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ORIGINAL ARTICLE

Antiviral activity and safety profile of silibinin in HCV patients with advanced fibrosis after liver transplantation: a randomized clinical trial

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Summary

Response to interferon-based therapies in HCV recurrence after liver transplantation (LT) is unsatisfactory, and major safety issues aroused in preliminary experience with boceprevir and telaprevir. As transplant community identified HCV viral clearance as a critical matter, efficacious and safe anti-HCV therapies are awaited. The aim of this study was to assess efficacy and safety of intravenous silibinin monotherapy in patients with established HCV recurrence after LT, nonresponders to pegylated interferon and ribavirin. This is a single center, prospective, randomized, parallel-group, double-blind, placebo-controlled, phase 2 trial including 20 patients randomly assigned (3:1) to receive daily 20 mg/kg of intravenous silibinin or saline as placebo, for 14 consecutive days. On day 14 of treatment, viral load decreased by 2.30 $\pm$ 1.32 in silibinin group versus no change in the placebo group ($P = 0.0002$). Sixteen days after the end of the treatment, viral load mean values were similar to baseline. Treatment resulted well tolerated apart from a transient and reversible increase in bilirubin. Neither changes in immunosuppressant through levels nor dosage adjustments were necessary. Silibinin monotherapy has a significant antiviral activity in patients with established HCV recurrence on the graft not responding to standard therapy and confirms safety and tolerability without interaction with immunosuppressive drugs (ClinicalTrials.gov number: NCT01518933).

Introduction

End-stage liver disease related to HCV infection is the most common indication for liver transplantation (LT) both in Europe and in USA. The results of LT for this indication are negatively affected by the high rate of disease recurrence [1], thus leading to a general acceptance that HCV is a severe drawback in liver transplant programs [2]. The suppression of HCV replication is regarded as the most relevant modifier of the natural history of HCV recurrent disease after LT [3–7].

At present, a combined regimen with pegylated interferon and ribavirin leads to sustained virological response (SVR) in approximately 30% of transplanted patients, which is significantly lower than in immunocompetent subjects. The main problem lies in the high rate of side effects and poor applicability: Significant proportions of patients are not exposed to appropriate therapy and/or

remains untreated due to comorbid conditions [8]. Moreover, transplanted patients are exposed to immunological risks related to interactions with the immune system (rejection and *de novo* autoimmune hepatitis) [9–11].

Given the importance of viral clearance in the post-transplant setting, new anti-HCV therapies are anxiously awaited [12,13].

Triple therapy with telaprevir and boceprevir represents a new area in the treatment for HCV infection. However, important issues aroused about their efficacy and safety in the transplant setting. While limited efficacy had been reported in preliminary experiences, important safety concerns had been highlighted [14–16]. The first limitations had been the interaction with immunosuppressants, which requires calcineurin inhibitors (CNIs) dose to be empirically reduced during protease inhibitors (PIs) exposure and consequently increased when PIs are discontinued. Therefore, an intensified monitoring of CNIs levels is required. Moreover, these regimens are associated with important toxicities mainly represented by severe anemia but also pancytopenia and severe infections accounting for cases of death [15–17].

Besides several direct-acting antivirals (DAA's) in phase 3 development, simeprevir and sofosbuvir recently reached marketplace. The promising efficacy results demonstrated in both treatment-naïve and experienced nontransplanted patients need confirmations in large, prospective, multicenter studies with special carefulness to the safety profile in the population of the multidrugs exposed transplant patients.

Silibinin, a 1:1 mixture of silybin A and silybin B, has been recently showed to have, besides its wide range of antioxidant, immunomodulatory, antiproliferative, and antifibrotic activities, also the capacity to inhibit HCV infection in cell culture [18–20]. The first clinical application showed a potent dose-dependent antiviral activity of intravenous silibinin (iv-SIL) in patients with HCV chronic hepatitis nonresponders to antiviral therapy [21]. Moreover, a very favorable safety profile with the only side effects represented by heat sensation and mild sweating during first infusion was reported. Therefore, the natural setting of application has been considered the liver transplant one [22,23]. And in fact, two recent studies explored its safety and efficacy in a prospective way in the peritransplant setting and confirmed the potent antiviral activity of iv-SIL in the transplant patients [24,25].

