JGG 2018;66:46-55

ORIGINAL INVESTIGATION

Efficacy and safety of direct-acting antivirals in elderly with chronic hepatitis C: results from a retrospective cohort study

R. Villani[1], I. Donatiello[2], F. Barone[2], F. Cavallone[1], G. Fioravanti[1], F. Di Cosimo[1], F. Bellanti[1], F. Sollitto[3], G. Vendemiale[1], G. Serviddio[1]

[1] C.U.R.E. (Centre for Liver Diseases Research and Treatment), Institute of Internal Medicine, Department of Medical and Surgical Sciences, University of Foggia, Italy; [2] Internal Medicine Unit, San Giovanni Hospital, Lagonegro, Potenza, Italy; [3] Department of Medical and Surgical Sciences, University of Foggia, Italy

Background. Seroprevalence of hepatitis C virus infection has increased over the last decade and because of hepatitis C virus acquisition time and age of most infected persons, the proportion of elderly with CHC is expected to increase over time. With the approval of direct-acting antivirals (DAAs), treatment access has expanded to interferon intolerant patient populations, including older age. However, elderly patients, especially those aged 75 years and older, have been excluded from most clinical trials and few data are available on safety and efficacy of DAAs in this special population.
Methods. We conducted a retrospective cohort study on three age subgroups of patients (< 65 years; 65-74 years and ≥ 75 years) treated with DAAs between March 2015 and March 2017. Two hundred and sixty-two patients were followed up with clinical and laboratory evaluations during antiviral therapy.
Results. HCV genotype distribution significantly differed among the three subgroups. Antiviral treatments were not different between younger and elderly groups. Sofosbuvir-based regimens were used in about 60% of patients without significant differences among the three age-subgroups. All patients except three achieved SVR12 (99.3% in elderly *vs* 98.3% in younger patients). A total of 62 patients (23.7%) showed at least one adverse event (AE). AEs were not higher in elderly patients.
Conclusions. Our data showed that DAAs in elderly CHC patients were as effective as youngers without any significant increase of adverse events.

Key words: HCV, Elderly, Direct-acting antivirals

INTRODUCTION

Chronic hepatitis C virus infection (CHC) is a major cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver related death in the Western world [1]. Global epidemiology of HCV infection shows that the seroprevalence of AntiHCV antibody has increased over the last decade from 2.3% to 2.8%, corresponding to > 185 million infections worldwide [2]. Although publication bias resulting in a geografic variability in HCV seroprevalence need to be considered, Italian population showed the highest prevalence of HCV infection and contributed highest number of data-points for the epidemiology of HCV in Europe [2 3].
High prevalence of global HCV infection necessitates renewed efforts in primary prevention, including vaccine development, as well as new approaches to secondary and tertiary prevention to reduce the burden of chronic liver disease and to improve survival for those who already have evidence of liver disease.
Because of hepatitis C virus (HCV) acquisition time (i.e. 1960-1980s) and age of acquisition (i.e. 20-40 years)

Received: May 27, 2018 - Accepted: June 1, 2018
Correspondence: Gaetano Serviddio, C.U.R.E. (Centre for Liver Diseases Research and Treatment), Institute of Internal Medicine, Department of Medical and Surgical Sciences, University of Foggia, 71122 Foggia, Italy - E-mail: gaetano.serviddio@unifg.it

of most infected persons, the proportion of elderly with CHC is expected to increase over time [4].

With the recent approval of interferon-free regimens (direct-acting antivirals or DAAs), treatment access has expanded to interferon ineligible/intolerant patient populations, including persons of older age [5].

Moreover, since novel HCV treatment regimens are well tolerated and the advancing age is an important risk factor for progression to cirrhosis and HCC, the number of elderly patients who will receive anti-HCV treatments is likely to increase [4].

Elderly patients, especially those aged 75 years and older, have been excluded from most clinical trials and the safety and efficacy of DAAs have not been specifically examined in this special population except for very small clinical trial [6] or in Japanese population by using asunaprevir and daclatasvir [7-10].

Generally, very few real-world data are available on DAAs treatment in old and very old patients.

Rodriguez-Osorio et al. reported 120 patients > 65 years with a SVR12 rate of 88,3% and a rate of AE of about 65% [11]; Conti et al. observed a 94,7% of SVR in HCV older patients recruited in North Italy centers [12]; Ippolito et al. showed no differences in terms of SVR in octogenarians but they enrolled highly selected patients with preserved glomerular renal filtration and mainly patients assuming only one concomitant medication [13]. Moreover, data from other observations were limited to a single treatment [14], included co-infected patients [15] and a single genotype [7 16].

Therefore, data on efficacy and safety of DAAs in these groups are requested.

In the present study, we retrospectively analyzed the efficacy and safety of six different DAAs treatments in a cohort of old (> 65 years) and very old (> 75 years) population from South Italy with CHC. Frequencies and distribution of concomitant medications were also analyzed in our study.

MATERIALS AND METHODS

Study population

We conducted a retrospective cohort study on 262 consecutively and prospectively treated patients with CHC with advanced fibrosis or cirrhosis referred to one single hepatological centre between March 2015 and March 2017, who started therapy with DAA as standard-of-care treatment for HCV-related chronic hepatitis. Eligible patients were aged 18 years and older with chronic HCV infection assessed by the presence of Anti-HCV antibody and detectable serum HCV RNA.

