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FULL PAPER

Efficacy of the "first wave" Direct Acting antivirals against HCV infection: results from the Italian LINA (Liver Network Activity) cohort

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SUMMARY

Approximately 71 million people are chronically infected with HCV worldwide. Recently, interferon-free therapies effective against HCV became available and nowadays, therapeutic strategies include a combination of two or three drugs with different mechanisms of action. In the present study, we reported real-life SVR rates in a large cohort of four prescribing centers in a high-endemic area of Southern Italy.
We conducted a prospective multicenter study among all the patients with chronic HCV infection, who received therapy with the first available interferon-free therapies between March 2015 and December 2017 and who referred to one of the 4 DAA-prescribing centers in Campania, Southern Italy. Patients with Child C cirrhosis, a diagnosis of active HCC at the baseline or who refused the consent form, were excluded.
Nine-hundred fifty-three patients were enrolled. Most of the enrolled patients had HCV genotype 1b infection (66.4%), were older than 65 years (64.1%) and had advanced liver fibrosis (Metavir > F4) (73.5%). The overall SVR12 rate was 98.5%. Patients with clinical cirrhosis had a similar SVR12 rate compared with those without cirrhosis (97.8% vs 99.2%, p=0.09), while patients with decompensated cirrhosis had a significantly lower rate of SVR12 compared with those without decompensated disease (95.3% vs 99.0%, p<0.05). Patients aged more than 65 years had a similar rate of SVR12 compared with patients aged ≤ 65 years (98.6% vs 98.0%, p=0.57). Among patients >65 years, those with clinical cirrhosis, as well as those with advanced liver fibrosis, had a similar SVR12 rate compared with the patients with a Metavir score < F4 (98.3% vs 99.0%, p=0.70 and 98.6% vs 98.6%, p=1.00, respectively).
In the present, real-life study, DAA regimens are effective and safe in patients with chronic HCV infection, regardless of age and stage of liver disease, providing very high rates of SVR12 (98.5%).

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INTRODUCTION

Hepatitis C virus (HCV) was discovered about 30 years ago (Pawlotsky *et al.,* 2015) and represents a major cause of end-stage liver disease, hepatocellular carcinoma, and other liver-related deaths.
Approximately 71 million people worldwide are chronically infected with HCV (WHO 2017). There are seven genotypes (GTs) of HCV and the most common is GT1 with the sub-genotype GT1b, representing 68% of all HCV GTs and being the most prevalent in the Western world (Gower *et al.,* 2014). Moreover, some HCV GTs have been associated with specific at-risk behaviors, such as GT3 and GT1a, and resulted mainly associated with intravenous drug use (Stroffolini *et al.,* 2004; Buonomo *et al.,* 2018).
For a long time, the cornerstone of HCV therapy has been based on a combination of two drugs (Interferon and ribavirin) which carried low rates of sustained virologic response (SVR) (about 40% in genotype 1b and up to 80% in genotype 2 or 3) and many side effects such as, among others, psychiatric disorders, thrombocytopenia, leucopenia, and flu-like syndrome (Pol *et al.,* 1999; Gentile *et al.,* 2005; Tosone *et al.,* 2007; Bourliere *et al.,* 2012). Moreover, in case of significant comorbidity or decompensated liver disease, the antiviral interferon-based treatment was contraindicated.
Recently, interferon-free therapies became available, and therapeutic strategies now include a combination of two or three drugs with different mechanisms of action (i.e., NS3/4A protease inhibitors, NS5B polymerase inhibitors and NS5A inhibitors). The advent of these drugs for interferon-sparing strategies can be divided into two big waves, with only Sofosbuvir (SOF) that "survives" from the first wave and therefore, is still prescribed with new-

