Safety and efficacy of direct-acting antivirals for the treatment of chronic hepatitis C in a real-world population aged 65 years and older

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SAFETY AND EFFICACY OF DIRECT ACTING ANTIVIRALS FOR THE TREATMENT OF CHRONIC HEPATITIS C IN A REAL-WORLD POPULATION AGED 65 YEARS AND OLDER

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LIST OF ABBREVIATIONS:

HCV, hepatitis C virus; IFN, interferon; RBV, ribavirin; DAA, direct acting antiviral; CHC, chronic hepatitis C; SVR, sustained virologic response; CTP, Child-Pugh-Turcotte; eGFR, estimated glomerular filtration rate; PLT, platelets; ALT, alanine transaminases; AST, aspartate transaminases; INR, international normalized ratio; EOT, end of treatment; MELD, Model for End-Stage Liver Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SVR12, sustained virologic response 12 weeks after completing treatment; ITT, intention-to-treat; PP, per-protocol; AE, adverse event; SAE, severe adverse event; SOF, sofosbuvir; DCV, daclatasvir; SMV, simeprevir; HCC, hepatocellular carcinoma; 3D, paritaprevir/ombitasvir/ritonavir/dasabuvir; LDV, ledipasvir; SVR4, sustained virologic response 4 weeks after completing treatment.

Summary. The availability of direct acting antiviral agents (DAA) regimens has expanded the pool of patients eligible for treatment. However, data on the virological response and tolerability of DAAs in elderly patients are lacking. We evaluated the efficacy and safety of DAAs in patients with advanced fibrosis/cirrhosis in real-life practice with the focus on those aged ≥65 years. Between January and December 2015, all consecutive patients with HCV-related advanced fibrosis/cirrhosis treated with DAA at eleven tertiary referral centers in Emilia Romagna (Italy) were enrolled. Regimen choice was based on viral genotype and stage of disease, according to guidelines. The primary endpoint was sustained virological response 12 weeks after the end of treatment (SVR12). Overall, 282/556 (50.7%) patients evaluated were elderly, most of them with cirrhosis. Antiviral therapy was stopped prematurely in 4 (1.4%)

patients. Two patients, both with cirrhosis, died during treatment due to worsening of liver/renal function. SVR12 was achieved by 94.7% and was comparable to that obtained in patients aged <65 (p=0.074). Similar data were also reported in subgroup of patients aged ≥75 years. All patients with advanced fibrosis achieved virologic response. SVR12 was 80.8% in Child-Pugh-Turcotte (CTP)-B cirrhosis and 95.4% in CTP-A (p=0.013). According to genotype, the SVR12 was achieved in 172/181 (95%) with genotype 1b cirrhosis and in 44/48 (91.7%) with genotype 2 cirrhosis.

In conclusions, in a real-world setting, DAAs are safe and effective in elderly patients with HCV-related advanced fibrosis/cirrhosis but SVR12 is lower with worsening CTP class.

INTRODUCTION

The mean age of hepatitis C virus (HCV)-infected population and the number of elderly patients with more advanced liver disease are gradually increasing[1-2]. Moreover, this cohort is expected to rise in the next 10 years[3], and will significantly contribute to higher patient mortality and resource utilization, heavily influencing public health and healthcare management worldwide. Although the eradication of HCV by antiviral therapy seems to reduce the risk of complications of liver disease[4-7], elderly patients have been considered a difficult-to-treat subgroup, given the higher risk of adverse events, discontinuations, and mortality[8]. In addition, advanced age has been reported as a predictor of nonresponse to interferon-based therapy[9-11]. The concomitant comorbidities, particularly metabolic and cardiovascular disease, along with renal, pulmonary, and hematologic conditions limited the use of pegylated interferon (IFN) and ribavirin (RBV) in these subjects. Now that scenario is rapidly changing, and interferon-free antiviral therapy

regimens with direct acting antivirals (DAA) have shown higher efficacy, shortened treatment duration, and a better safety profile[12-18]. All these regimens are expected to expand and revolutionize treatment options for patients with HCV and may provide a solution to continually postponed demand of treating the "baby boomers" with chronic hepatitis C (CHC)[19]. However, the high costs of these medications have resulted in controversy as to which patients should be offered therapy[20-21].

