Hepatology International (2019) 13:66–74
https://doi.org/10.1007/s12072-018-9914-6

ORIGINAL ARTICLE

Treatment with direct-acting antivirals improves the clinical outcome in patients with HCV-related decompensated cirrhosis: results from an Italian real-life cohort (Liver Network Activity—LINA cohort)

Ivan Gentile[1] · Riccardo Scotto[1] · Carmine Coppola[2] · Laura Staiano[2] · Daniela Caterina Amoruso[2] · Teresa De Simone[2] · Federica Portunato[3] · Stefania De Pascalis[3] · Salvatore Martini[3] · Margherita Macera[3] · Giulio Viceconte[1] · Grazia Tosone[1] · Antonio Riccardo Buonomo[1] · Guglielmo Borgia[1] · Nicola Coppola[3]

Received: 31 July 2018 / Accepted: 15 November 2018 / Published online: 6 December 2018

Abstract

Background Direct-acting antivirals (DAAs) are safe and effective for the treatment of HCV infection. However, data regarding their efficacy in patients with Child–Pugh B cirrhosis are scarce and their capability in improving liver function is debated. The aim of our study was to assess the clinical benefits of treatment with DAA in subjects with Child–Pugh B cirrhosis.

Methods We conducted a prospective multicentre study among patients with Child–Pugh B cirrhosis of an Italian real-life HCV cohort (LINA cohort) who received treatment with DAAs.

Results Among 89 patients enrolled, the rate of sustained virologic response 12 was 95.5%. No discontinuation occurred, no patient died during treatment. Most patients had Genotype 1 (1b 61.8%, 1a 11.2%). Conversely, 22.5%, 1.1% and 3.4% of patients had Genotype 2, 3 and 4, respectively. At last observation, 61.8% of patients switched to a Class A cirrhosis, 33.7% remained in Class B and 4.5 worsened to Child C ($p < 0.001$). Liver parameters significantly improved from baseline to 12 weeks after the end of treatment. Previous anti-HCV treatments and the presence of decompensated cirrhosis at 1 month of treatment were significantly associated with a decompensated cirrhosis at the last observation.

Conclusions Treatment with DAA in patients with Child–Pugh B cirrhosis is safe and leads to a very high rate of viral clearance, a significant rate of re-compensation and an improvement in liver function. Further studies are needed to assess the impact of treatment on survival and quality of life in long-term follow-up.

Keywords Direct-acting antivirals · Hepatitis C virus · Decompensated cirrhosis

Introduction

The availability of second generation direct-acting antivirals (DAA) effective against HCV chronic infection has radically changed the cure rate achievable by patients harbouring such virus [1–3]. Results from both registration trials and real-life cohorts reported high rates of sustained virologic response (namely, undetectable viral load 12 weeks after treatment, SVR12) after a treatment course with one of the approved DAA combinations available [4–10]. The use of a combination of at least two DAA allowed to avoid interferon administration (interferon-free combinations). Such peculiarity allowed patients with contraindications to interferon (e.g., decompensated cirrhosis) to be eligible for antiviral treatment. The sofosbuvir (SOF)-based combinations, either with ledipasvir (LDV), daclatasvir (DCV) or velpatasvir (VEL) ± ribavirin (RBV), showed to be safe and effective

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12072-018-9914-6) contains supplementary material, which is available to authorized users.

✉ Riccardo Scotto
riccardo.scotto@unina.it

[1] Section of Infectious Diseases, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

[2] Unit of Hepatology and Interventional Ultrasonography, Department of Internal Medicine, OORR Area Stabiese, Plesso Nuovo Gragnano, Naples, Italy

[3] Infectious Diseases Unit, Department of Mental Health and Public Medicine, University of Campania Luigi Vanvitelli, Caserta, Italy

in clinical trials when used in patients with decompensated cirrhosis [11–13].

However, real-life data on the treatment with DAA in patients with decompensated cirrhosis are conflicting. In fact, results from a large Spanish real-life cohort showed significant lower rates of SVR12 in patients with decompensated cirrhosis compared with those with Child–Pugh A cirrhosis [14], while an international multicentre cohort study reported similar SVR12 rates among patients with Child–Pugh A and Child–Pugh B/C cirrhosis [15].

Moreover, despite the high virological efficacy, data regarding clinical benefits of DAA on decompensated liver cirrhosis are scarce, especially in real-life settings [16, 17]. The aim of our study was to assess, in a cohort of subjects with a baseline decompensated cirrhosis, the rate of patients who have a compensated disease after treatment with DAAs.

Materials and methods

The complete study protocol is available as Supplementary File.

Study design

We conducted a prospective multicentre study involving all the patients with HCV chronic infection who received therapy with DAA between March 2015 and December 2017 and who referred to one of the following hospitals in Campania region, Southern Italy, which is an endemic area for HCV infection [18] (LINA cohort):

- University of Naples Federico II, Department of Clinical Medicine and Surgery—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 for the LINA cohort were:

1. Patients affected by chronic HCV hepatitis.
2. Treatment with DAA started between March 2015 and December 2017.
3. Age ≥ 18-year-old.

