV RNA during treatment. Relapse: detection of HCV RNA, which was not detected at the end of treatment or during the follow-up after treatment. EVR and SVR-12 treatment efficacy analyses were performed between both groups with modified intention to tract (mITT) and per protocol (PP). Patients who completed the treatment period and who had HCV RNA test results at the 12th week after end of treatment were included in the PP analysis. Patients with at least one HCV RNA test result in addition to pretreatment HCV RNA levels were included mITT analysis. All cases with unknown sustained viral responses (SVR-12) were considered as unresponsive in mITT analysis.

Figure 1. Study population flowchart
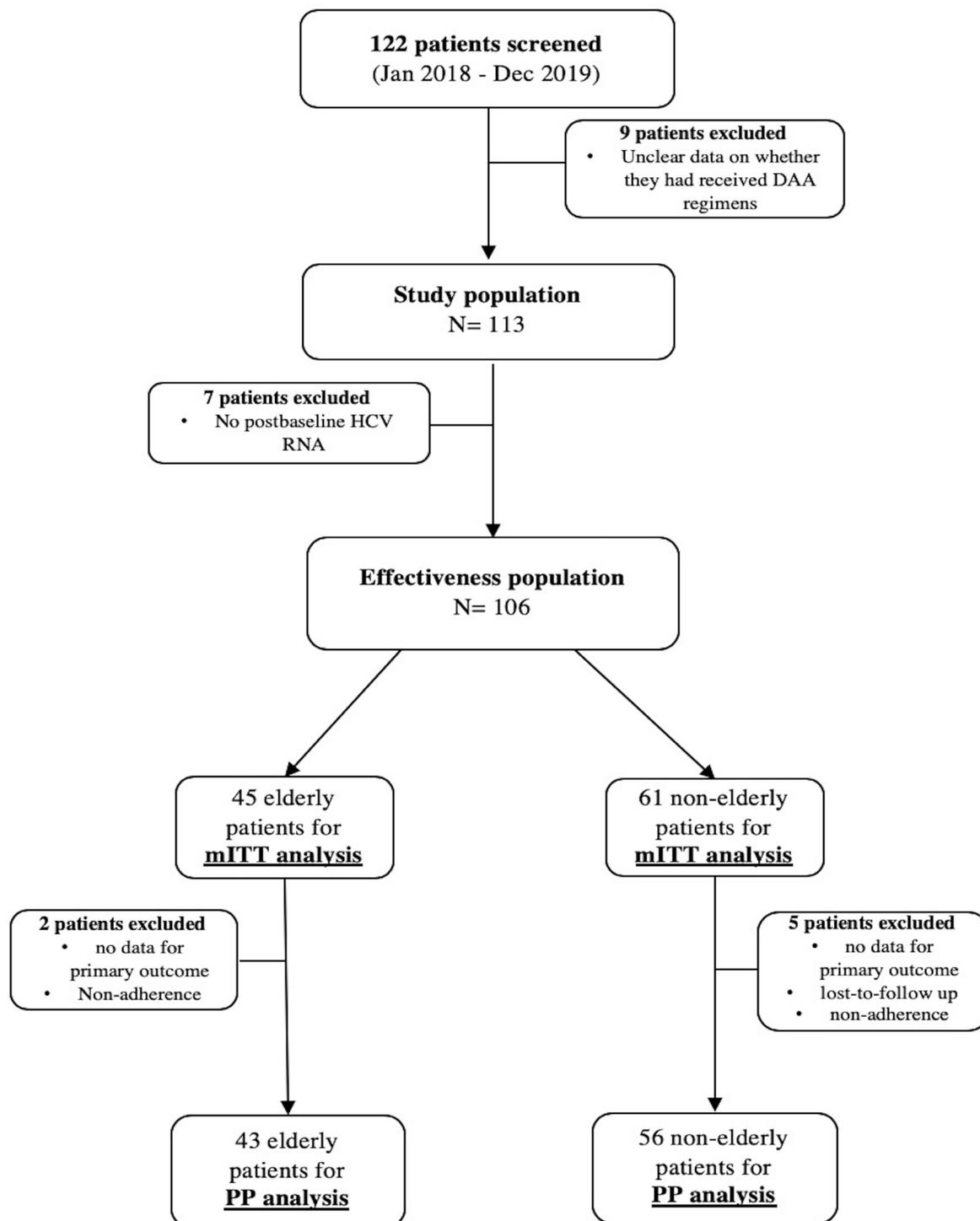
Statistical Analysis

IBM SPSS version 23.0 statistical package program (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The suitability of variables to normal distribution was tested using the Shapiro–Wilk test and histogram. Mean and standard deviation was used for variables that were normally distributed, median (median) and interquartile range was used for variables that were not normally distributed. The Chi-square test was used to compare categorical variables between groups. Biochemical and hematological parameters before and 12 weeks after treatment were compared between groups through the Wilcoxon test. P values below 0.05 were evaluated as statistically significant.