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ly-available companions (Gentile *et al.,* 2013a; Gentile *et al.,* 2014e; Gentile *et al.,* 2015a; Gentile *et al.,* 2015b). In detail, SOF and Dasabuvir (DAS) (NS5B polymerase inhibitor), Simeprevir (SIM), Paritaprevir (PAR) (NS3/4A protease inhibitors), Daclatasvir (DCV), Ombitasvir (OMB) and Ledipasvir (LDV) (NS5A inhibitors) are the first wave DAAs, while Grazoprevir, Glecaprevir, Voxilaprevir (NS3/4A protease inhibitors), Velpatasvir, Pibrentasvir, Elbasvir (NS5A inhibitors) and the "survived" SOF, represent the second wave of DAA agents. According to the recent literature, the two groups substantially differ in SVR rates (≈95% with new agents vs 90% obtained with the first available drugs) and in the overcoming of ribavirin (now only considered in the retreatment of advanced liver disease) (Gentile *et al.,* 2014a; Gentile *et al.,* 2014b; Gentile *et al.,* 2014c; Gentile *et al.,* 2014d; Gentile *et al.,* 2014g; Gentile *et al.,* 2016; Hezode and Bronowicki 2016; Li *et al.,* 2017; Carrion and Martin 2018; Cory *et al.,* 2018). At the moment, the treatment schedule consists of a treatment lasting from 8 to 24 weeks, depending on the patient's stage of fibrosis and previous antiviral treatments, with SVR rates that rose up to about 95% (Feld *et al.,* 2016; Hezode and Bronowicki 2016). However, these results on efficacy and safety derived from randomized controlled trials and few data are available in real-life settings (Ozono *et al.,* 2017; Trifan *et al.,* 2017).

Aim of this study was to report real-life data on efficacy safety and tolerability in a large cohort of four prescribing centers in a high-endemic area of Southern Italy.

PATIENTS AND METHODS

Study Design

A prospective multicenter study was planned. We enrolled all the patients with chronic HCV infection, who started therapy with DAAs between March 2015 and December 2017 at one of the 4 centers in Campania, Southern Italy, participating to the study (LINA cohort):

- University of Naples Federico II, Department of Clinical Medicine and Science - Section of Infectious Diseases.
- University of Campania, Luigi Vanvitelli, Infectious Diseases Unit, Department of Mental Health and Public Medicine.
- Azienda ospedaliera dei colli, HIV unit.
- OORR Area Stabiese - P.O. Gragnano. U.O.C. Medicina Interna, Epatologia ed Ecografia Interventistica.

Inclusion criteria were:

- Detectable plasmatic HCV-RNA within 3 months before enrolment.
- Age ≥ 18 years.
- DAA-based treatment with one of the following drug combinations: SOF+RBV, SOF+SIM±RBV, SOF+DCV±RBV, OMB/PAR/Ritonavir ± RBV, SOF/LDV±RBV Detectable plasmatic HCV-RNA within 3 months before enrolment.

Scheduled follow-up (FU) visits were: time of enrolment (TOE), one month after the beginning of treatment, at end of treatment and at 12 weeks after the end of treatment (12 weeks post-treatment, 12WPT). All the patients underwent a clinical exam and performed laboratory tests at TOE and at each FU visit. Child-Pugh and MELD score were calculated at each FU visit and at the date of last observation (LO). Plasmatic HCV-RNA detection was performed at EOT.

Patients who missed FU visit at EOT and/or 12WPT were excluded from the study. Other exclusion criteria were the presence of a Child C cirrhosis, a diagnosis of active HCC at the baseline or consent refusal.

The severity of liver disease was graduated according to the degree of liver fibrosis by Metavir stage or clinical signs. The Metavir score was estimated with a FibroScan© exam performed within 6 months before the beginning of the antiviral treatment. Moreover, clinical cirrhosis was identified according to the presence of clinical, biochemical and ultrasound signs including a blood platelet count lower than 100,000/mm^3, hypertrophy of the caudate lobe, nodularity of the liver surfaces, altered straightness of hepatic veins, ascites, porto-systemic encephalopathy, esophageal varices and ultrasound evidence characterizing liver cirrhosis (Nyblom *et al.,* 2004; Nyblom *et al.,* 2006; Afdhal *et al.,* 2008; Gentile *et al.,* 2009; Gentile *et al.,* 2013b; Gentile *et al.,* 2014f; Ramachandran *et al.,* 2014; Procopet and Berzigotti 2017). Decompensated cirrhosis was defined as a cirrhosis in Child-Pugh stage of at least B7, while advanced liver fibrosis was defined as the presence of Metavir score ≥F4 or clinical cirrhosis. Patients who previously received an interferon-based anti-HCV treatment were defined as treatment-experienced; patients who never received a previous treatment against HCV were defined as treatment-naïve.