Although in clinical trials there was no upper limit of age, the number of elderly patients, especially of those aged ≥75 years, was too small to determine whether they respond differently from younger patients[12-18]. Moreover, the proportion of elderly with advanced liver disease was too limited and data about the efficacy/safety in this group of patients are lacking. Thus, there is a need for further prospective trials to be conducted in elderly patients with advanced CHC, to better evaluate safety and efficacy of HCV treatment in this group. Many studies highlight the benefits of treating HCV beyond achieving sustained virologic response (SVR). Subjects who achieve SVR demonstrated improved quality of life, patient-related outcomes, and work productivity, irrespective of the severity of liver disease[22-24]. Younossi et al.[25] recently showed that subjects over 65 years of age also obtain a significant benefit in patient related outcomes after achieving SVR.

The aim of our multicentre study was to evaluate the efficacy and safety of the treatment with DAA-based regimens in a large cohort of HCV patients aged ≥65 years with advanced fibrosis/cirrhosis (including subgroup analysis of patients ≥75 years), in a real-life clinical setting.

MATERIALS AND METHODS

Study design and patients

This was a retrospective cohort study on consecutively and prospectively treated patients with HCV-related advanced fibrosis or cirrhosis, who received interferon-free regimens at eleven tertiary referral centers in Emilia Romagna (Italy), between January and December 2015.

Eligible patients were aged 18 years and older with HCV infection confirmed by both positive serum HCV antibody titers and serum HCV-RNA, using a real-time PCR-based method and documentation of liver fibrosis assessed by liver biopsy or a noninvasive test (Transient Elastography, Fibroscan) showing advanced fibrosis (Metavir F3 or Ishak 3-4) or cirrhosis (Metavir F4 or Ishak 5-6). Exclusion criteria included: 1) patients treated with non-conventional DAA-schedule; 2) with evidence of decompensated liver disease [Child-Pugh-Turcotte (CTP)-C]: 3) human immunodeficiency virus co-infection; 4) severe chronic kidney disease defined by estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2; 5) presence of malignant neoplastic disease or organ graft; 6) candidates for liver transplantation at the time of HCV treatment.

Treatment

Eligibility of each patient for treatment of HCV with DAAs was assessed following the priority criteria established by the national registry of the Italian Medicines Agency committee (AIFA)[26]. The choice of DAA and treatment duration (12/24 weeks) was based on viral genotype and stage of liver disease, according to the current guidelines available at the time of enrollment. At the discretion of treating physicians, weight-based RBV was used.

Efficacy and Safety Monitoring

Laboratory data included HCV-RNA, hemoglobin, platelets (PLT), alanine transaminases (ALT), aspartate transaminases (AST), albumin, total bilirubin, serum creatinine and international normalized ratio (INR) at baseline, after 4 and 12 weeks of treatment, at the end of treatment (EOT) and after 4 and 12 weeks of post-treatment follow-up. CTP and Model for End-Stage Liver Disease (MELD) scores were reported at the respective time points. Creatinine clearance was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula[27] with cut-off values for eGFR corresponding to: normal (>90 ml/min/1.73m2), mild decrease (60-89 ml/min/1.73m2), moderate decrease (30-59 ml/min/1.73m^2).

The primary endpoint was the proportion of patients who achieved SVR 12 weeks after completing treatment (SVR12). SVR12 results were calculated based on intention-to-treat (ITT) and per-protocol (PP) analysis. Viral breakthrough was defined as confirmed ≥1 log10 IU/ml increase from nadir of HCV-RNA, or HCV-RNA ≥15 IU/ml after confirmed undetectable. Post-treatment relapse was defined as confirmed HCV-RNA ≥15 IU/ml during follow-up in patients with undetectable HCV-RNA at the end of treatment. Comparisons were made between cohorts of patients aged ≥65 years and <65 years and subgroup analyses were performed for patients aged ≥75 years.