Patients with HIV co-infection or severe chronic kidney disease defined by estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2 or who received pegylated interferon as part of their treatment regimen were excluded.

Antiviral therapy and treatment duration (12 or 24 weeks) were indicated for each patient according to the viral genotype/subtype and the severity of liver disease according to the guidelines from Italian Association for the Study of Liver Diseases' available at the time of enrolment and according to the National Drug Agency reimbursement restriction.

All patients received one of the following six regimens:

1. sofosbuvir and simeprevir ± ribavirin;
2. sofosbuvir and ledipasvir ± ribavirin;
3. sofosbuvir and daclatasvir ± ribavirin;
4. sofosbuvir + ribavirin;
5. ombitasvir/paritaprevir/ritonavir + dasabuvir (3D) ± ribavirin;
6. ombitasvir/paritaprevir/ritonavir (2D) ± ribavirin.

For all genotypes weight-based ribavirin was administered according to discretion of physician.

Definition of old age

Patients of old age were defined as being 65 years and older. This population included the young-old patients (65-74 years) and old-old patients (≥ 75 years).

Assessment of efficacy data

Patients were followed up with clinical and laboratory evaluations during antiviral therapy. Virological response was assessed at week 4, at the end of treatment, and at 4 and 12 weeks after the end of treatment to determine the SVR. SVR4 and SVR12 were defined as undetectable HCV RNA 4 or 12 weeks after the treatment completion, respectively. Data were retrospectively and anonymously analysed.

Assessment of safety data

Safety assessments included laboratory data (hemoglobin, platelets, white blood cell count, alanine transaminases, aspartate transaminases, gamma-glutamyltransferase, alkaline phosphatase, albumin, total bilirubin, serum creatinine, international normalized ratio, plasma sodium and potassium concentration, creatinine clearance), physical examinations, evaluation of vital signs (respiratory rate, heart rate and blood pressure) and the reporting of adverse events (AE).

Safety data were assessed at baseline, at week 4, at the end of treatment, and at 12 weeks after the end of treatment. Adverse events were reported according to the Common Terminology Criteria for Adverse Events [17].

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used for estimating the glomerular filtration rate (GFR).

The occurrence of ribavirin (RBV) induced haemolytic anaemia was also assessed at each time point.

Significant anaemia was defined as an absolute decline in haemoglobin levels < 10 g/dL and/or a decline of greater than 3 g/dL.
At baseline and at the end of treatment, all patients were evaluated using abdominal ultrasound.
All patients with persistent ALT or AST > upper limit of normal (ULN) after 4 weeks of treatment underwent additional US analysis.

Statistical analysis

All statistical analyses and graphs were performed using SPSS (Statistical Package for the Social Sciences, version 20, Armonk, New York, NY, USA) and GraphPad Prism version 7 (La Jolla, CA, USA). Quantitative variables are shown as mean ± s.d. or median and range.
Comparisons between groups were made using parametric one way ANOVA, nonparametric Kruskal-Wallis test, chi-square test or Fisher's exact test where appropriate.
$P < 0.05$ was considered statistically significant. Univariate and multivariate logistic regression analysis was used to identify the associations between clinical parameters and virological response.

RESULTS

Patients population

Two hundred and sixty-two patients with HCV-related significant fibrosis (Metavir F3) or liver cirrhosis were treated with DAAs regimens during the study period.
120 patients (46%) were < 65 years old, 80 patients (30%) were 65-74 years and 62 patients (24%) were ≥ 75 years old.
Baseline clinical characteristics of included patients are provided in Table I.
No gender difference was found between patients aged < 65 and ≥ 65 years and between young – old and old-old patients.
Liver cirrhosis was found in 52.1% of elderly (42.5% of young-old patients and 64.5% of old-old patients) and in 38.3% of younger patients ($p = 0.559$), and pre-treatment Child-Pugh-Turcotte (CPT) score classification was comparable between patients aged < 65 and ≥ 65 years.
Diabetes mellitus was more prevalent in elderly. The highest incidence was observed in the young-old patients (47.5%) and it was significantly different from youngers ($p = 0.02$) and old-old patients ($p = 0.02$).
No significant differences were found in baseline serum liver function tests (i.e. ALT, AST, total bilirubin and PLT).
No patients had eGFR lower than 30 ml/min or required pre-treatment or in-treatment hemodialysis.
Pre-treatment serum HCV-RNA levels did not differ between the young patients and elderly and between the young-old and old-old patients.
HCV genotype distribution significantly differed among the three subgroups ($p < 0.001$). In all age subgroups Genotype 1 (G1) was the most common (youngers: 56.6%; young-old patients: 77.5%; old-old patients 64.5%). Genotype 2 prevalence was 18.3% in patients aged <65 years and 26.1% in older people (20% in young-old patients and 32.2% in old-old patients). Genotype 3 and 4 were responsible for a total 24.9% of all cases in younger group and less than 4% in patients aged ≥ 65 years (Tab. I).
The rate of IFN-experienced patients was lower in elderly than in youngers with a statistically significant difference (aged < 65 years: 41.6%; aged 65-75 years: 42.5%; aged ≥ 75 years: 16.1%). Finally, 10% of younger, 12.5% of young-old, and 3.2% of old-old patients had experienced protease inhibitor (PI) therapy. The rate of interferon-experienced patients was higher in olders groups.
Ribavirin was administered in 52 patients aged > 65, 14 patients aged 65-74 and 24 patients aged ≥ 75 years.
G1b and G4, irrespective of age and fibrosis, were treated without ribavirin except for those treated with 2D where ribavirin was weight-based dosed.