The indication for antiviral therapy and the choice of the IFN-free regimen and ribavirin was made according to the international guidelines and local availability (EASL 2008). The dose of the different DAAs and the duration of the regimen were chosen according to the international guidelines (EASL 2008).

The patients who were HCV-RNA-negative at month 3 after the end of the treatment were defined as having reached the SVR.

The primary endpoint of the study was to analyze the overall SVR12 rate after treatment with DAA. Secondary endpoints were:

- To analyze the SVR12 rates according to liver disease stage (no cirrhosis, cirrhosis and decompensated cirrhosis).
- To compare the SVR12 rates between patients aged >65 and ≤65 years.

Statistical analysis

The Kolmogorov-Smirnov test was applied to quantitative variables to check for Gaussian distribution. Data are given as mean ± standard deviation or as median and interquartile range (IQR) in case of Gaussian and non-Gaussian distribution, respectively. For categorical dichotomic variables, the χ^2 test (or Fisher's exact test if appropriate) was used for comparisons between unpaired groups. For all tests, a p-value <0.05 at two-sided test was considered statistically significant. Statistical analysis was carried out using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc. Chicago, IL, USA).

Ethical statement

The present prospective study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki-Sixth Version) for experiments involving humans. Written informed consent was obtained for all the patients involved into the study.

The protocol was submitted to Ethical Committee "Federico II" (Prot. 259/18).

RESULTS

A total of 953 patients were included in the study. The main clinical and laboratory characteristics of the enrolled patients are reported in *Table 1*. Most enrolled patients had HCV genotype 1b infection (633/953, 66.4%), were older than 65 years (611/953, 64.1%) and had advanced liver fibrosis (700/953, 73.5%). Treatment allocation, according to HCV genotype and treatment duration, is reported in *Table 2*. The most prescribed regimen was SOF+LDV for 24 weeks (204/953 patients, 21.4%).
The overall SVR12 rate was 98.5% (939/953 patients) and the highest SVR12 rates were reached by patients with genotype 1b and 2 (98.7% and 98.6%, respectively). No significant differences in the SVR12 were found among patients with HBV experienced patients (vs naïve), genotype 3 (vs others) or 1a (vs others).

Treatment efficacy according to liver disease stage

Patients with clinical cirrhosis had a similar SVR12 rate compared to those without cirrhosis (352/360, 97.8% vs 480/484, 99.2%, p=0.09), while patients with decompensated cirrhosis had a significantly lower rate of SVR12 compared to those without decompensated disease (82/86, 95.3% vs 584/590, 99.0%, p<0.05). Finally, no differences in SVR12 were observed among patients with advanced liver fibrosis compared to those with a Metavir score <F4 (689/700, 98.4% vs 250/253, 98.8%, p=1.0) (*Figure 1*). Among patients with advanced liver disease, those with GT1a and GT3 showed SVR12 rates of 95.7% (45/47) and 95.1% (39/41), respectively, while those with GT1b and GT2 had SVR12 rates of 98.5% (458/465) and 100% (127/127), respectively. When pooling patients with HCV GT1a and GT3, patients with advanced disease showed a significantly lower SVR12 rate compared with the SVR12 rate of patients with other GTs (84/88, 95.5% vs 605/612, 98.9%, p<0.05).

Table 1 - *Clinical and laboratory parameters of the enrolled patients (N=953).*

Age (years; median, IQR)	70 (62-75)
Male Sex (n, %)	475 (54.8)
HCV-RNA (IU/ml; median, IQR)	1,310,000 (414,000-3,100,000)
HCV Genotype (n, %)	
1a	64 (6.7)
1b	633 (66.4)
2	172 (18.0)
3	54 (5.7)
4	16 (1.7)
1 without subtype	14 (1.5)
Albumin (g/dL; median, IQR)	3.9 (3.5-4.1)
Platelets (elements/μL; median, IQR)	132,000 (88,000-183,250)
INR (median, IQR)	1.05 (1.00-1.15)
ALT (IU/l; median, IQR)	62 (38-94)
AST (IU/l; median, IQR)	58 (38-87)
GGT (IU/l; median, IQR)	50 (31-88)
Tot.Bil. (mg/dl; median, IQR)	0.82 (0.60-1.10)
Advanced liver fibrosis (Metavir score >F4 or clinical cirrhosis)	700 (73.5)
Clinical cirrhosis (n, %)	360 (37.8)
Child Pugh stage (n, %) (among clinical cirrhosis)	
A	260 (72)
B	100 (28)
MELD (among clinical cirrhosis) (median, IQR)	8 (7-11)
Treatment experienced (n, %)	419 (44.0)
HBV co-infection (n, %)	12 (1.3)