However, aside the fascinating pre-emptive approach, there is an urgent need of cure for the high number of patients with an already established HCV recurrent disease to improve the natural and accelerated progression of the disease toward severe fibrosis, decompensation, and graft and/or patient failure. These patients had in most cases failed standard therapy and/or were unsuitable for antiviral therapy for comorbidities.

Concerning this as a background, we designed this proof-of-concept prospectively randomized, placebo-controlled study, with the primary aim to investigate antiviral activity as well as safety of iv-SIL in patients with established HCV recurrence after LT, a setting never explored before.

Patients and methods

Study design and patients

This study was a prospective, randomized, parallel-group, double-blind, placebo-controlled, phase 2 trial. Patients enrolled in this study were stable (≥1 year) liver transplanted subjects with HCV recurrence, not responding to previous treatment with peginterferon-/ribavirin-based standard of care, who were assessed for eligibility in our Outpatients Liver Transplant Unit within the Gastroenterology Unit of the University Hospital of Bari between June and September 2011.

Eligible patients were males or females aged ≥18 and ≤70 with a ≥ 1 year post-transplant follow-up and diagnosed as having HCV recurrent hepatitis (biochemical data, positive viremia, and presence of liver fibrosis). Female patients of childbearing potential must agree on using a contraceptive method and must have a negative pregnancy test at screening. Exclusion criteria included active hepatocellular carcinoma or other neoplasia, active biliary tract anomalies, recent history of rejection, active interferon treatment, creatinine clearance <50 ml/min, history of substances abuse, or other factors limiting their ability to cooperate during the study.

This study was reviewed and approved from Ethics Committee of the Ospedale Policlinico—Università degli Studi di Bari, Italy, and patients gave their written informed consent to be part of the trial. This study is registered with ClinicalTrials.gov, number NCT01518933.

Randomization and masking

Eligible patients were randomly assigned (3:1) to receive daily infusion of iv-SIL (each delivering 20 mg/kg/day of silibinin) or saline as placebo for a maximum of 14 consecutive days.

Patients were randomly assigned to treatment groups by an interactive voice response system via a computer-generated random allocation sequence. Investigators and patients were blinded to treatment assignment throughout the study.

Procedures

From November 2011 to February 2012, 21 patients were enrolled. Twenty patients were randomized to receive

iv-SIL ($n = 15$) or placebo ($n = 5$) and received at least 80% of the assigned study drug. One patient failed to enter the randomization for the occurrence of renal impairment at screening visit. The 20 patients constitute the prospectively defined intention-to-treat population for the efficacy analysis as well as the safety population.

Methods

HCV-RNA levels were measured using the Abbott RealTime HCV assay (Abbott Molecular Laboratories. Abbott Park, Illinois, USA; dynamic range of quantification: 12–100 000 000 IU/ml). Immunosuppressive drug serum levels (cyclosporine, tacrolimus, everolimus, and rapamycin) had been analyzed in an institutional central laboratory using standardized commercial kits (Siemens Healthcare Diagnostics Dimension CSA, Siemens Healthcare Diagnostics Inc., Deerfield, Illinois, USA; EMIT 2000 Tacrolimus Assay, Siemens Healthcare Diagnostics Inc., Deerfield, Illinois, USA; Thermo Scientific Innofluor Certican, Thermo Fisher Scientific Clinical Diagnostics, Indianapolis, Indiana, USA; IMx Sirolimus Assay, Abbott Diagnostics Division. Abbott Park, Illinois, USA).

Study schedule and chronology

The study encompassed 5 clinical visits for efficacy/safety evaluations over a period of 30 days: a screening visit, 3 visits during treatment phase, and a follow-up visit. Flow of clinical evaluation and treatment schedule are detailed in Fig. 1. At each visit, adverse events had been monitored, recorded, and reported on the e-CRF, as well as the intake of concomitant medications.