This study was performed with the approval of Mustafa Kemal University Faculty of Medicine Retrospective Ethics Board (reference number: 04.06.2020-01).

RESULTS

During the study period, DAA regiment was administered to 122 cases. 106 cases meeting the criteria for inclusion were included in the study. Of the 106 cases, patients in 45 cases (42.5%) were 65 years old and patients in over 61 cases (57.7%) were younger than 65 years of age. Of the cases having patients aged 65 years and older, 24 patients were female and 21 patients were male. Of the patients who were younger than 65 years of age, 23 were female and 38 were male. Table 1 shows the demographic, primary clinical characteristics, and biochemical as well as hematological parameters of patients according to age groups. Four cases had previous treatment experience: in one of these cases, the patient was over 65 years old, and in three cases, the patients were younger than 65 years of age. All experienced patients had previously used the combination of IFN and RBV.

The most common genotype was 1b in patients aged 65 years and older (80%; n = 36) as well as in patients younger than 65 years (57%; n = 35) of age. However, the difference was statistically significant (p = 0.022). Figure 2 shows the genotype distributions of cases by age.

SOF ± LED ± RBV treatment was started in 11.1%, OBV + PTV/r ± DSV ± RBV treatment was started in 73.3%, and GLE + PIB treatment was started in 15.6% patients aged 65 years and older. SOF ± LED ± RBV treatment was started in 8.2%, OBV +PTV/r ± DSV ± RBV treatment was started in 73.8%, GLE +

Figure 2. The genotype distribution by age groups
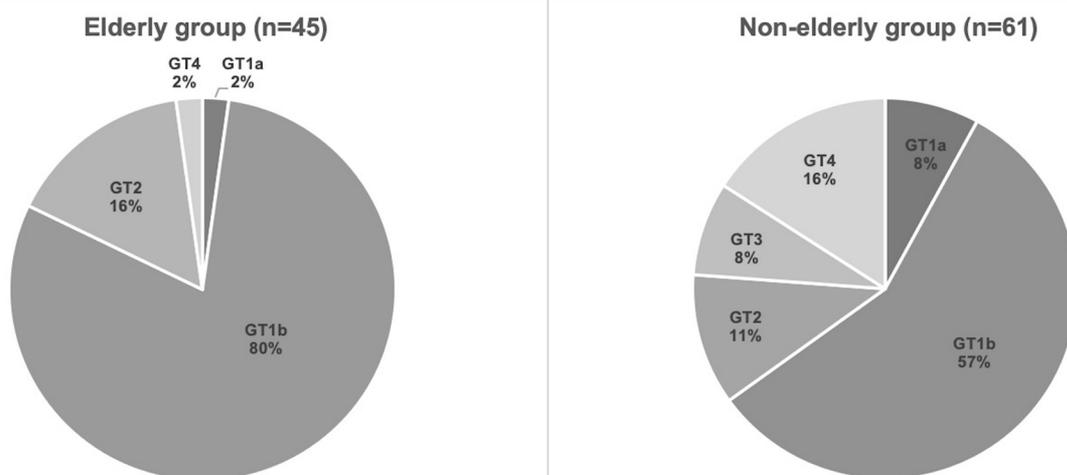
Table 1. Patients demographics and clinical characteristics at baseline by age groups in mITT population.

	Elderly (n=45)	Non-elderly (n=61)	p value
Age	73.6 ± 6.8	47.5 ± 14.32	<0.001
Gender, male	21 (46.6)	38 (62.2)	0.109
Cirrhosis	4 (8.9)	4 (6.6)	0.720
Treatment-experienced	1 (2.2)	3 (4.9)	0.635
Genotype 1	37 (82.2)	39 (63.9)	0.022
HCV RNA level	246000 (77600-14076712)	407300 (135547-1334478)	0.426
Biochemical parameters			
ALT	37 (19-56)	37 (18-58)	0.718
AST	35 (22-50)	35 (22-51)	0.898
BIL	0.70 (0.60-1.10)	0.70 (0.50-1.00)	0.162
ALB	4.30 (3.8-4.2)	4.26 ± 0.37	0.003
Crea	0.70 (0.60-0.90)	0.70 (0.60-0.90)	0.750
Hematological parameters			
HGB	12.73 ± 1.72	14.05 ± 2.31	0.001
PLT	239733 ± 86729	216213 ± 61696	0.232
INR	1.04 ± 0.11	1.02 ± 0.10	0.267

Data expressed as n (%), median (IQR) or mean ± SD. Bold font indicates statistical significance.
HCV RNA: hepatitis C virus ribonucleic acid, ALT: alanine aminotransferase, AST: aspartate aminotransferase,
BIL: bilirubin, ALB: albumin, Crea: creatinine, HGB: hemoglobin, PLT: platelet, INR: international normalized ratio.

