ORIGINAL ARTICLE

Efficacy and safety of daclatasvir-based antiviral therapy in hepatitis C virus recurrence after liver transplantation. Role of cirrhosis and genotype 3. A multicenter cohort study

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SUMMARY

Direct-acting antiviral agents (DAA) combining daclatasvir (DCV) have reported good outcomes in the recurrence of hepatitis C virus (HCV) infection after liver transplant (LT). However, its effect on the severe recurrence and the risk of death remains controversial. We evaluated the efficacy, predictors of survival, and safety of DAC-based regimens in a large real-world cohort. A total of 331 patients received DCV-based therapy. Duration of therapy and ribavirin use were at the investigator's discretion. The primary end point was sustained virological response (SVR) at week 12. A multivariate analysis of predictive factors of mortality was performed. Intention-to-treat (ITT) and per-protocol SVR were 93.05% and 96.9%. ITT-SVR was lower in cirrhosis ($n = 163$) (96.4% vs. 89.6% $P = 0.017$); the SVR in genotype 3 ($n = 91$) was similar, even in advanced fibrosis (96.7% vs. 88%, $P = 0.2$). Ten patients (3%) experienced virological failure. Therapy was stopped in 18 patients (5.44%), and ten died during treatment. A total of 22 patients (6.6%) died. Albumin (HR = 0.376; 95% CI 0.155–0.910) and baseline MELD (HR = 1.137; 95% CI: 1.061–1.218) were predictors of death. DCV-based DAA treatment is efficacious and safe in patients with HCV infection after LT. Baseline MELD score and serum albumin are predictors of survival irrespective of viral response.

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Key words
daclatasvir, efficacy and safety, Model for End-Stage Liver Disease, recurrence of HCV, survival prognostic model

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Introduction

End-stage liver disease due to infection by chronic hepatitis C virus (HCV) is a major problem worldwide. It is observed mainly in the context of liver transplant (LT), where the impact of recurrent graft infection clearly affects the natural history of the disease after transplantation. In fact, reinfection of the graft by HCV is almost universal and is usually associated with an accelerated course, thus severely affecting graft and patient survival [1]. Furthermore, viral clearance after LT is the most important independent factor associated with prognosis after LT in HCV-infected patients [2]. Second-generation direct-acting antiviral agents (DAAs) constitute a major advance for HCV-infected patients because of their antiviral potency and good tolerability. DAAs have expanded the applicability of therapy and have increased the likelihood of a viral response compared with previous IFN-based therapies [3]. When combined with other DAAs, the potent NS5A inhibitor daclatasvir (DCV) has shown a high rate of viral response with an excellent safety profile in several HCV-infected populations, including those with different genotypes and stages of liver disease [4]. The results obtained in pivotal clinical trials cannot be applied directly to real-world LT settings, where several conditions (e.g., immunosuppression, renal failure, severity of liver disease, and drug interactions) can affect the feasibility of treatment and outcome. Therefore, it is important to obtain more information on the efficacy and safety profile of DCV-based DAA regimens in LT patients in a real-world setting [5–9]. This aspect is particularly important in genotype 3 carriers, who have a poorer viral response after therapy, especially in advanced liver disease.

Previous studies of nontransplanted patients with advanced fibrosis have highlighted the impact of viral clearance on survival, even after successful eradication of HCV [10]. However, this issue has not been sufficiently addressed in LT patients with advanced liver disease after therapy with DAAs.

Therefore, we evaluated the efficacy and safety of DCV-based DAA regimens in patients with HCV recurrence after LT in a large Spanish multicenter real-world cohort, with emphasis on patients with cirrhosis and genotype 3 carriers. We also analyzed the predictors of survival in this context.

Patients and methods

Study design and description of therapy

We performed a multicenter retrospective observational study of prospectively collected data from a cohort of

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adult liver recipients (deceased donors, $n = 331$) from 23 Spanish LT units. All patients received antiviral treatment with DCV combined with other DAAs from February 8, 2014, to November 28, 2015.

