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Research Article

Ombitasvir/Paritaprevir/ritonavir/Dasabuvir ± Ribavirin is safe and effective in HCV infected patients in a real-life cohort from Latin America†

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Abstract

Information about the use of ombitasvir/paritaprevir/ritonavir/dasabuvir ± ribavirin (OBV/PTV/r/DSV±RBV) in real-clinical practice in Latin America is scarce. We aimed to confirm safety and effectiveness of OBV/PTV/r/DSV±RBV therapy in real-world setting. We analyzed a cohort of patients with genotype 1 infection treated with OBV/PTV/r/DSV±RBV. Data on demographics, clinical features, safety and virological response were retrospectively collected from 21 centers in Latin America. A total of 96 patients received OBV/PTV/r/DSV, associated with RBV in 68% of the cases. Most were genotype 1b (80%), 56 (58%) had cirrhosis and 45 (47%) failed prior HCV treatment. Adverse events occurred in 62% of patients. The most common adverse events were pruritus (21%), hyperbilirubinemia (17%) and asthenia (17%). Five patients discontinued therapy prematurely due to hepatic decompensation, three of them were Child-Pugh B at baseline and one patient died due to multi-organ failure. Follow up HCV-RNA 12 weeks after completion of therapy was evaluated in all the patients and sustained virologic response rate was 97%. No virologic breakthrough was detected. Our study confirms that OBV/PTV/r/DSV treatment is highly effective in patients with chronic HCV without cirrhosis or with Child-Pugh A cirrhosis in non-European populations. Adverse events were often mild and rarely led to treatment discontinuation except for patients with Child-Pugh B cirrhosis or with previous history of hepatic decompensation. These results can support the development of public strategies to expand the access of OBV/PTV/r + DSV and other DAAs combinations in order to reduce the burden of HCV infection in our region.
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Introduction

Chronic infection with hepatitis C virus (HCV) is a major health problem in Latin America, with about 8-10 million people chronically infected with HCV in the region.(Kershenobich *et al.*, 2011) Nearly 30% of those infected will develop cirrhosis and/or liver cancer, which has a high mortality and a significant cost to the health system.(Missiha, Ostrowski & Heathcote, 2008)

In recent years the treatment for HCV has evolved rapidly. The emergence of new direct-acting antivirals agents (DAA) against HCV infection has dramatically altered the landscape of treatment for HCV, achieving outstanding outcomes.(Lawitz *et al.*, 2014; Poordad *et al.*, 2014; 2016) Hepatitis C treatment with second generation DAAs are short, well tolerated and safe. The interferon-free, all-oral regimen of 3 DAAs comprises drugs from different families: ombitasvir (OBV; NS5A inhibitor), paritaprevir (PTV; protease inhibitor) associated with a booster ritonavir (r) and dasabuvir (DSV; non-nucleoside polymerase inhibitor). The efficacy and safety of OBV/PTV/r ± DSV regimen in patients without cirrhosis or with compensated cirrhosis has been demonstrated in different phase 3 clinical trials.(Feld *et al.*, 2014; Ferenci *et al.*, 2014; Poordad *et al.*, 2014; Feld *et al.*, 2016) Cure rate in this population exceeded 90% in all the subgroups with rate of severe adverse events lower than 5%.

The safety and effectiveness of OBV/PTV/r + DSV treatment has been corroborated in real-life cohorts from Europe.(Chamorro-de-Vega *et al.*, 2016; Flisiak *et al.*, 2016) Previous reports have described lower response rates for IFN-based antiviral therapy in Latin American patients and to our knowledge there is no information regarding the use of DAA regimens in this population.(Yu, Douglass, Qualls, Arora & Dunkelberg, 2009) Information about the use of any DAA regimen in real-world practice in Latin America is scarce. Knowing the safety profile of the OBV/PTV/r + DSV regimen in a Latin American cohort is relevant for treating physicians given the different race and ethnicities in this region when compare to Europe or the United States.

The aim of this study is to assess safety and effectiveness of OBV/PTV/r + DSV regimen with or without ribavirin (RBV) in genotype 1 HCV infected patients treated in a Latin American real life cohort.