Treatment efficacy among patients aged more than 65 years

Patients aged more than 65 years had a similar rate of SVR12 compared with patients aged ≤ 65 years (579/587, 98.6% vs 292/298, 98.0%, p=0.57). Among them, patients with HCV GT1a showed a SVR12 rate of 94.7% (18/19), while those with GT1b and GT2 had SVR12 rates of 98.6% (426/432) and 99.2% (124/125), respectively. Only 1 patient aged more than 65 years had HCV GT3 and he achieved the SVR12. When patients with HCV GT1a and GT3 were grouped, they showed a non-significant trend toward a lower SVR12 rate compared with the SVR12 rate of patients with other GTs (19/20, 95.0% vs 560/567, 98.8%, p=0.24). Among patients >65 years, those with clinical cirrhosis, as well as those with advanced liver fibrosis had a similar SVR12 rate compared with the patients with a Metavir score <F4 (238/242, 98.3% vs 286/289, 99.0%, p=0.70 and 437/443, 98.6% vs 142/144, 98.6%, p=1.00, respectively). Conversely, patients aged >65 years with decompensated cirrhosis had a significant lower SVR12 rate compared with patients without decompensated disease (60/63, 95.2% vs 365/368, 99.2%, p<0.05) (*Figure 2*).

DISCUSSION

In our large real-life cohort, we showed a very high rate of SVR12 (98.5%) among 953 HCV chronically infected patients, despite most of them (74.1%) had advanced liver fibrosis, which is one of the main factors associated with lower rates of SVR in DAA-treated patients (Ippolito *et al.,* 2017). It is noteworthy that such rate is even higher than that reported in pivotal trials among patients with advanced liver disease (Lawitz *et al.,* 2013; Poordad *et al.,* 2014; Charlton *et al.,* 2015). Interestingly, we found a very high rate of SVR12 among patients with advanced liver fibrosis and GT1a (95.7%) and GT3 (97.1%), which are considered difficult-to-treat genotypes. In particular, results from the ALLY-3 study, a registration trial for SOF+DCV+RBV treatment among patients with GT3 and decompensated cirrhosis (Nelson *et al.,* 2015), showed an overall rate of 90%, with rates of 88% and 92% among patients who received a 12-week and a 16-week treatment course, respectively. Moreover, the SVR12 rates observed in our cohort were very similar to the SVR12 rates reported from the registration trials in which the same DAAs of our study were used.
Most patients in our cohort were aged more than 65 years (median age 70 years, IQR: 62-75). In fact, the mean age of hepatitis C virus (HCV) infected population and the number of elderly patients with more advanced liver disease are gradually increasing (Thabut *et al.,* 2006). Moreover, this cohort is expected to rise in the next 10 years

Table 2 - *Treatment allocation of the enrolled patients and SVR12 rates (N=953).*