Study aims and endpoints

The efficacy outcome measure was the evaluation of antiviral effect of iv-SIL, as the proportion of patients with serum HCV-RNA decline ≥2 logs versus baseline at day 7 and day 14 after treatment start as well as after 16 days off treatment follow-up. Safety endpoints included adverse events, serious adverse events, grade 3 or 4 laboratory abnormalities, and deaths. We also recorded plasma levels of immunosuppressive drugs as well as changes in dosage. Patients underwent physical examinations and clinical laboratory tests at screening, days 1, 7, 14, and 30. We did electrocardiography at screening and at treatment end.

Statistical analysis

Statistical analyses on efficacy assessments were carried out on the intention-to-treat population, that is, on all randomized patients treated for at least 11 days.

Standard procedures depending on the underlying distribution were used to summarize all recorded and calculated variables in tables and listings. Descriptive statistics on ordinal and categorical variables were reported as numbers and percentages, whereas mean and standard deviation (and standard error) together with range and valid cases were used for continuous variables.

To provide a better estimate of the treatment effect during the study period, an ANCOVA for repeated measures was performed on HCV-RNA values. The baseline value was chosen as covariate in the model to cope with the individual variability. HCV-RNA values collected or estimated until month 3 were log10-transformed and considered as dependent variable of the model, whereas treatment, visit, and the interaction treatment visit were considered as independent variables. Log_{10}-transformed HCV-RNA levels at baseline were considered as covariate. The Fisher's exact test was applied to compare the proportions of patients with a partial virological response at the end of treatment between treatment groups. Safety analyses were carried out on safety population.

Results

The key clinical characteristics and virological features of both iv-SIL and placebo patients are summarized in Table 1. Baseline characteristics of patients were similar

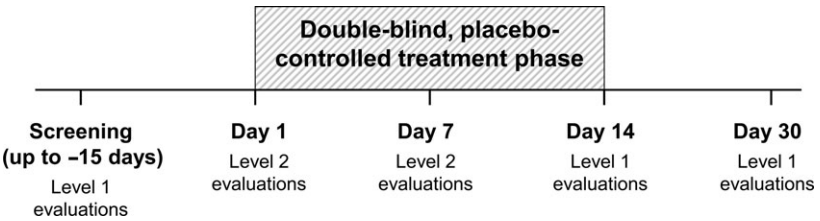

Figure 1 iv-SIL administration schedule and evaluations flowchart. The treatment phase consisted of 14 consecutive days. Each patient received daily infusion of iv-SIL (each delivering 20 mg/kg/day of silibinin) or saline as placebo. Levels of evaluations: screening, day 14 and day 30 visits consisted in vital signs recording, ECG, biochemistry, HCV-RNA, immunomodulators levels, and pregnancy test (Level 1 evaluations). Day 1 and day 7 visits consisted in vital signs recording, biochemistry, HCV-RNA, and immunomodulators levels (Level 2 evaluations).

Table 1. Baseline characteristics of the entire cohort ($N = 20$).

	iv-SIL $N = 15$	Placebo $N = 5$
Age (yrs, mean ± SD)	59.5 ± 6.8	58.2 ± 11.0
Sex, male [%, (*n*)]	87% (13)	100% (5)
HCV genotype (1/2/3; %)	80/7/13	100/0/0
IL28B genotype (CC/CT/TT;%)	26/27/47	60/20/20
HCV-RNA (log 10 IU/ml; mean ± sd)	6.34 ± 0.6	6.32 ± 0.5
FK/CyA/mTor* (*n*)	8/3/3	3/1/1
ALT (U/l; median)	94	62
GGT (U/l; median)	109	87
Total bilirubin (mg/dl; median)	0.85	0.78
Scheuer fibrosis score†—*n* (%)		
F1	2 (13)	1 (20)
F2-3	5 (33)	3 (60)
F4	4 (27)	0 (0)
Clinical cirrhosis	4 (27)	1 (20)
Child A/B/C—n	0/1/3	0/1/0
Meld, median	13	9
Post-LT follow-up (years; median)‡	8	2