Safety Assessments

Throughout the treatment period, safety assessments were carried out including laboratory assessments, physical examinations, evaluation of vital signs and the reporting of adverse events (AE). Safety data were collected from all patients from the time of starting treatment until the assessment of the primary endpoint. Clinic visits were conducted at approximately week 4, EOT,

and week 4 and 12 after treatment completion. Severe adverse events (SAE), including urgent clinic visits and/or hospitalizations were thoroughly reviewed to identify the causal relationship with treatment regimen and reported to local regulatory authority. Management of AE, as well as discontinuation of therapy due to side effects, was carried out according to caring physician decisions.

Statistical Analysis

Quantitative variables were expressed as median and range; the categorical variables as count number and proportions. Chi-square or Fisher's exact test and Mann-Whitney test were used to compare categorical and continuous variables as appropriate. Multivariate logistic regression models were constructed to examine associations between clinical parameters and SVR12. As independent variables, we selected those that influenced SVR12 according to the univariate analysis with a p value <0.01. Kendall's tau correlation coefficient (r) was used to evaluate the correlation of two variables. A strong correlation was considered if $0.700 < r < 1.000$. All analyses were performed using SPSS for Windows (Statistical Package for the Social Sciences, version 21.0, Armonk, New York, NY, USA).

RESULTS

Patient population

A total of 566 HCV infected patients with advanced liver disease were treated with interferon-free regimens during the study period. Ten patients (1.8%) were treated with non-conventional DAA-schedules [6 with sofosbuvir (SOF) plus RBV for HCV genotype 1/4 and 4 with daclatasvir (DCV)/simeprevir (SMV)/SOF for HCV genotype 1b] and were excluded. Among

the remaining patients, 282 (50.7%) were ≥65 years old (of whom 106 patients were ≥75 years) and 274 (49.3%) were <65 years old (Fig.1). A summary of baseline clinical characteristics of the cohort by age is provided in Table 1. As expected, the proportion of female was higher in patients aged ≥65 years than in patients aged <65 years (p<0.001). Liver cirrhosis was present in 86.5% of elderly and in 78.1% of younger (p=0.010), but pre-treatment CTP class distribution and MELD score were similar between the two groups. Elderly patients were more likely to have comorbidities including arterial hypertension, stage-3 kidney disease and history of previous hepatocellular carcinoma (HCC). Also diabetes mellitus was more prevalent in elderly even if not significant different from youngers (20.9% versus 16.8%, p=0.234). No significant differences were found in baseline serum liver function tests (i.e. ALT, AST, total bilirubin, INR and PLT) except for serum albumin that was significantly lower in the elderly cohort, as well as eGFR (p<0.001 for both). At baseline, serum HCV-RNA levels did not differ between the two groups. HCV genotype distribution significantly differed between the two cohorts, despite the majority of patients being infected with HCV genotype 1. Of note, the rate of treatment-experienced was lower in elderly than in younger (51.8% versus 60.6%, p=0.040). In elderly cohort, no significant differences were found in term of liver disease severity and genotypes distribution between aged≥75 and 64-75 years.

Safety profile and treatment discontinuation

The safety profile is shown in Table 2. A total of 154 patients (54.6%) ≥65 years of age experienced at least one AE. The frequency of AEs was higher for the ≥65 than for the <65 age group (p<0.001), even if treatment schedules were not comparable between two groups. There were no differences by subdividing the elderly cohort according to age (52.8% in aged 65-75 years versus 57.5% in aged≥75 years; p=0.461). Severe anemia was observed in more than 20%

of elderly, mostly in patients aged ≥75 years and with the addition of RBV the rate of AEs increased significantly (60.1% with RBV versus 42.7% without RBV; p=0.007). Dose reduction/discontinuation of the RBV daily dose was observed 25.9% of elderly and in 12.2 % of younger (p<0.001).

SAEs during treatment were recorded in 14 patients (5%) of elderly cohort, and the incidence of such events was comparable between patients aged 65-74 years and aged ≥75 years (5.1% and 4.7%, respectively; p=1). Notably, SAEs included hepatic decompensation in 4 patients (1.4%), severe anemia in 4 patients (1.4%), drug related photosensitivity in 2 patients (0.7%), pulmonary infection, atrial flutter, syncope and abdominal pain in a patient each. The majority of serious adverse events occurred in patients with cirrhosis at baseline (13 of 14 reported events; 92.9%) and approximately 80% of these had a MELD score greater than 10 before therapy (Supplementary Table 1). Similar data have been recorded in younger cohort.

