Journal of Infection 79 (2019) 30–35

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Higher relapse rate among HIV/HCV-coinfected patients receiving sofosbuvir/ledipasvir for 8 vs 12 weeks

Anaïs Corma-Gómez[a], Juan Macías[a,*], Dolores Merino Muñoz[b], Francisco Téllez[c,d], Rafael Granados[e], Luis E. Morano[f], Ignacio De Los Santos Gil[g], Francisco J. Vera-Méndez[h], Antonio Collado[i], Rosario Palacios[j], Juan A. Pineda[a]

[a] Unit of Infectious Diseases and Microbiology, Hospital Universitario de Valme, Seville, Spain
[b] Unit of Infectious Diseases, Hospitales Juan Ramón Jiménez e Infanta Elena, Huelva, Spain
[c] Unit of Infectious Diseases and Microbiology, Hospital Universitario de Puerto Real, Cádiz, Spain
[d] Instituto de Investigación e Innovación en Ciencias Biomédicas de la provincia de Cádiz (INiBICA), Cádiz, Spain
[e] Unit of Infectious Diseases, Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria, Spain
[f] Unit of Infectious Pathology, Hospital Universitario Alvaro Cunqueiro, Vigo, Spain
[g] Unit of Internal Medicine and Infectious Diseases, Hospital La Princesa, Madrid, Spain
[h] Section of Infectious Medicine/Service of Internal Medicine, Hospital General Universitario Santa Lucía, Cartagena, Spain
[i] Infectious Diseases Unit, Hospital Universitario Torrecárdenas, Almeria, Spain
[j] Unit of Infectious Diseases and Microbiology, Hospital Virgen de la Victoria, Málaga, Spain

ARTICLE INFO

Article history:
Accepted 10 May 2019
Available online 14 May 2019

Keywords:
Sofosbuvir
Ledipasvir
8 week treatment
HCV genotype 1
HIV-coinfection
Real-word

SUMMARY

Objectives: To compare the efficacy of sofosbuvir/ledipasvir (SOF/LDV) for 8 weeks (SL8) versus a 12-week course of SOF/LDV (SL12) among HIV/HCV-coinfected patients in clinical practice. In addition we compared sustained virological response (SVR) rates achieved with SL8 in HCV-monoinfected and HIV/HCV-coinfected patients in a real life setting.

Methods: HCV-infected patients were retrospectively selected from the HEPAVIR-DAA and GEHEP-MONO real-life prospective cohorts if they fulfilled the following criteria: 1) Infected with genotype 1; 2) Treatment with SL8 or SL12; 3) Treatment naïve prior to receiving SL8 or SL12; 4) Absence of cirrhosis; 5) Baseline HCV RNA$<6\times10^6$ IU/mL; 6) Reached the scheduled time-point for SVR (SVR12) assessment. SVR12 and relapse rates of HCV-monoinfected and HIV/HCV-coinfected patients were compared on an intention to treat basis. The responses with SL8 and SL12 were also compared.

Results: In the SL8 group, 107 (51%) HCV-monoinfected and 102 (49%) HIV/HCV-coinfected patients were included. One hundred and sixty-four (43%) HCV-monoinfected subjects and 220 (57%) HIV/HCV-coinfected patients received SL12. SVR12 rates for HIV/HCV-coinfected patients treated with SL8 vs SL12 were SVR12 92.2% vs. 97.3% ($p=0.044$) and the respective relapse rates were 4.9% vs. 0.5% ($p=0.013$). SVR12 rates for SL8 among HCV-monoinfected and HIV/HCV-coinfected patients were: 96.3% vs. 92.2% ($p=0.243$), respectively. The corresponding relapse rates were 0.9% vs. 4.9% ($p=0.112$).

Conclusion: HIV/HCV-coinfected patients reach high rates of SVR12 with SL8, although lower than with SL12, mainly due to a higher probability of relapse. SVR12 rates with SL8 are numerically lower and the proportion of relapses higher in HIV/HCVcoinfected patients than in HCV-monoinfected subjects.