PIB treatment was started in 18% patients younger than 65 years of age. No statistically significant difference was observed between the groups in terms of the agents used in the treatment (p = 0.893). Of the 106 cases, 9 had diabetes mellitus, 10 had hypertension, 5 had coronary artery disease, and 7 had chronic renal failure.
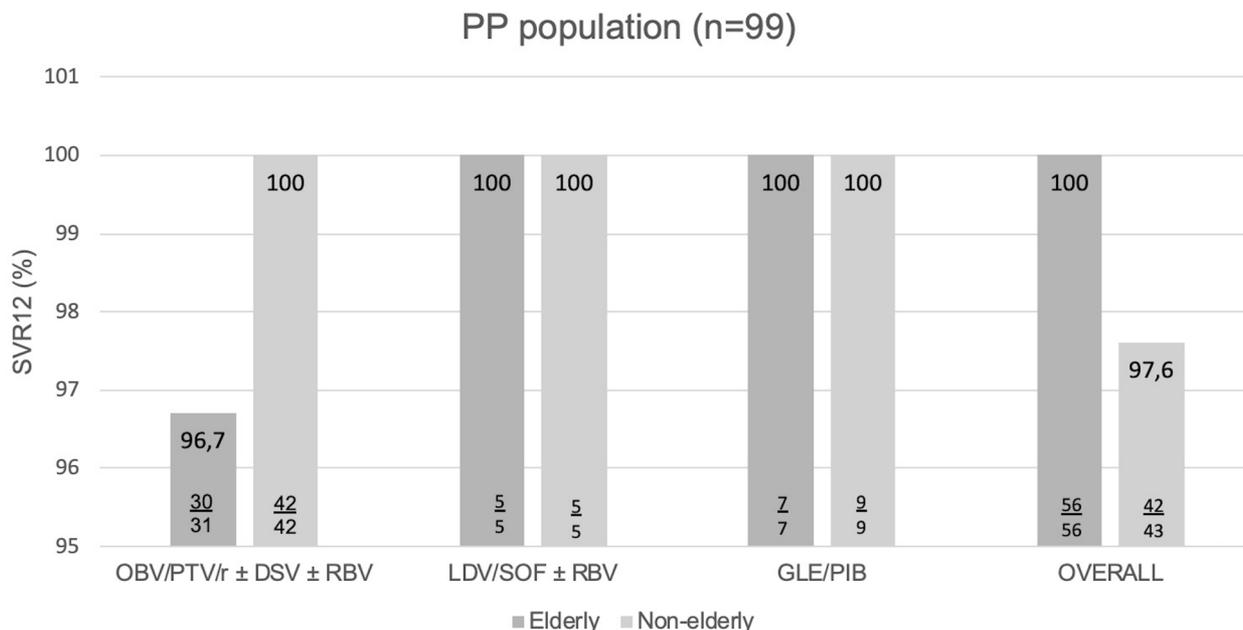
Early virological response (EVR) was observed in 102 cases. EVR was 97/102 (95.1%) in all treatment regimens. It was detected as 53/57 (93.4%) in patients aged 65 years and older and 44/45 (97.8%) in patients younger than 65 years of age. No statistically significant difference was observed between both groups (p = 0.290).

A total of 106 and 99 cases were included in mITT and PP populations, respectively, for treatment outcome analysis. SVR-12 rates of patients aged 65 years and older were similar compared to patients younger than 65 years of age. PP analysis was 97.6% (42/43) vs. 100% (56/56) and mITT analysis was 91.3% (43/45) vs. 91.8% (56/61), respectively. SVR-12 could not be studied in seven cases as the patients of these cases did not attend follow-up examinations post treatment. SVR-12 rates are presented in Figures 3 and 4 according to age and mITT and PP analysis. No breakthrough was observed during treatment. Relapse was detected in a female patient aged 74 years at 24 weeks after treatment cessation. This patient in this case did not have prior treatment experience, was of genotype 1b, and received OBV + PTV/r ± DSV treatment.