Antiviral therapy had to be stopped prematurely in 4 (1.4%) patients aged ≥65 and in 7 (2.6%) aged <65 (p=0.334), all with cirrhosis. In younger cohort, 3 (1.1%) patients died (2 due to worsening of liver function at week 14 and week 15 of treatment and 1 due to intracerebral hemorrhage at week 8). Among elderly, 2 (0.7%) patients died due to worsening of liver and/or renal function at week 4 and week 7 of treatment respectively. Notably, HCC occurred during treatment in 4 patients (3 aged <65 and 1 aged ≥65), all completed treatment achieving SVR12. A new or recurrent HCC was detected during follow-up in 8 patients (4 aged <65 and 4 aged ≥65).

Virological response

Overall, at ITT analysis, 515 (92.6%) patients achieved SVR12. Fig. 1 shows the SVR12 rates stratified by age and the presence or absence of cirrhosis. This proportion was slightly higher in

patients aged ≥65 years than in those aged <65 (94.7% versus 90.5%; p=0.074), but the two cohorts were not comparable in terms of genotypes and treatment regimens. In subgroup of patients aged ≥75 years, virological response was achieved by 98.1%.

Efficacy in elderly cohort

In elderly, SVR12 did not differ between treatment-experienced and treatment-naïve-patients (93.1% versus 96.4%; p=0.290) (Fig. 2). The presence of liver cirrhosis affected virological response: SVR12 was achieved in 93.9% of cirrhotic patients, in comparison with 100% observed in the 38 patients with advanced fibrosis. In patients with cirrhosis, CTP class significantly affected SVR12: (80.8% in CTP-B versus 95.4% in CTP-A; p=0.013). A trend towards a lower SVR12 was also observed in patients with MELD score ≥10 than in those with MELD score <10 (89.4% versus 95.5%; p=0.077). Undetectable HCV-RNA at weeks 4 of treatment was a poor predictor of SVR12 with a Kendall's tau correlation coefficient of 0.129. Conversely, a strong correlation was found between sustained virologic response 4 weeks after completing treatment (SVR4) and SVR12 with a Kendall's tau correlation coefficient of 0.928.
A virological relapse occurred in 13/282 (4.6%) patients (7 with genotype 1-b infection, 4 with genotype 2, 1 with genotype 3 and 1 with genotype 4). Interestingly, 2 patients had a relapse after four weeks of undetectable HCV-RNA after treatment completion.

Virological Response in Genotype 1b subjects

Two hundred and eight elderly patients had HCV genotype-1b infection; of them, 181 (87%) had cirrhosis. Overall, SVR12 was achieved in 95.7% (100% in patients with advanced fibrosis and 95% in those with cirrhosis, p=0.609). No difference in SVR12 was found in comparison with younger patients (p=0.134). According to treatment regimen, SVR12 was achieved in 93.1%

(95/102) of elderly patients treated with SOF/SMV±RBV, in 96.9% (62/64) with paritaprevir/ombitasvir/ritonavir/dasabuvir (3D)±RBV, in 100% (22/22) with SOF/DCV±RBV and in 100% (20/20) with ledipasvir (LDV)/SOF±RBV. Furthermore, in subgroup of patients ≥75 years the rate of SVR12 increased to 98.7% (77/78).

Virological Response in Genotype 2 subjects

Genotype 2- infected patients aged ≥65 years, all treated with SOF±RBV, achieved an overall SVR12 of 93.1% (54/58). Four out of 48 (8.3%) patients with cirrhosis relapsed. In patients aged <65 years, the virologic response rates was 95.2% (20/21). No difference was found comparing the two cohorts (p=1). As previously reported for genotype 1b, in patients aged ≥75 years the SVR12 increased to 96% (24/25).