Introduction

Hepatitis C virus (HCV) chronic infection is still a major public health problem. Recent estimations point to a global prevalence of 70 million people living with HCV chronic infection worldwide.[1] Most untreated HCV-infected individuals may be soon concentrated in countries in South America, Africa, South-east Asia and Eastern Europe, because access to treatments has been more difficult in those areas, mainly due to cost issues.[2] HIV infection is also highly prevalent in some specific countries of these regions[3] and, in this way, both epidemics do overlap. HIV and HCV coinfection is associated with a higher risk of fibrosis progression and death due to end-stage liver disease.[4–6] Thus, timely access to treatment of HIV/HCV-coinfected patients is a priority.

Sofosbuvir/Ledipasvir (SOF/LDV) is recommended as first line option to treat genotype 1 (G1) and 4-infected patients with a

* Corresponding author.
E-mail addresses: juan.macias.sanchez@gmail.com, jmacias@cica.es, jumasa@me.com (J. Macías).

https://doi.org/10.1016/j.jinf.2019.05.005
0163-4453/

standard duration of treatment of 12 weeks.[7–9] For G1, there is the option of shortening the length of treatment to 8 weeks, as the 8-week regimen was non-inferior to the 12-week course.[10] In addition, a post-hoc analysis showed that the rate of relapse after SOF/LDV for 8 weeks was lower among individuals with baseline HCV RNA levels below 6 million UI/mL.[10] Thus, current guidelines recommend a shorter duration in non-cirrhotic patients, without previous treatment experience and HCV viremia below that threshold.[8,9] A single tablet, once-daily, short-duration regimen can be particularly useful in difficult to follow populations and in low resource settings. Moreover, it is possible to retreat relapses to SOF/LDV for 8 weeks with longer courses of the same regimen with high efficacy.[11] Finally, SOF/LDV is now available as generic, and therefore cheaper, medicine in countries from South America, Africa and South-east Asia.

There are limited comparative data of the efficacy and safety of SOF/LDV 8-weeks between HCV-monoinfected and HIV/HCV-coinfected individuals.[12,13] Current guidelines provide controversial recommendations for treatment with short-duration SOF/LDV in HIV/HCV coinfection. For G1, European guidelines recommend no different duration of SOF/LDV for the HCV-monoinfected or the HIV/HCV-coinfected patients,[9] while USA guidelines recommend against SOF/LDV for a shortened length of time in HIV/HCV-coinfection.[8] Therefore, the aim of this study was to compare the efficacy in real life setting of an 8-week SOF/LDV regimen versus a 12-week of this combination among HIV/HCV-coinfected patients. In addition, SVR rates achieved with an 8-week SOF/LDV regimen among HCV-monoinfected and HIV/HCV-coinfected patients were also compared.

Patients and methods

Patients and study design

This study included patients from two prospective real-life cohorts of direct acting antiviral agents (DAA)-treated patients, conducted at 25 Infectious Diseases Units throughout Spain. In these cohorts, all subjects with HCV infection or HIV/HCV co-infection who initiated therapy with one or more DAA are followed since October 2011 (GEHEP-MONO Cohort, ClinicalTrials.gov ID: NCT02333292 and HEPAVIR-DAA Cohort, ClinicalTrials.gov ID: NCT02057003). For the present study, patients treated from October 2011 to September 2017 were retrospectively selected if they fulfilled the following criteria: 1) Infected with HCV genotype 1; 2) Began treatment with with SL8 or SL12; 3) Naïve for HCV treatment prior to receiving SL8 or SL12; 4) Absence of cirrhosis; 5) Baseline plasma HCV RNA level $<6 \times 10^6$ UI/mL; 6) Reached the scheduled time-point for SVR (SVR12) assessment.

Patient management and study definitions

Patients were classified in two groups: 1) Those who received an 8-week SOF/LDV regimen (SL8); 2) Those who received the same regimen for 12 weeks but met the selection criteria stated above, i.e. the criteria for the 8 weeks duration of SOF/LDV (SL12). The decision about the length of treatment was made by the physician in charge of each patient.

