Official journal of the Spanish Society of Chemotherapy

Original

Juan Carlos del Rio-Valencia
Rocío Asensi-Diez
Rocío Tamayo-Bermejo
Isabel Muñoz-Castillo

Effectiveness of 12 week ledipasvir/sofosbuvir and predictors of treatment failure in patients with hepatitis C

Hospital Regional Universitario de Málaga

Article history
Received: 30 November 2018; Revision Requested: 4 February 2019; Revision Received: 14 April 2019; Accepted: 6 June 2019

SUMMARY

Introduction. The efficacy of ledipasvir/sofosbuvir (LDV/SOF) have been demonstrated in randomized controlled trials, however, there is an unmet need for real-world effectiveness data. It is important to gather data regarding potential predictors of treatment failure with (LDV/SOF). Predictors of sustained virologic response (SVR) to all-oral HCV regimens can inform nuanced treatment decisions. The objectives of this study were to evaluate the effectiveness of LDV/SOF, SVR12 as main endpoint and SVR24 as second endpoint, and identify predictors of treatment failure.

Material and methods. Retrospective and observational study carried out from April 2015 to January 2016. Inclusion criteria: patients with HCV infection treated with LDV/SOF for 12 weeks during study period. The patients that were treated during 24 weeks were excluded as well as those treated with peg-interferon. Binary logistic regression was used to predict what variable was associated with treatment failure.

Results. A total of 122 patients were analyzed achieving SVR12 91.80% (112/122) of them. The patients with HCV genotype (GT) 1a or GT1b or GT4 achieved SVR12. Only one pre-treated non-cirrhotic HCV GT1 patients relapsed to treatment. The lowest SVR12 were obtained for GT3, 43.75%, (7/16). Everybody that got SVR12 achieved SVR24. None of the variables analyzed significantly influenced the SVR12, except GT (p=0.001). Almost all the relapses occurred in GT3.

Conclusion. LDV/SOF combination has been very effective to treat GT1 and GT4 infected patients, however, has constituted a suboptimal therapeutic option for those patients infected with GT3, regardless of the rest of the variables analyzed.

Keywords: Hepatitis C, ledipasvir/sofosbuvir, effectiveness, treatment failure, predictors.

Correspondence:
Juan Carlos del Rio-Valencia.
Hospital Regional Universitario de Málaga. Avenida de Carlos Haya s/n. CP.29010. Málaga.
Phone: 951291435.
Fax: 951291493.
E-mail: mailto:juancardelrio@telefonica.net.

Efectividad de ledipasvir/sofosbuvir durante 12 semanas de tratamiento y factores predictivos de fracaso del tratamiento en pacientes con hepatitis C

RESUMEN

Introducción. La eficacia de ledipasvir/sofosbuvir (LDV/SOF) se ha demostrado en ensayos clínicos, sin embargo, son necesarios más estudios sobre su eficacia en la práctica clínica. Además es importante estudiar los posibles factores predictivos de fracaso de tratamiento con LDV/SOF. Los factores predictivos de respuesta viral sostenida (RVS) a antivirales de acción directa pueden informar sobre decisiones de tratamiento. Los objetivos de este estudio fueron evaluar la efectividad de LDV/SOF, RVS12 como variable principal y RVS24 como secundaria, e identificar los factores predictivos de fracaso del tratamiento.

Material y métodos. Estudio retrospectivo y observacional realizado desde abril de 2015 a enero de 2016. Criterios de inclusión: pacientes con infección por VHC tratados con LDV/SOF durante 12 semanas. Se excluyeron los pacientes tratados durante 24 semanas y los tratados con peg-interferón. Aplicamos el método estadístico denominado regresión logística binaria para predecir qué variable estaba relacionada con el fracaso del tratamiento.

Resultados. Se analizaron 122 pacientes logrando el 91,80% (112/122) RVS12. Los pacientes infectados con genotipo (GT) 1a o GT1b o GT4 lograron RVS12. Solo un paciente, no cirrótico y previamente tratado, infectado con GT1 no alcanzó RVS12. Las tasas más bajas de RVS12 se obtuvieron para GT3, 43.75%, (7/16). Todos los pacientes que obtuvieron RVS12 lograron RVS24. Ninguna de las variables analizadas influyó significativamente en la RVS12, excepto GT (p=0.001). Casi todas las recaídas ocurrieron en GT3.

