



Treatment of Chronic HCV Infection with the New Direct Acting Antivirals (DAA): First Report of a Real World Experience in Southern Brazil

Hoel Sette-Jr, * Hugo Cheinquer, **,*** Fernando H. Wolff, **,***
Alexandre de Araujo, **,*** Silvia Coelho-Borges, **,*** Silvia R.P. Soares, * Mauricio F.A. Barros*

* Pró-Fígado, São Paulo, São Paulo, Brazil.

** Hospital de Clínicas de Porto Alegre e Programa de Pós-Graduação em Gastroenterologia e Hepatologia da Universidade Federal do Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil.

*** Hospital Moinhos de Vento, Porto Alegre, Rio Grande do Sul, Brazil.

ABSTRACT

Introduction and aim. There is almost no data regarding the efficacy of direct acting antivirals (DAAs) therapy in Brazil. The aim of this historical cohort study is to describe the sustained virologic response (SVR) rate among real-world compensated chronic hepatitis C patients in three hepatology centers from Southern Brazil. **Materials and methods.** Patients were included if they had at least 12 weeks follow-up after the end of therapy. Patients that were lost to follow-up or had treatment prematurely interrupted for any reason were considered treatment failure in this intention to treat analysis. **Results.** 219 patients were analyzed. Mean age was 57.4 ± 10.9 years and 142/219 (64.8%) were male. Genotype 1 was present in 166 patients (75.8%; 1a 29.2%, 1b 46.6%); Genotypes 2, 3 and 4 in 8 (3.7%), 43 (19.6%) and 2 (0.9%), respectively. 96 (43.8%) were cirrhotic. 134 (59.5%) were treatment experienced. DAA therapies were: sofosbuvir (SOF) + ribavirin (RBV) in 10 patients; SOF + simeprevir (SMV) \pm RBV in 73; SOF + pegylated interferon (PEG-IFN) + RBV in 6; SOF + daclatasvir (DCV) \pm RBV in 51, SOF + ledipasvir (LDV) \pm RBV in 61, and paritaprevir/ritonavir + ombitasvir + dasabuvir (PTVr/OBV/DSV) \pm RBV in 18 patients. SVR-12 was achieved in 208/219 (95%). Ten patients had virologic failure: 6 cirrhotic, 7 treatment experienced, and 6 either genotype 3 or 1a. No adverse event was attributed to the DAA therapy. **Conclusions.** Real world experience with DAA therapy in Southern Brazil showed a high rate of SVR and excellent tolerability. Failure to achieve SVR was mainly observed among patients with at least one negative predictor of response: cirrhosis and/or genotypes 1a or 3.

Key words. HCV. Chronic hepatitis C. Direct antiviral therapy. Real World. Brazil.

INTRODUCTION

Hepatitis C virus (HCV) is currently the main cause of end stage liver disease in the Western world. Remarkably, HCV is the only chronic viral infection in humans that can be cured.¹⁻⁴ The recent development of direct acting antivirals (DAAs) active against several targets in the HCV replication cycle has revolutionized HCV therapy. Indeed, sustained virological response (SVR) rates well above 90% have been reported in several phase III clinical trials and real-life observational studies, mostly from United States and Europe.⁵⁻²⁶ Use of DAA therapy has only recently

started in Latin America and there are still few real-life reports regarding the efficacy of this new treatment modality in the region. Thus, the purpose of the present study is to describe the SVR rate with different DAA regimens used for treatment of compensated chronic hepatitis C patients in three hepatology outpatient clinics in Southern Brazil.

MATERIAL AND METHODS

Since February 2014, consecutive compensated chronic HCV infected patients age 18 or older treated with DAA therapy from three hepatology outpatient clinics in South-

ern Brazil, one in São Paulo (Pró-Fígado) and two in Porto Alegre (Pró-Fígado Sul and Hospital Moinhos de Vento), were included in this observational cohort study. Patients were included if they had at least 12 weeks follow-up after the end of therapy. Patients that were lost to follow-up or had treatment prematurely interrupted for any reason were considered treatment failure in this intention to treat analysis.