Antiviral combinations (always including DCV) were prescribed at the discretion of investigators according to drug availability. The four regimens used were DCV-sofosbuvir (DCV-SOF) with and without ribavirin (RBV) and DAC-simeprevir (DCV-SMV) with and without ribavirin (RBV). Dosages were 150 mg qd for SMV, 400 mg qd for SOF, and 60 mg qd for DCV. RBV was administered at the investigator's discretion. The planned duration of treatment was 24 weeks in 243 patients (73.4%), although the investigators were allowed to shorten the treatment according to their clinical judgement. DCV was administered to 175 patients (52.8%) under the named patients program (compassionate use).

Clinical assessment and laboratory tests

End of treatment (EOT) response was defined as a negative HCV RNA value at the end of therapy; sustained virological response (SVR) at 12 weeks was defined as undetectable HCV RNA 12 weeks after EOT. Viral breakthrough during DCV-based therapy was defined as the presence of detectable serum HCV RNA in patients who had achieved undetectable HCV RNA while on treatment. Relapse was defined as detectable HCV RNA in patients who had achieved undetectable HCV RNA at EOT. HCV RNA levels were measured at each visit using a real-time polymerase chain reaction-based assay: COBAS AmpliPrep or COBAS TaqMan (Roche Molecular Systems, Pleasanton, CA, USA), with a lower limit of quantification of 15 IU/ml; or $m2000_{SP}$/$m2000_{RT}$ (Abbott Molecular, Des Plaines, IL, USA), with a lower limit of quantification of 12 IU/ml. HCV RNA was considered undetectable when it was below the lower limit of detection of local laboratories. HCV RNA was not evaluated centrally. A prespecified determination of resistance mutations was not performed.

Child–Turcotte–Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores were calculated at baseline (before starting therapy), EOT, and week 12 after EOT based on data provided by the local laboratories. The MELD score was also recorded at week 24 after EOT in patients with cirrhosis and a baseline MELD score ≥15 points. The severity of fibrosis at baseline was established by transient elastography or by liver biopsy. A clinical diagnosis of cirrhosis was also based on compatible clinical, biochemical, and imaging data. Cholestatic hepatitis was diagnosed by liver biopsy according to established criteria [11].

Safety assessment

Adverse event (AE)-related data were collected retrospectively using a prespecified questionnaire. AEs included anemia, viral or bacterial infections, hepatic decompensation, graft rejection, renal failure, death, or any other relevant clinical event according to the investigators' criteria.

Anemia was managed according to local criteria [reduction of the dose of ribavirin (RBV) and/or administration of erythropoietin].

Aims

The primary efficacy end point was SVR at 12 weeks after EOT. Secondary end points were survival, safety, and clinical impact on liver disease.

Statistical analysis

No sample size was predefined. Continuous variables are expressed as mean [SD] or median (range) as appropriate. Categorical variables are expressed as frequencies and percentages.

The main study end point was efficacy in terms of viral response. Therefore, SVR was assessed on an intention-to-treat (ITT) and per-protocol (PP) basis (see below).

Quantitative variables were compared using the *t*-test or Mann–Whitney test, as appropriate. The chi-square test was used to compare SVR rates between the populations.

Univariate and multivariate Cox models were developed (backward stepwise procedure) to find predictive factors of survival in patients with advanced fibrosis (F4 or liver-related clinical decompensation). *A priori*, we decided to include only baseline variables with a plausible association with the end point. The variables that reached significance in the univariate analysis ($P < 0.1$) were included in the multivariate analysis. To avoid overfitting and collinearity, the MELD score, rather than its individual components, was included in the model.

To simplify clinical interpretation of the final model, the variables independently associated with the end point were categorized according to the best Youden index. A simple risk score was then constructed using the selected cutoff values (see below). Kaplan–Meier survival curves for the different score values were plotted and compared using the log-rank method.

Written informed consent for treatment was obtained from each patient in the case of compassionate use. The protocol adhered to the Declaration of Helsinki and Spanish regulations on biomedical research and was approved by the local ethics committees.

Results

Main cohort characteristics

The study population comprised 331 liver recipients, that is, all the patients treated in the 23 adult LT units. The main characteristics of the patients are presented in Table 1. Most of the patients were male (263; 79.5%), with a median age of 56 years (35–82). Tacrolimus was used as the main immunosuppressive drug in most cases ($n = 222$; 67%). Genotype 1 was the predominant genotype ($n = 220$; 66.5%), while genotype 3 was present in 91 patients (27.5%). Eighteen patients (5.8%) were coinfected with HIV. Mean baseline HCV viral load was 6.37 [6.74] log10 IU/ml. Most patients ($n = 184$; 55.6%) did not respond to previous antiviral therapy administered after LT. Previous antiviral treatment is detailed in Table S1.