Exclusion criteria were:

1. Diagnosis of active hepatocellular carcinoma (HCC) at the baseline.
2. Child–Pugh C cirrhosis.
3. Consent refusal.

Among patients in the LINA cohort, for the present analysis, we included only those patients with a diagnosis of cirrhosis in class B according to Child–Pugh classification who completed 12 weeks of post-treatment (12WPT) observation. Figure 1 shows the flowchart of the included patients.

Scheduled follow-up visits were time of enrolment (TOE), 1 month after the beginning of treatment (1 month of therapy, 1MT), at the end of treatment (EOT) and at 12 weeks after the end of treatment (12WPT). All the patients underwent a clinical exam and performed laboratory tests at TOE and at each follow-up (FU) visit. Child–Pugh and MELD score were calculated at each FU visit and at the date of last observation (LO).

Clinical and laboratory adverse events were defined as per NIH definitions [19] during the monthly check-ups.

Study outcomes and sample size

The primary outcome of the study was to assess, in a cohort of patients with Child–Pugh B cirrhosis at baseline, the rate of patients with a Child–Pugh B cirrhosis 12 weeks after the end of the antiviral treatment.

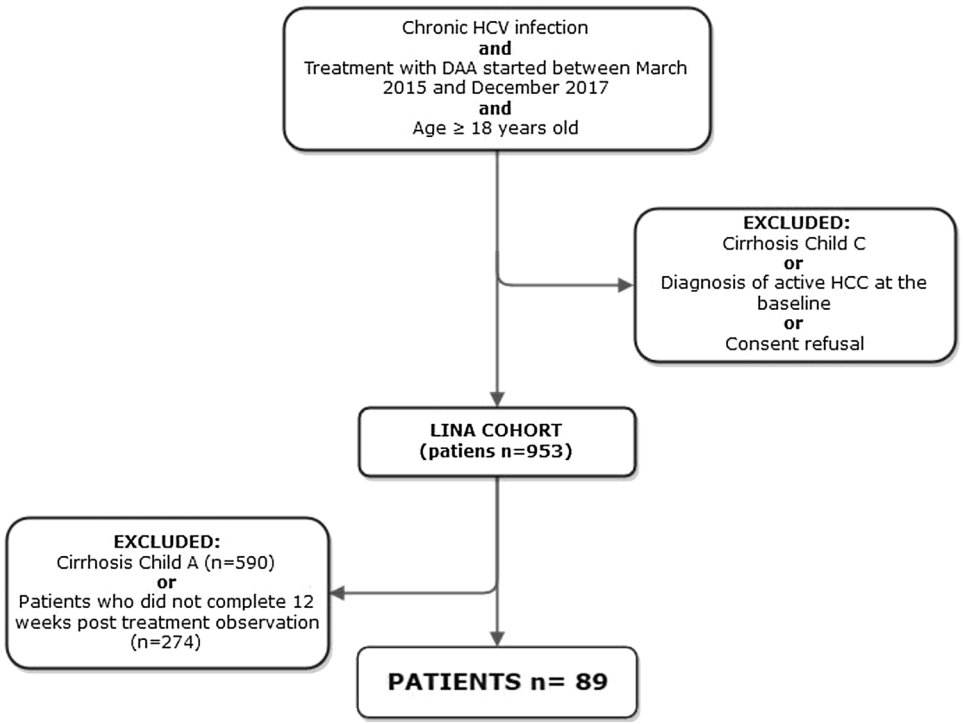
Secondary outcomes were:

- To estimate the safety of DAA in a real-life setting in term of treatment discontinuation.
- To analyse the course of liver disease in terms of MELD and CHILD–PUGH score during and after the treatment.
- To analyse the laboratory parameters of liver function and liver damage throughout and after the treatment with DAA.
- To estimate the real-life efficacy (SVR12) of DAA in patients with Child–Pugh B liver cirrhosis.
- To investigate the presence of predictive factors for decompensation of the liver disease after treatment with DAA.

Given the previously reported rate of 24% of patients in waiting list for liver transplantation who showed significant improvement in liver cirrhosis [17], a 40% rate of reduction in decompensated cirrhosis among patients who received DAA according to our definition was estimated. The calculated sample size was 61 (α-error: 0.05, power = 0.8).

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



DAA: direct-acting antivirals. HCC: hepatocellular carcinoma

Fig. 1 Flowchart of the cohort inclusion criteria

χ^2 test (or Fisher's exact test if appropriate) was used for comparisons between two unpaired groups, while the McNemar test and the Cochrane *Q* test were used for comparisons among paired groups (2 and 3 + groups, respectively). For continuous non-Gaussian-distributed data, the Wilcoxon test was used for comparisons between two paired groups, while the Friedman test was used for comparisons among 3 or more paired groups. Logistic regression model with backward conditional step for multivariate analysis was used. The variables that showed a p value < 0.2 at the univariate analysis were included in the multivariate model analysis. The cut-off values for the stepwise method were $p = 0.05$ for entry into the model and $p = 0.10$ for removal from the model. 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).