SVR12 was defined as undetectable plasma HCV RNA 12 weeks after the scheduled end of therapy. Relapse was defined as the re-emergence of plasma HCV viremia after undetectable HCV RNA at the end of therapy, provided that, if phylogenetic analysis was available, baseline and re-emergent strains showed a closer genetic distance. Reemergent HCV RNA was considered a relapse if it was detected at week 4 after the end of treatment without genotype switch. Otherwise, re-emergences were considered as reinfections.

Fibrosis was evaluated by transient elastography (FibroScan®, Echosens, France). Cirrhosis was diagnosed if liver stiffness value was equal or greater than 12.5 kPa.

Assessments and endpoints

The primary study outcome was the achievement of SVR12. Demographic and other baseline variables were determined prior to treatment initiation and included: Sex, age, HIV co-infection, genotype 1 subtype, plasma HCV-RNA levels, liver stiffness, and, for those with HIV coinfection, CD4 cell counts, HIV viremia and antiretroviral therapy.

Plasma HCV-RNA levels were measured by PCR, according to the available technique at each participant center (Cobas AmpliPrep/Cobas TaqMan HCV test v2.0; Roche Diagnostic Corporation, Pleasanton, CA, USA lower limit of quantification (LLOQ): 15 UI/mL; Abbott M2000 Real Time System, Abbott Diagnostic, Chicago, IL, US; LLOQ 12 UI/mL). HCV genotype was determined using Versant HCV genotype 2.0 Line Probe Assay (Siemens Healthcare GmbH, ErlaRgen, Germany) or by the Real Time Genotype II (Abbott diagnostic, Chicago IL, USA) procedure.

Data analysis

The primary analysis was performed on an intention to treat approach (ITT), which included all patients meeting the study selection criteria who were prescribed SOF/LDV. In the ITT analysis, all individuals with missing information on response were classified as non-responders. Secondarily, outcomes were reported as a per protocol analysis (PP), excluding those patients with missing data or who dropped-out. The SVR12 and relapse rates were compared between HIV/HCV-coinfected patients receiving 8 and 12 weeks of therapy. In addition, the response rates of each regimen were compared among HCV-monoinfected patients and HIV/HCV-coinfected individuals treated SL8.

Continuous variables were expressed as median (Q1–Q3) and categorical variables as frequencies (percentage), with 95% confidence intervals (95% CI) for the main outcome variables. The comparisons of SVR12 rates and other variables were analyzed using the $\chi 2$ test or Fisher's exact test (categorical variables) and the Student's t-test and the Mann-Whitney U test (continuous variables). Differences were considered significant for p values ≤ 0.05. All data analyses were performed using the SPSS statistical software package release 24.0 (IBM, Chicago, IL, USA). The 95% CI were calculated with EpiDat statistical software package release 4.2. (Available at: https://www.sergas.es/Saude-publica/EPIDAT-4-2).

Ethical statement

This study was designed and performed according to the Helsinki declaration and was approved by the local ethics committee. All patients gave written informed consent before being included in the cohorts.

Results

Characteristics of the study population

By September 2017, 2173 patients from the HEPAVIR and GEHEP cohorts had been treated with SOF/LDV. After excluding 1580 because not meeting the study eligibility criteria, 209 initiated SL8, and 384 received SL12. The disposition of patients is shown in Fig. 1.

The baseline characteristics of the patients, by their HIV status, receiving SL8 and SL12 are shown in Tables 1, 2 and 1supl. There

