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LIVER TRANSPLANTATION

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The Italian compassionate use of sofosbuvir in HCV patients waitlisted for liver transplantation: A national real-life experience

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Abstract

Background & Aims: This study aimed to assess the real-life clinical and virological outcomes of HCV waitlisted patients for liver transplantation (LT) who received sofosbuvir/ribavirin (SOF/R) within the Italian compassionate use program.

Methods: Clinical and virological data were collected in 224 patients with decompensated cirrhosis and/or hepatocellular carcinoma (HCC) receiving daily SOF/R until LT or up a maximum of 48 weeks.

Results: Of 100 transplanted patients, 51 were HCV-RNA negative for >4 weeks before LT (SVR12: 88%) and 49 negative for <4 weeks or still viraemic at transplant: 34 patients continued treatment after LT (bridging therapy) (SVR12: 88%), while 15 stopped treatment (SVR12: 53%). 98 patients completed SOF/R without LT (SVR12: 73%). In patients with advanced decompensated cirrhosis (basal MELD ≥15 and/or C-P ≥B8), a marked improvement of the scores occurred in about 50% of cases and

Abbreviations: DAA, direct-acting antivirals; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ITT, intention to treat; LT, liver transplantation; MELD, model of end-stage liver disease; R, ribavirin; SOF, sofosbuvir; SVR, sustained virological response.

The list of collaborators of the ITACOPS study group is provided in the Appendix.

almost 20% of decompensated patients without HCC reached a condition suitable for inactivation and delisting.

Conclusions: These real-life data indicate that in waitlisted patients: (i) bridging antiviral therapy can be an option for patients still viraemic or negative <4 weeks at LT; and (ii) clinical improvement to a condition suitable for delisting can occur even in patients with advanced decompensated cirrhosis.

KEYWORDS

bridging therapy, decompensated cirrhosis, delisting, direct-acting antivirals, hepatitis C, liver transplantation

1 | INTRODUCTION

The treatment paradigm for patients with decompensated hepatitis C (HCV) cirrhosis has changed dramatically after the introduction of the direct-acting antivirals (DAA) leading to sustained virological response (SVR) rates as high as 75%-90% in patients with Child-Pugh B and C cirrhosis.[1-4] Moreover, DAAs have a remarkably good safety profile even if a risk of inducing hepatic decompensation with NS3 protease inhibitors has been reported.[5] As a result, HCV-infection can be now effectively and safely cured in patients waiting for liver transplantation (LT).

A major goal of treating HCV infection in these patients is to avoid its recurrence after LT. Prevention of allograft reinfection may provide a relevant advantage in the post-transplant management, especially in areas where the donor age greatly increased above 60 years in the last decade, leading to a more severe HCV recurrence.[6] Treatment should be initiated if patients have sufficient time to achieve undetectable HCV-RNA before LT, but the timing to transplantation is often unpredictable. Thus, a reasonable alternative strategy is to differ therapy after LT, as the reported SVR rates in transplant recipients are higher than those with decompensated cirrhosis with an excellent drug safety profile.[7]

Treatment with DAAs before LT is also associated to an improvement of liver function in many patients, thus reducing waiting-list mortality and even leading to inactivation and withdrawal from the transplant list in some cases.[8,9] However, if liver function improves during treatment but does not eliminate the need for LT, these patients are at disadvantage for graft allocation when the system is based only on the MELD scoring system. Moreover, many patients with severe liver diseases have no reduction of Child-Pugh and MELD scores or continue to show disease progression following successful treatment, indicating the existence of a point of no return for recovery.[1-4]

Unfortunately, clinical evidences in the pretransplant setting are quite limited. In the pivotal study by Curry et al[10] including waitlisted patients with Child-Pugh score ≤B7 and hepatocellular carcinoma (HCC), the combination of sofosbuvir plus ribavirin (SOF/R) prevented HCV recurrence in 96% of patients with undetectable viraemia for at least 4 weeks before LT, but only in 36% with undetectable viraemia for less than 4 weeks. De-listing was reported in 18% of patients waiting for LT after treatment with SOF-based regimes in a French multicentre cohort.[9] More recently, a retrospective analysis of 103 patients listed in several European centres for decompensated cirrhosis without HCC showed that treatment with SOF-based regimens favoured, in a time-frame of 60 weeks, the inactivation from the list of about one-third of cases and delisting of about 20% of cases.[8] Thus, additional data are needed to clarify the open issues regarding DAAs treatment in patients waiting for LT.