	Genotype 1a		*Genotype 1b*		*Genotype 2*		*Genotype 3*		*Genotype 4*		*Other Genotype 1**		*All Genotypes*	
Treatment	*n, %*	*SVR12 (n, %)*	*n, %*	*SVR12 (n, %)*	*n, %*	*SVR12 (n, %)*	*n, %*	*SVR12 (n, %)*	*n, %*	*SVR12 (n, %)*	*n, %*	*SVR12 (n, %)*	*n, %*	*SVR12 (n, %)*
SOF+RBV	-	-	-	-	146 (15.3)	144 (98.6)	8 (0.8)	7 (87.5)	-	-	-	-	154 (16.2)	**151 (98.0)**
12 weeks	-	-	-	-	37 (3.9)	35 (94.6)	1 (0.1)	1 (100)	-	-	-	-	38 (4.0)	**36 (94.7)**
16 weeks	-	-	-	-	38 (4.0)	38 (100)	-	-	-	-	-	-	38 (4.0)	**38 (100)**
24 weeks	-	-	-	-	71 (7.4)	71 (100)	7 (0.7)	6 (85.7)	-	-	-	-	78 (8.2)	**77 (98.7)**
SOF+SIM	1 (0.1)	0 (0)	60 (6.3)	59 (98.3)	1 (0.1)	1 (100)	-	-	1 (0.1)	1 (100)	-	-	63 (6.6)	**61 (96.8)**
12 weeks	1 (0.1)	0 (0)	59 (6.2)	58 (98.3)	1 (0.1)	1 (100)	-	-	1 (0.1)	1 (100)	-	-	62 (6.5)	**60 (96.8)**
24 weeks	-	-	1 (0.1)	1 (100)	-	-	-	-	-	-	-	-	1 (0.1)	**1 (100)**
SOF+SIM+RBV 12 weeks	-	-	12 (1.3)	12 (100)	-	-	-	-	-	-	-	-	12 (1.3)	**12 (100)**
OMB/PAR/r+DAS	1 (0.1)	1 (100)	191 (20.0)	190 (99.5)	-	-	-	-	3 (0.3)	3 (100)	-	-	195 (20.5)	**194 (99.5)**
12 weeks	1 (0.1)	1 (100)	188 (19.7)	187 (99.5)	-	-	-	-	-	-	-	-	189 (19.8)	**188 (99.5)**
24 weeks	-	-	3 (0.3)	3 (100)	-	-	-	-	3 (0.3)	3 (100)	-	-	6 (0.6)	**6 (100)**
OMB/PAR/r+-DAS+RBV	9 (0.9)	9 (100)	68 (7.1)	68 (100)	-	-	-	-	2 (0.2)	2 (100)	-	-	79 (8.3)	**79 (100)**
12 weeks	3 (0.3)	3 (100)	68 (7.1)	68 (100)	-	-	-	-	1 (0.1)	1 (100)	-	-	72 (7.5)	**72 (100)**
24 weeks	6 (0.6)	6 (100)	-	-	-	-	-	-	1 (0.1)	1 (100)	-	-	7 (0.7)	**7 (100)**
SOF/LDV	23 (2.4)	22 (95.6)	224 (23.5)	222 (99.1)	-	-	-	-	5 (0.5)	5 (100)	5 (0.5)	5 (100)	257 (27.0)	**254 (98.8)**
12 weeks	5 (0.5)	5 (100)	46 (4.8)	46 (100)	-	-	-	-	1 (0.1)	1 (100)	1 (0.1)	1 (100)	53 (5.6)	**53 (100)**
24 weeks	18 (1.9)	17 (94.4)	178 (18.7)	176 (98.9)	-	-	-	-	4 (0.4)	4 (100)	4 (0.4)	4 (100)	204 (21.4)	**201 (98.5)**
SOF/LDV+RBV	20 (2.1)	20 (100)	50 (5.2)	46 (92.0)	1 (0.1)	1 (100)	-	-	3 (0.3)	3 (100)	4 (0.4)	4 (100)	78 (8.2)	**74 (94.9)**
12 weeks	11 (1.1)	11 (100)	26 (2.7)	23 (88.5)	-	-	-	-	2 (0.2)	2 (100)	2 (0.2)	2 (100)	41 (4.3)	**38 (92.7)**
24 weeks	9 (0.9)	9 (100)	24 (2.5)	23 (95.8)	1 (0.1)	1 (100)	-	-	1 (0.1)	1 (100)	2 (0.2)	2 (100)	37 (3.9)	**36 (97.3)**
SOF+DCV	7 (0.7)	7 (100)	28 (2.9)	28 (100)	24 (2.5)	24 (100)	33 (3.5)	33 (100)	1 (0.1)	1 (100)	1 (0.1)	1 (100)	94 (9.9)	**94 (100)**
12 weeks	1 (0.1)	1 (100)	5 (0.5)	5 (100)	23 (2.4)	23 (100)	10 (1.0)	10 (100)	-	-	-	-	39 (4.1)	**39 (100)**
24 weeks	6 (0.6)	6 (100)	23 (2.4)	23 (100)	1 (0.1)	1 (100)	23 (2.3)	23 (100)	1 (0.1)	1 (100)	1 (0.1)	1 (100)	55 (5.8)	**55 (100)**
SOF+DCV+RBV	3 (0.3)	3 (100)	3 (0.3)	3 (100)	-	-	13 (1.4)	12 (92.3)	1 (0.1)	1 (100)	-	-	20 (2.1)	**19 (95.0)**
12 weeks	2 (0.2)	2 (100)	3 (0.3)	3 (100)	-	-	-	-	-	1 (100)	-	-	6 (0.6)	**6 (100)**
24 weeks	1 (0.1)	1 (100)	-	-	-	-	13 (1.4)	12 (92.3)	1 (0.1)	-	-	-	14 (1.5)	**13 (92.9)**
GZR/EBR 12 wk	-	-	1 (0.1)	1 (100)	-	-	-	-		-	-	-	1 (0.1)	**1 (100)**
All Treatments	64 (6.7)	**62 (96.9)**	637 (66.8)	**629 (98.7)**	172 (18.0)	**170 (98.8)**	54 (5.7)	**52 (96.3)**	16 (1.7)	**16 (100)**	10 (1.0)	**10 (100)**	953 (100)	**939 (98.5)**

