Liver, Pancreas and Biliary Tract

Transjugular Intrahepatic Portosystemic Shunt does not affect the efficacy and safety of direct-acting antivirals in patients with advanced cirrhosis: A real-life, case-control study

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ABSTRACT

Background: Transjugular Intrahepatic Portosystemic Shunt (TIPS) is a well-established treatment for complications of portal hypertension.

Aims: To analyze the impact of TIPS on virologic response and safety profile in patients treated with direct-acting antivirals (DAAs).

Methods: We analyzed data from HCV-positive cirrhotic patients treated with DAAs. Twenty-one patients with previous TIPS placement were compared with 42 matched subjects without TIPS. Logistic regression was used to identify predictors of hepatic function worsening and adverse events.

Results: No differences were found between the two groups in particular regarding sustained virologic response (92.5 and 97.6% in TIPS vs no-TIPS, p = 0.559). Model for End-stage Liver Disease (MELD) of both TIPS and no-TIPS groups declined from baseline to week 24 of follow-up (from 12.5 ± 3.5 to 10.8 ± 3.4 and from 11.1 ± 3.5 to 10.3 ± 3.4, p = 0.044 and 0.025). There were no differences in adverse event rates. At univariate analysis, age was associated with MELD increase from baseline to week 24 (OR 1.111, 95% CI 1.019-1.211, p = 0.017), and patients with higher baseline MELD developed serious adverse events more frequently (OR 0.815, 95% CI 0.658–1.010, p = 0.062). Patients with or without TIPS did not show differences in transplant-free survival.

Conclusion: TIPS placement does not affect virologic response and clinical outcome of patients receiving DAAs.

1. Introduction

About 3% of the world population is infected with hepatitis C virus (HCV) infection and 150.000 new infections are registered every year in Western countries [1]. Twenty percent of patients with chronic hepatitis C (CHC) develop cirrhosis, and 700.000 deaths associated with complications of liver disease occur every year [2]. Until a few years ago, antiviral therapy based on interferon in association with ribavirin (RBV) was the only approach for infected patients, with modest rates of sustained virologic response (SVR) and significant side effects [3]. During the last few years, new antiviral molecules with a direct action against the virus have been developed, resulting in a dramatic change in the management of CHC [3]. In fact, most direct-acting antiviral (DAA) schedules induce high SVR rates with excellent safety profiles. At difference with interferon-based antiviral therapy, DAAs can be used in patients with advanced liver disease with good SVR rates [4] and a positive impact on patient survival [5]. Nonetheless, Curry et al. [6] reported

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that in patients in Child-Pugh-Turcotte (CTP) class B treated with DAAs, satisfactory SVR rate (83–94%) were associated with a relevant number of serious adverse events (SAE) compared to the same regimens in patients with chronic hepatitis or compensated cirrhosis (16–19% vs 2%) [6,7].

Transjugular Intrahepatic Portosystemic Shunt (TIPS) is a leading treatment option for the complications of portal hypertension. TIPS is indicated in portal hypertensive bleeding, refractory ascites and vascular liver diseases, resulting in improvement of patient survival [8–12]. Notably, TIPS strongly modifies splanchnic hemodynamics, determining substantial porto-systemic shunting [8]. TIPS placement might influence the pharmacokinetics of different drugs [13–15], and this is theoretically possible also for DAAs. The safety profile represents another open issue, considering the high rates of SAEs in patients with advanced liver disease [6]. These aspects have never been previously investigated.

In this study, we evaluated the impact of TIPS on SVR rate, drug safety profile and liver function in HCV-positive cirrhotic patients treated with DAAs.

2. Materials and methods

We analyzed biochemical, virological and clinical data of HCV-positive cirrhotic patients with functioning TIPS, consecutively treated with DAA-based therapies from September 2014 to April 2017. In all cases, TIPS was placed before starting DAA therapy. Cirrhotic patients without TIPS treated with DAAs in the same period of time were used as comparison. They were selected among HCV positive patients consecutively treated in the four tertiary participating centers, according to sex, age (±3 years) and CTP class (match 1:2). DAA schedule and treatment length were established following the recommendations of the Italian Medicines Agency committee [16].