At baseline, demographic data (gender and age) and clinical data (disease stage, HCV genotype and previous therapy) were collected. The following DAA regimens were used for 12 or 24 weeks: sofosbuvir (SOF) + ribavirin (RBV); SOF + simeprevir (SMV) ± RBV; SOF + pegylated interferon (PEG-IFN) + RBV; SOF + daclatasvir (DCV) ± RBV; SOF + ledipasvir (LDV) ± RBV, and paritaprevir/ritonavir + ombitasvir + dasabuvir (PTVr/OBV/DSV) ± RBV. The decision of treatment regimen was left entirely to the physician in charge of the patient, considering the availability of the drugs in Brazil. This study was conducted before drugs were available in the Brazilian Public Health System; therefore patient's ability to pay for the medication was also an issue in the decision process. There was no treatment protocol agreed by the participants and regimens were used according to published data at the time of treatment initiation. All physicians were highly experienced in HCV therapy and checked for interactions using Liverpool Hep Drug Interactions database (<http://www.hep-druginteractions.org/>) before starting therapy.

The liver disease stage (cirrhosis or no cirrhosis) was defined using biopsy or elastography (≥ 12.5 kPa). Main outcome was SVR-12 defined as undetectable HCV RNA using real time PCR with lower limit of detection (LLQ) < 15 IU/mL recorded at least 12 weeks after the end of treatment. Patients with eGFR < 30 or end stage renal failure or kidney transplant were not included. Patients with liver transplant and HIV co-infection were allowed in the cohort. Assessment of resistance associated substitutions (RAS) related to the most important RAS of the NS5A region (Y93H) was performed in 3 of 6 patients that failed a regimen including an NS5A drug. RAS detection was done using population sequencing with the Sanger method (20% cut-off). All analyses were conducted according to intention to treat.

The protocol was approved by Institutional Review Committee and conducted in accordance with the Declaration of Helsinki. All authors had complete access to the study data, reviewed and approved the final manuscript.

Results were reported as means with standard deviation and range. Proportions were used for descriptive statistics. χ^2 test was used for dichotomous variables, with $p < 0.05$ defining statistical significance. Statistical analysis was conducted using IBM SPSS Statistics 20.

RESULTS

A total of 219 chronic HCV infected patients treated with DAA therapy between February 2014 and April 2016 comprise the population of this real-life cohort study: 218 had an HCV RNA result twelve weeks after the end of therapy and one patient interrupted therapy. There was no major difference detected in patients characteristics among the three centers involved in the

Table 1. Patient characteristics (n = 219).

Male	142	(64.8)
Age (years)	57.4	± 10.9
Cirrhosis*	96	(43.8)
Liver stiffness (kPa)**	14.9	± 12.0
≤ 9.4 kPa**	76	(40.4)
9.5-12.4 kPa**	34	(15.5)
≥ 12.5 kPa**	78	(40.5)
ALT (mg/dL)	107.0	± 92.3
AST (mg/dL)	80.5	± 62.3
Bilirubin (mg/dL)	0.9	± 1.0
INR	1.09	± 0.18
Creatinin (mg/dL)	0.88	± 0.57
Platelets (thousand/ μ L)	161	± 67
Low platelets ($< 100,000/\mu$ L)	35	(18.4)
HCV genotype		
1a	64	(29.2)
1b	102	(46.6)
2	8	(3.7)
3	43	(19.6)
4	2	(0.9)
Treatment naive	85	(40.5)
Treatment regimen		
SOF/SMV ± RBV	73	(33.3)
SOF/DCV ± RBV	51	(23.3)
PTVr/OBV/DSV ± RBV	18	(8.2)
SOF/LDV ± RBV	61	(27.9)
SOF/RBV	10	(4.3)
SOF/Peg-IFN/RBV	6	(2.7)
Treatment duration		
12 weeks	174	(79.5)
24 weeks	45	(20.5)
Ribavirin use	80	(36.5)