*One patient was on mycophenolate monotherapy.
†Biopsy performed within 1 year before enrollment.
‡Years elapsed between the LT and the first study drug infusion.

across the treatment groups. Most patients were male (90%) and were infected with HCV genotype 1 (85%). The mean age was 59.2 ± 7.7 years, and the mean baseline HCV-RNA concentration was 6.33 ± 0.54 $\log_{10}$ IU/ml (range 5.29–7.38 IU/ml). Mean post-transplant follow-up was 89 ± 72 months (range 13–195). Fifty-five percent of patients had been already treated with interferon before transplant. Liver biopsy, performed within 1 year before enrollment, was available in 15 patients, and the distribution of patients according to fibrosis stage was as follows: F1 in 3, F2-3 in 8, and F4 in 4 patients. Five patients did not have a biopsy as they had clinical diagnosis of cirrhosis.

As far as immunosuppression, 11 patients (55%) were on tacrolimus; 4 pts were on cyclosporine-based therapy and 4 were on m-Tor inhibitors (3 sirolimus and 1 everolimus); one patient was on mycophenolate monotherapy.

Virological response

HCV-RNA kinetics differed significantly between iv-SIL and placebo-treated patients. While in patients treated with placebo, the viral load (VL) remained fairly constant during the 14-day treatment period and thereafter, in patients treated with iv-SIL, VL declined during the treatment period (Fig. 2). Starting from a mean baseline VL of 6.34 ± 0.6 and 6.32 ± 0.5 in iv-SIL and placebo group, respectively, HCV-RNA was lower in almost all patients of the iv-SIL group compared with placebo at day 7 after the start of treatment (4.75 ± 1.09 in iv-SIL treatment group and 6.22 ± 0.49 in placebo treatment group, ($P = 0.0057$, ANOVA); VL then continued to decline further up to the end of 14-day treatment period (4.04 ± 1.23 in iv-SIL treatment group and 6.38 ± 0.45 in placebo treatment group, $P = 0.0002$, ANOVA). Mean change from baseline in HCV-RNA at day 7 and day 14 was −1.59 $\log_{10}$ (range −3.45 ± 1.26) and −2.30 $\log_{10}$ IU/ml (range −4.35 ± 0.46), respectively. Decline in viral load in the two patients infected by genotype 3 in our cohort was 1.30 and 0.72 $\log_{10}$ IU/ml, respectively. The only patient with genotype 2 exhibit a reduction in RNA comparable to entire cohort (−2.28 $\log_{10}$ IU/ml).

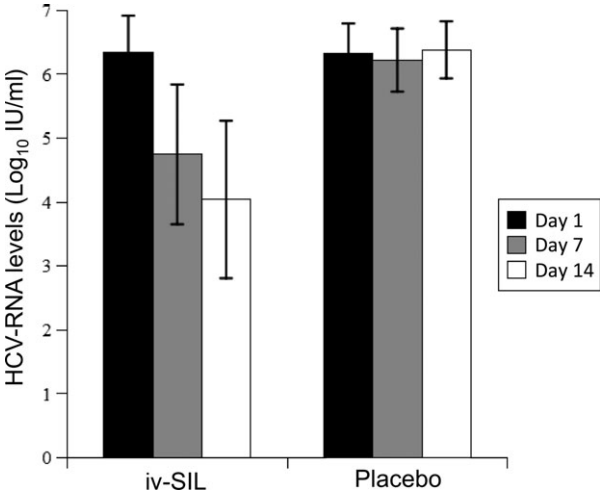

Figure 2 Virological response during treatment in patients treated with iv-SIL and in those treated with placebo (days 1, 7, and 14). Column represents mean, and error bars indicate standard deviation.