Factor influencing SVR12 rate in elderly patients with cirrhosis

In multivariate analysis, the only significant independent predictor of SVR12 in elderly was CTP-A [Odds Ratio: 0.202, 95%CI 0.063-0646; p=0.007]. Sex, genotype 1, naïve status, history of liver decompensation and/or HCC, diabetes, eGFR<60, MELD≥10 and RBV use were not significantly associated with SVR12 (Table 3).

DISCUSSION

Older patients with CHC will become an increasingly larger group over the next decade and they are expected to develop more cirrhosis and liver cancer with a significant increase in health-related disease costs. Therefore, achieving a SVR could halt the progression of liver disease. In Southern Europe, and especially in Italy, the treatment of aged patients with CHC is an important issue, because of the higher prevalence of HCV infection, and the older age of HCV carriers,

compared to other European countries, thus contributing to the disease burden and complications[28-31]. Progress in pharmacotherapy will continue to extend healthy life expectancy and a chance for HCV eradication in the elderly, historically considered poor candidates to IFN-based treatments, is now offered by new all-oral DAA regimens. Despite this, the experience with IFN-free regimens in these patients has been very limited in phase 3 studies, in which only few patients older than 65 years were included, often without advanced fibrosis or cirrhosis. Hence, evidence for the benefit of virologic response in elderly patients has yet to be clearly demonstrated.

In our knowledge, this study represents the largest experience on all-oral antiviral therapy in HCV patients aged ≥65 years with advanced liver disease, in a real-life setting. It reports the efficacy and safety of the available DAA regimens, but its retrospective cohort design and the real-life setting do not allow comparing the efficacy and safety of the different DAA regimens.

Several important findings emerged from our study. First, the results of our analysis demonstrate that all oral DAA-treatments were quite effective in elderly patients with advanced CHC and that older age was not a barrier to achieve a SVR12. Second, older age was not associated with increased SAEs during antiviral treatment.

In contrast with clinical trials[32], where patients over 65 years old with advanced fibrosis or cirrhosis were underrepresented, this study was carried out in a clinical practice setting where about 50% of this population consisted of elderly patients. As expected, in comparison with younger patients treated during the same period, elderly had more severe liver disease, a higher prevalence of HCC history and comorbidities as arterial hypertension and renal disease. During IFN-era, elderly patients were generally less treated than younger probably because they were excluded from the randomized controlled trials and physicians are reluctant to treat elderly

patients with antiviral therapy because of possible side effects[33]. In our country, the majority of elderly patients have a HCV genotype-1b or 2 infection, and this epidemiology have influenced the choice of antiviral regimens in our cohort and led to highly effective results. In fact, response rates were 100% in patients with advanced fibrosis and 94.7% in patients with cirrhosis (95% in GT-1b and 91.7% in GT-2). The high SVR12 rate observed in the latter group was also probably due to a high prevalence of subjects in CTP-A class (about 90%).

High efficacy in a real-world setting was recently reported also by Vermehren et al.[34] even if the sample size of elderly patients was lower than in our study and less than 50% had cirrhosis.

The majority of patients were treated with SOF/SMV regimen and viral eradication was obtained in 82/89 (92.1%) of those with cirrhosis. These results confirm data recently reported in a large prospective observational cohort study by Sulkowski et al.[35]. Efficacy of other DAA-regimens (as SOF/DCV±RBV and LDV/SOF±RBV) was even more encouraging even if the limited sample size does not allow definitive conclusions. Furthermore, the SVR12 rates observed in patients with genotype 2 treated with SOF plus RBV has yielded very favourable results, comparable to those of our younger population and higher than those reported in previous real-life studies[36-37]. In these clinical practice studies, authors reported SVR12 rates lower in patients with liver cirrhosis (83-87%) than in our cohort. Probably this difference is due to the use of a 24-week regimen of SOF and RBV in about 50% of our patients with cirrhosis, considering that extended treatment duration in cirrhotics has been shown to increase SVR[38].

Interestingly, and probably unexpectedly, our data showed that sex, diabetes, genotype 1, renal function, previous treatment failure and RBV use were not negatively associated with SVR12 in elderly patients with cirrhosis. Only severity of liver disease at baseline had a significant impact on SVR12. In fact, patients with CTP-A at the time of treatment initiation were more likely to

achieve SVR12 compared to those in CTP-B class (95.4% vs 80.8%, respectively, p=0.010). Similar trend has been previously reported in other studies[39-40].