Conclusiones. La combinación LDV/SOF ha sido muy efectiva para tratar a los pacientes infectados con GT1 y GT4, sin

embargo, ha constituido una opción terapéutica subóptima para los infectados con GT3, independientemente del resto de las variables analizadas.

Palabras claves: Hepatitis C, ledipasvir/sofosbuvir, efectividad, no respuesta tratamiento, factores predictivos

INTRODUCTION

Chronic hepatitis C (CHC) is a worldwide cause of liver-related morbidity and mortality. It affects over 185 million people, approximately 2–3% of the world's population. Although this prevalence may be relatively low overall, it varies by age group and is typically much higher in cohorts between the ages of 45 and 75. For example, in Central and East Asia, the prevalence peaks at 8.8–8.9% for those aged 55–64 [1].

Over the last several years, the management of CHC has been revolutionized by the development of cell-mediated targeted therapies [direct-acting antiviral agents (DAAs)] against hepatitis C virus (HCV). Indeed, we are at the beginning of a new era of HCV management, which is beneficial to patients and clinicians alike. Treatment regimen that have left behind was fraught with side effects, quality of life (QOL) impairment and high treatment failure rates. The new regimens are simple, safe, effective regimens of short duration with minimal side effects [2].

Six different genotypes of hepatitis C virus HCV (genotypes 1, 2, 3, 4, 5, 6) have been identified [3]. Genotype 1, specifically 1b, is the most common subtype worldwide affecting 42% of HCV-infected individuals [3]. This is followed by genotype 3 (26%), most commonly found in Pakistan and India, and genotype 4 (14%) which is most common in North Africa and the Middle East. In the US, genotype 1a is the most common, accounting for 58% of HCV infected individuals; genotype 1b accounts for 21%, genotype 2 accounts for 15% and genotype 3 accounts for 5% [3]. In Spain, different studies [4-6] have revealed that the most frequent genotype is genotype 1 (69.6%-78.4%), predominating the subtype 1b 35.1% and the second most prevalent subtype is 1a, 23.1% [6]; genotype 3 is the second in frequency (12.03-19.5%) [4, 6]; genotype 4 explains between 9.1-12.54% [4-6] and finally genotype 2 constitutes about 1.5-2.4% [4-6]. The genotype is clinically relevant given that some of current DAAs do not have pangenotypic efficacy. In addition, each genotype is associated with a different sustained virologic response (SVR) rate [2].

Although the efficacy of ledipasvir/sofosbuvir (LDV/SOF), a fixed-dose combination, have been demonstrated in randomized controlled trials, there is an unmet need for real-world effectiveness data and studies that assess the association of rates of SVR with specific clinical and demographic factors in the population. It is important to gather data regarding potential predictors of treatment failure with LDV/SOF. Studies have assessed the association between the rate of SVR12 with LDV/SOF in HCV genotype 1 infection and specific clinical and demographic factors, such as sex, history of treatment failure, presence of cirrhosis, basal viral load, concomitant use of medications that reduce the concentrations of LDV or SOF, and human immunodeficiency virus (HIV) coinfection [7].

Predictors of sustained virologic response (SVR) to all-oral HCV regimens can inform nuanced treatment decisions [8]. The objectives of this study were to evaluate the effectiveness of LDV/SOF treatment in HCV genotype 1, 3 and 4 as measured by the rate of SVR12 as main endpoint and SVR24 as second endpoint and to identify predictors of treatment failure in the patients.

MATERIAL AND METHODS

Retrospective and observational study carried out in a third level hospital. Study period: April 2015-February 2016. Inclusion criteria: Patients with HCV infection treated with LDV/SOF for 12 weeks during study period.

Exclusion Criteria: patients from whom adequate clinical and/or analytical information was not available for further analysis. The patients that were treated during 24 weeks were excluded as well as those treated with peg-interferon.