Most patients were experiencing a severe recurrence of hepatitis at the time of antiviral therapy: 163 (49.2%) had advanced fibrosis (F4 by transient elastography or by liver biopsy) or clinically evident cirrhosis. Interestingly, a large number of patients in this group (68 out of 163; 41.72%) had previous or current decompensation (ascites, pleural effusion, or encephalopathy). At baseline, 56 patients (34.36%) were CTP class B and 11 (6.7%) class C.

As expected, patients with liver decompensation had a higher mean MELD score [14.03 (5.6) points vs. 10.98 (4.11) points; $P < 0.0001$] and lower serum albumin values [3.17 (0.57) g/dl vs. 3.69 (0.62) g/dl; $P < 0.0001$] than patients with advanced fibrosis without decompensation. Twenty-three patients (6.9%) had fibrosing cholestatic hepatitis at baseline, with a mean MELD score of 14.29 (1.3) points.

Characteristics of therapy

Overall, the mean interval between LT and initiation of antiviral therapy was 60.73 [60.28] months. This period was significantly longer in patients with advanced fibrosis than in patients with cholestatic hepatitis [77.74 (59.3) vs. 13.73 (16.03) months; $P < 0.05$] or with less advanced fibrosis [77.74 (59.3) vs. 49.84 (59.4); $P < 0.0001$].

Direct-acting antiviral agents-based regimens are shown in Table S2. The most frequent combination of oral antiviral drugs was DCV plus SOF (322 of 331 patients, 97.3%). RBV was used in 44% of patients and more frequently in men (49% vs. 27.9%; $P = 0.002$), genotype 3-infected patients (64.8% vs. 36.4%; $P = 0.000$), and patients with less severe recurrence (56.5% in F1, F2, and F3 patients vs. 34.4% in F4 patients; $P = 0.000$). RBV was also more frequently used in shorter schedules (62.5% in 12 weeks vs. 38.3% in 24 weeks). Nine of 10 patients who relapsed did not receive RBV as part of antiviral therapy.

Overall, 313 of 331 patients (94.56%) completed the scheduled therapy and were considered the PP population; the reasons for discontinuation were death during antiviral therapy ($n = 12$ patients: 10 due to complications of liver disease and 2 who died early after retransplantation, which was performed, while the patients were receiving DAA-based therapy after having achieved undetectable RNA levels), severe thrombocytopenia observed within the first week ($n = 1$), bacteremia at week 21 ($n = 1$), and new therapeutic recommendations during the compassionate use program, in which therapy was stopped at week 16 ($n = 3$). One patient underwent retransplantation at week 9 of therapy and achieved an SVR.

Virological response

All patients who completed treatment had undetectable RNA at the end of therapy. No viral breakthrough was observed. Ten patients who had completed the scheduled therapy relapsed (3%); interestingly, relapse was not observed in patients who had received at least 9 weeks of therapy and interrupted treatment thereafter. The characteristics of patients who experienced a relapse are shown in Table S3.

Sustained virological response rates according to the ITT and PP analyses were 93.05% and 96.9%, respectively (Fig. 1). Remarkably, all patients who had cholestatic hepatitis and finished therapy reached SVR at week 12. However, SVR-ITT was lower in patients with advanced fibrosis (F4) (89.6% vs. 96.4%; $P = 0.017$). Similarly, the SVR rate was greater in patients who received RBV in both the ITT population (97.3% vs. 89.6%; $P = 0.008$) and in the PP population (99.3% vs. 94.8%; $P = 0.024$). Sixty-one patients (18.4%) received antiviral therapy within the first 12 months after liver transplantation. There were no differences in the

Table 1. Baseline characteristics of patients.