Enrollment criteria were age >18 years and HCV infection as established by both positive serum HCV antibody and serum HCV-RNA, using a real-time polymerase chain reaction-based method. Patients had evidence of cirrhosis as assessed by liver biopsy, vibration-controlled transient elastography with FibroScan®, or by the presence of complications. Other causes of liver disease including alcohol abuse, and previous liver transplantation were exclusion criteria.

In all patients with previous TIPS placement, shunt patency was documented by radiologic follow-up. All enrolled patients underwent at least one Doppler ultrasound within six months from the beginning of antiviral therapy with the following signs of optimal function [17]: whole color saturation in three segments of the stent (portal, midportion, and hepatic sites) without any evidence of filling defects or focal aliasing; high-velocity turbulent flow into the stent with a gradual velocity shift during respiration; hepatofugal flow in the portal vein branches; hepatic artery flow increase.

Laboratory assessment, including HCV-RNA levels, was conducted at baseline, end of antiviral treatment, and 12 and 24 weeks after the end of DAA. Model for End-Stage Liver Disease (MELD) and MELD corrected by serum sodium (MELD-Na) were calculated at all time points. Delta values were calculated (week 24 of follow-up − baseline) for all the main laboratory values. HCV-RNA levels were measured with COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative Test, v2.0 (limit 15 IU/ml).

We registered DAA-related and unrelated adverse events (AEs) (untoward medical occurrence associated with the use of antiviral therapy) and SAEs (death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions) [18]. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Patients gave their written informed consent to undergo antiviral therapy with DAAs.

2.1. Statistical analysis

A physician trained in statistics encoded all samples into a dedicated database in an anonymous form. Data are expressed as the mean (±standard deviation) or median (with range), as applicable. Confidence interval (CI) is shown where appropriate. Comparisons between groups were made by Chi square-test and Fisher's exact test for qualitative variables, and Mann–Whitney U-test for continuous ordinal data, respectively. Wilcoxon test was utilized to assess tendencies and specific rank test for significance. Logistic regression was performed to identify the predictors of liver function impairment, AEs and SAEs. Presence of TIPS was analyzed as potential predictor in all outcome analyses. A significance level of 0.05 was considered for all tests. The SPSS software version 21.0 (MJ Norusis, Chicago, US) was used for all statistical analyses.

3. Results

3.1. Baseline characteristics

We enrolled 21 HCV-positive cirrhotic patients with previous TIPS placement and 42 cirrhotic subjects without TIPS, matched for gender, age and CTP class. The main demographic and baseline clinical characteristics of the two groups (TIPS and no-TIPS) are summarized in Table 1. Additional clinical and technical data of patients included in the TIPS group are reported in Supplementary Table 1. Notably, a fraction of patients had under-dilated TIPS according to an approach described in a recently published study [19]. Patients with TIPS and the counterparts were comparable for all other clinical and virologic characteristics. Genotype 1b was the most represented, and sofosbuvir/ledipasvir the most frequently used antiviral schedule. RBV was added to DAA in approximately half of the cases, in both groups.

3.2. Virologic response

All patients concluded the antiviral therapy. All patients, regardless of the presence of TIPS, reached the SVR12 but not all maintained the virologic response at 24 weeks of follow-up (SVR24 92.5% vs 97.6% in TIPS and no-TIPS, respectively, p = 0.559). One patient in each group had a virologic relapse: in the TIPS group, a 49 years old male, genotype 4, CTP class A, treated for 24 weeks with sofosbuvir/ledipasvir without RBV; in the no-TIPS group, a 42 years old male, genotype 1a, CTP class B, treated for 24 weeks with sofosbuvir/ledipasvir without RBV.

3.3. Changes in laboratory parameters and liver function

The behavior of laboratory tests at baseline (T0), end of treatment (EOT) and week 24 of follow-up (W24) is reported in Table 2. Patients with TIPS and no-TIPS were in general comparable for all laboratory assessments, although those with TIPS had higher median values of total bilirubin at EOT and at W24 in comparison with patients without TIPS.