Results

Among the 953 patients enrolled in the LINA cohort, 89 were included in the study according to the inclusion/exclusion criteria. Clinical parameters of the 89 patients with Child–Pugh B cirrhosis are shown in Table 1. No patients underwent liver transplantation throughout the whole follow-up and until LO.

Table 1 Clinical parameters of the enrolled patients ($N = 89$)

Age (years; median, IQR)	72 (67–76)
Male sex (*n*, %)	41 (46.1)
HCV-RNA (IU/ml; median, IQR)	466,400 (90,682–1,519,730)
HCV genotype (*n*, %)	
1a	10 (11.2)
1b	55 (61.8)
2	20 (22.5)
3	1 (1.1)
4	3 (3.4)
MELD (median, IQR)	11 (9–14)
Treatment experienced (*n*, %)	37 (41.6)
HIV co-infection (*n*, %)	2 (2.2)
HBV co-infection (*n*, %)	1 (1.1)
Cryoglobulinemic syndrome (*n*, %)	3 (3.4)

Treatment efficacy

SOF + LDV for 24 weeks was the most prescribed treatment in our cohort (34/89 patients, 38.2%). Among patients with HCV genotype 2, 14 (70%) received SOF + RBV while 6 (30%) received SOF + DCV when this treatment became available for genotype 2 patients with contraindications to RBV (e.g. anemia, coronary diseases, severe pulmonary diseases).

All patients except 3 had HCV-RNA < 15 IU/ml at one month of treatment (86/89, 96.6%), while 85/89 patients achieved SVR12. Therefore, the overall SVR12 rate was 95.5%. All patients with HCV genotype 2 achieved the SVR12 (20/20) while patients with genotype 1a and 1b achieved SVR12 rates of 80% (8/10) and 96.4% (53/54), respectively. Rates of SVR12 according to HCV genotype and treatment are shown in Table 2. Two of the patients who failed the cure received SOF plus simeprevir for 12 weeks (one treatment-experienced genotype 1a and one treatment-naïve genotype 1b), while the other two patients received SOF+LDV for 24 weeks (treatment-experienced genotype 1a) and SOF+LDV+RBV for 24 weeks (treatment-experienced genotype 1b). All the 89 patients completed the treatment, no discontinuation occurred. Regarding biochemical efficacy, aminotransferase decreased rapidly during treatment. We underline that neither enzyme lowering agents nor other liver protecting agents were used during the treatment with DAA in any of the enrolled patients.

For what concerns the tolerability, a total of 27 treatment-related clinical and laboratory adverse events (AEs) were experienced by 25 patients (28.1%). The most frequently observed AE was anemia, which occurred in 10/89 patients (11.2%). Anemia was experienced by 4/24 (16.7%) patients who received RBV and by 6/65 (9.2%) patients who received a RBV-free regimen, respectively ($p = 0.45$). Eight patients (9.0%) had mild–moderate asthenia, while three (3.4%) showed an episode of delirium. All these AEs were completely reversible and they resolved after the end of the treatment. Only one patient with a delirium episode during treatment (SOF+LDV without RBV) had a diagnosis of psychosis after the end of the treatment; he had no previous diagnosis of psychiatric comorbidities. Notably, 2 patients (2.2%) experienced a herpes simplex reactivation which resolved with appropriate treatment (acyclovir). Only 1 (1.1%) patient experienced severe headache that required symptomatic treatment (grade 3 according to NIH definitions); it was reversible at the end of the treatment. Finally, two patients experienced a rare AE: respectively, hyperkeratosis, and a cryoglobulinemic vasculitis reactivation. Both improved after appropriate treatment.

Changes in liver function parameters during the study period

During the observation period (median 11 months, IQR 6–21), rates of patients with persistent decompensated liver disease were significantly lower at each observation time point when compared to the TOE. Namely, rates of patients who switched from a decompensated to a compensated liver cirrhosis progressively increased during the observation from 45.5% at 1MT to 61.8% at LO ($p < 0.001$, Fig. 2). Two out of 89 (2.2%) and 1/89 (1.1%) patients had HIV- and HBV-co-infection, respectively. They were all assuming specific antiviral treatment and they all had suppressed HIV/HBV viremia at TOE and in the previous 3 years. They all achieved SVR12 and they all had compensated cirrhosis at LO. Among the 85 patients who achieved the SVR12, 55 (64.7%) were compensated at LO, while none of the 4 patients who failed to achieve the SVR12 was compensated at LO ($p < 0.05$). Most of the analysed parameters showed significant reductions at each observation time point compared to TOE (for all the comparisons of clinical and laboratory parameters at different times of observation see Table 3). Only 4/89 patients (4.5%) showed a worsening of liver disease after the end of the treatment (namely, from Child–Pugh B to Child–Pugh C cirrhosis), while 3/89 patients (3.4%) showed at least one episode of liver decompensation during the treatment. All the 3 patients who had a decompensation episode during the treatment, eventually achieved the SVR12. Only 1 of these had compensated cirrhosis at 12WPT and at LO. Two out of three received SOF + LDV for 24 weeks while 1 received SOF + DVC for 24 weeks. They all had HCV-RNA plasmatic concentration below the lower limit of detectability at 1MT.