Distribution of direct-acting antivirals treatment and efficacy

The distribution of antiviral treatments was not statistically different between the youngers and elderly (Tab. I); sofosbuvir-based regimens were used in about 60% of patients without significant differences among the three age subgroups.
Sixteen percent of patients treated with 2D or 3D-based and 26% of sof-based treatment showed undetectable HCV-RNA by 4 weeks of therapy without differences among age subgroups.
All patients except 3 achieved SVR12 (99.3% in elderly *vs* 98.3% in younger patients) (Fig. 1).
Two were from sofosbuvir/ledipasvir G1b group and one was a sofosbuvir + daclatasvir treated patient with G3 infection. All were cirrhotic and showed mutations in NS5A region. Figures 2-4 show SVR rates according to baseline features (genotype, DAA regimen and liver fibrosis).

Safety of direct-acting antivirals

Sixty-two adverse events (AE) were reported in our study population (Tab. II). The number of AE was not higher in elderly patients than in younger. The analysis of age subgroup showed a difference of AE that did not reach a statistically significant level (30% in aged 65-75 years versus 27% in aged ≥ 75 years).
Five patients treated with sofosbuvir had grade 2

Table I. Baseline characteristic of study popultion and DAAs regimens according to age groups.

Variable	< 65 (n = 120)	p§	≥ 65 (n = 142)	p#	≥ 75 (n = 62)
Age, years	55 (35-64)		73 (65-88)		79 (75-85)
Male gender (n/%)	80 (66.7%)	< 0.001	66 (46.5%)	0.496	32 (51.6%)
Cirrhosis (n/%)	46 (38.3%)	0.559	74 (52.1%)	0.100	40 (64.5%)
CPT Class A B	 44 2	> 0.999	 68 6	0.738	 36 4
Type 2 diabetes	28 (23.3%)	< 0.001	50 (35.2%)	0.023	12 (19.3%)
IFN-experienced	50 (41.6%)	> 0.999	44 (31%)	0.026	10 (16.1%)
PI-experienced	12 (10%)	0.647	12 (8.5%)	0.235	2 (3.2%)
HCV genotype 1a 1b 2 3 4	 22 (18.3) 46 (38.3%) 22 (18.3%) 16 (13.3%) 14 (11.6%)	< 0.001	 0 102 (71.8%) 36 (25.4%) 2 (1.4%) 2 (1.4%)	0.634	 0 40 (64.5%) 20 (32.2%) 0 2 (3.22%)
DAA treatment schedule SOF+RBV SOF+SIM ± RBV SOF+LDV ± RBV SOF+DCV ± RBV OBV+PTV+R ± DASABUVIR ± RBV	 24 (20%) 18 (15%) 4 (3.3%) 26 (21.7%) 48 (40%)	0.296	 34 (24%) 20 (14%) 18 (12.7%) 14 (9.9%) 56 (39.4%)	0.387	 20 (32.3%) 8 (12.9%) 10 (16.1%) 2 (3.2%) 22 (35.5%)
Use of ribavirin (n/%)	52 (43.3%)	0.001	38 (26.8%)	0.087	24 (38.7%)
Treatment duration (n/%) 12 weeks 24 weeks	 80 (66.7%) 40 (33.3%)	0.382	 92 (64.8%) 48 (33.8%)	0.224	 34 (54.8%) 26 (45.2%)
Log_{10} HCV RNA, U/ml	5.69 (3.04-6.83)	0.481	4.51 (2.38-7.73)	0.348	5.36 (3.03-6.68)
AST, U/L	58.5 (15-305)	0.696	54 (17-302)	0.934	52 (23-302)
ALT, U/L	73 (12-272)	0.144	55 (12-327)	0.110	45 (17-327)

§ comparison between patients aged < 65 years and ≥ 65 years.
# comparison between patients aged ≥ 65 years and ≥ 75 years.

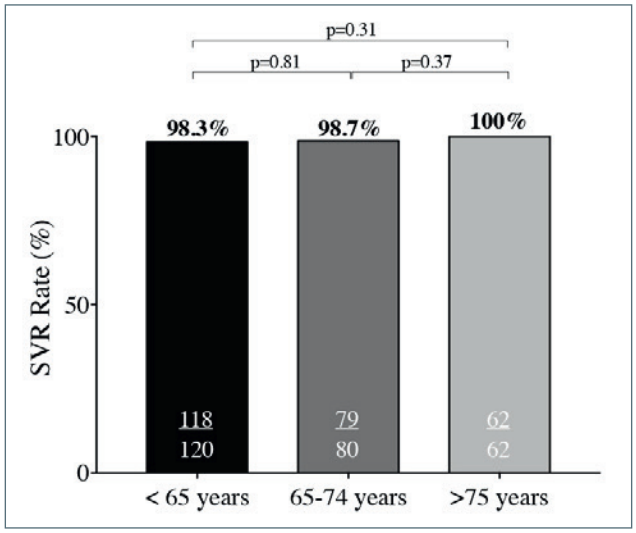

Figure 1. SVR rates according to age groups. SVR rates were not statistically different between the youngers and elderly.