In the present study, the levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin significantly decreased and albumin levels

Figure 3. SVR12 rates according to DAA regimens in PP population by age groups


DISCUSSION

Elderly individuals have traditionally received less HCV treatment than young patients (11). In the meta-analysis of Yang et al., SVR rates of IFN/RBV treatment were found to be low in patients aged 65 years and older compared to patients younger than 65 years of age; in contrast, relapse was found to be significantly higher (12). Saab et al. reviewed four clinical trials and found that DAA and SVR-12 rates were similar between patients aged 65 years and older and patients younger than 65 years (13). Real-world data were used herein, and SVR-12 rates were found to be similar between patients aged 65 years and older and patients younger than 65 years treated with new DAAs Clinical and real-world studies, new DAAs have higher SVR rates than IFN-based treatments, and SVR-12 rates of new DAAs

significantly increased with DAA treatment in both elderly and younger patients.

are above 90% (14-16). Real-world data on DAA treatment in elderly and advanced elderly patients is very limited. To the best of our knowledge, there is no other study comparing real-world data in Turkey on DAA treatment in patients aged 65 years and older and patients younger than 65 years of age. We believe that the present study is important because it is the first study to investigate real-world data on the elderly in Turkey.

Saab et al. retrospectively evaluated the results of four clinical trials. SVR was 98% in patients with HCV aged 65 years and older using LED/SOF GT-1 and 97% in patients under 65 years of age (13). Herein, SVR-12 was determined to be 100% - and 100% in both groups, respectively, owing to the small sample size. Sherigar et al. evaluated the results of 80 patients using LED/SOF in their study, and they found an SVR-12 rate of 94% (17). Dultz et al. found the SVR-12 rate to be 95% and 94% in non-cirrhotic and cirrhotic patients over 70 years of age receiving GT-1b and LED/SOF ± RBV treatment. In

Figure 4. SVR12 rates according to DAA regimens in mITT population by age groups
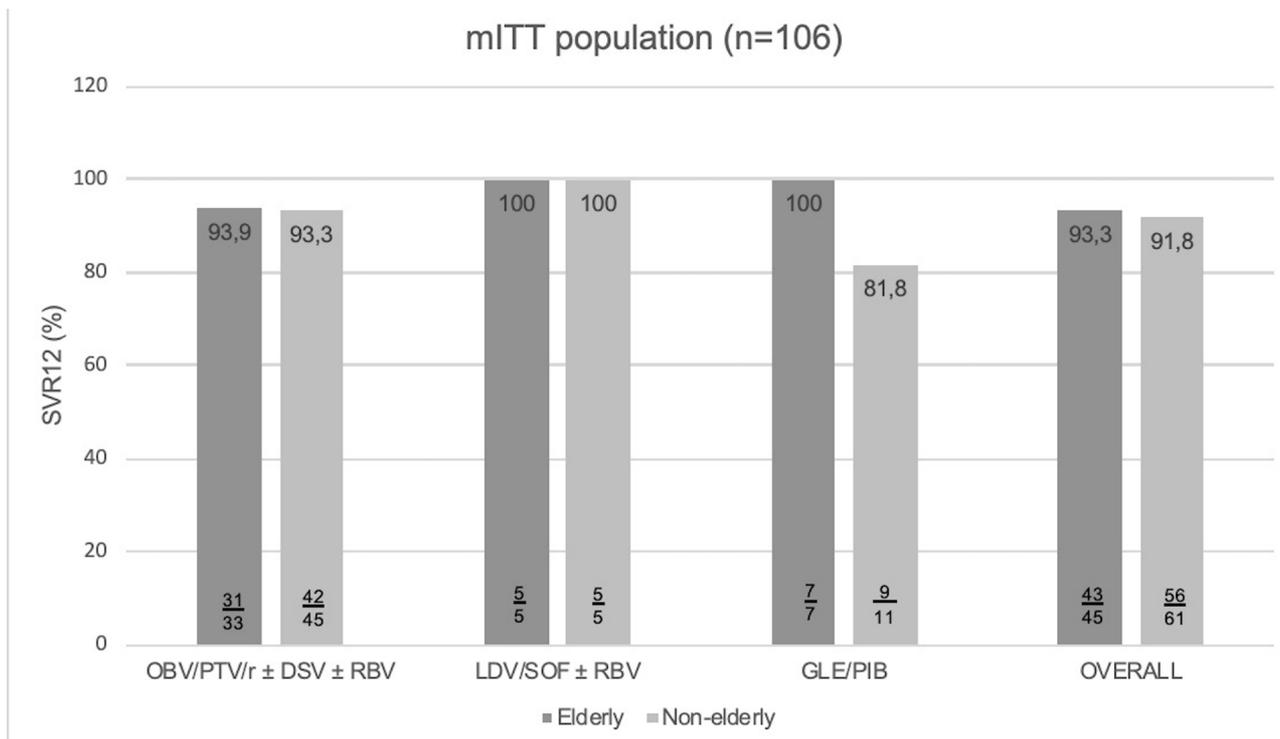
noncirrhotic and cirrhotic patients younger than 70 years of age, SVR-12 was 95% vs. 91%, respectively (14). In their studies including real-world data, Lens et al. found an SVR-12 rate of 96% in patients who received LED/SOF ± RBV treatment (15). In these studies, it was found that SVR-12 was high in elderly patients receiving LED/SOF ± RBV treatment.