Here we report the real-life virological and clinical outcomes of a large cohort of 224 patients waitlisted for LT affected by HCV-related cirrhosis with or without HCC, who received SOF/R within the frame of a national compassionate program.

Key points

- Viral eradication is associated to an improvement of liver function in about half of patients awaiting liver transplantation.
- A condition of inactivation and then de-listing can be reached in almost 20% of non-HCC patients even in some of those with a severely compromised liver function.
- A decrease of MELD score after 4 weeks of therapy can help to identify patients with the highest chances to achieve inactivation.
- Pretransplant sofosbuvir plus ribavirin antiviral treatment can prevent graft reinfection in almost 90% of the recipients provided that bridging therapy is performed in those patients still viraemic or negative for less than 4 weeks at transplantation.

2 | PATIENTS AND METHODS

2.1 | Patients and design of the study

Patients waiting for LT in Italian transplant centres and participating from June 2014 to December 2014 to the Italian compassionate program for

the use of SOF (ITACOPS) were included in this prospective, observational cohort study. ITACOPS was promoted by the Italian Association for the Study of the Liver (AISF) and the Italian Society of Infectious and Tropical Diseases (SIMIT) and endorsed by the Italian Medicines Agency (AIFA). SOF was kindly provided by Gilead Sciences at no cost for Italian National Health System.

Inclusion criteria were: age >18 years, registration in a LT waiting list, decompensated cirrhosis (Child-Pugh ≥B7), and HCC within Milan criteria independently of the severity of the underlying liver disease. Exclusion criteria were: MELD score ≥25, creatinine clearance ≤30 mL/min, according with the SOF Summary of Product Characteristics, pregnant/nursing women, and history of significant drug allergy to nucleoside/nucleotide analogues.

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and all patients gave their written consent to participate in the study. The study was approved by the Ethical Committee of the S. Orsola-Malpighi University Hospital of Bologna and by Ethical Committees of all participating centres.

2.2 | Treatments

Patients were enrolled to receive daily SOF (400 mg daily) plus weight-based R (1000-1200 mg daily) until LT or for a maximum of 24 weeks (genotype 2) or 48 weeks (all other genotypes). Investigators were allowed to add a second DAA if obtained for the compassionate use. All patients were also treated for decompensated cirrhosis and HCC according to the standard of care.

2.3 | Monitoring

Patients receiving therapy were reviewed at treatment weeks 2, 4, 8, 12, 16, 20, 24, 36 and 48 and at post-treatment weeks 4 and 12. Clinical status, including grade of ascites and hepatic encephalopathy (HE), and laboratory parameters, measured by the local accredited laboratories, were recorded on eCRF (Ibis Informatica, Milan, Italy). HCV-RNA assessment was performed either by Roche High-Pure-System/COBAS(®) TaqMan(®) v2.0 assay (LLOQ 15 IU/mL; Roche Diagnostics, Indianapolis, IN, USA) or by Abbott real time assay (LLOQ 12 IU/mL; Abbott Molecular Inc., Des Plaines, IL, USA). MELD and Child-Pugh scores were calculated using site-derived laboratory and clinical parameters. Estimated glomerular filtration rate (eGFR) was using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[11]

2.4 | Statistical analysis

Data were expressed as absolute number and percentages for discrete variables and as median and minimum/maximum values for quantitative variables. For continuous variables normality of distribution and homogeneity of variances were assessed by the Kolmogorov–Smirnov and Levene test, respectively, afterward differences between groups were evaluated by the Unpaired Student's *t*-test or Mann–Whitney *U* test as appropriate. Spearman's rank correlation method was used to test the relationship between continuous data. Grouping variables were analysed by means of the Chi-square test or Fisher exact test. Change in MELD and Child-Pugh scores over treatment weeks was evaluated by a paired data Wilcoxon rank test, while the cumulative probability of clinical scores improvement through the treatment weeks was estimated by the Kaplan–Meier method followed by the Log Rank test to evaluate the difference between groups. All tests were two-tailed and *P* values less than .05 were considered statistically significant. The statistical analysis was performed by the Statistical Package for Social Sciences (SPSS) software version 23 (IBM corporation, Armonk, NY, USA).

3 | RESULTS

3.1 | Patients

Between June 2014 and December 2014, 243 patients listed for LT in the Italian transplant centres received SOF/R within the national ITACOPS program. As shown in Figure 1, of these 243 patients, 19 (7.8%) were excluded by the present analysis because the data were not provided by the investigators or were insufficient to assess the virological and clinical outcomes.