RBV was not used in 34.6% (66/191) of elderly patients with HCV-genotype 1 or 4 cirrhosis due to the presence of anemia at baseline (68.2%) or concomitant cardiovascular disease (18.2%), for intolerance to a previous RBV-containing treatment (7.6%) and for treating physicians' choice (6%). Despite this, no difference was found in terms of SVR12 compared to patients treated with RBV. In HCV-genotype 2 or 3 patients treated with SOF+RBV (which was the only schedule available for these genotypes during the study period), hematopoietic growth factor supplementation and dose reduction were successful used to manage the anemia.

Our study confirms previous observations reported by others[41] that undetectable viremia after 4 weeks of treatment is not a predictor of SVR12. Conversely, also in our experience SVR4 continues to be a strong predictor of SVR12 and only 2 patients relapsed in our cohort after achieving SVR4[42].

All the DAA regimens were generally well tolerated, with only less than 2% of patients discontinuing treatment due to adverse events. SAEs were observed in about 5% of patients nevertheless two patients died during treatment due to worsening of liver and/or renal function. Anaemia was frequent in this cohort of patients aged ≥65 years and mostly managed with RBV dose reductions or discontinuation. Hyperbilirubinemia was well tolerated in most patients, did not require premature discontinuation of treatment and resolved within a few weeks after treatment discontinuation. Most common AEs corresponded to those previously reported in pivotal phase III studies[12-18].

In addition, our findings demonstrated that the rate of AEs in patients aged 65-74 years was not different from that observed in patients aged 75 years or older. In this setting, fatigue and skin

complaints were confirmed to be the most common AEs. Finally, some complications of liver disease occurred during the short period of the study, including HCC. Recently some studies, also from our group[43-45], reported increased rates of HCC recurrence in patients treated with DAAs suspecting a deregulation of the anti-tumor response after the sharp decrease of HCV viral load induced by DAA. To date, data on the effect of HCV eradication after DAA in patients who have already developed HCC are still few and not conclusive and it is as yet unclear if interferon-free treatment could result in patients being free from the HCC occurrence[46-48]. Until now, there are no findings supporting the role of the age *per se* as a risk factor for the development of HCC after interferon-free treatment. Therefore, all patients with cirrhosis remain at increased risk for HCC even after they have been cleared HCV. This observation highlights the need for these patients to continue a regular screening for liver complications, even after SVR.

Some limitations should be considered in the interpretation of our results, including the retrospective design and the lack of data on the emergence of resistance-associated viral strains. Furthermore, the short follow-up period (12 weeks) limits our ability to assess the long-term impact of SVR on those patients. Another objection could be that we arbitrarily defined as "elderly" those patients aged 65 years or above. Nonetheless, in the cohort of patients over 75 years of age data about efficacy and safety of IFN-free regimens were superimposable, suggesting that prescription of these new treatments should not be limited by any age.

In conclusion, the results of this study demonstrate that age *per se* does not influence the success of IFN-free treatments in elderly patients with CHC, and that all the DAA regimens seem well tolerated and safe, also in subjects with advanced liver disease and in those aged 75 years or older. Based on these evidences, there are no reasons to deny treatment with new DAA using the

age as a criterion for prescription. Nonetheless, some conditions may limit the use of these drugs in elderly subjects such as the presence of severe comorbidities, affecting the short-term life expectancy, and/or the risk of serious drug interactions. Therefore, a careful assessment of the patient's geriatric status is mandatory. Finally, a longer follow-up of this cohort may provide additional useful information about the lifetime utility of HCV eradication in terms of reduction of outcomes and survival.

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FIGURE LEGENDS

Fig.1: Flow chart of the SVR12 rates stratified by age and the presence or absence of cirrhosis. DAA, direct acting antiviral; SVR12, sustained virologic response 12 weeks after completing treatment.

Fig.2: SVR12 for patients aged ≥65 years according to various baseline features. CTP, Child-Pugh-Turcotte; MELD, Model for End-Stage Liver Disease.