At day 7 and day 14 of treatment, VL was ≥2 $\log_{10}$ lower than at baseline in 40% (6/15) and 60% (9/15) in patients receiving iv-SIL versus no patients in the placebo group (Fisher's exact test, $P = 0.03$).

Sixteen days after the end of the treatment, VL mean values were similar to baseline (6.11 ± 0.72 in iv-SIL group and 6.23 ± 0.40 in placebo group).

Biochemical response

Serum ALT levels at baseline were comparable between the two groups, 94 (32–406) vs. 78 (49–132) in the iv-SIL and placebo group, respectively.

The time course of ALT (Fig. 3) clearly shows distinct trends in the two groups. Median ALT values in patients randomized to iv-SIL decreased during the treatment

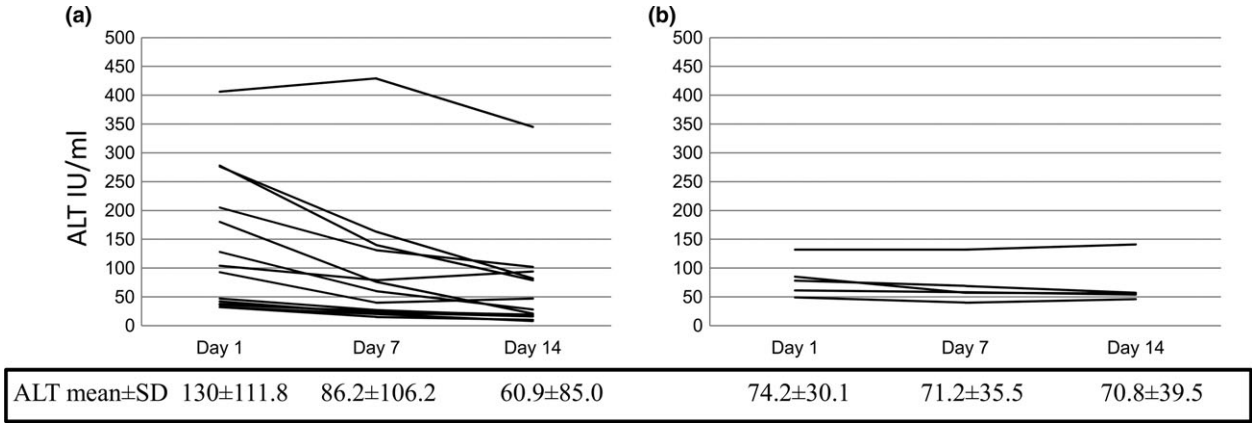

Figure 3 ALT time course during treatment in iv-SIL (a) and placebo group (b). The time course of ALT concentrations clearly shows distinct trends in the two groups. Mean ALT values in iv-SIL group decreased during the treatment period and were 60.9 ± 85.0 U/l (i.e., below the ULN) at EOT, where the median was 26.0 U/l. In placebo group, mean ALT remained stable during treatment period.

period and were 26 (8–345) (i.e., below the ULN) at day 14. In patients randomized to placebo, mean ALT remained. There were no changes in other liver function tests during treatment with iv-SIL.

Safety

Safety was analyzed in all 20 randomized patients who received at least one dose of the study medication. Most of adverse events were mild or moderate (78%) and/or related to study drug (67%).

As far as the serious adverse events are concerned, a total of 2 serious adverse events were reported during the study, both (anastomotic biliary stenosis and fever of unknown origin) occurred in one patient who received iv-SIL and were considered not related to the study medication.

The observed adverse events are reported in Table 2. There was a numerical trend versus a higher occurrence rate in iv-SIL than in placebo-treated patients.