Thus, the study population consisted of 224 patients. The demographic and baseline clinical and laboratory characteristics of these patients are reported in Table 1. Median age was 56 years and 74% were male. Genotype 1b (44%) was the most frequent genotype followed by genotype 3 and 1a. HCC was present in 107 patients (48%). As expected, MELD and Child-Pugh score were lower in HCC than non-HCC patients (MELD: 10.5 [6-23] vs 15 [9-24], Child-Pugh: 7 [5-12] vs 8 [7-12] respectively). Nine patients were also positive for the antibody against HIV and four patients for serum HBsAg.

Of the 224 patients, 26 patients discontinued prematurely treatment (24 [3-47] weeks): 11 patients died for complications of cirrhosis, three patients presented a treatment virological failure (two non-responders and one virological breakthrough), six patients were forced to interrupt therapy due to severe anaemia, four patients decided to interrupt the study, and two patients were excluded for medical decision (progression of HCC in one case and scarce adherence to treatment in the other).

As a result, 198 patients reached the end of treatment: 100 were transplanted during treatment and 98 completed the course of therapy without LT.

3.2 | Treatments

According to the study protocol, SOF was given in association with R in all patients. However, the starting dose of R was lower than the suggested weight-based dosage (1000-1200 mg daily) in 119 (59%) patients. Thus, the median initial R daily dose was 800 mg (200-1200 mg). Genotype 1 patients were treated for 48 weeks, while genotype 2 patients for 24 weeks. Seven of 50 patients with genotype 3 received SOF/R for 24 weeks according to investigator's choice. Furthermore, 22 (9.8%) patients were also treated with a second DAA obtained through a company-driven compassionate program (18 patients with

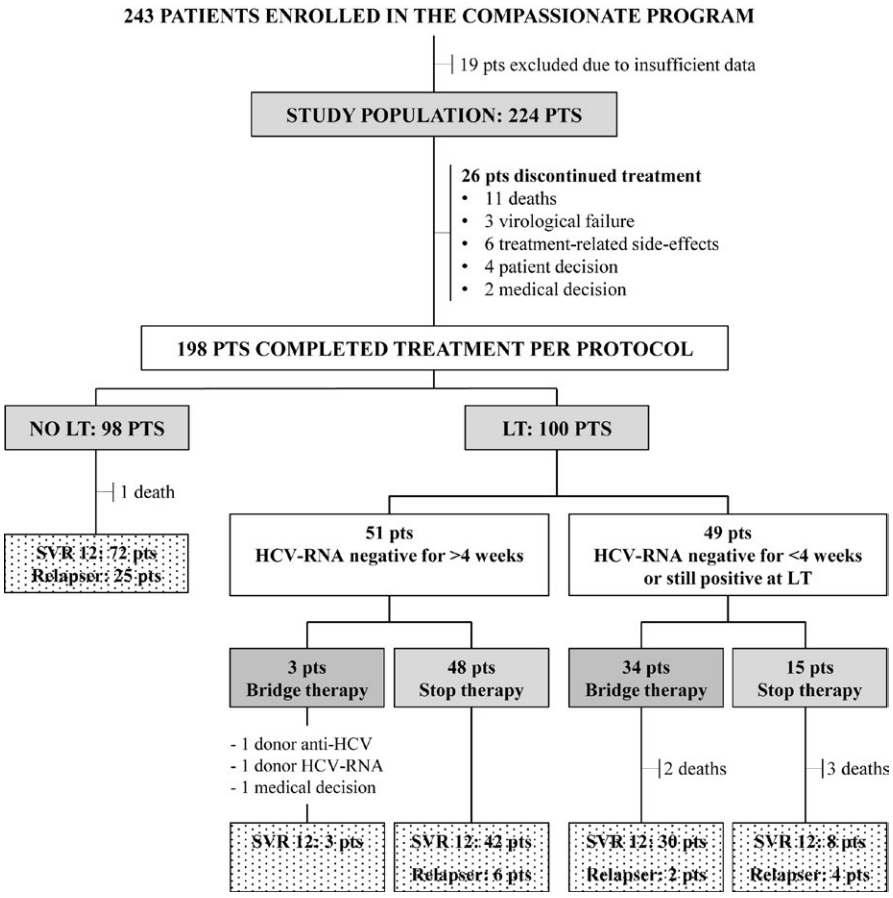

FIGURE 1 Clinical and virological outcome of waitlisted patients enrolled in the compassionate national program for the use of sofosbuvir. LT, liver transplantation; SVR, sustained virological response

daclatasvir [12 genotype 1, 4 genotype 3, and 2 genotype 4] and four patients with simeprevir [all genotype 1]) and their length of treatment was 12 or 24 weeks. Clinical and virological outcomes of the 22 patients receiving a second DAA are reported in Fig. S1.