Methods

Study design and patients.

This retrospective, multicenter cohort study included patients from Argentina, Chile, Colombia and Uruguay with HCV chronic infection genotype 1 who received at least one dose of OBV/PTV/r + DSV regimen associated or not to RBV. Eligible patients were adults (older than 18 years of age) with or without cirrhosis and treatment-naïve or treatment-experienced (previously treated with an interferon-based therapy with or without first generation protease inhibitors). Patients coinfected with human immunodeficiency virus (HIV) were included in the analysis and those who underwent an orthotopic liver transplantation (OLT) or presented renal insufficiency requiring hemodialysis were

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excluded. Patients who failed second generation DAAs or received OBV/PTV/r + DSV regimen as part of a clinical trial were also excluded.

The study was conducted according to the principles of the Declaration of Helsinki. The local institutional review board of each center approved the study.

Data collection

A standardized form was developed for this study. Physicians collected the data from each eligible patient under their care during the study period. Every patient was identified with a code. Detailed demographic, laboratory, clinical and outcome information for all enrolled patients was provided. All data records were checked for missing values and inconsistencies, queries were referred to the participating institution, and corrections were made at the data coordinating center. Treatment was either part of a compassionate use program or prescribed by treating physician by July 30th, 2016.

Cirrhosis was defined by the presence of METAVIR stage 4 fibrosis on liver biopsy (The French METAVIR Cooperative Study Group., 1994) or transient elastography with a cutoff >12.5 kPa or at least two of the following criteria: 1) platelet count less than 120,000/mm^3, 2) endoscopic evidence of varices or portal hypertensive gastropathy, and/or 3) radiographic evidence of liver nodularity.

Treatment was administered as recommended by international guidelines (http://www.hcvguidelines.org/full-report/): OBV/PTV /r 25/150/100 mg once a day + DSV 250 mg twice a day. Use of RBV and its dose adjustments were not protocolized, but were at discretion of the treating physician.

Outcome assessment

Effectiveness

Primary virologic outcome was achievement of sustained virologic response (SVR) defined as an undetectable HCV RNA at least 12 weeks after completion or early discontinuation of HCV therapy. Secondary virologic outcome included end of treatment (EOT) response defined as achievement of undetectable HCV RNA at the completion or early discontinuation of HCV therapy. Virological outcomes were calculated based on intention-to-treat (ITT) analysis.

Safety

Safety data were collected from all patients from the time of starting treatment until completion or early discontinuation. Standard laboratory tests including Model for End-stage Liver Disease (MELD) score and Child-Turcotte-Pugh (CTP) score parameters. Frequency of clinic visits and laboratory tests were performed according to the treating physician´s discretion. The primary safety outcome was hepatic decompensation, defined as the development of

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ascites, hepatic encephalopathy or variceal bleeding. Secondary safety outcomes included MELD score change from baseline to end of treatment. Serious adverse events (SAEs) including urgent clinic visits, hospitalizations and/or death were thoroughly reviewed to identify the causal relationship with treatment regimen. All patients were included in the analysis of safety outcomes. Adverse events severity were classified according to National Cancer Institute common toxicity criteria.(Dueck *et al.*, 2015)

Statistical analysis

Data are presented as percentages or as means and SD. The normality distribution of different variables was tested with the Shapiro-Wilk test. A comparison of baseline parameters between patient groups was performed with the Student *t* test, the Mann-Whitney or median nonparametric test, and the chi-square test for categorical parameters. All analyses were performed with SPSS, version 17.0 (SPSS, Inc., Chicago, IL).