Fig.3: SVR12 for patients aged <65 and ≥65 years in HCV genotype 1b and genotype 2. A subgroup analysis is shown for patients aged ≥75 years.

Table 1. Baseline characteristics of patients with chronic hepatitis C who started therapy with Direct Acting Antivirals according to age group

Variable	Age groups (years)			p[#]
	<65 (n=274)	≥65 (n=282)	≥75 (n=106)	
Age, years	54 (21-64)	73 (65-85)	78 (75-85)	<0.001
Male gender	184 (67.2%)	138 (48.9%)	58 (54.7%)	<0.001
BMI, Kg/m^2	25.6 (18.6-40.8)	25.4 (17.6-39.8)	24.2 (18.6-39.8)	0.043
Cirrhosis	214 (78.1%)	244 (86.5%)	93 (87.7%)	0.010
Advanced fibrosis	60 (21.9%)	38 (13.5%)	13 (12.3%)	
CPT class*:				
▪ A	191 (89.3%)	218 (89.3%)	85 (91.4%)	1
▪ B	23 (10.7%)	26 (10.7%)	8 (8.6%)	
MELD	8 (6-18)	8 (6-17)	8 (6-17)	0.843
MELD ≥10*	53 (24.8%)	66 (27.1%)	23 (24.7%)	0.595
History of previous HCC	20 (7.3%)	65 (23%)	30 (28.3%)	<0.001
History of liver decompensation*	27 (12.6%)	38 (15.6%)	14 (15.1%)	0.365
Arterial hypertension	58 (21.2%)	139 (49.3%)	58 (54.7%)	<0.001
Type 2 diabetes	46 (16.8%)	59 (20.9%)	23 (21.7%)	0.234
Stage-3 kidney disease	3 (1.1%)	39 (13.8%)	23 (21.7%)	<0.001
Treatment-experienced	166 (60.6%)	146 (51.8%)	62 (58.5%)	0.040
HCV-genotype:				
▪ 1a	53 (19.3%)	4 (1.4%)	1 (0.9%)	
▪ 1b	111 (40.5%)	208 (73.8%)	78 (73.6%)	
▪ 2	21 (7.7%)	58 (20.6%)	25 (23.6%)	<0.001
▪ 3	62 (22.6%)	6 (2.1%)	/	
▪ 4	27 (9.9%)	6 (2.1%)	2 (1.9%)	
DAA treatment schedule:				
▪ SOF+RBV	48 (17.5%)	60 (21.3%)	25 (23.6%)	

▪ SOF/SMV±RBV	95 (34.7%)	106 (37.6%)	37 (34.9%)	
▪ SOF/LDV±RBV	25 (9.1%)	20 (7.1%)	9 (8.5%)	0.002
▪ SOF/DCV±RBV	51 (18.6%)	27 (9.6%)	9 (8.5%)	
▪ 3D±RBV	44 (16.1%)	66 (23.4%)	25 (23.6%)	
▪ OBV/PTV/r±RBV	11 (4%)	3 (1.1%)	1 (0.9%)	
Use of RBV	196 (71.5%)	193 (68.4%)	77 (72.6%)	0.460
Treatment duration[§]				
▪ 12 weeks	151 (56.6%)	211 (75.9%)	80 (75.5%)	<0.001
▪ 24 weeks	116 (43.4%)	67 (24.1%)	26 (24.5%)	
HCV-RNA ≥800000 U/ml	155 (56.6%)	155 (55%)	62 (58.5%)	0.733
Log_{10} HCV-RNA, U/ml	6 (2.4-7.1)	6 (3.1-7.3)	6 (4.5-7.2)	0.947
AST, U/l	62 (10-344)	66 (11-1029)	70 (11-331)	0.638
ALT, U/l	69 (14-327)	64 (14-784)	61 (16-376)	0.060
Total bilirubin, mg/dl	0.86 (0.22-5.91)	0.84 (0.23-4.07)	0.83 (0.34-3.29)	0.520
INR	1.11 (0.7-1.62)	1.10 (0.8-1.68)	1.12 (0.9-1.68)	0.886
Albumin, g/dl	4 (2.1-5.0)	3.8 (2.7-4.9)	3.8 (2.8-4.9)	<0.001
eGFR, ml/min/1.73m^2	101 (30-130)	84 (33-106)	76 (36-97)	<0.001
Hemoglobin, g/dl	14.4 (9.5-18.3)	13.4 (8.3-18.2)	13.2 (8.3-16.3)	<0.001
PLT, x10^3/mmc	112 (19-713)	117 (15-406)	111 (15-406)	0.857

Data are given as median (range) or as number of cases (%).