3.3 | Clinical and virological outcomes

Virological clearance, as defined by HCV-RNA not detected, occurred in 204 (91%) patients during treatment. The median time to clearance was 4 weeks (min/max 1-28). Seventeen (7.6%) patients received LT (median treatment duration 4 [0-13] weeks) or discontinued prematurely the drugs (median treatment duration 6 [3-17] weeks) when they were still viraemic; two patients failed to clear HCV-RNA and one patient showed a virological breakthrough.

Of the 98 patients who completed the planned course of therapy without LT, in agreement to what already reported,[12] 73% of the patients showed a SVR12 according to the Intention-To-Treat (ITT) analysis, while the remaining relapsed, except one patient who died for bacterial infection after having obtained the SVR4 (Figure 1).

Although not included in the initial study protocol, many investigators decided to continue treatment after LT (bridging therapy), considering the available data of a high probability of viral recurrence if the period of HCV-RNA clearance before LT was shorter than 4 weeks.[10] Bridging therapy was in fact performed in 37 of the 100 patients who received LT. Of these 37 patients, 19 were still HCV-RNA positive at LT and 15 patients were negative for less than 4 weeks: two patients died after LT due to multiple organ failure and two patients presented a virological relapse. In the remaining 3 cases of bridging therapy with undetectable HCV-RNA for more than 4 weeks, two received a graft from a HCV positive donor, and in the third the period of clearance before LT was only 5 weeks: all these three patients reached an SVR12. Taken together, SVR12 was 88% (33/37) according to the ITT analysis and 94% (33/35) excluding the two deaths (Figure 1). The median DAA treatment duration was 6 (0-37) weeks before LT and 17 (4-27) weeks after LT.

Fifteen patients negative for less than 4 weeks at LT stopped therapy: three patients died for early LT complications and four patients presented a virological relapse. Thus, SVR12 was 53% according to ITT analysis (8/15) and 67% (8/12) excluding the three deaths (Figure 1).

Finally, 48 patients stopped therapy at LT being the HCV-RNA undetectable for more than 4 weeks with an SVR12 of 88% (42/48).

Overall, in transplanted patients SVR12 was achieved in 83% (83/100) of the patients, by ITT analysis, and 87% (83/95) excluding the five deaths.

The virological outcome in the different subgroups according the HCV genotypes is reported in Fig. S2.

3.4 | Effect of treatment on liver function

To determine the effect of treatment on liver function, we first analysed the changes in MELD (n = 126) and Child-Pugh (n = 124) scores in the patients who were not transplanted in the initial 24 weeks of the study with data available at baseline and after 24 weeks of therapy.

TABLE 1 Anthropometric, virological, clinical and biochemical parameters of 224 patients at study inclusion. Data are expressed as median (min-max value) or frequencies [n (%)]

	Median (min-max)/n (%)
Anthropometric	
Age (y)	56 (25-70)
Weight (kg)	73 (35-115)
Gender (male)	165 (74)
Virological	
Genotype (1/2/3/4)	134/17/50/23 (61/7/22/10)
HCV-RNA [log(IU/mL)]	5.5 (0.9-7.3)
Previous treatment	123 (55)
HBsAg positive	4 (1.7)
HIV positive	9 (4.0)
Clinical	
HCC	107 (48)
Ascites (none/mild/severe)	73/125/27 (33/55/12)
HE (none/mild/severe)	122/94/8 (54/42/4)
Child-Pugh class (A/B/C) (all pts)	46/135/43 (21/60/19)
Child-Pugh score (all pts)	8 (5-12)
Child-Pugh score (pts with HCC)	7 (5-12)
Child-Pugh score (pts without HCC)	8 (7-12)
MELD (all pts)	13 (6-24)
MELD (pts with HCC)	10.5 (6-23)
MELD (pts without HCC)	15 (9-24)
Biochemical	
Bilirubin (mg/dL)	5.5 (0.4-19.7)
INR	1.3 (1-2.3)
Albumin (g/dL)	3.4 (1.5-5.2)
Creatinine (mg/dL)	0.8 (0.5-1.5)
eGFR (ml/min/1.73 m^2)	101.2 (31.6-128.4)
AST (IU/L)	75 (17-544)
ALT (IU/L)	59 (9-522)
Hb (g/dL)	11.8 (7.7-16.7)
Platelets (10^9/L)	66 (12-285)