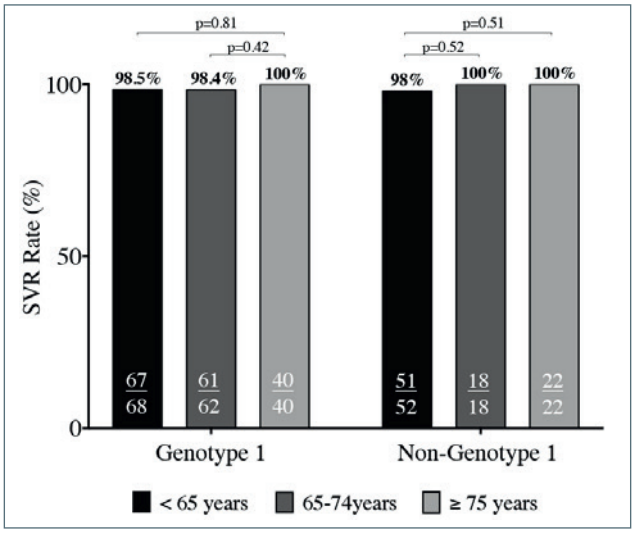

Figure 2. SVR12 for treated patients according to age and genotype. Virological response was not statistically different among the three age subgroups.

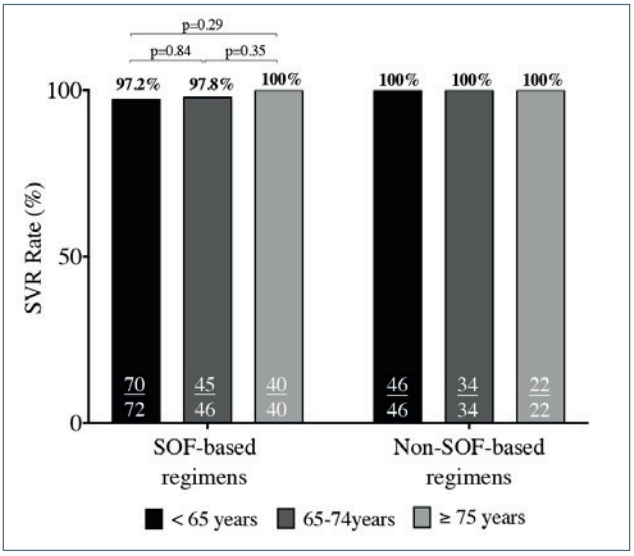

Figure 3. SVR12 for treated patients according to age and DAA regimen. Virological response was not statistically different among the three age subgroups.

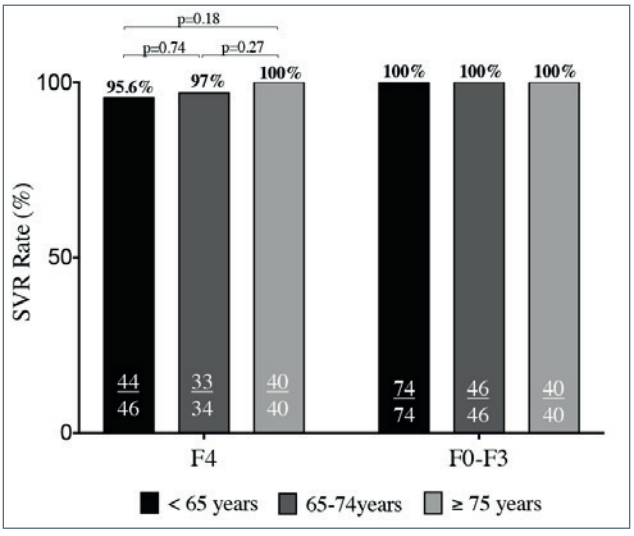

Figure 4. SVR12 for treated patients according to age and liver fibrosis. All patients except 3 achieved SVR12. All were cirrhotic and showed mutations in NS5A region. However virological response was not statistically different among the three age subgroups.

hyperbilirubinemia and one treated with 3D had grade 3 hyperbilirubinemia, respectively. All were cirrhotic and one of them assumed ribavirin.

Significant anemia was observed in 4 patients included in the old-old age group. All were G2-infected patients and were treated with sofosbuvir plus ribavirin.

A ribavirin dose reduction was required in 16 patients, 6 in the younger and 10 in the in ≥ 75 year-old groups. No dose reduction was needed in patients aged 65-75 years and erythropoetin was never used.

No hepatic decompensation was observed. One patient aged ≥ 75 years treated with 3D-based treatment reported pleural effusion resolved spontaneously at the end of the treatment.

Antiviral therapy was discontinued just in one patient aged < 65 years after only 8 weeks for acute ischemic stroke. The patient was in treatment with 3D regimen and reached SVR12 anyway.