The information was obtained from the electronic clinical/medical records and dispensing records from outpatient software (Cafydim® and ATHOS-Prisma®) Pharmacy Service.

Outcomes collected: Demographic variables: age and sex. Clinical data: basal viral load (viral RNA content before starting therapy) (VL), SVR at week 12 (SVR12), defined as HCV RNA titres lower than 15 IU/mL 12 weeks after the final of treatment, SVR at week 24 (SVR24), defined as HCV RNA titres lower than 15 IU/mL 24 weeks after the final of treatment. HCV-RNA levels were measured by the COBAS TaqMan HCV Test v2.0 (RCTM) (Roche Molecular Diagnostics) with a lower limit quantification (LLOQ) of 15 IU/ml. Respect to fibrosis grade, patients were categorized depending on the fibrosis grade according to METAVIR scale (F0-F4). Fibrosis stage was determined by non-invasive device: Fibroscan®. F4 patients were considered as cirrhotic. Other variables picked up were: platelet levels (cel/µl), albumin concentration (g/dl), transaminases hepatic levels (IU/L): aspartate transaminase (AST) and alanine transaminase (ALT) and bilirubin concentration (mg/dl).

We also have assessed whether patients had had liver transplant, HIV co-infection or had been treated previously for HCV and adherence.

The main endpoint measured was the SVR12 and the second endpoint was: SVR24.

Adherence variable: Adherence was measured according to pharmacy dispensing records.

In the event that one of the patients was admitted to our hospital, the Pharmacy Service provided the DAA agents during the entire hospitalization period. According to this, the adherence calculation also took into account the registration of dispensed medication by unit dose to hospitalized patients.

Statistical analysis. The variables collected were ex-

pressed as median (range) or mean and standard deviation. Binary logistic regression was used to identify independent clinical and demographic factors associated with treatment failure. All analyses were performed by using SPSS v.17. Here p values < 0.05 were considered statistically significant.

RESULTS

In the study period, in our hospital, 124 HCV patients were treated with LDV/SOF. Two patients were excluded due to insufficient clinical or analytical information. The genotypic distribution of all patients is summarized in table 1.

Baseline characteristics. Of the 122 patients included in the study, 78 (63.93%) were male, with mean age of 56.23 ± 9.14 years. Cirrhosis was present in 33.60% (n=41) of the cohort. Also, 15 patients (12.29%) had received liver transplant, and 48 patients (39.34%) were pre-treated patients for HCV. In addition, 32 patients (26.23%) were HIV co-infected and 78 (63.93%) had VL higher than 800,000 IU/mL. We measured other serum biomarkers related to stage of liver fibrosis and liver function such as platelet, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and also bilirubin [9]. The median platelet count was 176,000 (27,000-375,000) cel/µl, the mean albumin was 4.00 ± 0 .45 g/dL. The median AST, ALT and total bilirubin were 50 (18-244) IU/L, 64 (12-346) IU/L and 0.66 (0.18-3.15) mg/dL, respectively. Baseline demographics, analytical and clinical characteristics of enrolled patients are summarized in table 2.

Table 1 Genotypic distribution of different patients treated from April 2015 to February 2016.

Genotypic distribution	Number of patients (%)
GT 1 non-a non-b	12 (9.68%)
GT 1a	29 (23.38%)
GT 1b	46 (37.10%)
GT 3	16 (12.90%)
GT 4	21 (16.94%)
Total	124 (100.00%)

Table 2 Baseline characteristics of all enrolled patients.