[#]p values quoted for the differences between the <65 and ≥65 age groups. *Calculated on patients with cirrhosis. [§]Calculated on patients reaching end of treatment.

BMI, body mass index; CPT, Child Pugh Turcotte; MELD, Model for End stage Liver Disease; HCC, hepatocellular carcinoma; SOF, sofosbuvir; RBV, ribavirin; SMV, simeprevir; LDV, ledipasvir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir/dasasbuvir; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; DAA, direct acting antiviral; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; eGFR, glomerular filtration rate; PLT, platelet count.

Table 2. AEs and laboratory abnormalities by age

Variable	Age group (years)					
	<65 (n=274)	**≥65 (n=282)**	**p**	**65-74 (n=176)**	**≥75 (n=106)**	**p**
Total AEs	106 (38.7%)	154 (54.6%)	<0.001	93 (52.8%)	61 (57.5%)	0.461
Serious AEs	12 (4.4%)	14 (5%)	0.740	9 (5.1%)	5 (4.7%)	1
Death	3 (1.1%)	2 (0.7%)	0.681	2 (1.1%)	0	0.529
Discontinuation due to serious AE	7 (2.6%)	4 (1.4%)	0.334	4 (2.3%)	0	0.301
Common AEs (>2%):						
▪ Fatigue	52 (19%)	60 (21.3%)	0.497	31 (17.6%)	29 (27.4)	0.071
▪ Skin complaints (rash, pruritus, or photosensitivity)	23 (8.4%)	43 (15.2%)	0.012	24 (13.6%)	19 (17.9%)	0.393
▪ Depression/irritability	10 (3.6%)	9 (3.2%)	0.764	8 (4.5%)	1 (0.9%)	0.160
▪ Gastrointestinal complaints (nausea, dyspepsia)	9 (3.3%)	8 (2.8%)	0.764	4 (2.3%)	4 (3.8%)	0.479
▪ Arthralgia/myalgia	6 (2.2%)	6 (2.1%)	1	4 (2.3%)	2 (1.9%)	1
Treatment-related laboratory abnormality:						
▪ Total Bilirubin ≥4 mg/dl	11 (4%)	15 (5.3%)	0.466	10 (5.7%)	5 (4.7%)	0.792
▪ Hemoglobin <10 g/dL	52 (19%)	58 (20.6%)	0.639	30 (17%)	28 (26.4%)	0.069
RBV dose reduction or discontinuation*	24 (12.2%)	50 (25.9%)	<0.001	30 (25.9%)	20 (26%)	1

Data are given as number of cases (%).

* Calculated on 193 patients treated with RBV (196 in aged <65 years, 116 in aged 65-74 years and 77 in aged ≥75 years).

AE, adverse event; RBV, ribavirin.

Table 3. Univariate and multivariate analyses of variables associated with SVR in elderly patients with cirrhosis by Multivariate logistic regression

	Univariate Analysis	Multivariate Analysis		
Variable	**p**	**Odds Ratio**	**95%CI**	**p**
Male vs Female	0.427			
Genotype 1 vs non-1	0.161			
Naïve vs Experienced	0.237			
History of decompensation vs no	0.012			
decompensation	0.495			
History of HCC vs no HCC	0.663			
Diabetes vs No-Diabetes	0.873			
eGFR≥60 ml/min vs <60 ml/min	0.086			
MELD<10 vs ≥10	0.007	0.202	0.063-0646	0.007
CTP-A vs CTP-B	0.943			
RBV use vs no-RBV use				

HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; eGFR, glomerular filtration rate; CTP, Child-Turcotte-Pugh; RBV, ribavirin.