	Whole cohort *N* = 331	Genotype 3 *N* = 91
Male (%)	263 (79.5)	77 (84.6)
Age (range), years	56 (35–82)	55 (42–82)
Immunosuppressive drug, no. (%)	Tacrolimus: 222 (67.1)	63 (71.6)
	Mycophenolate mofetil: 125 (37.8)	31 (37.8)
	Cyclosporine: 53 (16)	11 (13.4)
	mTOR inhibitors: 46 (13.9)	18 (22.2)
	Prednisone: 33 (9.7)	6 (7.4)
	Azathioprine: 2 (0.6)	1 (1.2)
Genotype, no. (%)		
1	220 (66.5)	
2	2 (0.6)	
3	91 (27.5)	91
4	18 (5.4)	
HIV coinfection	18 (5.8)	6 (6.8)
Mean baseline viral load log10 [SD]	6.37 [6.74]	6.47 [6.79]
Fibrosis, no. (%)		
0	18 (5.4)	7 (7.7)
1	29 (8.8)	17 (18)
2	43 (13)	19 (20.9)
3	55 (16.6)	17 (18.7)
4	163 (49.2)	30 (33)
Cholestatic hepatitis	23 (6.9)	1 (1.1)
Mean [SD] baseline MELD score in F4 (points) (*n* = 160 in the complete cohort and *n* = 29 in the G3 cohort)	12.11 [4.98]	10.71 [3.98]
Mean [SD] baseline MELD score in patients with decompensated cirrhosis (points)	14.03 [5.6]	12.29 [5.1]
Mean [SD]baseline serum albumin in patients with decompensated cirrhosis (g/dl) (*n* = 68 in the complete cohort and *n* = 7 in the G3 cohort)	3.17 [0.57]	3.55 [0.57]
Mean [SD] baseline serum albumin in patients with compensated cirrhosis (g/dl) (*n* = 84 in the complete cohort and *n* = 21 in the G3 cohort)	3.69 [0.62]	3.85 [0.45]
Mean [SD] baseline Child–Pugh–Turcotte score in patients with previous decompensation, *n* (%)*	Child B 56 [83.6] Child C 11 [16.4]	Child B 6 (100) [100]

Quantitative variables are shown as mean [SD] or as median (range), as appropriate. Categorical variables are shown as *N* (%).
*The Child–Pugh–Turcotte score could not be calculated in 1 patient.

SVR-ITT between patients treated within the first year after recurrence and patients treated thereafter (93.4% vs. 93%; P = NS). Furthermore, there were no differences in SVR rate with the different combinations of DAAs. Interestingly, SVR in genotype 3 carriers was similar to that observed in the whole cohort, even in patients with advanced fibrosis (96.7% vs. 88%; $P = 0.2$).

Clinical outcome after therapy

All variables reflecting liver function and severity of liver disease improved in most cases. Overall, liver disease tended to improve at the 12th week after therapy in patients with advanced recurrence after transplantation (F4 or decompensated cirrhosis)