	GT1 (n=10)	GT1a (n=29)	GT1b (n=46)	GT3 (n=16)	GT4 (n=21)	TOTAL (n=122)	P value
Age (years); mean ± SD	59.09 ± 9.56	58.43 ± 10.33	58.59 ± 10.18	53.05 ± 9.05	52.00 ± 6.60	56.23 ± 9.14	0.398
Sex							0.09
Male	5	25	21	12	15	78	
Female	5	4	25	4	6	44	
Stage of fibrosis							0.682
F4	3	10	14	7	7	41	
F3	5	8	15	6	7	41	
F2	2	8	16	2	4	32	
F1	-	3	1	1	3	8	
Liver transplant	2	3	9	1	0	15	0.625
Previously treated	3	11	20	4	10	48	0.528
HIV co-infected	2	12	3	1	14	32	0.243
Basal VL > 800,000 U/ml	8	24	34	6	6	78	0.338
Platelet; median (range)	147,000 cel/µl (51,000-214,000)	192,000 cel/µl (27,000-307,000)	176,000 cel/µl (32,000-375,0000)	152,000 cel/µl (96,000-326,000)	185,000 cel/µl (50,000-243,000)	176,000 cel/µl (27,000-375,000)	0.226
Albumin; mean ± SD	4.02 ± 0.51 g/dL	4.04 ± 0.50 g/dL	4.05 ± 0.48 g/dL	3.91 ± 0.47 g/dL	4.00 ± 0.29 g/dL	4.00 ± 0.45 g/dL	0.439
AST; median (range)	65 IU/L (37-127)	50 IU/L (20-210)	48 IU/L (18-244)	57 IU/L (23-170)	49 IU/L (24-108)	50 IU/L (18-244)	0.324
ALT; median (range)	65 IU/L (31-115)	64 IU/L (12-253)	56 IU/L (13-346)	70 IU/L (26-162)	59 IU/L (33-217)	64 IU/L (12-346)	0.125
Bilirubin; median (range)	0.80 mg/dL (0.39-3.15)	0.65 mg/dL (0.18-2.34)	0.66 mg/dL (0.21-1.63)	0.74 mg/dL (0.36-2.06)	0.54 mg/dL (0.28-0.97)	0.66 mg/dL (0.18-3.15)	0.268

Finally, we analyzed the treatment adherence and it was of 100% in all patients. Therefore, this variable was not included in the binary logistic regression analysis.

Sustained virologic response (SVR). Of the 122 patients included in the study, 112 patients (91.80%) achieved SVR12. If we analyze the different genotypes, we observe that 98.82% (84/85) of patients with GT1 achieved SVR12, however; only 43.75% (7/16) of all GT3-infected patients treated with LDV/SOF reached SVR12 and 100% (21/21) of the GT4-infected patients treated got SVR12 (figure 1).

A binary logistic regression analysis was carried out to determine if there were factors associated with treatment failure, and it was found that none of the baseline variables analyzed in table 2 had a significant influence on SVR12 ($p > 0.05$), except GT ($p = 0.001$). In fact, almost all relapses occurred in patients GT3-infected patients.

a) Genotype 1

If we analyze the different subgroups of patients, we observe that all patients achieved SVR12 except one pre-treated non-cirrhotic HCV GT1. Everybody that reached SVR12 achieved SVR24 (figure 2).

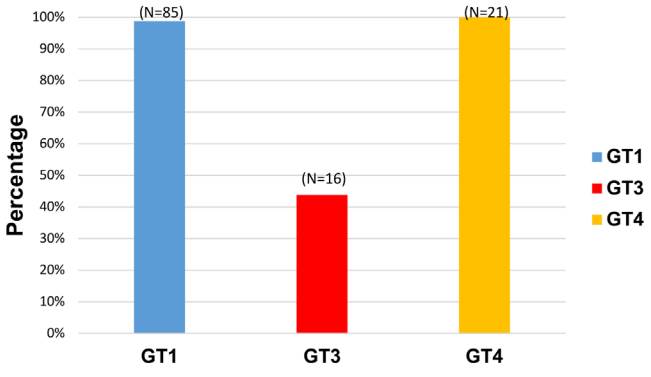

Figure 1 Percentage of patients who have achieved Sustained Virologic Response at 12 weeks (SVR12) depending on the genotypes. GT1= genotype 1, GT3= genotype 3, GT4= genotype 4.