The results of the longitudinal analysis are provided as Supplementary File.

Predictive factors for lack of improvement in liver function

At the univariate analysis, a history of previous antiviral treatment (OR 2.60, 95 CI 1.08–6.28; $p < 0.05$) and the presence of decompensated cirrhosis at 1MT (OR 57.75, 95 CI 7.33–454.88; $p < 0.001$) were significantly associated with a decompensated cirrhosis at LO. Conversely, a MELD score > 11 at baseline, the presence of decompensated cirrhosis at EOT, HCV genotype, HCV-RNA ≥ 800.000 IU/ml at baseline, HCV-RNA detectable at 1MT and at EOT were not predictive for decompensated cirrhosis at LO (Table 4). At the multivariate analysis, either a previous anti-HCV treatment (OR 4.75, 95 CI 1.34–16.87; $p < 0.05$) and the presence of decompensated cirrhosis at 1MT (OR 67.28, 95 CI 7.48–605.03; $p < 0.001$) persisted significantly associated with decompensated cirrhosis at LO (Table 4) when considering in the analysis also HCV genotype 2 vs. others and HCV-RNA ≥ 800.000 IU/ml.

Discussion

In this sub-cohort of 89 patients with Child–Pugh B HCV-related liver cirrhosis, we showed that treatment with DAAs not only leads to high rates of SVR12 (95.5%), but also ensures a significant improvement in liver function.

Table 2 Treatment allocation of the enrolled patients and SVR12 rates ($N=89$)

Treatments	Genotype 1a		Genotype 1b		Genotype 2		Genotype 3		Genotype 4		All Genotypes	
	n, %	SVR12 (*n*, %)	*n*, %	SVR12 (*n*, %)	*n*, %	SVR12 (*n*, %)	*n*, %	SVR12 (*n*, %)	*n*, %	SVR12 (*n*, %)	*n*, %	SVR12 (*n*, %)
SOF + RBV	–	–	–	–	14 (15.7)	14 (100)	–	–	–	–	14 (15.7)	14 (100)
16 weeks	–	–	–	–	6 (6.7)	6 (100)	–	–	–	–	6 (6.7)	6 (100)
24 weeks	–	–	–	–	8 (9.0)	8 (100)	–	–	–	–	8 (9.0)	8 (100)
SOF + SIM 12 weeks	1 (1.1)	0 (0)	12 (13.5)	11 (91.7)	–	–	–	–	1 (1.1)	1 (100)	14 (15.7)	12 (85.7)
SOF + SIM + RBV 12 weeks	–	–	1 (1.1)	1 (100)	–	–	–	–	–	–	1 (1.1)	1 (100)
OMB/PAR/r + DAS 12 weeks	–	–	3 (3.4)	3 (100)	–	–	–	–	–	–	3 (3.4)	3 (100)
OMB/PAR/r + DAS + RBV 12 weeks	–	–	1 (1.1)	1 (100)	–	–	–	–	–	–	1 (1.1)	1 (100)
SOF/LDV 24 weeks	5 (5.6)	4 (80)	28 (31.5)	28 (100)	–	–	–	–	1 (1.1)	1 (100)	34 (38.2)	33 (97.0)
SOF/LDV + RBV	–	–	6 (6.7)	5 (83.3)	–	–	–	–	–	–	6 (6.7)	5 (83.3)
12 weeks	–	–	3 (3.4)	3 (100)	–	–	–	–	–	–	3 (3.4)	3 (100)
24 weeks	–	–	3 (3.4)	2 (66.7)	–	–	–	–	–	–	3 (3.4)	2 (66.6)
SOF + DCV	2 (2.2)	2 (100)	4 (4.5)	4 (100)	6 (6.7)	6 (100)	–	–	1 (1.1)	1 (100)	13 (14.6)	13 (100)
12 weeks	–	–	–	–	6 (6.7)	6 (100)	–	–	–	–	6 (6.7)	6 (100)
24 weeks	2 (2.2)	2 (100)	4 (4.5)	4 (100)	–	–	–	–	1 (100)	1 (100)	7 (7.9)	7 (100)
SOF + DCV + RBV	2 (2.2)	2 (100)	–	–	–	–	1 (1.1)	1 (100)	–	–	3 (3.4)	3 (100)
12 weeks	1 (1.1)	1 (100)	–	–	–	–	–	1 (100)	–	–	1 (1.1)	1 (100)
24 weeks	1 (1.1)	1 (100)	–	–	–	–	1 (1.1)	–	–		2 (2.2)	2 (100)
All treatments	10 (11.2)	8 (80)	55 (61.8)	53 (96.4)	20 (22.5)	20 (100)	1 (1.1)	1 (100)	3 (3.4)	3 (100)	89 (100)	85 (95.5)