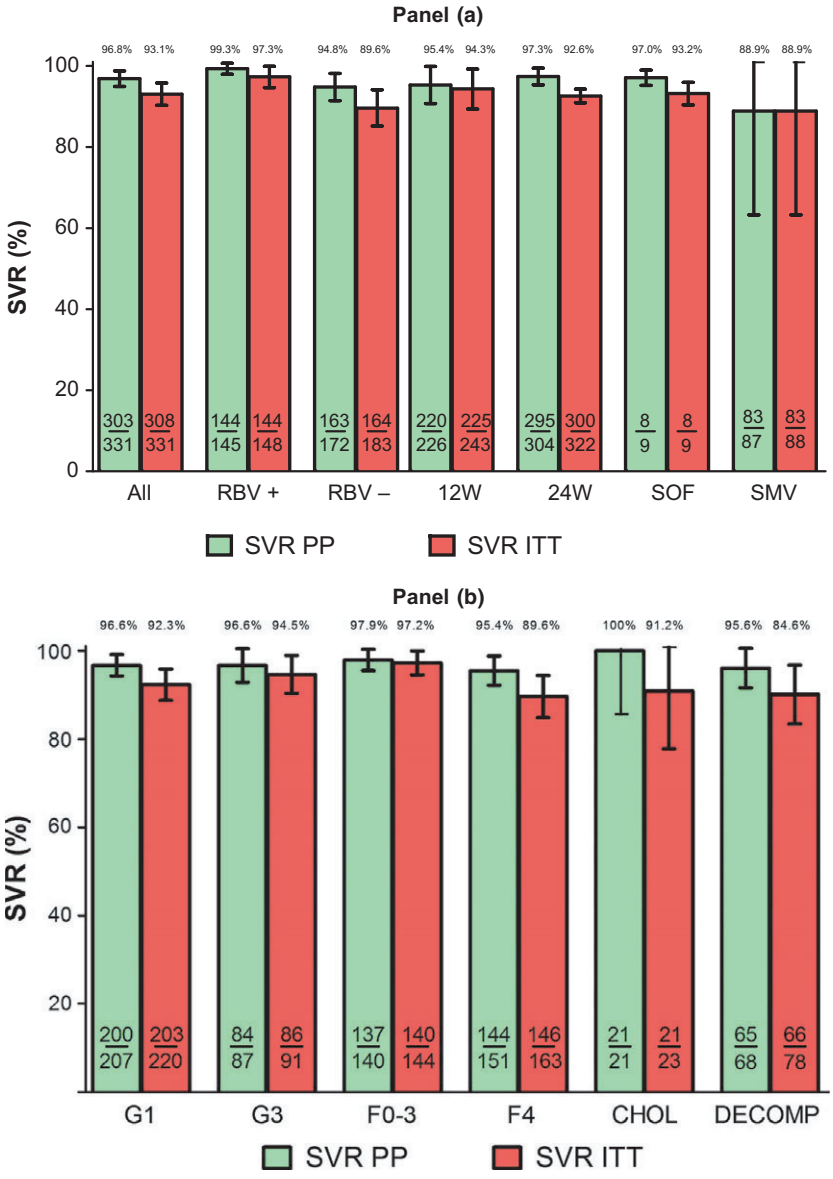

Figure 1 Sustained virological response per protocol (SVR-PP, green) and by intention to treat (SVR-ITT, red). Panel a: According to therapy, Panel b: According to the characteristics of the infection and stage of liver disease. Panel a: All, all patients; RBV, ribavirin; 12W, week 12 of therapy; 24W, week 24 of therapy; SOF, sofosbuvir; SMV, simeprevir. Panel b: G1, genotype 1; G3, genotype 3; F0-3, stage fibrosis below F4; F4, fibrosis stage F4 and clinical cirrhosis; CHOL, cholestatic hepatitis C; Decomp, clinical decompensation.

(Fig. 2, Panel a shows the Delta MELD for the whole cohort). The baseline MELD score improved in most cases (49.6%) or remained unchanged (19.5%) at this point.

We also specifically assessed changes in liver function among candidates for retransplantation, defined as a baseline MELD score greater than 15 points. Interestingly, the mean decrease in the MELD score was significantly greater in cirrhotic patients with a baseline score above 15 at baseline than in the rest of the cirrhotic population [2.69 (0.98) vs. 0.12 (0.34); $P = 0.002$]. Finally, the MELD score improved in 62.5% of patients, worsened in 29.2% of patients, and remained unchanged in 8.3% of patients with more severe liver disease (Fig. 2, Panel b).

Mortality and predictors of survival

Twelve patients died during antiviral therapy: 10 of complications of decompensated cirrhosis and two with cholestatic hepatitis who died early after retransplantation. A further 10 patients died after therapy with DAAs: 1 who relapsed died of liver cirrhosis, and 9 who died after achieving an SVR. Most died of complications of liver disease. The characteristics of the patients who died are summarized in Table S4. The mortality rate was similar in patients who were treated before and after 12 months after liver transplantation (4.9% vs. 7%; $P = 0.89$).

The variables associated with survival of F4 patients in both the univariate and the multivariate analyses are