A special mention is required for bilirubin trend during treatment. In fact, while at baseline, median total bilirubin values were comparable between the two groups ($P = 0.49$), a transient and reversible increase in bilirubin was observed in 93% of patients who received iv- SIL—from 0.85 (0.61–8.3) to 1.74 (0.96–23.96) mg/dl. No major changes were observed in patients receiving placebo. Two patients treated with iv-SIL were judged as having a clinically significant (not serious) increase in bilirubin (total bilirubin maximum value 13.55 mg/dl and 6.31 mg/dl, respectively). Of note, in another patient on iv-SIL, total bilirubin rose to a maximum value on treatment of 23.96 mg/dl, but this increase was considered a sign of the biliary anastomotic stenosis and biliary gallstones, and the patient was suffering from as a sequelae of his LT. Sixteen days after the end of treatment, bilirubin values returned comparable to baseline in almost all patients (Fig. 4).

Table 2. Adverse events reported in iv-SIL and Placebo group during the treatment period.

	iv-SIL *n* (%)	Placebo *n* (%)
Feeling hot	14 (93.3%)	0 (0.0%)
Diarrhea	10 (66. 7%)	0 (0.0%)
Headache	5 (33.3%)	1 (20.0%)
Vomiting	5 (33.3%)	0 (0.0%)
Asthenia	3 (20.0%)	2 (40.0%)
Feeling cold	3 (20.0%)	1 (20.0%)
Abdominal pain	3 (20.0%)	0 (0.0%)
Pruritus	2 (13.3%)	1 (20.0%)
Ascites	2 (13.3%)	0 (0.0%)
Hyperbilirubinemia	2 (13.3%)	0 (0.0%)
Nausea	2 (13.3%)	0 (0.0%)
Pyrexia	2 (13.3%)	0 (0.0%)
Erythema	1 (6.7%)	1 (20.0%)
Anemia	1 (6.7%)	0 (0.0%)
Biliary anastomosis complication	1 (6.7%)	0 (0.0%)
Cholelithiasis	1 (6.7%)	0 (0.0%)
Depression	0 (0.0%)	1 (20.0%)
Dyspnea	0 (0.0%)	1 (20.0%)
Hyperhidrosis	0 (0.0%)	1 (20.0%)
Hypertension	0 (0.0%)	1 (20.0%)
Hypotension	0 (0.0%)	1 (20.0%)

Immunosuppression

Most of the patients were on tacrolimus-based therapy (55%). Apart from the patient who suffered from severe cholestasis and who experienced rise in tacrolimus blood levels, no other patient required modifications of the

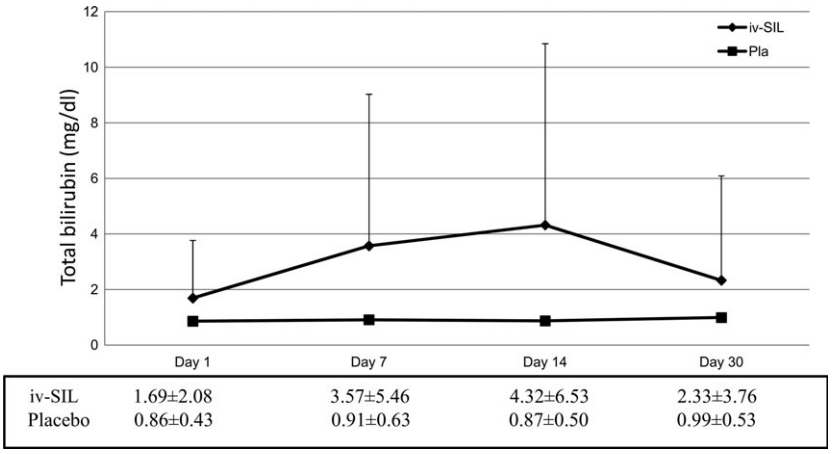

Figure 4 Time course of total bilirubin during the study in iv-SIL group (n = 15) and Placebo group (n = 5). A transient and reversible increase in bilirubin was observed in almost all patients who received iv-SIL (on average of about 2.5 xULN) while no major changes were observed in patients receiving placebo. At day 16 after the end of treatment bilirubin value returned similar to day 1 value in almost all patients.