* Cirrhosis defined by transient hepatic elastography > 12.5 kPa, characteristic findings on ultrasound, gastroesophageal varices on upper endoscopy, or Metavir F4 and/or Ishak ≥ 5 on hepatic biopsy. ** Measured by transient hepatic elastography. Data available for 188/219 patients. ALT: alanine-aminotransferase. AST: aspartate-aminotransferase. INR: international normalized ratio. SOF: sofosbuvir. SMV: simeprevir. RBV: ribavirin. DCV: daclatasvir. PTVr/OBV/DSV: paritaprevir/ritonavir, ombitasvir, dasabuvir. LDV: ledipasvir. Peg-IFN: pegylated interferon. MELD: Model of End Stage Liver Disease.

study, therefore data was decided to be shown altogether.

Demographic and clinical data are depicted in table 1. Similar to other reported series, there was a male predominance and most patients were Caucasians infected with HCV genotype 1. It is important to highlight that almost half of all the patients included were genotype 1b. For most patients (188/219) liver stiffness was measured using transient hepatic elastography. Results showed significant fibrosis in most of our patients: mean 14.9 ± 12.0 kPa; median 10.8 kPa; range 3.5-69.1 kPa. Among the 96 patients with cirrhosis, 79% had MELD scores < 10, and 95% < 12. Only two patient were decompensated in the beginning of treatment, with MELD scores of 22 and 25.

Posttreatment HCV RNA result at least 12 weeks after the end of treatment was available for 218 patients. In one patient this data was not available because he died during treatment and was considered as treatment failure.

Among 219 patients, SVR was achieved by 208 (95%).

The rates of SVR according to the presence or absence of cirrhosis was 92.7% and 96.7%, respectively. Only genotype 3 cirrhotic patients had an SVR below 90%. Overall SVR-12 results according to HCV genotype and disease stage are shown in table 2.

SVR-12 results in patients with genotypes 1, 2 and 3 according to DAA regimen and disease stage are summarized in tables 3, 4 and 5, respectively. Patients treated with SOF + SMV had genotype 1 and the majority was treated for 12 weeks with or without RBV, independent of disease stage. Among genotype 1 patients treated with SOF + DCV, it was noted that most cirrhotics received either 12 weeks with RBV or 24 weeks without RBV. All patients with genotype 2 achieved SVR, independent of DAA regimen or treatment duration. Among genotype 3 patients treated with SOF + DCV, 9 of 10 (90%) of the cirrhotic patients received either 12 weeks with RBV or 24 weeks with or without RBV. All 2 patients with genotype 4 were non-cirrhotic and achieved SVR-12, one with SOF + DCV 12

Table 2. Sustained virological response according to HCV Genotype and disease stage (n = 219).

SVR n (%)	Overall n = 219	G1 n = 166	G2 n = 8	G3 n = 43	G4 n = 2
Overall	208 (95.0)	159 (95.8)	8 (100)	39 (90.7)	2 (100)
Patients with cirrhosis	89 (92.7)	64 (94.1)	4 (100)	21 (87.5)	-
Patients without cirrhosis	119 (96.7)	95 (96.9)	4 (100)	18 (94.7)	2 (100)

G1: HCV genotype 1. G2: HCV genotype 2. G3: HCV genotype 3. G4: HCV genotype 4. SVR: sustained virological response.

Table 3. SVR-12 among 166 HCV genotype 1 patients according to DAA regimen and disease stage.