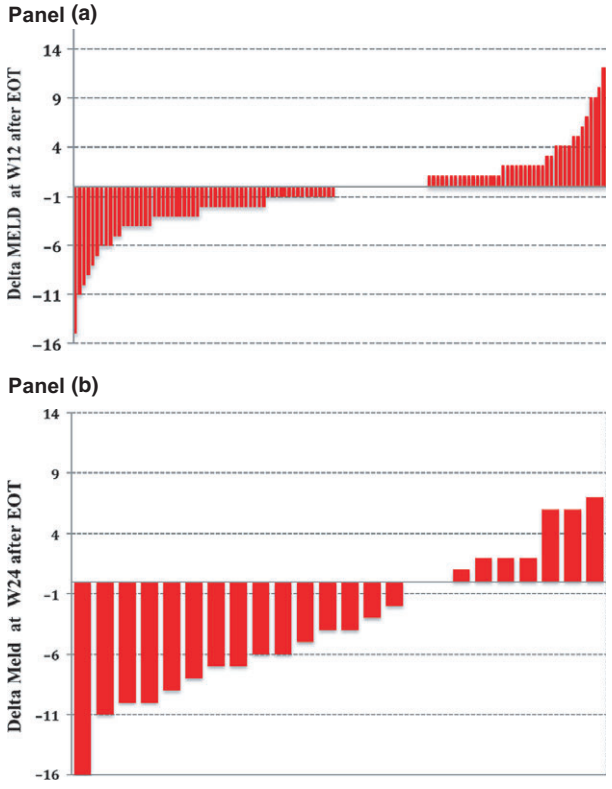

Figure 2 Changes in Model for End-Stage Liver Disease (MELD) score (Delta MELD). Panel a: Delta MELD at week 12 after therapy, in patients with F4 or findings of cirrhosis. Panel b: Delta MELD at week 24 after therapy in patients with F4 or findings of cirrhosis and baseline MELD ≥15 points.

shown in Table 2. The baseline MELD score, serum albumin values, and previous or current liver decompensation were associated with survival in the univariate analysis. Only the MELD score and serum albumin values were retained in the multivariate model. Cutoff values of 15 points for the MELD score and 3.3 g/dl for serum albumin values were obtained after a ROC curve analysis. A simple score was obtained by assigning zero or 1 point according to the presence or absence of the risk factor with the previously mentioned cutoff. Thus, there were three possible scores: 0 points when no risk factor was observed, 1 point when only 1 risk factor was present, and 2 points when both risk factors were present. The Kaplan–Meier survival curve estimation according to this calculated risk score can be seen in Fig. 3. As shown, the probability of survival was significantly lower in patients with a score of 1 or 2 (chi-square for trend, 22.37; $P < 0.001$).

Safety

Direct-acting antiviral agents were generally well tolerated. Importantly, AEs were recorded differently if the patient was treated within the named patient program or in the open-phase regimen, thus precluding a homogeneous report. However, most reported AEs were mild to moderate in severity and were mainly described by the investigators as associated with the underlying liver disease. The most frequent AE was anemia, which was commonly associated with the use of RBV. RBV was discontinued in 21/137 patients (15.3%), and 40 additional patients required their RBV dose to be adjusted. Four patients (1.2%) had severe bacterial infection requiring hospital admission; outcome was favorable in all four cases. Finally, two patients (0.6%) developed malignancies (lymphoproliferative disorder and recurrence of hepatocellular carcinoma).

Table 2. : Multivariate analysis of mortality during or after treatment.

Variable	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
Age	1.019 (0.970–1.071)	0.455		
Sex	0.474 (0.139–1.610)	0.231		
Baseline MELD score	1.177 (1.108–1.249)	0.000	1.137 (1.061–1.218)	0.003
Regimen prescribed	2.328 (0.673–8.053)	0.182		
Baseline serum albumin	0.257 (0.109–0.601)	0.002	0.376 (0.155–0.910)	0.030
Baseline serum bilirubin	1.064 (1.027–1.101)	0.000		
Baseline serum creatinine	2.256 (1.241–3.942)	0.004		
Baseline INR	3.486 (1.415–8.586)	0.006		
Previous antiviral therapy	1.529 (0.587–3.980)	0.384		
Use of ribavirin	0.445 (0.149–1.329)	0.147		
Genotype	0.943 (0.587–1.514)	0.809		
Interval between liver transplant and antiviral therapy	1.003 (0.996–1.010)	0.408		
Liver decompensation at baseline	4.123 (1.597–10.644)	0.003	0.417 (0.115–1.505)	NS

INR, international normalized ratio; HR, hazard ratio; CI, confidence interval.