HCC recurrence occurred in three patients; two of them completed treatment but died before achieving SVR12 and were excluded from final analysis.

Indipendent predictor of SVR12 rate in elderly patients

A multivariate analysis was performed to verify the independent factors significantly associated with SVR12 in overall study population. No statistically significant association was found for age, gender, genotype, stage of liver fibrosis, antiviral regimens, diabetes and ribavirin use (Tab. III).

Frequencies of concomitant medications

Frequencies and distribution of concomitant medications were reported in our study (Fig. 5).

Overall, the number of patients who took ACE inhibitors/ATII receptor blockers, diuretics, beta-blockers, calcium channel blockers, insulin, platelet aggregation inhibitors and PPI was significantly higher in patients aged ≥ 65 compared to < 65 years wheras no significant differences were found for statins and oral antidiabetic drugs (Tab. IV).

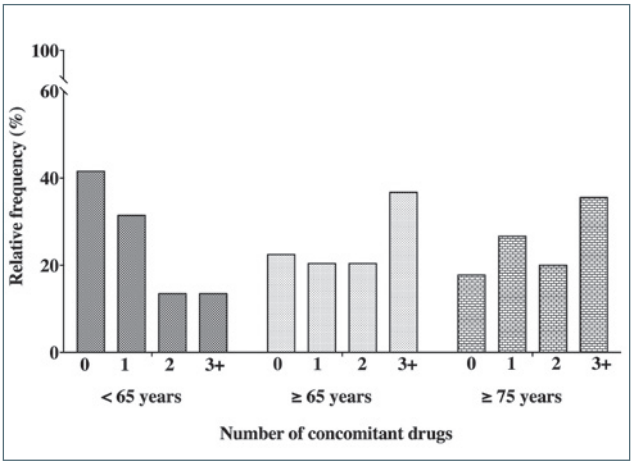

Figure 5. Frequencies and distribution of concomitant medications reported in our study. Elderly assumed more frequently 3 or more concomitant medications as compared to < 65 years patients (36.7% *vs* 13.4%; p = 0.0003).

Table II. AEs and laboratory abnormalities by age.

Variable	< 65 (n = 120)	p§	≥ 65 (n = 142)	p#	≥ 75 (n = 62)
Serious AEs	0		0		0
Death	0		0		0
Discontinuation due to serious AE	0		0		0
Fatigue	8	0.036	21	0.607	9
Skin complaints (rash/pruritus)	2	> 0.999	2	0.548	0
Insomnia	2	> 0.999	2	0.548	0
Gastrointestinal complaints (nausea/dyspepsia)	4	0.707	6	0.717	2
Headache	0	0.501	2	0.548	0
Irritability	1	> 0.999	1	0.516	1
Laboratory abnormality Grade 3 o 4 hyperbilirubinemia Hemoglobin 8-10 g/dl Hemoglobin < 8 g/dl	 4 0 0	0.917	 2 0 0	0.180	 0 4 0
RBV dose reduction or discontinuation (N event/N patients with ribavirin use)	6/52	< 0.001	10/14	0.100	10/24
Pleural effusion	0	> 0.999	1	0.516	1

comparison between patients aged ≥ 65 years and ≥ 75 years.
§ comparison between patients aged < 65 years and ≥ 65 years.

Table III. Variables associated with SVR in patients treated with Direct-Acting Antivirals (n = 242). The significance of association was assessed by performing an univariate and multivariate logistic regression analysis. No association was found for gender, genotype, liver fibrosis, age, antiviral regimen, IFN treatment or Diabetes.

Variable	Univariate analysis	Multivariate analysis	
	p	OR [95% CI]	p
Gender	0.291	2.782 [0.281-27.592]	0.382
Genotype (G1)	0.991	0.527 [0.049-4.963]	0.550
Cirrhosis	0.354	0.462 [0.071-3.021]	0.420
Age (≥ 65 years)	0.326	2.386 [0.363-15.695]	0.366
Sofosbuvir-based regimens	0.721	1.329 [0.196-9.024]	0.771
IFN-experience	0.292	4.151 [0.433-39.835]	0.217
Diabetes	0.582	2.007 [0.195-20.669]	0.558
Ribavirin	0.785	0.898 [0.104-7.783]	0.922

The most common drugs taken by elderly were diuretics (50% in ≥ 65 years and 71% in ≥ 75 years *vs* 14.1% in < 65 years) and ACE inhibitors/ATII receptor blockers (41.5% in ≥ 65 years and 45.1% in ≥ 75 years *vs* 20.8% in < 65 years).

Elderly assumed more frequently 3 or more concomitant medications as compared to < 65 years patients (36.7% *vs* 13.4%; p < 0.001).

A subgroup analysis for antiviral regimen was also performed: in the group of < 65 years, patients on 2D/3D regimen took more frequently ACE inhibitors/ATII receptor blockers (p < 0.05) and calcium channel blockers (p < 0.05) than those on sofosbuvir-based therapy; on the other hand, PPIs were more frequently found in ³ 65 years treated with sofosbuvir-based regimen (Tab. V).

DISCUSSION

The age of patients chronically infected by HCV has increased over the last decades and, due to the life expectancy in industrialized countries [18], older CHC patients will become an increasingly larger group over time.