	SOF/SMV n (%)	SOF/DCV n (%)	PTVr/OBV/DSV n (%)	SOF/LDV n (%)	Total n (%)
Cirrhotic (n = 68)	31 (91.2)	7 (87.5)	11 (100)	15 (100)	64 (94.1)
With RBV					
12 weeks	9 (90)	2 (66.7)	6 (100)	1 (100)	18 (90)
24 weeks	3 (100)	-	2 (100)	1 (100)	6 (100)
No RBV					
12 weeks	16 (88.9)	2 (100)	3 (100)	9 (100)	30 (93.8)
24 weeks	3 (100)	3 (100)	-	4 (100)	10 (100)
Non-cirrhotic (n = 98)	33 (97.1)	10 (90.9)	6 (85.7)	46 (100)	95 (96.9)
With RBV					
12 weeks	7 (87.5)	2 (100)	5 (83.3)	3 (100)	17 (89.4)
24 weeks	1 (100)	2 (100)	-	1 (100)	4 (100)
No RBV					
12 weeks	24 (100)	5 (83.3)	1 (100)	39 (100)	69 (98.5)
24 weeks	1 (100)	1 (100)	-	3 (100)	5 (100)

DAA: direct acting antivirals. SOF: sofosbuvir. SMV: simeprevir. RBV: ribavirin. DCV: daclatasvir. PTVr/OBV/DSV: paritaprevir/ritonavir, ombitasvir, dasabuvir. LDV: ledipasvir. Peg-IFN: pegylated interferon. SVR: sustained virological response.

Table 4. SVR-12 among 8 HCV genotype 2 patients according to DAA regimen and disease stage.

	SOF/DCV n (%)	SOF/RBV n (%)	Total n (%)
Cirrhotic (n = 4)			
12 weeks	-	3 (100)	3 (100)
24 weeks	1 (100)	-	1 (100)
Non-cirrhotic (n = 4)			
12 weeks	-	3 (100)	3 (100)
24 weeks	1 (100)	-	1 (100)

DAA: direct acting antivirals. SOF: sofosbuvir. DCV: daclatasvir. RBV: ribavirin. SVR: sustained virological response.

Table 5. SVR-12 among 43 HCV genotype 3 patients according to DAA regimen and disease stage.

	SOF/DCV n (%)	SOF/PEG/RBV n (%)	SOF/RBV n (%)	Total n (%)
Cirrhotic (n = 24)				
With RBV				
12 weeks	2 (100)	5 (100)	3 (100)	10 (100)
24 weeks	4 (80)	-	3 (100)	7 (70)
No RBV				
12 weeks	1 (100)	NA	NA	1 (100)
24 weeks	3 (60)	NA	NA	3 (60)
Non-cirrhotic (n = 19)				
With RBV				
12 weeks	6 (100)	-	1 (100)	7 (100)
24 weeks	-	-	3 (100)	3 (100)
No RBV				
12 weeks	6 (85.7)	NA	NA	6 (85.7)
24 weeks	2 (100)	NA	NA	2 (100)

DAA: direct acting antivirals. SOF: sofosbuvir. RBV: ribavirin. DCV: daclatasvir. Peg-IFN: pegylated interferon. SVR: sustained virological response.

Table 6. Detailed characteristics of 11 patients who did not achieve SVR.

	Gender	Age (years)	Gen	Cirrhosis	Naive	Regimen	Duration (weeks)	Elastography (KPa)	RAS
1	Male	52	1b	Yes	Yes	SOF + SMV	12	12.9	ND
2	Female	60	1b	No	Yes	SOF + SMV + RBV	12	5.2	ND
3	Male	39	1b	Yes	No	SOF + SMV + RBV	12	24.7	ND
4	Female	61	1b	Yes	No	SOF + SMV	12	27	ND
5	Male	55	1a	No	Yes	SOF + DCV	12	NA	Y93H
6	Male	55	3a	Yes	No	SOF + DCV	24	10.1	ND
7	Male	56	3a	Yes	No	SOF + DCV	24	38.5	Y93H
8	Male	60	3a	Yes	No	SOF + DCV + RBV	24	32	Y93H
9	Male	54	3a	No	No	SOF + DCV	12	9.5	ND
10	Male	66	1a	No	No	3D + RBV	12	11.5	ND
11*	Male	64	1b	Yes	No	SOF + DCV + RBV	12	22.0	ND