Analyzing the modifications along the three time points, aminotransferases and γGT levels decreased in both groups, while total bilirubin significantly declined only in patients without TIPS. Mean MELD scores at each time point and their trend during and after antiviral therapy are reported in Table 2 and in Fig. 1. Patients of the two groups had statistically equivalent MELD and MELD-Na scores at T0 and W24. Patients with TIPS showed a significantly higher mean MELD and MELD-Na at EOT in comparison with subjects with no-TIPS. Mean MELD score dropped from T0 to EOT and

Table 1
Baseline characteristics of patients included in the TIPS and no-TIPS groups.

	TIPS	no-TIPS	χ2-Fisher/MW-U P value
N	21	42	
Male n (%)	18 (85.7)	36 (85.7)	1.000
Age (years, mean ± SD)	58 ± 10	61 ± 10	0.385
Genotype n (%)			
1a	4 (19)	8 (19)	1.000
1b	9 (42.9)	21 (50)	0.395
2	1 (4.8)	2 (4.8)	1.000
3	3 (14.3)	8 (19)	0.564
4	4 (19)	3 (7.1)	0.160
HCV-RNA (UI/ml) (median, R)	352977. 8740–12723486	380000. 2750–12295107	0.683
CTP score n (%)			
A6	9 (42.8)	18 (42.8)	1.000
B7	3 (14.3)	15 (35.7)	0.137
B8	8 (38.1)	5 (11.9)	0.023
B9	0 (0)	2 (4.8)	0.548
C10	1 (4.8)	2 (4.8)	1.000
MELD (mean ± SD)	12.5 ± 3.5	11.1 ± 3.5	0.177
MELD-Na (mean ± SD)	13.6 ± 3.5	12.4 ± 5.2	0.055
DAA regimen n (%)			
SOF/SIM	0	2 (4.8)	0.441
SOF/LPV	11 (52.4)	18 (42.9)	0.327
SOF/DCV	7 (33.3)	14 (33.3)	1.000
SOF	2 (9.5)	3 (7.1)	0.545
OBV/PTV/RTV/DSV	0	4 (9.5)	0.188
OBV/PTV/RTV	1 (4.8)	1 (2.4)	0.559
RBV n (%)	9 (42.9)	20 (47.6)	0.465
Length of therapy 12/24 week n (%)	0 (0)/21 (100%)	6 (14.3)/36 (85.7)	0.077

TIPS: Transjugular Intrahepatic Portosystemic Shunt; χ2: Chi square; MW-U: Mann–Whitney U test; SD: standard deviation; R: range; CTP: Child-Turcotte-Pugh; MELD: Model for End-stage Liver Disease; SOF: sofosbuvir; SMV: simeprevir; LPV: ledipasvir; DCV: daclatasvir; OBV: ombitasvir; PTV: paritaprevir; RTV: ritonavir; DSV: dasabuvir; RBV: ribavirin.

Table 2
Laboratory parameters in cirrhotic patients with or without TIPS undergoing therapy with DAA.

	TIPS			no-TIPS		
	T0	EOT	W24	T0	EOT	W24
PLT (×10^9/mmc) (median, R)	79. 36–161	78. 33–172	78. 36–164	98. 19–222	92, 19–259	98. 20–206
Bilirubin (mg/dl) (median, R)	1.8. 0.8–7.2	1.7. 1.1–4.6[b]	1.3. 0.5–3.4[b]	1.3. 0.4–8.6	1.3, 0.2–6.7[a]	1. 0.4–5.5[a]
AST (IU/ml) (median, R)	61. 28–154	31. 14–63[a]	30. 17–55[a]	73. 21–519	28, 16–66[a]	25. 13–71[a]
ALT (IU/ml) (median, R)	47. 21–151	23. 9–48[a]	21. 10–52[a]	60. 11–405	20, 11–48[a]	21. 10–58[a]
γGT (IU/ml) (median, R)	53. 10–303	36. 7–246[a]	33. 8–120[a]	67. 16–303	41, 12–121[a]	42. 12–119[a]
ALP (IU/ml, median, R)	100. 62–233	99. 46–193	104. 57–200[b]	126. 58.490	123, 59–635[a]	157. 22–801
Creatinine (mg/dl, mean ± SD)	0.9 ± 0.2	0.8 ± 0.3	1 ± 0.4	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
MELD score (mean ± SD)	12.5 ± 3.5	12.7 ± 3[b]	10.8 ± 3.4[a]	11.1 ± 3.5	10.5 ± 3.4[a]	10.3 ± 3.4[a]
MELD-Na score (mean ± SD)	13.6 ± 3.5	13.7 ± 3.2[b]	11.7 ± 3.4[a]	12.4 ± 5.2	11 ± 4.2	10.4 ± 3.4[a]