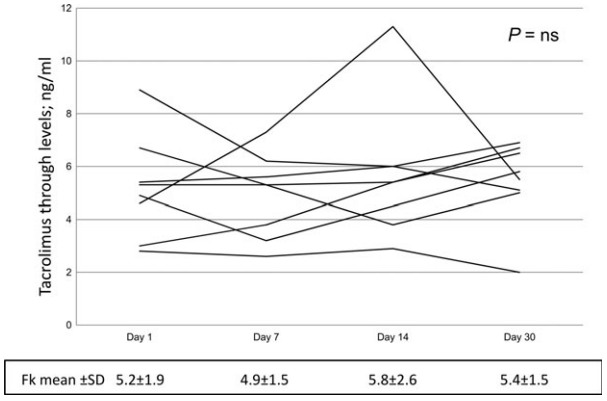

Figure 5 Tacrolimus through levels in 9 iv-SIL patients. The serum level concentrations of tacrolimus remained stable throughout the study. Only one patient who suffered from anastomotic stricture and severe cholestasis experienced rises in blood levels.

dosages of the immunosuppressants to maintain the target ranges. And in fact, as shown in Fig. 5, the mean ± SD through level concentrations of tacrolimus did not change throughout the study as well as those of cyclosporine (data not shown). Interestingly, no interaction was reported also with -Tor inhibitors (neither sirolimus nor everolimus).

Discussion

Administration of iv-SIL (20 mg/kg/d) monotherapy for 14 days, in patients with established HCV recurrence on the graft after LT not responding to standard therapy with pegylated interferon and ribavirin, resulted in a significant decrease in viral load with a mean decline in HCV-RNA of -2.30 $\log_{10}$ IU/ml.

Our findings confirm, in a different setting of patients, the recent data coming from two studies from Spain which explored the ability of iv-SIL to prevent HCV recurrence on the graft after transplant.

In the first study, iv-SIL was administered during the anhepatic phase and continued up for 21 days after transplant [24]. Marino *et al.*, treated cirrhotic patients for up to 21 consecutive days pre-LT and then for 7 consecutive days post-LT [25]. Even if the approaches proposed failed to induce the eradication of the virus, nevertheless, a potent antiviral activity of iv-SIL monotherapy when applied in the perioperative period was reported.

The pre-emptive strategy is actually the most intriguing one, and further studies are ongoing to determine the optimal duration of iv-SIL. However, the most frequent clinical situation now is represented by patients already transplanted in recent years and with an established and progressing disease. Most of these patients resembled the "difficult to treat" population in respect to treatment. And in fact, a significant proportion of patients in the Italian RECOLT HCV transplant cohorts had unfavorable treatment characteristics: 69% of 464 patients were genotype 1, 75% were male, diabetes was present in half of them, 84% had high viral load, and 79% had Ishak fibrosis stage >4 [7,26].

Therefore, and differently from the results showed in the Spanish patients, our study applies to a setting of patients who could be considered the worst category of patients in the HCV virological scenario. In fact, most of them had more than one negative predictive factors for viral response: severe fibrosis, genotype 1 in most cases, high viral load, already treated before transplant, and retreated after transplant. The "nonresponders" category of transplant patients make difficult to wait for good results with the use of boceprevir or telaprevir. Registration trials with

PIs in immunocompetent patients provided evidence for the existence of a relationship between SVR rates and the pattern of previous response to standard therapy, the non-responders patients being the most penalized subjects with only 32% rates of SVR when treated with telaprevir-based regimes [27,28]. And in fact, the results of triple therapy in transplanted patients deserve in-depth reflection in terms of efficacy and safety [15–17, 29]. Besides the limited efficacy and the high rate of adverse events, additional fears with PIs use in transplant setting relate to the clinical implications of the emergence of resistant variants, of the intriguing pill burden, and of the required association with interferon and ribavirin to be effective. These facts wiped away the idea we had to routinely apply this therapy to the transplant population and prompt efforts to alternative strategies.