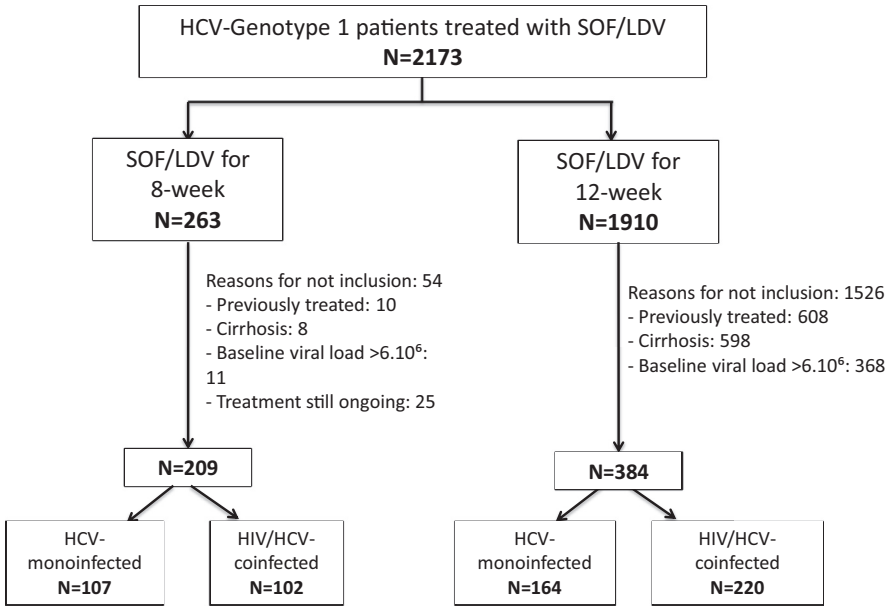

Fig. 1. Patient disposition.
Abbreviations: HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SOF/LDV: sofosbuvir/ledipasvir.

Table 1
Baseline demographic and clinical characteristics of HIV/HCV-coinfected patients with SOF/LDV for 8 or 12 weeks ($N = 332$).

Characteristics	8 weeks ($N = 102$)	12 weeks ($N = 220$)	*p*-value
Age (years)*	49.0 (45.0–53.0)	49.0 (46.0–53.0)	0.204
Sex n (%)			
Male	74 (73%)	178 (81%)	0.091
Risk Factors n (%)			
IDU	79 (77%)	147 (67%)	0.052
Genotype n (%)			
1a	50 (49%)	156 (71%)	
1b	25 (25%)	32 (15%)	<0.001
1 other	27 (27%)	32 (15%)	
HCV RNA ($\log_{10}$ IU/ml)*	5.89 (5.47–6.35)	6.28 (5.87–6.53)	<0.001
Undetectable HIV RNA, n (%)	99 (97%)	206 (94%)	0.561
CD4, cells/mm³*	683 (434–1040)	580 (380–846)	0.022
Liver stiffness (KPa)*	8.1 (6.1–9.5)	8.5 (7.2–10.3)	0.043

Abbreviations: IDU: injecting drug users.
* Median (IQR).

Table 2
Baseline demographic and clinical characteristics of patients with an SOF/LDV 8-week regimen ($N = 209$).

Characteristics	HCV ($N = 107$)	HIV/HCV ($N = 102$)	*p*-value
Age (years)*	51.0 (45.0–63.0)	49.0 (45.0–53.0)	**0.029**
Sex n (%)			
Male	67 (63%)	74 (73%)	0.126
Risk Factors n (%)			
IDU	45 (42%)	79 (77%)	0.000
Genotype n (%)			
1a	40 (37%)	50 (49%)	
1b	45 (42%)	25 (25%)	**0.027**
1 other	22 (21%)	27 (26%)	
HCV RNA ($\log_{10}$ IU/ml)*	6.04 (5.44–6.41)	5.89 (5.47–6.35)	0.605
Liver Stiffness (Kpa)*	7.9 (6.0–8.9)	8.1 (6.1–9.5)	0.349

Abbreviations: IDU: injecting drug users.
* Median (IQR).

was a greater proportion of men and of injecting drug users (IDU) in the HIV/HCV group. Genotype 1a was more frequent in the HIV/HCV cohort. HIV coinfection was present in 48.8% of patients receiving SL8, and in 57.3% of those receiving SL12. Antiretroviral therapy taken by the HIV/HCV-coinfected patients during the study is listed in Table 2supl.