T0: start of DAA treatment; EOT: end of antiviral therapy; W24: week 24 of follow-up after the end of antiviral therapy; R: range; PLT: platelets; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γGT: gamma glutamyl transferase; ALP: alkaline phosphatase; MELD: Model for End-Stage Liver Disease.
[a] Significant difference with respect to T0 (Wilcoxon test, p < 0.05).
[b] Significant difference compared to the same time point in no-TIPS (Mann–Whitney U test, p < 0.05).

Table 3
Comparison of changes in laboratory parameters before and after antiviral treatment in cirrhotic patients with or without TIPS.

Delta value (W24 – T0)	TIPS	no-TIPS	P value
ΔPLT (×10^9/mmc) median (R)	+2 (−61 to +54)	+4 (−42 to +49)	0.406
ΔBilirubin (mg/dl) median (R)	−0.4 (−6.7 to +2.5)	−0.3 (−15 to +1)	0.994
ΔAST (IU/ml) median (R)	−29 (−137 to +9)	−48 (−448 to −1)	0.055
ΔALT (IU/ml) median (R)	−25 (−144 to +12)	−41 (−347 to +35)	0.079
ΔγGT (IU/ml) median (R)	−20 (−141 to +37)	−22 (−218 to +99)	0.569
ΔALP (IU/ml) median (R)	−6 (−141 to +39)	+8 (−153 to +347)	0.354
ΔCreatinine (mg/dl) mean ± SD	+0.1 ± 0.2	+0.05 ± 0.2	0.331
ΔMELD score mean ± SD	−1.7 ± 3.4	−0.7 ± 2.6	0.039
ΔMELD-Na score mean ± SD	−2 ± 3.9	−2 ± 5.1	0.433

T0: start of DAA treatment; W24: week 24 of follow-up after the end of antiviral therapy; MW-U: Mann–Whitney U test; R: range; PLT: platelets; AST: aspartate aminotransferase; ALT: alanine aminotransferase; γGT: gamma glutamyl transferase; ALP: alkaline phosphatase; MELD: Model for End-Stage Liver Disease; MELD-Na: Model for End-Stage Liver Disease corrected by serum sodium.

from T0 to W24 in the control group. Patients with TIPS showed a significant decrease of mean MELD from T0 to W24 but not from T0 to EOT. In both groups, MELD-Na significantly decreased from T0 to W24. Delta values (W24 – T0) of the analyzed laboratory parameters are reported in Table 3. Patients with TIPS showed a significantly greater mean delta-MELD than patients without TIPS.
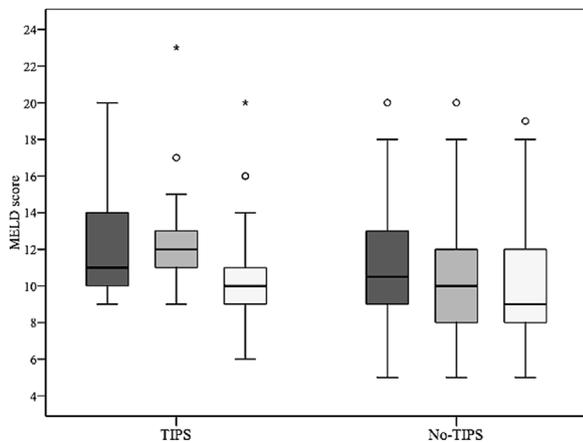
Fig. 1. Distribution of MELD score (ranging from 6 to 40, with higher values indicating more advanced liver disease) according to the previous TIPS placement. MELD at beginning of antiviral treatment (dark grey bar), MELD calculated at the end of antiviral therapy (light grey bar), MELD at week 24 from the end of treatment (white bar). The horizontal bar inside the box indicates the median value. The points represent the outliers, defined as values not falling in the inner fences. The asterisks are the extreme outliers, defined as values more than three times the height of the boxes.