SVR12 sustained virological response at 12 weeks post-treatment, *Wk* weeks, *SOF* sofosbuvir, *RBV* ribavirin, *SIM* simeprevir, *OMB* ombitasvir, *PAR* paritaprevir, *r* ritonavir, *DAS* dasabuvir, *LDV* ledipasvir, *DCV* daclatasvir

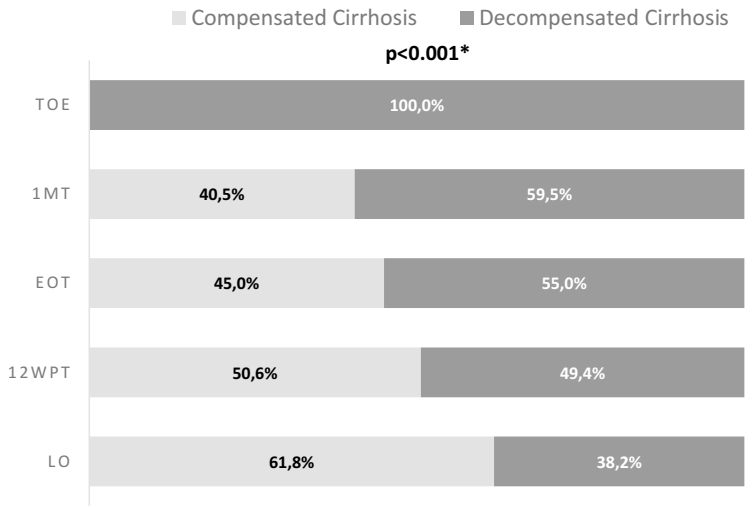


Fig. 2 Rates of patients with compensated/decompensated cirrhosis at the different times of observation

*Cochrane Q test
TOE: time of enrolment. 1MT: one month of treatment. EOT: end of treatment. 12WPT: twelve weeks post treatment. LO: last observation

The 95.5% rate of SVR12 is higher than previously reported from other real-life settings [14, 15]. Actually, in a phase II study, Lawitz et al. [20] reported a 100% rate of SVR12 among patients defined as "decompensated liver disease" but they also enrolled patients with a score of 5 according to Child–Pugh classification, which represents a compensated phase of liver disease. Furthermore, Chang et al. [21] showed a similar SVR12 rate (93%) in a cohort of 110 patients with advanced liver disease. However, only 37 patients in their cohort had decompensated liver cirrhosis and, among them, SVR12 rate was 84%. Moreover, they included in the decompensated group also patients classified as A5 in Child–Pugh classification but with esophageal varices.

For what concerns the primary outcome of the study, we showed an astonishing improvement in liver function, with a progressive increase in patients who switched from a decompensated to a compensated phase of the liver disease through the follow-up and up to 61.8% at last observation. In the largest real-life cohort aimed to evaluate the impact of DAA on liver decompensation, a significant reduction in MELD score was reported in treated patients compared to untreated ones (− 0.85, SD 2.54 vs + 0.75, SD 3.54; $p < 0.001$) [16]. However, such data only refer to a 3-month post-treatment observation and the study was not aimed at analysing the rates of patients who switched from decompensated to compensated cirrhosis at 12WPT. Similar results were obtained in a retrospective analysis performed in a cohort of patients enlisted for liver transplantation [17] who showed a significant reduction of MELD score and Child–Pugh score after treatment with DAA. Moreover, 24% of patients with decompensated cirrhosis without HCC were excluded from liver transplantation waiting list due to improvements in MELD score and in clinical outcomes. Despite these data derived from a specifically designed population (patients who were enlisted for liver transplantation and who mainly received DAA treatment by compassionate use or expanded access programme), similar results are awaited in real-life settings. Also studies in pre-DAA era showed that viral clearance after an interferon-based regimen led to a significant reduction in portal hypertension [22, 23], which is a surrogate marker of reduced incidence of complications [24, 25]. Recently, similar results were shown in a cohort of HIV/HCV co-infected patients who received treatment with DAA [26].

As expected, most of the laboratory parameters of liver injury and liver function significantly improved during the study time. While the improvement in injury parameters (e.g. AST and ALT) reflects the HCV clearance, the improvement in function parameters (e.g., albumin) and in parameters related to portal hypertension (e.g., platelets) is probably referable to a partial recovery of liver function. Moreover, in our study, an increase in albumin levels was observed as well (from 3.1 at TOE to 3.6 at 12WPT g/dl, $p < 0.001$). This may have clinical consequences. In fact, in a study by Backus et al., albumin concentration was the only parameter associated with mortality together with the non-treatment of infected patients [27]. Finally, the observed increase in neutrophil count might have an impact on the occurrence of infections, which are known to worsen the prognosis of patients with liver cirrhosis [28].