They are expected to develop cirrhosis and liver cancer with a relevant increase in health-related disease costs [12].

To date reports on antiviral treatment of elderly patients have been limited to side effects and intolerance to IFN-based regimens with final SVR rates lower than youngers.

Although the epidemiology data of HCV infection are

Table IV. Distribution of most common concomitant medication used in patients treated with DAAs.

Drugs	< 65 (n = 120)	p§	≥ 65 (n = 142)	p#	≥ 75 years (n = 62)
ACE-Inhibitors/ATII receptor blockers	25 (20.8%)		59 (41.5%)		28 (45.1%)
Ramipril	12		10		6
Enalapril	0		6		1
Lisinopril	0		3		3
Delapril	1		0		0
Zofenopril	0	< .001	1	0.631	1
Candesartan	1		3		0
Irbesartan	3		6		3
Losartan	1		6		3
Olmesartan	3		22		8
Telmisartan	3		4		0
Valsartan	1		4		3
Diuretics	17 (14.1%)		71 (50%)		44 (71%)
			27		
Furosemide	6	< .001	32	0.005	15
Hydroclorothiazide	7		11		20
Potassium canrenoate	3		1		8
Ca2+ Channel Blockers	1				1
Beta-Blockers	13 (10.8%)		47 (33%)		23 (37%)
Bisoprolol	4		10		7
Carvedilol	3	< .001	7	0.580	4
Nebivolol	3		16		5
Propranolol	3		6		3
Atenolol	0		7		3
Sotalol	0		1		1
Statins	2 (1.6%)		9 (6.3%)		6 (8%)
Atorvastatin	1		4		4
Rosuvastatin	0	0.060	3	0.400	1
Simvastatin	0		1		0
Pravastatin	0		1		1
Lovastatin	1		0		0
Calcium channel blockers	6 (5%)		24 (16.9%)		12 (19.3%)
Amlodipine	4		9		4
Lacidipine	1	0.002	3	0.672	2
Barnidipine	1		1		1
Lercanidipine	0		8		3
Nifedipine	0		2		1
Diltiazem	0		1		1
Oral antidiabetic drugs	16 (13.3%)	0.736	21 (14.8%)	0.321	6 (9.7%)
Insulin	6 (5%)	0.002	24 (16.9%)	0.304	7 (11.3%)
Platelet Aggregation inhibitors	13 (10.8%)		29 (20.4%)		15 (24.2%)
Acetyl salicylic acid	11	0.035	23	0.547	9
Clopidogrel	2		3		3
Ticlopidin	0		3		3
PPI	22 (15.5%)		51 (35.9%)		23 (37%)
Pantoprazole	9	0.001	18	0.871	6
Esomeprazole	6		4		3
Lansoprazole	5		16		11
Omeprazole	2		9		3

comparison between patients aged ≥ 65 years and ≥ 75 years.
§ comparison between patients aged < 65 years and ≥ 65 years.

limited because of publication bias and selective nature of the survey population, Italy showed high rate of chronic hepatitis C with a geographic and age-dependent gradient [19 20]. In Northern Italy the prevalence of CHC was found to be 3.2% ranging from < 1% of younger than 40 years up to 10% in older than 60 years [19]. Several authors reported in Southern Italy prevalence of HCV infection [3 20 21].

Moreover, Southern Italy has the largest number of elderly patients with chronic hepatitis C and therefore data about efficacy and safety of DAA-based therapy are required.

In our retrospective analysis 132 patients aged > 65 years coming from South Italy were analyzed and showed that DAAs is as effective as in patients aged < 65 years.

Small studies have recently showed SVR rates comparable to younger but high risk of adverse events when DAAs were used in CHC patients; one was conducted in Spain and reported 65% of side effects mainly related to ribavirin and protease inhibitors [11]; the second used data from sofosbuvir/ledipasvir registration trials but included only 24 patients older than 75 years [22].

Conti et al. recently reported data from a Northern Italian elderly population and showed an overall SVR rate comparable to that obtained in patients aged < 65 years. In their cohort, genotype distribution was significantly different between elderly and youngers, many elderly subjects had cirrhosis and sofosbuvir-based regimen was mostly administered (75%) [12].

In our retrospective analysis we included a large number of Southern Italian elderly patients (n = 132) and first of all our analysis demonstrated that IFN-free treatment is as effective in elderly as in patients aged < 65 years.

A larger number of our patients received 3D or 2D antiviral regimen with comparable efficacy and safety profiles to sofosbuvir-based therapy.

Almost all our cirrhotic patients were in CPT-A class. Patients with CPT-B class cirrhosis showed an SVR rate, viral kinetics and biochemical response comparable with class A patients. However, the number of CPT-B class patients was too small.

Most patients in our study were treated using ribavirin-free regimens without affecting SVR rate. Ribavirin is still considered important in clinical trial for interferon-free DAA combinations because it can increase SVR rates in some subgroups of patients, particularly those that historically have been considered the most difficult to cure [23]. Data from first-generation DAA studies showed that ribavirin dosage reduction did not negatively impact SVR rates unless it was reduced by more than 50% of the recommended dosage [24]. On the other hand, highly potent DAA combinations achieve SVR12 in more than 90% of patients with or without ribavirin. Therefore more data are required to evaluate its role in viral response and relapse.