*Genotype 1 with no subtype available.
SVR12: sustained virological response at 12 weeks post-treatment. Wk: weeks. SOF: sofosfbuvir. RBV: ribavirin. SIM: simeprevir. OMB: ombitasvir. PAR: paritaprevir. r: ritonavir. DAS: dasabuvir. LDV: ledipasvir. DCV: daclatasvir. GZR: grazoprevir. EBR: elbasvir.

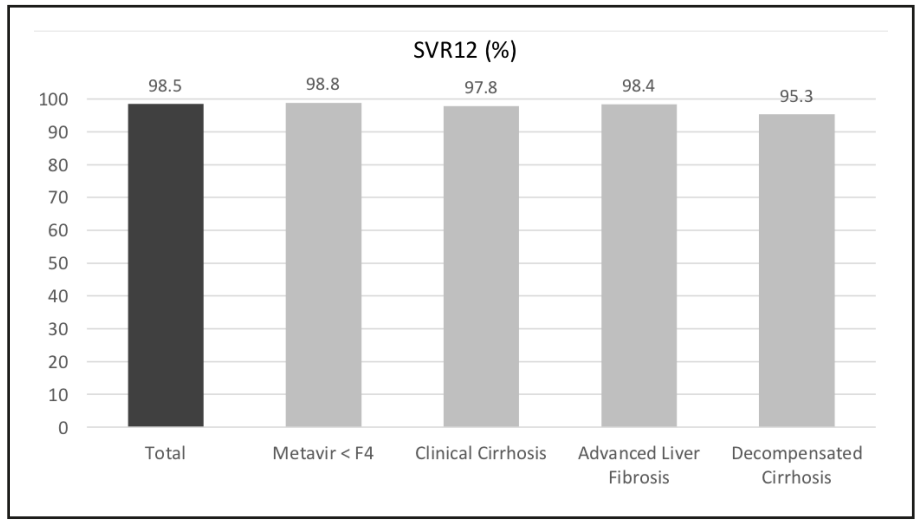

Figure 1 - *SVR12 rates among patients with different stages of liver disease.*

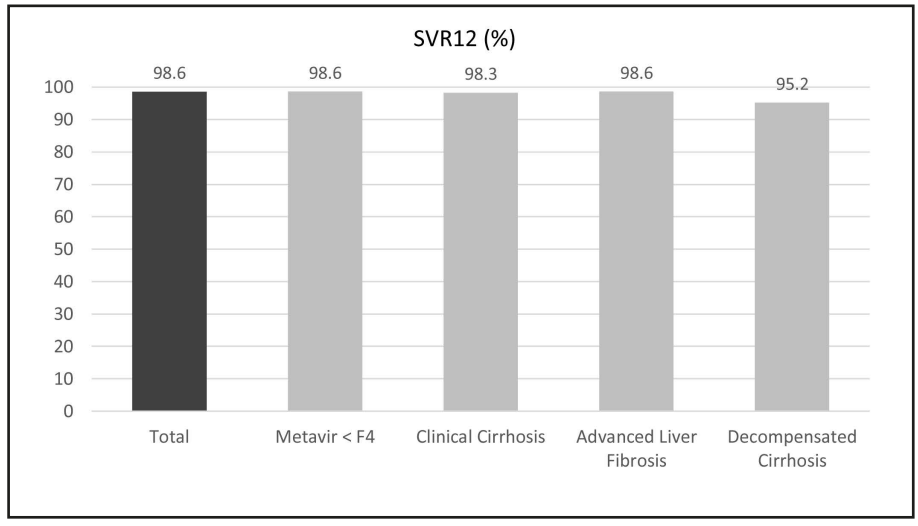

Figure 2 - *SVR12 rates among patients aged > 65 years with different stages of liver disease.*

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 (Bruno *et al.,* 2007; Singal *et al.,* 2010; Bruno *et al.,* 2016), elderly patients have been considered a difficult-to-treat subgroup, given the higher risk of adverse events, drug-to-drug interactions, discontinuations and mortality (Iwasaki *et al.,* 2006; Afdhal *et al.,* 2014).

Despite such concerns, patients aged >65 years in our cohort achieved a very high SVR12 rate (98.6%), that was similar to the SVR12 rate achieved by patients aged ≤65 years (98.0%) Although there was no upper age limit in DAA registration trials, the number of elderly patients enrolled, especially of those aged >65 years, was too small to determine whether they achieved different SVR12 rates compared with younger patients. For instance, in the TURQUOISE-II trial (Poordad *et al.,* 2014), the average age of the enrolled patients was 57.1±7.0 years among those who received OMB/PAR/r + RBV for 12 weeks, while it was 56.5±7.9 years among patients who received the same treatment for 24 weeks. Patients in the SAPPHIRE-I trial also had a similar average age (Feld *et al.,* 2014). Moreover, in the ION-1 trial (Afdhal *et al.,* 2014), the median age of the enrolled patients was 52 years (range: 18-75) among those who received SOF/LDV for 12 weeks, while it was 53 (range: 22-80) among those who received SOF/LDV for 24 weeks. Finally, patients enrolled in the ALLY-3 study (Leroy *et al.,* 2016) who received SOF+DCV+RBV for 12 weeks, had a median age of 53 years (range: 36-73), while the median age of those who received the same treatment for 16 weeks was 56 years (range: 42-62)