Accumulating evidences are supporting the benefits of treating all the patients with HCV-related liver disease including those with a decompensated liver disease for several reasons. First, as we demonstrated in our study, the treatment-induced HCV clearance leads to an improvement

Table 3 Clinical and laboratory parameters of the enrolled patients at different times of observation

	TOE	1MT	*p**	EOT	*p**	12WPT	*p**	LO	*p**
Decompensated cirrhosis (*n*, %)	89 (100)	53 (59.6)	**< 0.001**	49 (55.1)	**< 0.001**	44 (49.4)	**< 0.001**	34 (38.2)	**< 0.001**
Child–Pugh Score									
A	0 (0)	36 (40.4)	**< 0.001**	40 (44.9)	**< 0.001**	45 (50.6)	**< 0.001**	55 (61.8)	**< 0.001**
B	89 (100)	52 (58.4)	**< 0.001**	47 (52.8)	**< 0.001**	43 (48.3)	**< 0.001**	30 (33.7)	**< 0.001**
C	0 (0)	1 (1.1)	1.000	2 (2.2)	1.000	1 (1.1)	1.000	4 (4.5)	0.375
MELD (median, IQR)	11 (10–14)	10 (9–12)	0.393	10 (8–12)	0.274	10 (8–12)	0.105	10 (9–13)	0.236
HCV-RNA undetectable (*n*, %)	0 (0)	78 (87.6)	**< 0.001**	86 (96.6)	**< 0.001**	85 (95.5)	**< 0.001**	85 (95.5)	**< 0.001**
AST (IU/l; median, IQR)	62 (44–101)	30 (23–40)	**< 0.001**	29 (21–36)	**< 0.001**	29 (23–37)	**< 0.001**	–	–
ALT (IU/l; median, IQR)	50 (31–78)	19 (15–30)	**< 0.001**	20 (15–27)	**<0.001**	20 (17–28)	**< 0.001**	–	–
GGT (IU/l; median, IQR)	50 (30–94)	40 (24–62)	**< 0.001**	30 (20–54)	**< 0.001**	33 (22–60)	**< 0.001**	–	–
Tot.Bil. (mg/dl; median, IQR)	1.46 (1.00–2.54)	1.37 (1.00–2.20)	0.493	1.18 (1.00–2.00)	0.345	1.20 (1.00–2.00)	0.164	–	–
INR (median, IQR)	1.1 (1.0–1.3)	1.1 (1.0–1.3)	0.406	1.1 (1.0–1.3)	0.129	1.1 (1.0–1.4)	0.643	–	–
Albumin (g/dl, median, IQR)	3.1 (3.0–3.8)	3.1 (3.0–3.8)	0.115	3.4 (3.0–4.0)	**< 0.05**	3.6 (3.0–4.0)	**< 0.001**	–	–
AFP (IU/l, median, IQR)	9.9 (4.3–21.8)	6.8 (4.0–11.5)	0.422	6.7 (5.0–9.0)	0.093	5.2 (3.7–8.0)	0.227	–	–
WBC (cells/ µl × 10^3, median, IQR)	3.7 (2.8–4.9)	4.4 (3.0–5.2)	**< 0.01**	3.9 (3.0–5.2)	**< 0.05**	4.1 (3.1–5.3)	0.111	–	–
NEU (cells/ µl × 10^3, median, IQR)	2.1 (1.5–2.9)	2.4 (1.7–3.0)	**< 0.05**	2.1 (1.7–3.1)	0.072	2.3 (1.7–3.1)	**< 0.05**		
PLT (cells/ µl × 10^3, median, IQR)	73.5 (52.2–110.8)	79.0 (57.5–113.5)	0.224	82.0 (53.0–110.0)	0.058	81.0 (53.0–110.0)	**< 0.05**	–	–

Bold refers significant *p* values

TOE time of enrolment, *1MT* one month of treatment, *EOT* end of treatment, *LO* last observation, *12WPT* twelve weeks post-treatment, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GGT* gamma-glutamyl transpeptidase, *Tot.Bil* total bilirubin, *INR* international normalised ratio, *AFP* alpha-fetoprotein, *WBC* white blood cells, *NEU* neutrophils, *PLT* platelets

*Comparisons were made with baseline values. The McNemar test and the Wilcoxon test were use when appropriate (dichotomic and continuous variables, respectively)

in liver function in patients with decompensated liver cirrhosis and a subsequent re-compensation of the disease. Secondly, the presumed higher risk of HCC development after DAA treatment has been ruled out from many studies [29, 30]. At last, the universal treatment of HCV-infected patients can lead to the desired HCV eradication by 2030 as called by the WHO [31].