Table V. Distribution of most common concomitant medication by age and DAA regimen.

Drugs	< 65 years (n = 120)			≥ 65 years (n = 142)			≥ 75 years (n = 62)		
	Sof-based treatment (n = 7)	2D/3D (n = 48)	p	Sof-based treatment (n = 86)	2D/3D (n = 56)	p	Sof-based treatment (n = 40)	2D/3D (n = 22)	p
ACE-Inhibitors/ATII receptor blockers	10 (13.9%)	15 (31.2%)	0.04	37 (43%)	22 (39.3%)	0.79	19 (47.5%)	9 (41%)	0.82
Diuretics	11 (15.3%)	6 (12.5%)	0.87	49 (57%)	22 (39.3%)	0.06	29 (72.5%)	15 (68.1%)	0.95
Beta-Blockers	8 (11.1%)	5 (10.4%)	0.86	31 (36%)	16 (28.6%)	0.46	15 (37.5%)	8 (36.4%)	0.95
Statins	2 (2.8%)	0 (0%)	0.52	6 (7%)	3 (5.3%)	0.97	5 (12.5%)	1 (4.5%)	0.41
Calcium channel Blockers	1 (1.4%)	5 (10.4%)	0.04	13 (15.1%)	11 (19.6%)	0.63	7 (17.5%)	5 (22.7%)	0.87
Oral Antidiabetic Drugs	7 (9.7%)	9 (18.8%)	0.25	11 (12.8%)	10 (17.8%)	0.55	5 (12.5%)	1 (4.5%)	0.41
Insulin	3 (4.2%)	3 (6.3%)	0.68	15 (17.4%)	9 (16%)	0.98	4 (10%)	3 (13.6%)	0.69
Platelet Aggregation inhibitors	6 (8.3%)	7 (14.6%)	0.43	16 (18.6%)	13 (23.3%)	0.65	11 (27.5%)	4 (18.2%)	0.54
PPI	10 (13.9%)	12 (25%)	0.19	37 (43%)	14 (25%)	0.04	16 (40%)	7 (31.8%)	0.72

Regardless of virus genotype, in our cohort SVR rate was 99.3% in elderly and the only one patient who relapsed in this age-group did not take ribavirin. Moreover in our cohort, low dose ribavirin was used in comparison with dosage reported during "old" interferon-based treatment without affecting SVR rates.

Four cases of severe anemia was recorded in old-old patients and about 40% of them required a dose reduction suggesting that adverse effects occurred more commonly in patient aged ≥ 75 years treated with ribavirin-containing antiviral combinations.

Therefore our data provided a rationale against the use of ribavirin in patients aged ≥ 75 years whereas all DAAs combination can be effectively and safely used.

Potential pharmacokinetic interactions of common drugs administered with DAAs were analyzed in the present study and revealed that elderly patients took significantly more drugs than patients < 65 years. More than one third of our elderly patients (36.7%) took 3 or more concomitant drugs potentially interacting with DAAs; however, DAAs efficacy was not different.

PPI therapy has recently reported to be associated with a 26% increased risk of SVR failure when compared to non-users [25]. Our data showed high response rates regardless PPI use and age.

We observed a low percentage of AEs (24%) that were significantly lower than those reported in approval studies (60-95%) [26-31]; the discrepancy is probably related to the nature of the study design. In fact, in other real-world analyses the AE frequency ranged between 24 and 76% [12 16 32]. We should take into account that our analysis was carried out in a tertiary referral center for chronic viral hepatitis.

In any case, our physicians carefully evaluated the opportunity of any other drug before starting DAAs therapy and any potential interative drug was suspended if not strictly needed.

Our observations confirmed the data from other reports that showed a similar frequency of AEs between old and very old patients [5].

In conclusion, the results of our study demonstrate that age does not influence the success of DAA treatment and that all DAA regimens are well tolerated and safe, even in those aged 75 years or older. Although our patients commonly assumed many concomitant medications, compliance, efficacy and safety were not affected by DAAs.

We believe that a careful evaluation of baseline therapy of the old patients before starting DAAs is mandatory and may avoid treatment failure.

Acknowledgments

The authors are sincerely grateful to Carla Rovai and Lucia Barbera for their contribution in data collection.

Declaration of Sources of Funding

This study was not funded.

Conflict of Interest

The authors declare no conflicts of interest.

References

1 Westbrook RH, Dusheiko G. *Natural history of hepatitis C*. J Hepatol 2014;61(Suppl. 1):S58-68.

2 Mohd Hanafiah K, Groeger J, Flaxman AD, et al. *Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence.* Hepatology 2013;57:1333-42.

3 Guadagnino V, Stroffolini T, Rapicetta M, et al. *Prevalence, risk factors, and genotype distribution of hepatitis C virus infection in the general population: a community-based survey in southern Italy.* Hepatology 1997;26:1006-11.

4 El-Serag HB, Kramer J, Duan Z, et al. *Epidemiology and outcomes of hepatitis C infection in elderly US veterans*. J Viral Hepat 2016;23:687-96.