* Patient died during therapy and was considered treatment failure. Gen: HCV genotype. RAS: resistance associated substitutions after treatment failure. ND: not done.

weeks and the other with SOF + PEG + RBV 12 weeks. Table 6 describes all 11 patients that did not achieve SVR, including one patient that died during therapy of a non-established cause. It was observed that all failures were due to relapse and 10 of 11 had one of the following characteristics: genotype 1a, genotype 3, and/or cirrhosis. Unexpectedly, there was one patient with genotype 1b, treatment naïve and without cirrhosis that failed therapy in the present study. All patients completed therapy, except for the one that died. No patient interrupted therapy due to adverse event. There was no hepatocellular carcinoma or liver decompensation during the study period, but data regarding the occurrence of these events during follow-up after the end of therapy were not systematically reviewed.

DISCUSSION

The present study confirms the high efficacy of DAA therapy which was already reported in phase III trials and other real world observational studies. The majority of patients in this study were genotype 1, followed by genotypes 3, 2 and 4, reflecting the HCV genotype distribution in Brazil.

Overall SVR was 95%, being slightly higher in noncirrhotic compared to cirrhotic patients. The only group with somewhat suboptimal response was comprised of genotype 3 cirrhotic patients, which showed SVR below 90%. This observation confirms other reports, corroborating the fact that this is currently one of the most difficult populations to cure with the available DAA regimens.^{9,10}

Interestingly, among patients with genotypes 1 and 2 there was no major difference in SVR 12 between cirrhotic and non-cirrhotic, independent of DAA regimen used. On the other hand, genotype 3 patients showed an SVR absolute difference of 7.2% between cirrhotic and non-cirrhotic.

Ribavirin use and treatment duration was determined by the attending physician. There was no remarkable difference in SVR-12 related to these variables. However this data has to be taken with caution due to the small number of patients in some arms of the subgroup analysis. Therefore, a definite conclusion on the role of ribavirin use and extending therapy beyond 12 weeks cannot be established based solely on the basis of our findings. Nevertheless, we examined our sample of 28 genotype 1 cirrhotic patients treated with SOF + SMV ± RBV for 12 weeks and did not detect a significant difference in SVR-12 rate regarding RBV use or not (90 vs. 88.9%, respectively).

This result seems to indicate that RBV does not influence SVR with this regimen and replicates the findings of other real-life studies.¹⁹⁻²⁴ Nevertheless it is important to highlight that SVR rates reported with this regimen in cir-

rhotic patients with genotype 1 was higher among Real Life studies from Europe²²⁻²⁶ compared to the ones conducted in the United States,^{18,21} probably reflecting the proportion of genotype 1a with Q80K mutation in the study population. We did not look for baseline resistance substitutions in this cohort, however most of our patients were genotype 1b and Q80K seems to be infrequent in Brazil.²⁷ However the fact that the phase III trial with SOF + SMV for 12 weeks in compensated HCV cirrhotic patients with genotype 1 did not include an arm with RBV leaves this question still open for interpretation.⁶ Interestingly, all cirrhotic patients treated with SOF + SMV ± RBV for 24 weeks achieved SVR in our study.

Regarding our 15 cirrhotic patients with genotype 3 treated with SOF + DCV ± RBV for 12 or 24 weeks, we could not detect an influence of either duration of therapy or RBV use in SVR-12, probably due to the small sample size in this subgroup. Nevertheless, the fact that less than 80% of our genotype 3 cirrhotic patients achieved SVR-12 with this regimen indicates the need of further improvement in interferon-free therapy for this population. This result is in agreement with other reports from phase III trials and Real World cohorts that found suboptimal SVR rates in this most difficult to treat population. In this regard, the results from our region do not differ from other parts of the world.^{9,10,19,20} Indeed, Nelson, *et al.*⁹ in the ALLY-3 phase III study found an SVR rate of only 63% among HCV genotype 3 cirrhotic patients treated with SOF + DCV for 12 weeks without RBV. Remarkably, addition of RBV and/or extension to 24 weeks seems to improve SVR rate in this patient population to 80-90%, as shown in the ALLY-3 plus¹⁰ and European Compassionate Use Program.¹⁹ On the other hand, the 70% SVR rate showed in the United Kingdom experience probably reflects the more advanced stage of the cirrhotics included in that study.²⁰