Furthermore, given our results regarding the predictive factors for lack of improvement in liver function, patients who previously received an IFN-based regimen have a lower chance of getting benefit from treatment with DAA. In fact, treatment-experienced patients had a 4.75-fold risk of not having a clinical improvement after treatment, probably due to the long course of the diseases and the occurrence of non-reversible liver damage. It is not possible to state whether HCV clearance is associated with improvement of liver function due to the paucity of patients who did not reach SVR12 in our cohort. However, it is notable that the other only predictive factor for lack of improvement was the presence of decompensated liver cirrhosis at 1 month of treatment (OR 67.28, CI 95 7.48–605.03 at the multivariate analysis).

Our study had some limitations. First, whether the sample size was powered enough for the primary outcome, it was

Table 4 Regression logistic analysis for decompensated cirrhosis at last observation

	Univariate analysis			Multivariate analysis		
	OR	95 CI	*p*	OR	95 CI	*p*
Treatment experienced	2.60	1.08–6.28	< 0.05	4.75	1.34–16.87	< 0.05
APRI > 1 at TOE	1.89	0.45–7.95	0.384	–	–	–
FIB-4 > 3.25 at TOE	1.55	0.27–9.02	0.626	–	–	–
MELD > 11 at TOE	1.80	0.44–7.28	0.410	–	–	–
Decompensated cirrhosis at 1MT	57.75	7.33–454.88	< 0.001	67.28	7.48–605.03	< 0.001
Decompensated cirrhosis at EOT	0.62	0.04–10.30	0.741	–	–	–
Genotype 1a	1.72	0.46–6.46	0.419	–	–	–
Genotype 1b	1.50	0.61–3.68	0.373	–	–	–
Genotype 2	0.32	0.10–1.07	0.065	1.22	0.24–6.13	0.804
Genotype 3	#	#	#	–	–	–
Genotype 4	0.80	0.07–9.21	0.860	–	–	–
HCV-RNA ≥ 800.000 (IU/ml)	2.44	0.95–6.27	0.063	0.57	0.17–1.93	0.369
HCV-RNA detectable at 1MT	2.14	0.60–7.66	0.241	–	–	–
HCV-RNA detectable at EOT	1.61	0.10–26.56	0.741	–	–	–
SVR12	≈	≈	≈	–	–	–

TOE time of enrolment, *1MT* one month of treatment, *EOT* end of treatment, *SVR12* sustained virologic response at 12 weeks post-treatment

#Not analysable, only one patient had HCV genotype 3 infection

≈Not analysable: all patients without SVR12 were decompensated at last observation

not large enough to draw accurate conclusions regarding the longitudinal changes in liver function parameters. However, we showed significant changes even in a restricted sample. Moreover, we missed several data regarding laboratory parameters at LO, thus precluding us to analyse longitudinal changes in the middle and long term. Finally, as mentioned above, the paucity of patients who did not reach SVR precluded us to analyse clear relationship between HCV clearance and re-compensation of liver disease.

In conclusion, the treatment with antiviral agents of patients with HCV-related Child–Pugh B liver cirrhosis is safe and leads to a very high rate of viral clearance, a significant rate of re-compensation, and an improvement in liver function and in serological markers of fibrosis. Further studies are needed to assess the impact of treatment on survival and quality of life in the long-term follow-up.

Funding Not applicable.

Compliance with ethical standards

Conflict of interest Ivan Gentile was consultant for Abbvie, Merck Sharp & Dohme and Cardiome. He received a grant (in the framework of Fellowship program) from Gilead Sciences. Guglielmo Borgia was consultant for Abbvie. He received grants from Abbvie, Merck Sharp & Dohme, Pfizer. Nicola Coppola received grants from ViiV Healthcare, Janssen-Cilag, and Gilead Sciences; personal fees from Gilead Sciences, Abbvie, Bristol-Myers Squibb and Merck Sharp & Dohme. Riccardo Scotto, Carmine Coppola, Laura Staiano, Daniela Caterina Amoruso, Teresa De Simone, Federica Portunato, Stefania De Pascalis, Salvatore Martini, Margherita Macera, Giulio Viceconte, Grazia Tosone and Antonio Riccardo Buonomo have no conflict of interest to declare.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

References

1. Borgia G, Maraolo AE, Buonomo AR, Scotto R, Gentile I. The therapeutic potential of new investigational hepatitis C virus translation inhibitors. Expert Opin Investig Drugs 2016;25(10):1209–1214
2. Gentile I, Maraolo AE, Buonomo AR, Zappulo E, Borgia G. The discovery of sofosbuvir: a revolution for therapy of chronic hepatitis C. Expert Opin Drug Discov 2015;10(12):1363–1377
3. Gentile I, Scotto R, Zappulo E, Buonomo AR, Pinchera B, Borgia G. Investigational direct-acting antivirals in hepatitis C treatment: the latest drugs in clinical development. Expert Opin Investig Drugs 2016;25(5):557–572
4. Curry MP, Tapper EB, Bacon B, et al. Effectiveness of 8- or 12-weeks of ledipasvir and sofosbuvir in real-world treatment-naive, genotype 1 hepatitis C infected patients. Aliment Pharmacol Ther 2017;46(5):540–548
5. Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology (Baltimore, MD) 2015;61(4):1127–1135