Results

Population characteristics

A total of 96 patients with HCV chronic infection, genotype 1, were treated with OBV/PTV/r + DSV regimen. Baseline demographics and clinical characteristics are shown in **Table 1**. Twelve weeks therapy was administered to 80 (83%) patients and RBV was added in 66 (68%). Patients who received RBV were similar with those not treated with RBV. Median age of the cohort was 57.7 years, with 54% female and 16% with diabetes. All the patients were Hispanics with no African Americans included in our cohort. A total of 41 (43%) patients were treatment experienced, including 4 (4%) patients with previous boceprevir or telaprevir triple therapy. Extrahepatic manifestations associated with HCV infection were reported in 11 (12%) patients, being cryoglobulinemic vasculitis the most frequent one presented in 4 patients. All cirrhotic patients were CTP A at the moment of initiating OBV/PTV/r ± DSV therapy except for 7 who were CTP B. Overall, 31 (30.6%) patients had baseline surrogate markers for hepatic dysfunction, 15%, 13% and 13% of the patients presented hypoalbuminemia, hyperbilirubinemia and INR lower than 1.5, respectively. Thrombocytopenia was present in 49% of the patients.

Effectiveness

All the patients who completed OBV/PTV/r + DSV regimen presented undetectable HCV RNA 12 weeks after completion of treatment. Overall, SVR12 was achieved by 97% (93/96) (**Figure 1**). Among those patients who completed the scheduled therapy, all achieved EOT and SVR12, with no virologic breakthrough reported. Only 3 patients failed to achieve SVR12. Of these, one patient discontinued therapy due to serious adverse events and one

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developed septic shock and died. The remaining patient discontinued treatment because of an event unrelated to HCV therapy. One patient discontinued therapy at week 7 of treatment after developing encephalopathy but still accomplished SVR12. MELD score in cirrhotic patients decreased at least 1 point between baseline and post-treatment week 12 in 41% of the cases (**Figure 2**).

Safety

Adverse events were reported in 60 (62%) patients; most were mild and occurred more frequently in those treated with RBV (**Table 2**). The most common adverse events were pruritus (21% of patients) and nausea (17%). Total bilirubin level >3 mg/dL was only reported in patients receiving RBV (17%). Hemoglobin drop ≥3 g/dL was observed in 23% patients. Decline in hemoglobin level below 10 g/dL was described in 6% of patients whereas values below 8 g/dL were not reported. All the patients who developed significant hemoglobin drop received RBV and in all cases anemia was managed by RBV dose reduction. During post-treatment follow up one case of HCC was identified in a patient that had originally showed no lesion on the liver ultrasound examination at baseline.

Serious adverse events were reported in 5 patients who were all treated with RBV and were related with hepatic decompensation (**Table 3**). According to treating physicians, in 3 cases decompensation was associated with ongoing antiviral therapy. Four patients presented previous history of ascites and/or encephalopathy and 3 patients were CTP B at baseline. One death occurred during treatment secondary to pneumonia and septic shock. Another patient discontinued therapy after 7 weeks when he presented hyperbilirubinemia (14 mg/dL) but still achieved SVR12. A third patient discontinued treatment after developing ascites and encephalopathy at day 10 of treatment. Adrenal insufficiency was diagnosed in one patient after 4 days of therapy when he presented encephalopathy and hyponatremia. The patient was placed on corticosteroid replacement therapy and OBV/PTV/r + DSV regimen was reinitiated 2 months later achieving SVR12. Another patient discontinued therapy after 5 days when breast cancer was diagnosed.

Discussion

In our Latin American cohort of genotype 1 HCV-infected patients treated with OBV/PTV/r + DSV ± RBV we observed a SVR12 rate over 97%, nearly matching the rates reported in clinical trials.(Poordad *et al.*, 2014; Zeuzem *et al.*, 2014; Feld *et al.*, 2016) Therapy was safe and well tolerated except in those patients with CTP B or previous history of ascites and/or encephalopathy. Furthermore, the use of RBV was significantly associated with a higher incidence of adverse events.

The regimen also proved to be effective in compensated cirrhotic patients. These findings are consistent with

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the results of clinical trials and real-world studies.(Kwo *et al.*, 2014; Sulkowski *et al.*, 2015; Flisiak *et al.*, 2016; Pockros *et al.*, 2016) Patients co-infected with HIV were taking stable atazanavir or raltegravir-inclusive antiretroviral regimen. No serious adverse events were reported in this subgroup but we must keep in mind that the sample size was too small to make any definitive conclusions.