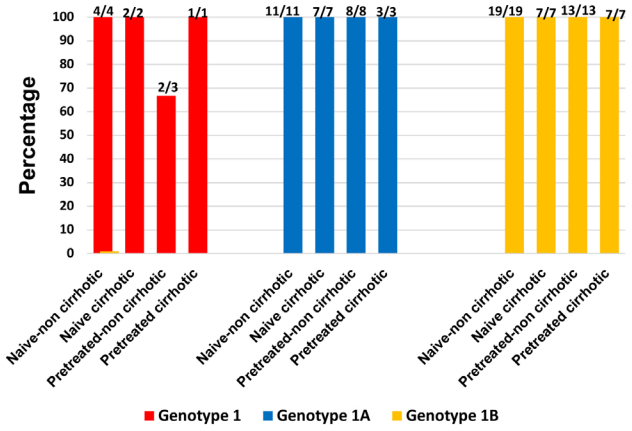

Figure 2 Sustained Virologic Response at 12 weeks (SVR12) rates of hepatitis C virus (HCV) genotype 1-infected patients (n=85). SVR12 of all patients with chronic HCV genotype 1 infection treated with ledipasvir/sofosbuvir.

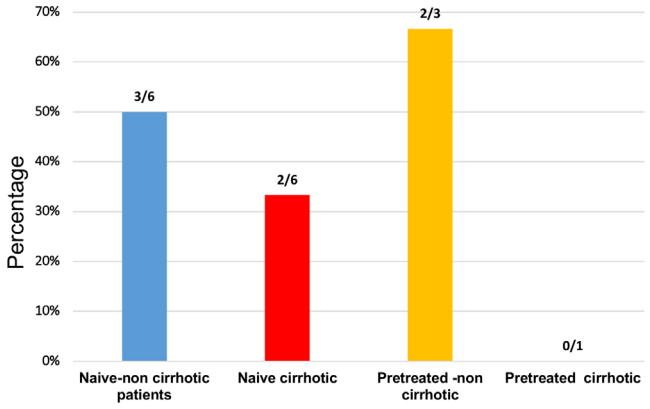

Figure 3 Percentage of different subgroups of genotype 3-infected patients (n=16) who have achieved Sustained Virologic Response at 12 weeks (SVR12) with ledipasvir/sofosbuvir.

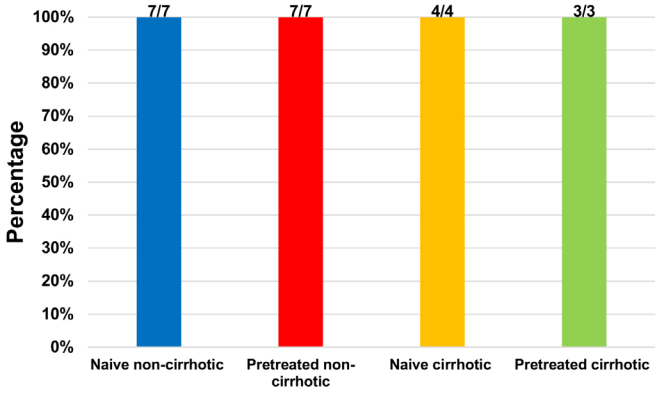

Figure 4 Percentage of different subgroups of genotype 4-infected patients (n=21) who have achieved Sustained Virologic Response at 12 weeks (SVR12) with ledipasvir/sofosbuvir.

b) Genotype 3

If we analyze the different subgroups of patients we observe that: 50% (N=3) of naive-non cirrhotic patients achieved SVR12; 33.33% (N=2) of naive cirrhotic got SVR12; 66.66% (N=2) of pre-treated-non cirrhotic patients reached SVR12 and nobody of pre-treated cirrhotic patients achieved SVR12. Everybody that achieved SVR12 achieved SVR24 (figure 3).

c) Genotype 4

As to GT4, the different subgroups reached SVR12 and like GT1 and GT3 everyone, that achieved SVR12, got SVR24 (figure 4).

DISCUSSION

In this study, we have investigated the real-world effectiveness of the regimen LDV/SOF administered for 12 weeks in patients infected with hepatitis C virus (HCV) genotype 1, 3 and 4 who met inclusion criteria explained in materials and methods. Also, we have identified factors associated with SVR in these patients treated in routine clinical practice.