6. Bonora S, Puoti M. Use of daclatasvir in HCV/HIV-coinfected patients in a real-life setting. AIDS Rev 2017;19(1):24–34
7. Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet (London, England) 2015;385(9986):2502–2509
8. Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014;147(2):359–365
9. Mendizabal M, Haddad L, Gallardo PE, et al. Ombitasvir/paritaprevir/ritonavir/dasabuvir ± ribavirin is safe and effective in HCV-infected patients in a real-life cohort from Latin America. J Med Virol 2017;89(9):1590–1596
10. Gheorghe L, Iacob S, Curescu M, et al. Real-life use of 3 direct-acting antiviral regimen in a large cohort of patients with genotype-1b HCV compensated cirrhosis. J Gastrointest Liver Dis JGLD 2017;26(3):275–281
11. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016;16(6):685–697
12. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology (Baltimore, MD) 2016;63(5):1493–1505
13. Younossi ZM, Stepanova M, Charlton M, et al. Patient-reported outcomes with sofosbuvir and velpatasvir with or without ribavirin for hepatitis C virus-related decompensated cirrhosis: an exploratory analysis from the randomised, open-label ASTRAL-4 phase 3 trial. Lancet Gastroenterol Hepatol 2016;1(2):122–132
14. Fernandez Carrillo C, Lens S, Llop E, et al. Treatment of hepatitis C virus infection in patients with cirrhosis and predictive value of model for end-stage liver disease: analysis of data from the Hepa-C registry. Hepatology (Baltimore, MD) 2017;65(6):1810–1822
15. Maan R, van Tilborg M, Deterding K, et al. Safety and effectiveness of direct-acting antiviral agents for treatment of patients with chronic hepatitis C virus infection and cirrhosis. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc 2016;14(12):1821–1830
16. Foster GR, Irving WL, Cheung MC, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016;64(6):1224–1231
17. Pascasio JM, Vinaixa C, Ferrer MT, et al. Clinical outcomes of patients undergoing antiviral therapy while awaiting liver transplantation. J Hepatol 2017;67(6):1168–1176
18. Buonomo AR, Scotto R, Pinchera B, et al. Epidemiology and risk factors for hepatitis C virus genotypes in a high prevalence region in Italy. New Microbiol 2018;41(1):26–29
19. National Institutes of Health. Common terminology criteria for adverse events (CTCAE) version 4.0. https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed Aug 2018
20. Lawitz E, Poordad F, Gutierrez JA, et al. Simeprevir, daclatasvir and sofosbuvir for hepatitis C virus-infected patients with decompensated liver disease. J Viral Hepat 2017;24(4):287–294
21. Chang CY, Nguyen P, Le A, et al. Real-world experience with interferon-free, direct acting antiviral therapies in Asian Americans with chronic hepatitis C and advanced liver disease. Medicine 2017;96(6):e6128
22. Rincon D, Ripoll C, Lo Iacono O, et al. Antiviral therapy decreases hepatic venous pressure gradient in patients with chronic hepatitis C and advanced fibrosis. Am J Gastroenterol 2006;101(10):2269–2274
23. Roberts S, Gordon A, McLean C, et al. Effect of sustained viral response on hepatic venous pressure gradient in hepatitis C-related cirrhosis. Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc 2007;5(8):932–937
24. de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63(3):743–752
25. Hernandez-Gea V, Aracil C, Colomo A, et al. Development of ascites in compensated cirrhosis with severe portal hypertension treated with beta-blockers. Am J Gastroenterol 2012;107(3):418–427
26. Schwabl P, Mandorfer M, Steiner S, et al. Interferon-free regimens improve portal hypertension and histological necroinflammation in HIV/HCV patients with advanced liver disease. Aliment Pharmacol Ther 2017;45(1):139–149
27. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Direct-acting antiviral sustained virologic response: impact on mortality in patients without advanced liver disease. Hepatology 2018;68(3):827–838
28. Gentile I, Buonomo AR, Scotto R, Zappulo E, Borgia G. Infections worsen prognosis of patients with cirrhosis irrespective of the liver disease stage. Eur J Intern Med 2017;46:e45–e47
29. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology 2017;153(4):996–1005
30. Buonomo AR, Gentile I, Borgia G. Direct acting antiviral agents and hepatocellular carcinoma development: don't take it for granted. Transl Gastroenterol Hepatol 2017;2:101
31. World Health Organization. Combating hepatitis B and C to reach elimination by 2030. Advocacy Brief. 2016. http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016.04_eng.pdf?ua=1. Accessed Mar 2018