Treatment outcomes according to HIV status

The SVR12 rate (95%CI) for HIV/HCV-coinfected patients was significantly lower in subjects treated with SL8 (92.2% [85.1%–96.6%]) than in those who received SL12 (97.3% [94.2%–99.0%]; $p = 0.044$). Among HCV-monoinfected patients, SVR12 rate to SL8 group was similar to SL12: 96.3% (90.7%–98.9%) and 98.2% (94.7%–99.6%) respectively ($p = 0.440$). The rates of relapse (95%CI) among HIV/HCV-coinfected treated with SL8 where significantly higher (4.9% [1.6%–11.1%]) than in those who received SL12 (0.5% [0.0%–2.5%]; $p = 0.013$). In HCV-monoinfected patients, the relapse rates (95%CI) were 0.9% (0.0%–9.1%) among subjects treated with SL8 and 1.2% (0.1%–4.3%) in those undergoing SL12 ($p = 1.000$). Treatment outcomes comparisons between HIV/HCV-coinfected patients receiving SL8 and those receiving SL12 are shown in Fig. 2.

In the PP analysis, SVR12 rate (95%CI) among HIV/HCV-coinfected patients with SL8 regimen was 95.9% (89.9%–98.9%; 94/98) and for those undergoing a SL12 course 100.0% (123/123; $p = 0.009$).

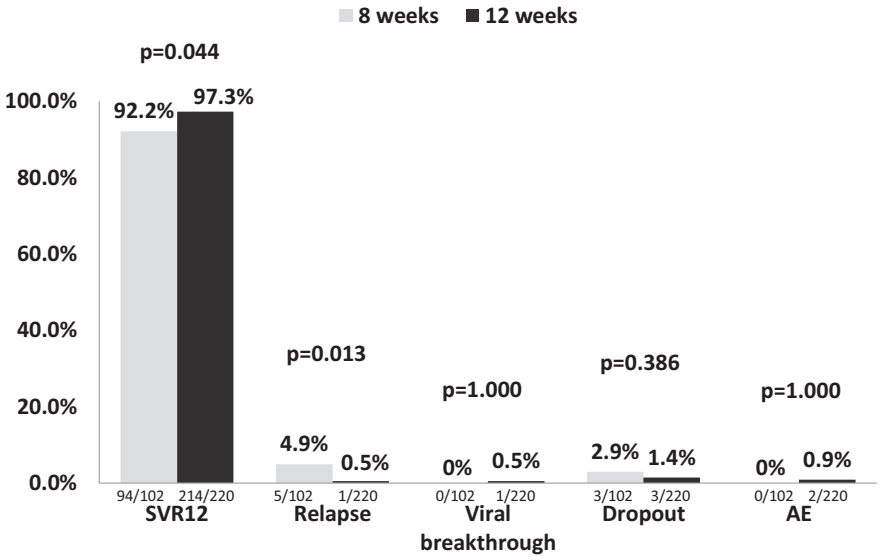

Fig. 2. Treatment outcomes among HIV/HCV-coinfected patients treated with 8 or 12-week SOF/LDV regimen.
Abbreviations: HCV-G1: Hepatitis C virus genotype 1; HIV: Human immunodeficiency virus; SOF/LDV: sofosbuvir/ledipasvir; SVR12: sustained viral response 12 weeks after treatment; AE: discontinuation due to adverse events.

Among patients treated for 8 weeks, 6 relapses were detected, 5 among HIV/HCV-coinfected patients and 1 among HCV-monoinfected subject. Phylogenetic assessment of sequences was carried out in 3 HIV/HCV-coinfected patients and none of them met criteria of re-infection. The other 3 plasma HCV viremia re-emergences were considered relapses as they were detected by week 4 after the end of treatment without genotype switching, and without reinfection risk factors. Among patients receiving a 12-week regimen, 3 relapses were identified. No phylogenetic analyses could be conducted in those patients.

Of the 5 HIV/HCV-coinfected patients receiving SL8 who relapsed, 3 were genotype 1a and the other 2, genotype 1b. The only HIV/HCV-coinfected patient treated with SL12 who failed to respond was genotype 1a. Among HCV-monoinfected patients, one patient infected by genotype 1a treated with SL8 relapsed. In those undergoing SL12, there were 2 relapses, both infected by genotype 1b.