Interferon-free regimens with second-generation DAA's are showing promising efficacy results in phase 3 studies in nontransplant setting. Data regarding safety and efficacy of the new DAA's in liver transplant recipients are lacking except for sofosbuvir which, combined with ascending dose of Ribavirin for 24 weeks, was associated with a 77% week 4 post-treatment response rate and excellent tolerability in a recent pilot study [30]. The relapse rate seen in this study recalls a similar observation reported in a naïve immunocompetent population with unfavorable treatment characteristics treated with sofosbuvir and ribavirin. Male sex, advanced fibrosis, and high viral load at baseline resulted significantly associated with relapse. Noteworthy, the odds of relapse were 5.74 for patients having baseline HCV-RNA >800 000 IU/ml [31] And if the addiction of IFN would be necessary to achieve HCV eradication in this very difficult categories of patients, the costs are expected to be very high not only for the drugs but also for the management of the PEG/RBV toxicity, which is the Achilles heel in liver transplant patients. In view of the effective ≥2 log decline in viral load already at day 14 following monotherapy in a cohort of difficult to treat patients as our own, it could be speculated that silibinin could be used in a lead in phase, prior to antivirals initiation, to take advantage of a pre-treatment low viral load. Moreover, the antioxidant, anti-inflammatory and antifibrotic effects of silibinin may reduce liver damage of non-viral origin such as the drug-induced liver injury which, in transplant patients, is reported to be 100-fold higher in respect to general population [32]. Another finding in our study is that no patient experienced breakthrough thus suggesting absence of resistance. The low number of cases in our study does not support a conclusive evidence on the resistance profile of silibinin. The mechanisms by which SIL inhibits HCV *in vivo* are currently under debate. Different mechanisms interfering with RNA replication had been described. Recently, Esser-Nobis isolated a mutation in the HCV non-structural 4B (NS4B) protein conferring partial resistance to SIL treatment *in vitro* and *in vivo* [33]). If this finding led authors to conclude that NS4B is a candidate target for inhibition of viral RNA replication by SIL, the other way around, strengthened the possibility that SIL, due to its mode of action and unique resistance profile, represents a promising candidate of future sequential or combined therapies. We cannot confirm in our study the finding by Aghemo of failure of iv-SIL to inhibit HCV-RNA replication in an HCV genotype 2 patient [34]. Indeed, in the sole patient with HCV-2 in our study, iv-SIL exposure led to a decline in HCV-RNA from 6.54 to 4.26 $\log_{10}$ IU/ml (change vs. screening—2.28 $\log_{10}$ IU/ml) that is, at the same extent of HCV-1 patients. Instead, two patients, infected by genotype 3, showed a rather low decline in RNA (−1.30 and −0.72 $\log_{10}$ IU/ml). These data, taken together, suggest that SIL antiviral effect might not be genotype dependent.

A relevant finding of this study is the very low rate of adverse events and, notably, the absence of interactions with immunosuppressants. A stable through levels was observed for calcineurin inhibitors as well as for 3 patients on sirolimus and one on everolimus. And in fact, no change was necessary in the administered schedule of antirejection drugs thus adding to this approach manageability over safety.

The limitations of our study are sample size and the use of an intravenous route of administration, which could be inconvenient in clinical practice. Another limitation is represented by the occurrence of hyperbilirubinemia. The mechanism of this alteration, which is anyway transient and reversible, may be related to an inhibition on hepatocellular uptake and efflux transport systems for organic anions [35].

In conclusions, this proof-of-concept randomized, double-blind, placebo-controlled study indicates, for the first time, that intravenous silibinin has a proper antiviral activity and is well tolerated also in patients with established HCV recurrence on the graft thus encouraging the evaluation of iv-SIL in a combined/sequential therapy with other antiviral drugs.

Authorship

MR: designed and performed the study, analyzed the data and wrote the paper. MA, NB, LR: designed the study. AC, NMC, MZ, RSB: performed the study. GG: performed statistical analysis. SFR: performed the study and collected the data, wrote the paper. AL: designed and performed the study, analyzed the data and wrote the paper.

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