Regarding the safety profile of OBV/PTV/r + DSV therapy, the majority of adverse events were mild, and strongly associated with use of RBV. Pruritus, nausea, headache and asthenia were the most common adverse events, in agreement with the results of previous clinical trials and real-life studies.(Poordad *et al.*, 2014; Chamorro-de-Vega *et al.*, 2016; Flisiak *et al.*, 2016) In our study, hyperbilirubinemia and anemia were also present in patients with RBV co-administration but no ALT elevation was reported. Decline of hemoglobin level below 10 g/dL was infrequently reported and no blood transfusions were required. Seventy percent of the patients received RBV according to the recommendations of the summary characteristics of the product. Recently, the TURQUOISE-III trial has shown that the addition of RBV is not necessary for cirrhotic patients infected with genotype 1b and this recommendation has been incorporated by international guidelines.(Feld *et al.*, 2016)

In our study no virologic breakthrough was detected. All the patients who completed treatment presented undetectable HCV RNA at EOT, and remained undetectable 12 weeks after completion of therapy. Current guidelines from the European Association for the Study of the liver and the AASLD/IDSA recommend HCV RNA measurement at weeks 2 and/or 4 only as means to monitor compliance and treatment efficacy.("http://www.hcvguidelines.org/full-report/ ," 2016; Liver, 2016) The concept of response-guided therapy is no longer effective with the interferon-free regimens. In clinical routine, the treating physician decides HCV RNA measurements frequency. With available data the final treatment outcome cannot be define on how on-treatment HCV RNA results are during OBV/PTV/r + DSV regimen.

Treatment with OBV/PTV/r + DSV is not recommended in patients with CTP B or C cirrhosis.(Liver, 2016) Post-marketing reports of hepatic decompensation were described; however, the causal association between its use and the development of liver failure has not been established.(*http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlerts-forHumanMedicalProducts/ucm468757.htm*) In our series, CTP B patients were included before these recommendations were released by the Food and Drugs Administration and 3 of them developed on-treatment liver failure and one died. Two studies reported outcomes of OBV/PTV/r + DSV in patients with CTP B, although the 25 patients achieved SVR12, 8 patients experienced serious adverse events.(Mantry *et al.*, 2015; Flisiak *et al.*, 2016) We suggest that in patients with current signs of hepatic functional impairment or history of hepatic decompensation,

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alternative therapeutic options should be evaluated.

Low- and middle-income countries account for more than 80% of the global HCV burden but most patients with HCV infection remain untreated.(Jayasekera, Barry, Roberts & Nguyen, 2014) This great disparity is the consequence of low detection rate of HCV-infected patients and the high cost of DAA therapy. Approval of second-wave DAAs in Latin America occurred 2-3 years later than in developed countries, so safety and effectiveness of these new therapies in our region is limited. Latin America lacks of adequate representative real-world cohorts concerning the use of any interferon-free regimen, either at country or regional levels. Regional differences in the predictors of response might result in differences in real world effectiveness. For example, a recent study reported the absence of Q80K polymorphism in 114 HCV-infected patients from Argentina, a well known predictor of low response when using protease inhibitors.(Martinez *et al.*, 2016)

While this study includes a large cohort of diverse patients treated in clinical practice, using standardized follow up protocols, as in any study, there are some limitations. First, owing to its retrospective design and reliance on medical records from routine clinical practice, some mild to moderate adverse events might be omitted. Second, given the inclusion of multiple centers from different countries, there was likely variability in criteria for adverse events management as well as threshold for discontinuing treatment. However, we consider that capturing the real life clinical use of OBV/PTV/r + DSV in different clinical situations is a strength that increases the generalizability of our findings.

Our study confirms that OBV/PTV/r + DSV treatment strategy is highly effective in patients with chronic HCV without cirrhosis or with CTP A cirrhosis in non-European populations. Adverse events were often mild and rarely led to treatment discontinuation except for patients with CTP B cirrhosis or with previous history of hepatic decompensation. The high effectiveness and safety of these drugs in a Latin American context could support the need for public strategies to expand the access of OBV/PTV/r + DSV and other DAAs combinations in order to reduce the burden of HCV infection in our region.