Our population was 122 patients, whose genotypic distribution was similar to that published in other studies in Spain [5, 6], regarding to GT1, concretely, the percentage of genotype 1 of our patients was 70.16% vs. 69.6%-78.4%.) As to genotype 3 was 12.90% vs. 12.03%-19.5% and genotype 4 was 16.94% vs. 9.1-12.54%, genotypic distribution a little bit different and it may be explained by the fact that a lot of GT3-4 infected patients were treated with other treatment regimens.

a) Genotype 1

LDV/SOF has showed high rates of SVR12 in our study: 98.82% (n=84/85). This rate was similar to SVR12 rate (95%) derived from the study Ramos et al. (2017). We analyzed different subgroups of patients treated with LDV/SOF and we observed that all naive patients achieved SVR12 (100%, n=50/50), same result as ION-1 study (99%, 211/213) [10]. As to pre-treated patients, 97.17% (34/35) obtained SVR12, it is similar to ION-2 study [11] where SVR12 rate was of 94% (202/215). However, it is important to underline that the sample size in the ION-1 and ION-2 studies was bigger than our study and basal conditions of the patients could differ.

b) Genotype 3

Patients with HCV genotype 3 are at a higher risk of liver disease progression and hepatocellular carcinoma development [12, 13]. However, compared with other HCV genotypes, DAAs combinations have lower efficacy against genotype 3 in patients with liver cirrhosis. In our study, the global SVR12 in patients with genotype 3 HCV infection was 43.75% (7/16), however, in ELECTRON-2 clinical trial [14] was 16/25 (64%). This difference could be explained because in ELECTORN-2 study, only naive patients were treated with this treatment regimen, conversely, in our study, four patients were pre-treated and seven of the totals were cirrhotic. In ELECTRON-2 study, we do not know if any patients were cirrhotic or not.

These results are aligned with the treatment regimens as valuable options for genotype 3 recommended by *European Association for the Study of the Liver* (*EASL*) (guideline 2016), moment in which the study was carried out. EASL determines that in patients infected with HCV genotype 3, the combination of LDV/SOF is not recommended because LDV is considerably less potent against genotype 3 than velpatasvir (VEL) or daclatasvir (DCV) [15].

c) Genotype 4

Patients with HCV GT4 [15] infection are poorly represented in pivotal clinical trials of second-generation DAAs and in most real world studies. In our cohort, 100% (21/21) of all patients with HCV GT4 infection achieved SVR12, that is to say, a similar SVR12 rate to other real world studies such as Ramos et al. 2017 [5] where 100% (n=11) of the patients got SVR12, respectively. Likewise, the SVR12 rates achieved in this study with the treatment SOF/LDV match the results obtained in published clinical trials, ION-4 [16] with SVR12=96% (n=322/335).

On the other hand, we have found that every subject who achieved SVR12 subsequently got SVR24, however according to other studies between 0.4%-2% of the subjects who achieved a SVR12 subsequently relapsed at week 24 (did not achieve SVR24) [5, 7, 18]. These studies demonstrated that in DAAs regimens, both with or without interferon, SVR12 and SVR24 are closely correlated.

According to results obtained and the logistic regression analysis made to identify independent clinical and demographic factors associated with treatment failure, we can affirm that LDV/SOF combination is very effective to treat GT-1 and GT-4 infected patients but not for those with GT-3. These outcomes match the results achieved by Kouris G et al. [7], in which analyzed the effectiveness of LDV/SOF and predictors of treatment failure in patients with HCV GT-1 infection. None of the included variables were found to be associated with statistically significant differences in odds treatment failure. The same result we got in our cohort, however, we also assessed if the genotype variable could be an important factor of treatment failure observing that GT-3 is a decisive predictor of SVR12 failure. According to the study of Serfaty L. et al. [19] observed that baseline NS5A resistance-associated substitutions (RASs) were more important than the baseline viral load for predicting the efficacy of elbasvir/grazoprevir in participants with HCV GT-1 infection.