MELD decreased in 45% of cases, increased in 33% and remained stable in 22% (P = .292), while Child-Pugh decreased in 53% of cases, increased in 19% and remained stable in 28% (P = .001). Notably, when patients were divided according to the severity of liver disease, a significant improvement of the scores was observed only in those with basal MELD ≥15 (n = 50; P = .019) or Child-Pugh ≥8 (n = 67; P = .001). In these latter subgroups, the median drop of MELD score was 3.5 points with a wide range comprised between 1 and 15, while the median Child-Pugh reduction was 2 points with a range between 1 and 4.

Due to this high variability, we then decided to assess the cumulative probability of having a decrease of at least 3 points in the MELD score and at least 2 points in the Child-Pugh score, an extent that may reflect a relevant clinical improvement (Figure 2). In patients with less severe disease identified by MELD <15 or Child-Pugh <B8, the probability of having such a decrease in the MELD score was about 20% and 30% after 24 and 48 weeks, respectively, while the probability in the Child-Pugh score was about 20% and 35% after 24 and 48 weeks respectively. When we consider the subgroup with a more severe liver disease, the probability was significantly higher for both prognostic scores, being around 35% after 24 weeks and 65% after 48 weeks for MELD and 50% after 24 weeks and 60% after 48 weeks for Child-Pugh.

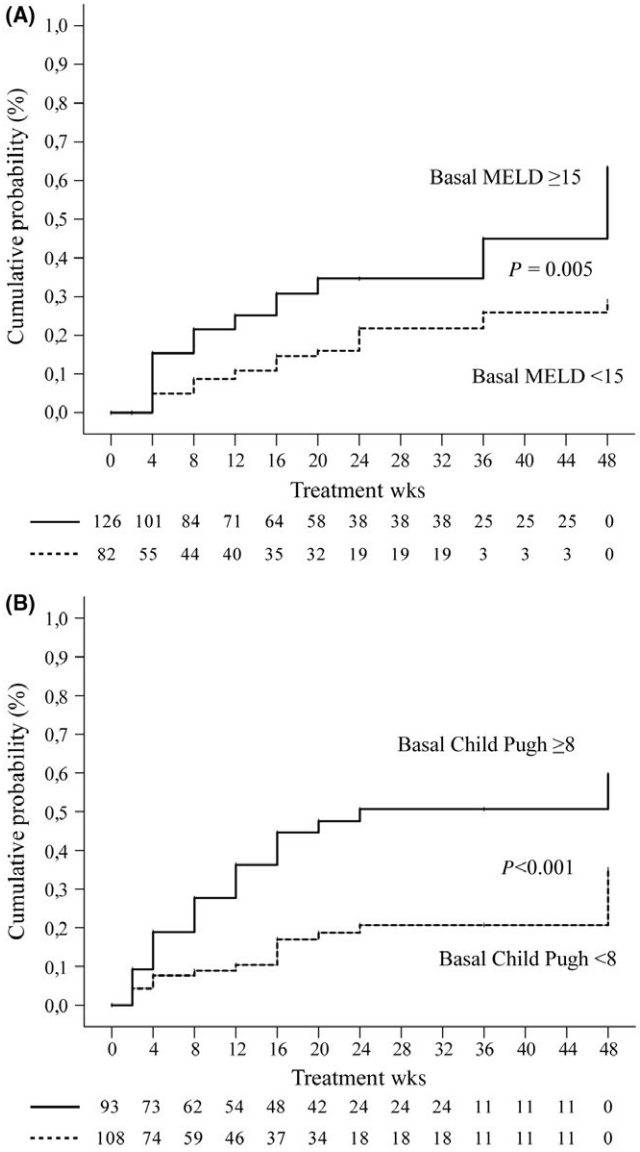

FIGURE 2 Cumulative probability of presenting a reduction in at least 3 points in the MELD score of patients with a basal score ≥15 or <15 (Panel A) and of at least 2 points in the Child-Pugh score of patients with a basal score ≥B8 or <B8 (Panel B)

3.5 | Effect of treatment on potential inactivation and delisting

To assess whether the clinical improvement may lead to inactivation and delisting of patients, we analyzed the clinical outcome of the 90 patients with basal MELD ≥15 and/or Child-Pugh ≥8 without HCC,

thus with a clear indication to OLT based on clinical liver decompensation (Figure 3A). We also decided to consider patients as potential candidates for inactivation and delisting when they reached a condition defined by Child-Pugh class A invariably associated to MELD score <15.