Lens et al. found an SVR-12 rate of 98.3% with OBV + PTV/r ± DSV ± RBV treatment in elderly patients containing real-world data (15). Sheregar et al. investigated patients receiving OBV + PTV/r ± DSV ± RBV treatment and found an SVR-12 rate of 100% in patients aged 65 years and older as well as patients younger than 65 years (17). Herein, SVR-12 was found to be 93.9% (31/33) in patients aged 65 years and older and 93.3% in patients under 65 years of age. Dultz et al. found that SVR-12 was 91% vs. 91% in noncirrhotic and cirrhotic patients over 70 years of age who received GT1b and OBV + PTV/r

± DSV ± RBV treatment. SVR-12 was 93% vs. 94% in noncirrhotic and cirrhotic patients aged 70 years or younger (14). Although these studies show regional differences, the fact that SVR-12 is above 90% in elderly patients is important in terms of showing that chronic HCV cases are treatable regardless of age.

GLE + PIB have been found to be effective and safe in noncirrhotic cases in many phase III trials such as ENDURANCE 1-4 and SURVEYOR. These studies include patients over 65 years of age. These studies reported no failure of treatment with previous drug combinations and advanced age (18-20). Foster et al. examined real-world data in patients receiving GLE + PIB treatment, and found that SVR-12 was 97.9% in patients aged 65 years and older and 97.3% in patients younger than 65 years, and there was no statistical difference between the age groups (21). Herein, SVR-12 in patients receiving GLE + PIB treatment was determined to be 100%

in patients aged 65 years and older and 81.8% in patients younger than 65 years. Low SVR in patients younger than 65 years in the present study may be associated with the small sample size. For this reason, further studies with larger case series should be conducted in the elderly population in Turkey.

SVR rates can vary according to genotypes (GT). Sherigar et al. found that SVR rates with DAA were lower in the elderly with GT 1 genotype compared to younger patients (17). Backus et al. did not find a significant difference between treatment naive and treatment experienced elderly and young cases with GT 1 genotype; however, they found that SVR-12 was significantly lower in GT 2 treatment experienced elderly patients compared to young patients (22). In the study conducted by Su et al., GT 1 cases had higher SVR-12 than GT 2, 3, and 4 cases. In GT 3 cases, SVR-12 was lower than other genotypes (16). In the present study, there was no significant difference in SVR-12 rates between genotypes. This may be due to the small sample size in our study.

In our study, genotype 1b was the most common in the distribution of genotype in both age groups, but this rate was low in younger than 65 years, genotype 3 and 4 were found higher. We think that this may be due to the use of IV drugs and the increase in international contact.

Tapper et al. detected relapse in 44 patients who received LED + SOF treatment (23). Sherigar et al. detected treatment failure in 12 cases. Five of the cases were 65 years old and older and seven were younger than 65 years. They detected relapse in eight cases, partial response in three cases, and virological breakthrough in one case. They found that age was not a factor in both groups in terms of treatment failure and poor virological response. In five out of 12 patients with treatment failure, they detected HIV coinfection (17). In the present study, there were no cases of HIV coinfection. We detected relapse in one case aged 65 years and older. Therefore, we recommend that further multicentric studies with numerous cases should be conducted.

The limitations of this study include its retrospective design, investigation of regional data, and the small number of cases investigated. Another limitation is that the safety and side effects of DAAs were not evaluated herein.

CONCLUSION

In the present study, SVR rates were found to be similar in elderly patients compared to younger patients, but there is very limited information about the effectiveness and safety of new and recently approve; however, very limited information on DAAs is available in the Turkish elderly population. Although majority DAA clinical trials include advanced age populations, the proportion of elderly patients is small. This study presents the first real-world data examining patients aged 65 years and older and patients younger than 65 years in Turkey. Short treatment times with new DAAs can reduce drug-related side effects in the elderly. Therefore, we recommend that further multicentric studies that examine the safety, efficacy, and side effects of new DAAs in elderly people should be conducted.

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