SOF (NS4B) is a pangenotypic nucleotide polymerase inhibitor with potent activity against all 6 HCV genotypes in both in vitro replicon assays and extensive clinical use. LDV is a potent and well-tolerated NS5A inhibitor with activity against replicons of genotypes 1a,1b, 4, 5 and 6, with 50% effective concentration (EC50) values ranging from 0.006 nM (genotype 1b) to 1.1 nM (genotype 6a) [14]. However, LDV is much less active against genotype 3a HCV in vitro, with an average EC50 of 168 nM against wild-type virus.

In addition to EC50, another important factor that we should keep in mind is the Resistance-Associated Substitution (RAS). However, the genotypic presence of a RAS does not necessarily translate to a phenotypic treatment failure. Like advanced cirrhosis or prior treatment experience, the presence of RAS represent an important factor in overall treatment outcomes, and when combined with other negative predictors may result in treatment failure. The clinical relevance of resistance testing has been limited to RASs in the NS5A gene. Two RASs in particular, Y93H and A30K, have emerged as the most clinically relevant polymorphisms in HCV-3 with the currently approved regimens, and are present at baseline in up to 8.3 and 6.3% of all HCV-3-infected patients, respectively [14]. To put this in perspective, the 1000-fold shift seen with the signature Y93H resistance-associated substitution in a genotype 1a virus results in an EC50 of approximately 6 nM with a clinically significant reduction in activity. Hence, one might expect that even at baseline the genotype 3 virus is effectively resistant to LDV [20]. However, in the ELECTRON-2 study, 26 patients randomized to receive LDV/SOF+RBV and everybody achieved SVR12, including 6 patients with compensated cirrhosis. These results clearly show that RBV is important but also suggest that LDV is more active against genotype 3 HCV than predicted based on the replicon data alone [20]. Cell culture assays that can assess all stages of the life cycle are limited, particularly for genotype 3 HCV; however, recent advances that allow replication of serum-derived virus may allow for a deeper investigation into the activity of LDV against genotype 3 HCV. It is also possible that RBV and/or SOF increase the sensitivity of genotype 3 HCV to LDV [20].

This study has the usual limitations related to its observational and retrospective design, electronic data collection and the small number of patients included in each arm of treatment. In addition, resistance testing was not performed; thus, we were unable to assess the impact of this factor. On the other hand, we have not analyzed concomitant drugs, except HIV drugs, therefore, we do not know the influence of this factor on the effectiveness and it could be analyzed in future studies.

In addition, it is important to note that this study was carried out between 2015-2016 and the EASL HCV treatment guidelines of those years recommended LDV/SOF to treat pre-treated patients with GT1a and GT4 [21]. However, the EASL HCV treatment guidelines (2018) do not recommend its use for these patients [15]. With respect to genotype 3, both guidelines do not recommend LDV/SOF to treat this genotype infection, but this fixed-dose combination was used to treat GT3 infection according to the therapeutic strategy established by the Ministry of Health, Consumption and Social Welfare in Spain in 2015 [22].

In conclusion in our patient cohort, LDV/SOF combination is very effective to treat GT-1 and GT-4 infected patients, however, constitutes a suboptimal therapeutic option for those patients infected with GT-3, regardless of the rest of the variables analyzed.

FUNDING

None to declare.

CONFLICT OF INTEREST

The authors declare that they have not conflict of interest.