During the entire period of observation of 60 weeks, 36 patients were transplanted and 2 died for complications of liver disease. We also excluded five patients with a follow-up shorter than 24 weeks. Of the remaining 47 patients (median follow-up: 48 weeks [min/max: 24-60]), 15 became Child-Pugh class A associated to a MELD score <15 at the last available follow-up. Thus, 17.4% of patients presented clinical scores suitable for inactivation and then delisting (Figure 3B). Figure 3C shows changes of the MELD and Child-Pugh scores observed in these 15 patients from baseline to the last visit available (median follow-up: 56 weeks [min/max: 24-60]). Interestingly, the pre-treatment highest MELD was 22 and Child-Pugh was C10.

To identify predictors of inactivation, we compared at the univariate analysis both static factors (demographic, virological and clinical characteristics at baseline) and dynamic factors (improvement of MELD and Child-Pugh scores and of their individual components after 4 weeks of therapy) between the 15 patients who became Child-Pugh class A with MELD <15 and the 71 patients who did not. Among the static factors, predictors of inactivation were baseline lower Child-Pugh score and absence of HE, while the Delta MELD score, Delta albumin, Delta bilirubin and Delta INR were associated to potential inactivation among the dynamic parameters (Table S1). Finally, the cumulative probability to become candidates for inactivation increases progressively with the extent of MELD score improvement, reaching a level of about 65% in those patients who improved their MELD of at least 2 points after 4 weeks of therapy. Furthermore, a condition suitable for inactivation is reached faster in patients presenting a greater week 0-4 Delta MELD (Fig. S3).

3.6 | Tolerability of treatment

No serious drug reactions were associated to SOF treatment. As expected, the major side-effect related to R was anaemia, which required dose reduction in about 30% of cases, erythropoietin administration in 18% of cases, and blood transfusions in 11% of cases. Antiviral treatment was discontinued due to anaemia only in six patients.