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Figure Legends

Figure 1. Virologic response to OBV/PTV/r/DSV ± RBV therapy

Figure 2. Change in MELD SVR12 in cirrhotic patients

Table 1. Baseline demographics and clinical characteristics

Variable	Study population (n=96)
Age, years (±SD)	57.7 (11.9)
Female gender, n	53 (54)
BMI, kg/m2 (±SD)	25.2 (3.4)
Treatment history, n (%) Naïve Non-responder PR Non-responder PI	 51 (53) 41 (43) 4 (4)
Cirrhosis, n (%)	56 (58)
HCV genotype, n (%) 1a 1b 1 (subgenotyping not available)	 16 (17) 77 (80) 3 (3)
HIV, n (%)	7 (9)
HCV RNA level IU/mL (log)	2,668,180 (6,18)
Bilirubin mg/dL,(±SD)	1.1 (0.6)
ALT IU/L (±SD)	90 (73)
INR (±SD)	1.16 (0.15)
Hemoglobin g/dL (±SD)	13.9 (1.6)
Platelets /mm3 (±SD)	148,500 (77,835)
Creatinine mg/dL (±SD)	0.83 (0.18)
Child-Pugh score (±SD) *	5.7 (0.9)
MELD score (±SD) *	9.6 (2.2)
Ribavirin use, n (%)	66 (68)

ALT, alanine aminotransferase; BMI, body mass index; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; MELD, model for end-stage liver disease; PI, protease inhibitor; PR, pegylated interferon + ribavirin; RBV, ribavirin; SD, standard deviation
* Only cirrhotic patients were included

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Table 2. Summary of adverse events

	All (n=96)	With RBV (n=66)	Without RBV (n=30)	P
Any AE, n (%)	60 (62)	55 (83)	10 (33)	<0.0001
Serious AE, n (%)				
Hepatic decompensation	3 (3)	3 (5)	0	NS
Death	1 (1)	1 (1)	0	
Drug related AE leading to treatment discontinuation, n (%)	3 (3)	3 (5)	0	NS
Most common AEs, n (%)*				
Asthenia	16 (17)	14 (21)	2 (7)	0.08
Headache	13 (14)	12 (18)	1 (3)	0.05
Pruritus	20 (21)	15 (23)	5 (17)	0.6
Insomnia	8 (8)	6 (9)	2 (7)	0.6
Rash	12 (12)	12 (18)	0	0.008
Diarrhea	8 (8)	7 (11)	1 (3)	0.4
Nausea/Vomiting	15 (16)	14 (21)	1 (3)	0.03
Chemical or hematological abnormality, n (%)				
Total Bilirubin >3 mg/dL	16 (17)	16 (24)	0	0.002
Hemoglobin drop >3 g/dL	22 (23)	22 (33)	0	<0.0001

AE, adverse events; NS, not significant; RBV, ribavirin

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Table 3. Characteristics of patients who developed hepatic decompensation during treatment.

	1	2	3	4	5
Age	73	50	66	56	57
Gender	F	M	F	M	M
Previous hepatic decompensation . Ascites . Encephalopathy	 No No	 Yes No	 Yes No	 Yes Yes	 Yes Yes
Decompensation related to therapy	No	Yes	Yes	Yes	No
Cause of discontinuation	Breast cancer	Ascites, encephalopathy, pneumonia	Ascites, encephalopathy	Hyperbilirubinemia	Adrenal insufficiency
Time until discontinuation	5 days	10 weeks	10 days	7 weeks	4 days
Death	No	Yes	No	No	No
Platelets /mm3	76,000	42,200	59,000	102,000	75,000
Albumin mg/dL	3.3	3.0	2.9	3.4	3.3
MELD score	9	13	13	10	11
Child-Pugh	A (5)	A (6)	B (7)	B (9)	B (8)
SVR12	No	No	No	Yes	Yes