Regarding DAA experience in Latin America, there are a few preliminary reports that have been presented mainly as abstracts in regional meetings (Table 7). The limitation of real-life studies such as the present work resides mainly in the fact that it is non-randomized, allowing for selection bias. This study was conducted before the Brazilian Ministry of Health started providing free therapy, patients included in this cohort represent mainly private patients that had access to therapy through their personal insurance or out of pocket. These patients comprise a large segment of the Brazilian population, however we cannot affirm that they represent the whole population of HCV infected patients in Brazil. On the other hand, the high number of patients included tends to compensate for that. Except for the lower SVR rate observed in genotype 3 patients with cirrhosis, we could not find significant clinical or laboratory differences that impact on SVR rates among patients

Table 7. Preliminary results of recently reported real-life DAA therapy in Latin America.

Author (reference)	N	Genotype	DAA regimen	Cirrhosis	SVR-12* n/N (%)
Mendizabal M, <i>et al.</i> ²⁸	83	1, 4	PTVr/OBV/DSV ± RBV	59%	56/56 (100)
Soza A, <i>et al.</i> ²⁹	44	1b	ASV/DCV	86%	24/28 (86)
Vargas J, <i>et al.</i> ³⁰	71	1b (97%)	ASV/DCV, PTVr/OBV/DSV, SOF/DCV, SOF/LDV	64%	39/44 (89)
Chirino-Sprung RA, <i>et al.</i> ³¹	84	1b (70%)	Seven different DAA regimens not specified in abstract	45%	81/84 (96)
Naveira MCM, <i>et al.</i> ³²	2,851	1, 2, 3	SOF/SMV ± RBV, SOF/DCV ± RBV	NR	243/257 (95)
Ferrada A, <i>et al.</i> ³³	25	1b (84%)	ASV/DCV, PTVr/OBV/DSV	84%	18/20 (90)
Malé-Velázquez R, <i>et al.</i> ³⁴	50	1, 2, 3	Eight different DAA regimens not specified in abstract	58%	42/44 (95)

DAA: direct acting antivirals. SOF: sofosbuvir. SMV: simeprevir. RBV: ribavirin. DCV: daclatasvir. PTVr/OBV/DSV: paritaprevir/ritonavir, ombitasvir, dasabuvir. LDV: ledipasvir. ASV: asunaprevir. NR: not reported. *SVR-12: sustained virological response as described in the abstract.

treated with DAA regimens used in the present study. It is important to note that the overwhelming majority of the 11 patients who failed therapy in our cohort had at least one of the following negative predictors of response: cirrhosis, genotype 1a or genotype 3. In fact, among all non-cirrhotic patients with genotype 1b there was only one with virological failure, confirming that this population is currently one of the easiest to cure with the available DAA regimens.

Finally, it is our conclusion that real-life experience with DAA therapy in compensated chronic HCV infected patients from Southern Brazil showed a high rate of SVR and excellent tolerability, despite the high frequency of patients with cirrhosis and previous failure to interferon based therapy included in the study population. The remarkable efficacy and tolerability of the DAA regimens used in our cohort is in full agreement with the published phase III trials. Results such as this renew our hope that this new therapeutic modality, coupled with measures to increase diagnosis and access to care, will eventually achieve the ultimate goal of eliminating HCV as a threat to public health worldwide.