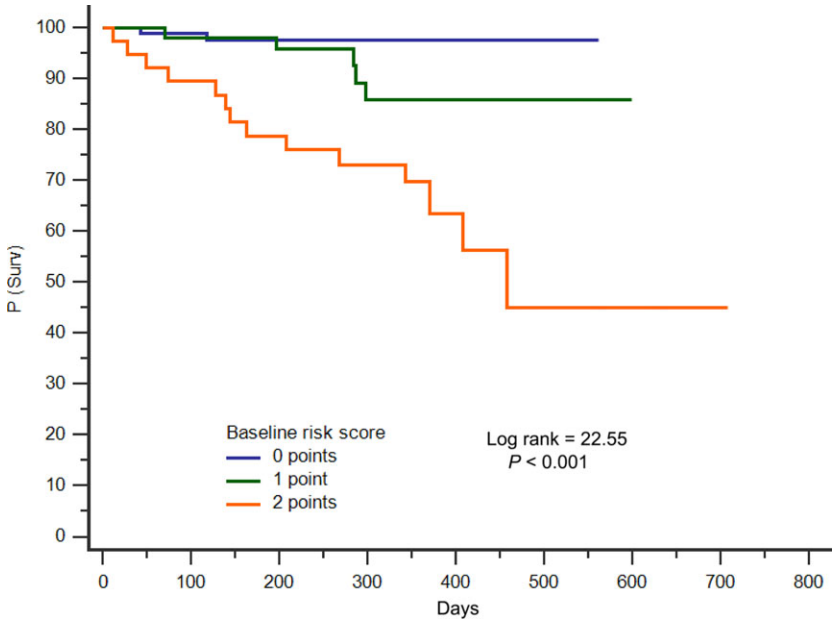

Figure 3 Kaplan–Meier survival estimation according to the calculated risk score. Blue: 0 points, Green: 1 point, Yellow: 2 points. Factors for scoring: baseline albuminemia ≤3.3 g/dl and baseline model for end-stage liver disease ≥15.

Immunosuppression

Most patients (n = 275, 83.1%) were receiving a calcineurin inhibitor-based regimen [mainly tacrolimus (67.1%)] at baseline. Changes in immunosuppressive therapy were required in 82 patients (32.5%). Although most doses were adjusted during DAA-based therapy (n = 66, 26.2%), some patients required changes in immunosuppressive medications after DAAs (n = 5, 2%) or during and after DAAs (n = 11, 4.4%). No episodes of rejection were reported.

Discussion

Recurrence of HCV infection has a considerable impact on patient outcome after LT, leading to a marked increase in liver-related morbidity and mortality [1]. To modify the natural history of this severe condition, any therapeutic approach has to fulfill three main objectives: antiviral efficacy, reduced severity of liver disease, and safety.

In the present large-scale, multicenter, real-world study, we clearly showed that administration of various DAA-based regimens, all of which contained DCV, a pangenotypic NS5A inhibitor, is a highly efficacious and safe therapeutic strategy in patients with recurrent HCV infection after LT. Furthermore, this approach leads to a modest improvement in the severity of recurrent liver disease in patients with advanced fibrosis.

The antiviral effect we observed was obtained irrespective of the DAA combination selected and of its duration. This finding is consistent with the pangenotypic activity of SOF and DAC, the most frequently used combination in our study. RBV seems to increase the SVR rate, although this finding may not be conclusive, because RBV was not prescribed homogeneously among centers.

Our results agree with those of initial short reports [5,6] and with more recently reported data from a French cohort and from an international compassionate use program [7–9]. Remarkably, the SVR-PP observed in the present study was achieved despite the fact that almost half of the cohort had advanced fibrosis (F4 by elastography or liver biopsy, with a significant number of patients with decompensated disease), a finding more frequently observed in our cohort than in the aforementioned studies. However, it is important to note that according to an ITT analysis, the SVR rate was significantly lower in patients with advanced fibrosis, mainly owing to the mortality observed during therapy in this group. Interestingly, the SVR rate was similar in genotype 3 carriers, a population that has traditionally been associated with decreased antiviral efficacy. Furthermore, a large majority of patients had previously received unsuccessful IFN-based therapy. Overall, these findings indicate that antiviral efficacy was maintained even in the worst clinical scenarios. However, the relatively low number of G3-infected patients with cirrhosis in our series limits the strength of this conclusion. Importantly, virological suppression was also observed across the study centers, thus clearly indicating the applicability of this approach.