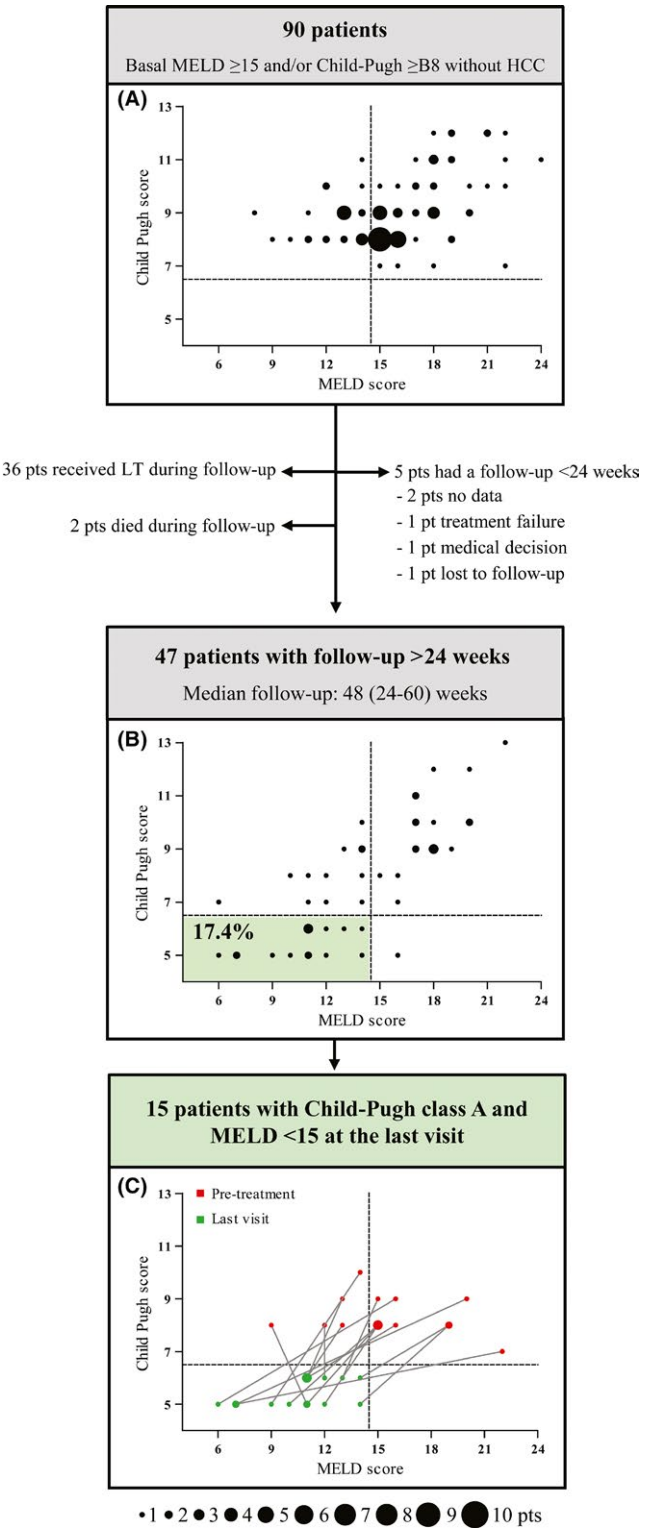

FIGURE 3 Clinical improvement suitable for inactivation and delisting in patients on liver transplant waiting-list without HCC and MELD ≥15 and/or Child-Pugh ≥ B8. Panel A, distribution of MELD and Child-Pugh score before treatment initiation. Panel B, distribution of MELD and Child-Pugh at the last available visit in the 47 patients with at least 24 wk of follow-up. Panel C, changes from baseline to the last visit available in MELD and Child-Pugh scores of the 15 patients reaching a condition suitable for inactivation and delisting (Child-Pugh class A with MELD score <15). HCC, hepatocellular carcinoma; LT, liver transplantation

A significant correlation was found between the starting dose of R and the eGFR (Spearman rho coefficient 0.199, P = .005). Finally, side-effects related to R were more frequently observed in patients with a lower basal eGFR although the difference did not reach the statistical significance (Fig. S4).

4 | DISCUSSION

We have here reported a multicentre, real-life experience in 224 pre-transplant patients with or without HCC who have received priority access to SOF through a compassionate use national program. Although SOF/R is now considered a sub-optimal therapy since the new DAA combinations achieve much higher SVR rates and require a shorter course of therapy,[1-4] our proof-of-concept study provides some new highlights on the effects of viral eradication in LT candidates, a setting where data are still limited.

The first piece of information regards the impact of pre-LT treatment on the prevention of the almost universal graft reinfection. Curry et al[10] showed that antiviral treatment can effectively prevent HCV recurrence only if the patients have undetectable HCV-RNA for at least 30 days before LT. However, these data were confined to Child A patients with HCC. Two novel data emerge from the analysis of our patients who were transplanted and achieved an overall SVR12 in 87% of cases: first, antiviral treatment can avoid graft reinfection also in Child B and C patients; second, very high SVR can be obtained even in patients negative at transplantation for less than 30 days or still positive while on treatment by continuing antiviral therapy after LT (bridging therapy). Taking into consideration the landmark study by Curry et al[10] and the report of an individual case of bridging therapy available at that time,[13] most of our clinicians decided to perform bridging therapy in the majority of patients who were still positive or HCV-RNA negative for less than 30 days at LT, achieving an SVR12 of 94% in those who survived after surgery, which was much higher than the 67% observed in those who stopped therapy at the time of LT. A detailed description of the clinical course of our patients receiving bridging therapy has been recently published.[14]

It can be argued that in patients with a very short expected waiting time antiviral therapy can be differed and started after hepatitis recurrence since the SVR rates in transplant patients are higher than those observed in decompensated cirrhosis.[1,2,15] However, it can also occur that patients in stable conditions, for whom the full course of therapy is expected to be completed, develop an acute complication that leads to a rapid clinical deterioration and to high priority for organ allocation. For the few patients on antiviral treatment who are still viraemic at the time of LT or who did not achieve viral clearance for at least 30 days, the recommendations of the European Liver and Intestine Transplant Association (ELITA), based on the expert opinion, state that bridging therapy can be considered.[16] Our study provides real data in favour of the efficacy and safety of this approach.