FINANCIAL SUPPORT

This study did not have financial support

REFERENCES

- Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatology* 2014; 61: 45-57.
- Li B, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2011; 9: 509-16.
- Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenon MS, Brinkley SC, Moore RD, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults co-infected with HIV/ HCV. *JAMA* 2012; 308: 370-8.
- van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; 308: 2584-93.
- Kwo P, Gitlin N, Nahass R, Bernstein D, Etkorn K, Rojter S, Schiff E, et al. Simeprevir plus sofosbuvir (12 and 8 weeks) in hepatitis C virus genotype 1-infected patients without cirrhosis: OPTIMIST-1, a phase 3, randomized study. *Hepatology* 2016; 64: 370-80.
- Lawitz E, Matusow G, DeJesus E, Yoshida EM, Felizarta F, Ghalib R, Godofsky E, et al. Simeprevir plus sofosbuvir in patients with chronic hepatitis C virus genotype 1 infection and cirrhosis: A phase 3 study (OPTIMIST-2). *Hepatology* 2016; 64: 360-9.
- Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, McPhee F, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology* 2016; 63: 1493-505.
- Wyles DL, Ruane PJ, Sulkowski MS, Dieterich D, Luetkemeyer A, Morgan TR, Sherman KE, et al. Daclatasvir plus Sofosbuvir for HCV in Patients Coinfected with HIV-1. *N Engl J Med* 2015; 373: 714-25.
- Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, Freilich BF, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015; 61: 1127-35.
- Leroy V, Angus P, Bronowicki JP, Dore GJ, Hezode C, Piantino S, Pol S, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology* 2016; 63: 1430-41.
- Afdhal N, Zeuzem S, Kwo P, Choijkier M, Gitlin N, Puoti M, Romero-Gomez M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; 370: 1889-98.
- Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; 370: 1483-93.
- Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, Fried MW, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology* 2015; 149: 649-59.
- Andreone P, Colombo MG, Enejosa JV, Koksai I, Ferenci P, Maieron A, Müllhaupt B, et al. ABT-450, ritonavir, ombitasvir,