5 Vermehren J, Peiffer KH, 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;44:856-65.

6 Snyder HS, Ali B, Gonzalez HC, et al. *Efficacy and safety of sofosbuvir-based direct acting antivirals for hepatitis C in septuagenarians and octogenarians.* J Clin Exp Hepatol 2017;7:93-6.

7 Tarao K, Tanaka K, Nozaki A, et al. *Efficacy and safety of dual therapy with daclatasvir and asunaprevir in elderly patients.* World J Hepatol 2017;9:544-50.

8 Toyoda H, Kumada T, Tada T, et al. *Efficacy and tolerability of an IFN-free regimen with DCV/ASV for elderly patients infected with HCV genotype 1B*. J Hepatol 2017;66:521-7.

9 Akuta N, Sezaki H, Suzuki F, et al. *Favorable efficacy of daclatasvir plus asunaprevir in treatment of elderly Japanese patients infected with HCV genotype 1b aged 70 and older.* J Med Virol 2017;89:91-8.

10 Fujii H, Umemura A, Nishikawa T, et al. *Real-world efficacy of daclatasvir and asunaprevir with respect to resistance-associated substitutions.* World J Hepatol 2017;9:1064-72.

11 Rodriguez-Osorio I, Cid P, Morano L, et al. *Real life experience with direct-acting antivirals agents against hepatitis C infection in elderly patients.* J Clin Virol 2017;88:58-61.

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

13 Ippolito AM, Iacobellis A, Milella M, et al. *Hepatitis C virus clearance in older adults.* J Am Geriatr Soc 2018;66:85-91.

14 Latt NL, Yanny BT, Gharibian D, et al. *Eight-week ledipasvir/sofosbuvir in non-cirrhotic, treatment-naive hepatitis C genotype-1 patients with hepatitis C virus-RNA < 6 million:*

single center, real world effectiveness and safety. World J Gastroenterol 2017;23:4759-66.

15 Bhattacharya D, Belperio PS, Shahoumian TA, et al. *Effectiveness of all-oral antiviral regimens in 996 human immunodeficiency virus/hepatitis C virus genotype 1-coinfected patients treated in routine practice*. Clin Infect Dis 2017;64:1711-20.

16 Atsukawa M, Tsubota A, Kondo C, et al. *Effectiveness and safety of community-based treatment with sofosbuvir plus ribavirin for elderly patients with genotype 2 chronic hepatitis C.* Dig Liver Dis 2017;49:1029-35.

17 Common Terminology Criteria for Adverse Events (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. version 4.0 - 2010).

18 Gramenzi A, Conti F, Camma C, et al. *Hepatitis C in the elderly: a multicentre cross-sectional study by the Italian Association for the Study of the Liver*. Dig Liver Dis 2012;44:674-80.

19 Bellentani S, Tiribelli C. *The spectrum of liver disease in the general population: lesson from the Dionysos study*. J Hepatol 2001;35:531-7.

20 Cozzolongo R, Osella AR, Elba S, et al. *Epidemiology of HCV infection in the general population: a survey in a southern Italian town.* Am J Gastroenterol 2009;104:2740-6.

21 Maio G, d'Argenio P, Stroffolini T, et al. *Hepatitis C virus infection and alanine transaminase levels in the general population: a survey in a southern Italian town.* J Hepatol 2000;33:116-20.

22 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;63:1112-9.

23 Feld JJ, Jacobson IM, Sulkowski MS, et al. *Ribavirin revisited in the era of direct-acting antiviral therapy for hepatitis C virus infection*. Liver Int 2017;37:5-18.

24 Poordad F, Lawitz E, Reddy KR, et al. *Effects of ribavirin dose reduction vs erythropoietin for boceprevir-related anemia in patients with chronic hepatitis C virus genotype 1 infection – a randomized trial.* Gastroenterology 2013;145:1035-44.

25 Wijarnpreecha K, Chesdachai S, Thongprayoon C, et al. *Efficacy and safety of direct-acting antivirals in hepatitis C virus-infected patients taking proton pump inhibitors*. J Clin Transl Hepatol 2017;5:327-34.

26 Afdhal N, Reddy KR, Nelson DR, et al. *Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection*. N Engl J Med 2014;370:1483-93.

27 Afdhal N, Zeuzem S, Kwo P, et al. *Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection.* N Engl J Med 2014;370:1889-98.

28 Lawitz E, Sulkowski MS, Ghalib R, et al. *Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study.* Lancet 2014;384:1756-65.

29 Bourliere M, Bronowicki JP, de Ledinghen V, et al. *Ledipasvir-sofosbuvir with or without ribavirin to treat patients with HCV genotype 1 infection and cirrhosis non-responsive to previous protease-inhibitor therapy: a randomised, double-blind, phase 2 trial (SIRIUS).* Lancet Infect Dis 2015;15:397-404.

30 Forns X, Gordon SC, Zuckerman E, et al. *Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent.* J Hepatol 2015;63:564-72.

31 Foster GR, Afdhal N, Roberts SK, et al. *Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection.* N Engl J Med 2015;373:2608-17.

32 Omata M, Nishiguchi S, Ueno Y, et al. *Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial.* J Viral Hepat 2014;21:762-8.