Moreover, as opposed to real-life experience, the proportion of elderly patients with advanced liver disease was too limited and data about the efficacy in this group of patients are lacking. Finally, the efficacy of DAA in elderly patients was assessed in only a few real-life cohorts. In fact, in 2017, *Trifan et al. (Trifan et al., 2017)* showed an SVR 12 rate of 97.4% among 117 patients aged ≥70 years who received the 3D pack combination plus RBV for 12 weeks. Finally, results from a Japanese real-life cohort (Ozono *et al.,* 2017) showed a SVR12 rate of 98.7% among 79 patients treated with SOF/LDV for 12 weeks. However, patients with decompensated cirrhosis were excluded from both the studies, as well as patients with HCV GTs other than 1.

In conclusion, among patients enrolled in our real-life cohort, we reported very high rates of SVR12, regardless of HCV genotype and age and excellent safety and tolerability profiles. We also showed that "first wave" DAA regimens are effective in patients with advanced fibrosis and clinical cirrhosis. Even though SVR12 rates were significantly lower in patients with decompensated cirrhosis (95.3% and 95.2% in the whole cohort and among patients aged > 65 years, respectively), such rates confirm high effectiveness. These very high rates of SVR together with screening and linkage to care policies are the keystone for the global HCV eradication advocated by the WHO.

Conflict of interests

IG was consultant for Abbvie, MSD and Cardiome. He received a grant (in the framework of Fellowship program) from Gilead Sciences. NC received grants from ViiV Healthcare, Janssen-Cilag, and Gilead Sciences; personal fees from Gilead Sciences, Abbvie, Bristol-Myers Squibb and Merck Sharp & Dohme.

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