MELD score declined from T0 to W24 in the vast majority of patients while it increased in 14.3% of patients with TIPS (3/21) and in 16.7% of no-TIPS (7/42) (p = 0.559). At univariate analysis, only patients' age was significantly associated with the increase in MELD score (from T0 to W24) [Odds Ratio (OR) 1.111, 95% CI 1.019–1.211, p = 0.017]. In particular, mean age was 67 ± 7 in patients with increased MELD, and 59 ± 10 years in those who decreased MELD. The presence of TIPS or time between TIPS placement and start of DAA therapy did not emerge as significant variables either in the preliminary univariate test or in the multivariate model.

3.4. Safety

The main safety outcomes are summarized in Table 4. Comparing TIPS and no-TIPS, no significant differences were found in the incidence of AE. The most common DAA-related AE was fatigue. HCC occurrence during antiviral therapy was the most frequent SAE unrelated to DAA. No DAA-related SAEs were registered. No patients discontinued treatment prematurely because of an AE or SAE.

Male gender was the only feature that tended to be associated with the occurrence of AE (OR 0.148, 95% CI 0.018–1.241, p = 0.078). AEs were reported in 40.4% of males (21/52) and in 9.1% of females (1/11). No predictors of DAA-related AE were detected.

At univariate analysis for the predictors of SAE, MELD score at T0 emerged as the only factor with a P value <0.1 (OR 0.815, 95% CI 0.658–1.010, p = 0.062). Patients who experienced a SAE showed a mean baseline MELD score of 14 ± 5, compared to 11 ± 3 in the other patients. The presence of TIPS or time between TIPS placement and start of DAA therapy did not emerge as significant variables either in the preliminary univariate test or in the multivariate model.

3.5. Long-term outcome

No patient died or was transplanted during the antiviral therapy. During the 2-year follow-up period, 1 patient died (no-TIPS group) while 3 patients with TIPS and 1 no-TIPS were transplanted. Two-year cumulative survival of patients with TIPS was 100% while survival of no-TIPS was 97.4% (p = 0.549). Death and transplantation occurred in all cases for progression of the underlying liver disease, and were not related to DAA therapy. The patient who

Table 4
Adverse events in cirrhotic patients with or without TIPS undergoing treatment with DAA.

	TIPS	no-TIPS	χ2-Fisher P value
N	21	42	
AEs (overall) n (%)	9 (42.9)	13 (31)	0.255
AEs (DAA-related) n (%)	3 (14.3)	10 (23.8)	0.297
Fatigue	3 (100)	7 (70)	
Skin rash	0	2 (20)	
Nausea	0	1 (10)	
AEs (not DAA-related) n (%)	6 (28.6)	3 (7.1)	0.031
Ascites	2 (33.3)	0	
Rectal bleeding	1 (16.7)	0	
Skin infection	1 (16.7)	0	
Hepatic Hencephalopathy	1 (16.7)	0	
Depression	1 (16.7)	2 (66.7)	
Anaemia	0	1 (33.3)	
Withdrawal of antiviral for AE	0	0	1.000
SAEs (overall) n (%)	1 (4.8)	6 (14.3)	0.248
SAEs (DAA-related) n (%)	0	0	1.000
SAEs (not DAA-related) n (%)	1 (4.8)	6 (14.3)	0.248
HCC	1 (100)	3 (50)	
Liver failure	0	1 (16.7)	
SBP	0	1 (16.7)	
Portal thrombosis	0	1 (16.7)	
Withdrawal of antiviral for SAE n (%)	0	0	1.000
Death during treatment n (%)	0	0	1.000
Death during 2-year follow-up n (%)	0	1 (2.4)	0.667
LT during treatment n (%)	0	0	1.000
LT during 2-year follow-up n (%)	3 (14.3)	1 (2.4)	0.104

χ2: Chi square; AE: adverse event; DAA: direct acting antivirals; SAE. serious adverse event; HCC: hepatocellular carcinoma; SBP: spontaneous bacterial peritonitis; LT: Liver Transplant.

died was a 60 years old male, genotype 1b, CTP B, treated with ombitasvir/paritaprevir/ritonavir plus dasabuvir and RBV for 12 weeks with achievement of RVR, SVR12 and SVR24. The cause of death was a complication of bowel obstruction.