MELD, model for end-stage liver disease; SVR, sustained virologic response

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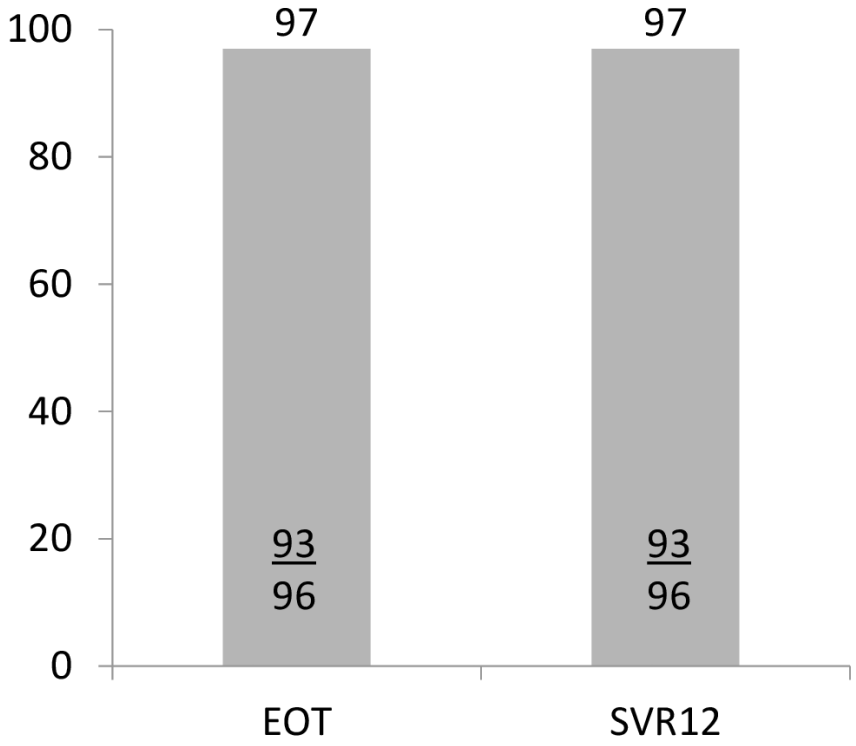
Figure 1. Virologic response to OBV/PTV/r/DSV ± RBV therapy



EOT, end of treatment; SVR12, sustained virologic response 12 weeks after completing treatment

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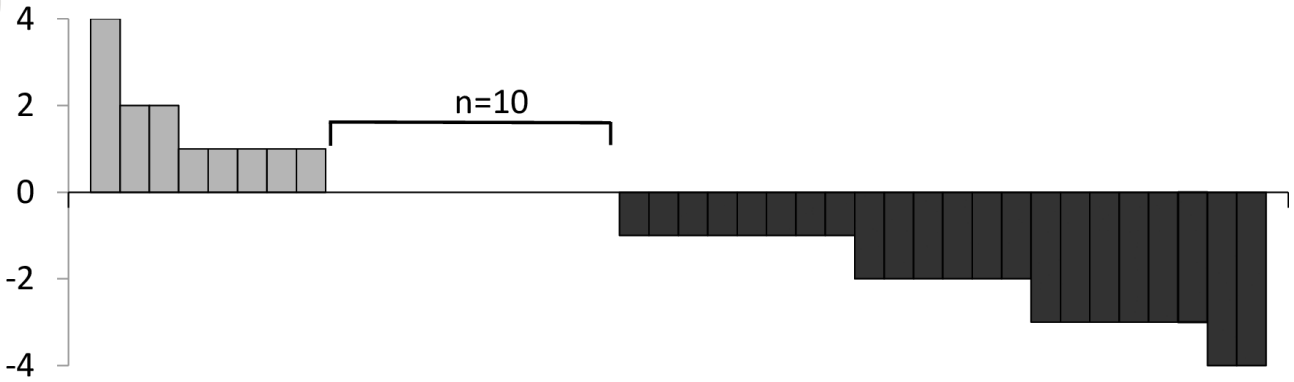
Figure 2. Change in MELD SVR12 in cirrhotic patients



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