- and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. *Gastroenterology* 2014; 147: 359-65.
15. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, Tam E, et al. PEARL-III Study; PEARL-IV Study. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med* 2014; 370: 1983-92.
 16. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, Shiffmann ML, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014; 370: 1973-82.
 17. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, De Jesus E, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naïve patients: the COSMOS randomised study. *Lancet* 2014; 384: 1756-65.
 18. Dieterich D, Bacon BR, Flamm SL, Kowdley KV, Milligan S, Tsai N, Younossi Z, et al. Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network: academic and community treatment of a real-world, heterogeneous population. *Hepatology* 2014; 60: 220A.
 19. Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, Berg T, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. *Gut* 2016 [Epub ahead of print].
 20. Foster GR, Irving WL, Cheung MCM, Walker AJ, Hudson BE, Verma S, McLaughlan J, et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol* 2016; 64: 1224-31.
 21. Sulkowski MS, Vargas HE, Di Bisceglie AM, Kuo A, Reddy KR, Lim JK, Morelli G, et al, for the HCV-TARGET Study Group. Effectiveness of Simeprevir Plus Sofosbuvir, With or Without Ribavirin, in Real-World Patients With HCV Genotype 1 Infection. *Gastroenterology* 2016; 150: 419-29.
 22. Gallego A, Alvarado E, Gely C, Pagès N, Masip M, Margall N, Torras X, et al. Treatment with sofosbuvir + simeprevir for 12 weeks in HCV compensated cirrhosis (genotypes 1 and 4); the use of ribavirin does not influence sustained viral response. *J Hepatol* 2016; 64: S741.
 23. Salomoni E, Gianni E, Gragnani L, Oliveri F, Brunetto MR, Luchi S, Bartolozzy D, et al. High SVR rates with SMV + SOF in HCV GT1 and GT4 patients with cirrhosis or advanced fibrosis: a real practice analysis from a large regional database in Tuscany, Italy. *J Hepatol* 2016; 64: S761-S762.
 24. Ramos H, Gómes J, Linares P, Martín I, Almohalla C, Jorquera F, García I, et al. Simeprevir and Sofosbuvir with or without ribavirin in genotype 1 chronic hepatitis C patients: efficacy and safety in real life. *J Hepatol* 2016; 64: S765-S766.
 25. Gaeta GB, Menzaghi B, D'Offizzi G, Giorgini A, Lazzarin A, Babudieri S, Brunetto M, et al. Effectiveness of simeprevir treatment for hepatitis C in real practice: preliminary results from the Stily Italian Observational Study. *J Hepatol* 2016; 64: S770-S771.
 26. Mariño Z, Pascasio JM, Sánchez-Antolin G, Baliellas C, Prieto M, Moreno JM, Carrion JA, et al. Safety and efficacy of sofosbuvir plus simeprevir in a Spanish Cohort of 622 cirrhotic patients infected with genotypes 1 or 4. *J Hepatol* 2016; 64: S831.
 27. Lisboa-Neto G, Noble CF, Pinho JR, Malta FM, Gomes-Gouveia MS, Alvarado-Mora MV, da Silva MH, et al. Resistance mutations are rare among protease inhibitor treatment-naïve hepatitis C genotype-1 patients with or without HIV coinfection. *Antivir Ther* 2015; 20: 281-7.
 28. Mendizabal M, Gallardo PE, Haddad L, Adrover R, Ferrada A, Aravena E, Roblero JP, et al. Safety and effectiveness of Paritaprevir/r/Ombitasvir/Dasabuvir ± Ribavirin in Genotype 1 and 4 HCV infected patients treated in real life settings: A South American cohort experience. *Ann Hepatol* 2016; 15: A992-3.
 29. Soza A, Monroy H, Labbé P, Urzúa A, Aravena E, Holguín J, Varón A, et al. Effectiveness of asunaprevir plus daclatasvir in patients with hepatitis C virus and advanced fibrosis: real-world experience from the LALREAN Network. *Ann Hepatol* 2016; 15: A998.
 30. Vargas JI, Monroy H, Beckmann A, Arrese M, Nenítez C, Barrera F, Soza A. Results of all-oral therapy for chronic hepatitis C in a single center. *Ann Hepatol* 2016; 15: A1000.
 31. Chirino-Sprung RA, Dehesa M, Wolpert E, Corona-Lau C, García-Juarez I, Moctezuma-Velázquez C, Sánchez-Avila JF, et al. Chronic hepatitis C treatment with direct acting antiviral agents in a real life setting. *Ann Hepatol* 2016; 15: A999.
 32. Naveira MCM, Almeida EC, Cattapan E, Fernandes N, Gomes JN, Graner B, Santos ME, et al. New antivirals for hepatitis C in Brazil: preliminary effectiveness analysis with current national databases. *Ann Hepatol* 2016; 15: A999.
 33. Ferrada A, Urzúa A, Pérez-Luco T, Molina n, González K, Aravena E, Arancibia JP, et al. Two interferon-free regimens for genotype 1 hepatitis C. Report of treatment "real life" in patients in Chile. *Ann Hepatol* 2016; 15: A993.
 34. Malé-Velázquez R, De La Cabada-Bauche J, Mireles-Alvarez CA, Hernández-Jaime M, Medina-Medrano MA, Colunga-Lozano LE, De La Torre González P, et al. Real life experience with interferon-free direct acting antivirals (IFDAA) in Mexican patients with chronic hepatitis C infection. *Ann Hepatol* 2016; 15: A994.

Correspondence and reprint request:

Hugo Cheinquer, Ph.D., M.D.

Ramiro Barcelos, No. 2350, ZP 90035-903, Porto Alegre, Brazil

Tels.: +55 51 33598307, +55 51 99816760

E-mail: drhugo@terra.com.br; hcheinquer@gmail.com