The second contribution of the present study is related to the impact of antiviral treatment on liver function and inactivation/delisting for waitlisted patients. Consistently with previous studies,[1-4] 40%-50% of our patients presented, after 24 weeks of therapy, an improvement of their MELD and Child-Pugh scores, which was clearly more evident in patients with a more severe disease, as defined by MELD ≥15 or Child-Pugh ≥B8.

Based on the median decrease of MELD and Child-Pugh scores in this latter subgroup of patients, we have also calculated the probability of having an improvement of at least 3 points of MELD and 2 points of Child-Pugh during the entire length of the study. Three interesting results emerged from this analysis: first, the probability was significantly higher in patients with a more advanced disease; second, about half of patients present a decrease of their scores of such an extent which may be of clinical relevance; and third, the improvement becomes manifest already few weeks after the initiation of therapy in some patients and occurs within 24 weeks in most of them.

If obtaining a clinical improvement or even blocking the progression of the disease obviously represents a goal of therapy in all patients with decompensated cirrhosis who do not have indication for LT, this may be not the case of waitlisted patients as the MELD improvement can also reduce the priority for LT in the centres where organ allocation is based on disease severity (the so called "MELD purgatory"). Thus, in this specific setting, a critical issue appears to determine which patients can be inactivated and then delisted as a result of viral eradication.

Belli et al[8] have shown that, in patients with HCV-related cirrhosis treated with DAAs, 27.6% of patients have been effectively inactivated and 10.3% delisted after 48 weeks, even if these results could have been influenced by the behaviour and policies of the different transplant centres. In our study, we do not have information regarding the real inactivation and de-listing rate. Thus, to investigate the effect of antiviral treatment on these critical outcomes, we first identified the cohort of 90 patients for whom the indication for LT was clearly justified by the severity of the disease (MELD ≥15 and/or Child-Pugh ≥B8) and not by the presence of HCC or by other MELD exceptions. Then, we arbitrary defined a condition that can be reasonably associated to inactivation and de-listing in the clinical practice: Child-Pugh A invariably associated to MELD <15. During follow-up, 15 (17.6%) patients reached this condition after a median length of treatment equal to 36 weeks, which was consistent with the rates of inactivation reported by Belli et al (15.5% at 24 weeks and 27.6% at 48 weeks).[8] It is important to note that none of our 15 patients had a basal MELD >22 and a Child-Pugh >C10.

Beside a baseline lower Child-Pugh score and less HE prevalence, patients who reached the condition suitable for inactivation had a significantly greater improvement of MELD scores and its components as well as of serum albumin after 4 weeks of therapy compared to those who did not. As a result, the delta MELD between 0 and 4 weeks was found able to stratify patients for achieving a condition of potential inactivation with a probability after 48 weeks of about 20% if MELD after 4 weeks increased, 50% if MELD remained stable or decreased 1 point, and 65% if decreased of at least 2 points. Taken together, these data suggest that non-HCC patients even with a quite advance liver disease still carry a considerable possibility to avoid LT for clinical improvement and a decrease of the MELD score within 4 weeks of treatment may help to identify patients with higher chances.

In conclusion, the Italian SOF compassionate use program showed that a pretransplant therapeutic approach can prevent graft reinfection in almost 90% of the recipients provided that bridging therapy is performed in those patients still viraemic or negative for less than 4 weeks

at transplantation. Furthermore, viral eradication is associated to an improvement of liver function in more than half of the cases, which can reach a condition of inactivation and then de-listing in almost 20% of non-HCC patients including some with a severely compromised liver function.

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CONFLICT OF INTEREST

Silvia Martini (advisory board for Gilead Sciences); Paolo Caraceni (speaking bureau for Bristol-Meyer-Squibb and Gilead Sciences), Stefano Fagiuoli (speaking bureau for Gilead Sciences, Merck-Sharp & Dome, Abbvie, Janssen, Bristol-Meyer-Squibb, Novartis, Bayer, Italchimici); Paola Carrai (advisory board for Gilead Sciences and Jannsen); Francesca Donato (speaking bureau for Merck-Sharp & Dome, Abbvie, Bristol-Meyer-Squibb); Maria Rendina (speaking bureau for Biotest, Kedrion, Grifols, Gilead Sciences, Abbvie, Bristol-Meyer-Squibb, Consultant for Biotest, Kedrion, Grifols, Gilead Sciences, Abbvie). All other authors have no conflicts of interest to declare.

DISCLOSURE

The views expressed in this work are personal and may not be understood or quoted as being made on behalf of or reflecting the position of AIFA, EMA or of one of their committees or working parties.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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APPENDIX

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