4. Discussion

Patients with HCV-related advanced liver disease might benefit from both TIPS placement and DAA therapy [6,8–12]. However, TIPS leads to porto-systemic shunting [8] and its impact on drug pharmacokinetics and consequently on efficacy and safety is uncertain. While DAA therapy is generally safe in CHC and compensated cirrhosis [6,7], in patients with advanced liver disease, relevant rates of SAE were observed [6,7]. In this study, we demonstrated for the first time that patients with previous placement of TIPS can achieve optimal rates of SVR24 (92.5%) and a significant decrease in MELD and MELD-Na score from T0 to W24. In particular, both SVR rate and the improvement of liver function in patients with prior placement of TIPS treated with DAA are coherent with previous studies in patients with advanced cirrhosis without TIPS [6,20]. It should be noted that in patients with TIPS the decline of MELD was somehow slower than in patients without TIPS. However, in patients with TIPS a significantly higher delta-MELD than in patients without TIPS was observed.

Notably, at two years of follow-up, patients with and without TIPS showed a comparable percentage of hard clinical outcomes (LT and death). Surprisingly, patients with TIPS tended to develop a lower number of DAA-related AEs and SAEs with respect to patients without TIPS, although this difference was not significant. While it is conceivable that the reduction in portal pressure could have an impact on some of the AEs, data from larger series of patients are necessary before definitive conclusions on this issue may be drawn.

We also analyzed the whole population of patients with severe liver disease, irrespective of TIPS, trying to identify independent predictors of MELD increase from T0 to W24, and of AEs and SAEs.

Indeed, while in the majority of patients MELD score decreased from T0 to the end of follow-up (W24), in a subgroup of patients the score increased (14.3% of patients with TIPS and 16.7% without TIPS). Elderly patients were at higher risk of MELD increase, confirming that age is a determinant of the likelihood to improve liver function, possible due to differences in hepatic functional reserve. These results are in agreement with those of Conti et al. [21], who demonstrated that patients with advanced fibrosis or cirrhosis aged ≥65 years, and treated with DAA, had a worsening of CTP class, at difference from younger patients. Gender emerged as a borderline predictor of the appearance of AE during DAA treatment. In fact, males showed four times as many AEs as females. Although this is an original and potentially interesting finding, the low number of females enrolled in this study does not allow to draw any definitive conclusions. Further studies should explore possible gender differences in terms of SVR and safety profile in this population.

Patients with higher MELD score at T0 displayed a higher risk of SAE. This finding is not surprising since only SAEs associated with advanced liver disease itself and not related to DAAs were registered. Notably, we could not analyze the possible predictors of SVR or of transplant or death due to the low number of events.

We have to acknowledge a few limitations of this study, including the relatively small number of patients enrolled. However, this is the first real-life study analyzing whole laboratory, virological, and clinical outcomes of patients treated with DAA after TIPS. Because DAAs have been introduced in clinical practice only few years ago, the length of follow-up reported in the present study (2 years) is adequate to confirm the excellent results of DAA-based therapy also in patients with advanced liver disease. The observational design of the study represents a further limitation, although the 1:2 matching can assure an acceptable strength of the study design. The study adds real life-based knowledge in the context of advanced cirrhosis, a condition where additional post-registration information may still be of value [22]. Future studies should be undertaken to evaluate whether the outcomes observed in TIPS patients treated with DAA are different from those of patients with TIPS not undergoing antiviral therapy. In the cohorts available in our centers, these latter patients had TIPS placed several years before and this would create a bias in the comparison. Another limitation of this study is the lack of pharmacokinetic data in the two groups of patients. These data, which could establish whether, and to what extent, DAAs plasma levels are different in patients with TIPS, deserve to be obtained in future studies.

In conclusion, DAA-based antiviral therapy may be safely and effectively used after TIPS placement. Cirrhotic patients with and without TIPS treated with DAA have similar long-term outcomes and comparable chances to improve their liver function.

Conflict of interest

Appendix A. Supplementary data

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