REFERENCES

1. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57(4):1333–42. DOI: 10.1002/hep.26141
2. Lam BP, Jeffers T, Younoszai Z, Fazel Y, Younossi ZM. The changing landscape of hepatitis C virus therapy: focus on interferon-free treatment. Therap Adv Gastroenterol. 2015;8(5):298–312. DOI: 10.1177/1756283X15587481
3. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61(1):77–87. DOI:10.1002/hep.27259
4. Del Rio-Valencia JC, Asensi-Diez R, Villalobos-Torres L, Munoz Castillo I. Direct-acting antiviral agents in patients with hepatitis C genotype 1-4 infections in a tertiary hospital. Rev Esp Quimioter. 2018;31(3):226–36. PMID: 29771105
5. Ramos H, Linares P, Badia E, Martin I, Gomez J, Almohalla C, et al. Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting. World J Gastrointest Pharmacol Ther. 2017;8(2):137–46. DOI: 10.4292/wjgpt.v8.i2.
6. Gutierrez-Aroca JB, Ruiz-Martinez P, Rodriguez-Ruiz L, Casal-Roman M. Distribution of the genotype of the Hepatitis C Virus in Cordoba-Spain. Rev Esp Quimioter. 2018;31(2):164-165. PMID: 29616511
7. Kouris G, Hydery T, Greenwood BC, Lavitas P, Price M, Clements K, et al. Effectiveness of Ledipasvir/Sofosbuvir and Predictors of Treatment Failure in Members with Hepatitis C Genotype 1 Infection: A Retrospective Cohort Study in a Medicaid Population. J Manag care Spec Pharm. 2018;24(7):591–7. DOI: 10.18553/jmcp.2018.24.7.591
8. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness and predictors of sustained virological response with all-oral therapy in 21,242 hepatitis C genotype-1 patients. Antivir Ther. 2017;22(6):481–93. DOI: 10.3851/IMP3117
9. Bang CS, Kang HY, Choi GH, Kim SB, Lee W, Song IH. The Performance of Serum Biomarkers for Predicting Fibrosis in Patients with Chronic Viral Hepatitis. Korean J Gastroenterol. 2017;69(5):298–307. DOI: 10.4166/kjg.2017.69.5.298
10. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889–98. DOI: 10.1056/NEJMoa1402454
11. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir A KP. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014;370(16):1483–93. DOI: 10.1056/NEJMoa1316366

12. Bochud P-Y, Cai T, Overbeck K, Bochud M, Dufour J-F, Mullhaupt B, et al. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. J Hepatol. 2009;51(4):655–66. DOI: 10.1016/j.jhep.2009.05.016

13. Nkontchou G, Ziol M, Aout M, Lhabadie M, Baazia Y, Mahmoudi A, et al. HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. J Viral Hepat. 2011;18(10):e516-22. DOI: 10.1111/j.1365-2893.2011.01441

14. Gane EJ, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. Gastroenterology. 2015;149(6):1454–1461.e1. DOI: 10.1053/j.gastro.2015.07.063

15. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018; 69(2):461-511. DOI:10.1016/j.jhep.2018.03.026

16. Naggie S, Cooper C, Saag M, Workowski K, Ruane P, Towner WJ, et al. Ledipasvir and Sofosbuvir for HCV in Patients Coinfected with HIV-1. N Engl J Med. 2015;373(8):705–13. DOI: 10.1056/NEJMoa1501315

17. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, et al. Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. Gastroenterology. 2013;144(7):1450–1455.e2. DOI: 10.1053/j.gastro.2013.02.039

18. Yoshida EM, Sulkowski MS, Gane EJ, Herring RWJ, Ratziu V, Ding X, et al. Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology. 2015;61(1):41–5. DOI: 10.1002/hep.27366

19. Serfaty L, Jacobson I, Rockstroh J, Altice FL, Hwang P, Barr E, et al. The accuracy of baseline viral load for predicting the efficacy of elbasvir/grazoprevir in participants with hepatitis C virus genotype 1a infection: an integrated analysis. J Viral Hepat. 2019;26(3):329-336 . DOI: 10.1111/jvh.13037

20. Feld JJ, Ramji A, Shafran SD, Willems B, Marotta P, Huchet E, et al. Ledipasvir-Sofosbuvir Plus Ribavirin in Treatment-Naive Patients With Hepatitis C Virus Genotype 3 Infection: An Open-Label Study. Clin Infect Dis. 2017; 65(1):13-19. DOI: 10.1093/cid/cix289

21. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66(1):153-94. DOI:10.1016/j.jhep.2016.09.001

22. Ministerio de Sanidad, Consumo y Bienestar Social. Estrategia terapéutica para la hepatitis crónica causada por el virus de hepatitis C en el Sistema Nacional de Salud. Recomendaciones generales y pautas actuales de tratamiento [web page]. Madrid 2015. [Accessed 2019 February 10]. Available at: http://aeeh.es/wp-content/uploads/2015/04/a77478e2a1147600cb9979b5992281cb.pdf