When assessing antiviral therapy, it is also important to evaluate the impact of DAAs on clinical outcome, especially in patients with advanced graft disease. Consistent with findings reported elsewhere [12–14], we observed an improvement in the MELD score at week 12 after therapy. In fact, we observed a decrease in the MELD score in half of the patients with cirrhosis. Interestingly, the magnitude of this decrease was greater in patients with a MELD score >15 points. However, short-term MELD changes per se may not accurately predict clinical outcome and risk of death in this complex population. It is likely that some of the patients with decompensated cirrhosis after recurrence of HCV infection had reached a point where antiviral therapy was less effective in improving liver function. Furthermore, the limits of severity of liver disease that mark the futility of antiviral treatment remain controversial. This may be even more important after LT, when the issue of retransplantation is also controversial. Therefore, we used a multivariate approach to analyze the influence of baseline variables on the survival of patients with cirrhosis. Interestingly, we found that baseline MELD score and serum albumin values were independent predictors of survival. The combination of both variables in a simple score clearly identified those patients with a markedly low risk of death and can help in the clinical decision-making process. This finding is similar to that observed in previous studies performed mainly in nontransplanted patients and consistent with recent data from the Spanish registry [15]. We can speculate that in liver recipients, in whom the intensity of fibrosis formation and the severity of its consequences are clearly accelerated, the suppression of viral replication alone cannot reverse the natural course of the disease. Reversibility has been demonstrated in the post-transplant setting and appears to be similar to that observed in the nontransplant patient [16]. Considering the potential influence of the interval between recurrence and the initiation of therapy, we analyzed outcomes according to this variable separately but found no changes. Nevertheless, it seems reasonable to start antiviral therapy early, before advanced fibrosis and, especially, before liver failure occurs.

As for ribavirin, it is noteworthy that although its use was not associated with survival, the majority of patients who relapsed (9 out of 10) did not receive RBV as a part of their therapeutic regimen. However, the lack of a standardized protocol to administer RBV in this real-world study precludes a definitive conclusion.

The third relevant issue when addressing DAAs in the context of liver transplantation is safety. As in other clinical scenarios involving DAAs, DCV-based regimens proved to be extremely safe, with a very low number of severe AEs, which were most probably associated with the underlying liver disease. Only ribavirin dose modifications were clinically relevant. Although immunosuppressive drug doses were frequently adjusted, there were no rejection episodes during therapy. Our results are consistent with preliminary data showing that the DCV + SOF was safe and effective in LT recipients, with varying severity of liver disease [6–9,17,18].

The strengths of our study include the enrollment of more than 300 patients, making ours the largest cohort to date in a real-world multicenter study. Importantly, we included a large number patients with advanced fibrosis and infected with HCV genotype 3, thus accurately reflecting clinical practice. This is particularly relevant, because the data obtained in phase II and III trials, which were performed mainly in the nontransplant setting, may not be directly applied in the real-world setting of recurrence of advanced HCV infection. We also provided an accurate assessment of the baseline risk of death, which may help in the clinical decision-making process, especially when considering the futility of antiviral therapy.

Our study is not without limitations. First, there was no control group, and we do not know whether all treated patients in each unit were finally included. However, the large representation of sicker patients clearly validates our results. Additionally, the selection of the DAA regimen was not homogeneous and was based on the individual judgement of the attending physician. Furthermore, the study protocol did not include baseline antiviral resistance tests, which, if applied, have the potential to influence the probability of viral response. Finally, as AEs were not registered according to a standardized protocol, their magnitude could have been underestimated.

In summary, we found that DCV-based DAA regimens are an efficacious and safe option for management of recurrence of advanced HCV infection after LT. Additionally, a baseline evaluation of the MELD score and serum albumin values could help in the assessment of prognosis, irrespective of the viral response.

Authorship

MS, MP and LLC: participated in the study conception and design, data collection and analysis, and critical review of the manuscript. MS and RB: conducted the statistical analyses and participated in drafting and

critical review of the manuscript. All authors contributed patient data, reviewed manuscript drafts, and reviewed and approved the final draft of the manuscript.

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BMS provided daclatasvir for patients under a named patient regimen.

Conflict of interest

MS has been a clinical investigator, speaker, and/or consultant for Astellas, Novartis, Bristol-Myers Squibb, AbbVie, and Gilead Sciences.

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SUPPORTING INFORMATION

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

Table S1. Previous post-transplant antiviral treatments.

Table S2. DAA treatment schedules.

Table S3. Characteristics of patients who experienced viral relapse.

Table S4. Characteristics of the patients who died during or after therapy.

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