The presence of resistance associated substitutions in the HCV genome was assessed in 3 out of 5 HIV/HCV-coinfected patients who relapsed after receiving SL8. No resistance associated substitutions were detected in the NS5A region. In one HIV/HCV-coinfected patient who relapsed after SL12, resistance associated substitutions were detected in the NS5A region (H58L and Q30R). The presence of resistance associated substitutions in HCV-monoinfected patients could not been assessed.

Treatment outcomes according to the length of therapy

In patients treated during 8 weeks with SOF/LDV, SVR12 rates (95%CI) were numerically lower among HIV/HCV-coinfected patients [92.2% (85.1%–96.6%)] than for HCV-monoinfected subjects [96.3% (90.7%–98.9%); $p = 0.243$], and relapse rates were higher: 4.9% (1.6%–11.1%) versus 0.9% (0.0%–9.1%) respectively ($p = 0.112$). Conversely, SVR12 and relapse rates (95%CI) were similar among HCV-monoinfected and HIV/HCV-coinfected patients who received SL12: SVR12 rates were 98.2% (94.7%–99.6%) for HCV-monoinfected subjects and 97.3% (94.2%–99.0%) for HIV/HCV-coinfected patients ($p = 0.738$); and relapse rates (95%CI) were 1.2% (0.1%–4.3%) for HCV-monoinfected subjects and 0.5% (0.0%–2.5%) for HIV/HCV-coinfected patients ($p = 0.578$).

By PP approach, SVR12 rate (95%CI) was 99.0% (94.7%–99.9%; 103/104) in HCV-monoinfected patients and 95.9% (89.9%–98.9%; 94/98) in HIV/HCV-coinfected patients ($p = 0.201$), in the SL8 group.

Discussion

This study suggests that SVR12 rates with an 8-week SOF/LDV regimen are lower than with a 12-week course of this combination among HIV/HCV-coinfected patients. This is driven by a higher probability of relapse with short duration therapy. Accordingly, SVR12 rates SOF/LDV 8 weeks are numerically lower and the proportion of relapses higher in HIV/HCV-coinfected patients compared with HCV-monoinfected subjects.

In the present study, HIV/HCV-coinfected patients receiving SL8 were less likely to reach SVR12, analyzed on an ITT approach, than those treated with SL12, but fulfilling criteria for SL8 treatment. This lower rate of response to SL8 in the HIV/HCV-coinfected group was not attributable to losses to follow-up or discontinuations due to adverse events, but it was the result of a higher probability of virologic failure because of relapses. The higher rate of relapses suggests that the SL8 regimen is less potent than the SL12 in HIV/HCV-coinfection. Nevertheless, in our study, HIV/HCV-coinfected patients who relapsed to SL8, in whom resistance was evaluated, did not show emergent resistance associated substitutions. NS5A resistance associated substitutions are less frequent after relapse to SOF/LDV for 8 weeks than relapses after SOF/LDV for 12 weeks.[11] In a study of retreatments after failure to treatment containing SOF/LDV, Lawitz et al. found that retreatment with SOF/LDV for 24 weeks achieved SVR12 rates of 80% among those who relapsed to 8 weeks regimens, compared with 46% of those relapsing after 12 weeks regimens.[11] Since relapses after SL8 seem to respond to longer durations of SOF/LDV, these individuals could be retreated with SOF/LDV for a more prolonged period of time or with alternative options.

The rates of relapse that we found among HIV/HCV-coinfected patients receiving SL8 are in agreement with those previously reported for HIV/HCV-coinfected individuals treated with SL8.[12,13] As we observed in the present study, which included a larger sample size HIV/HCV-coinfected patient, relapses were more frequent

in the SL8 than in the SL12 treated groups.[12,13] The AASLD/IDSA guidelines do not support this shortened length of SOF/LDV in HIV/HCV-coinfection[8] because of the lack of specific clinical trials and the scant observational data. In addition, in other recent studies, 6 weeks of SOF/LDV therapy for acute HCV in HIV-coinfected patients achieved low SVR rates, below 80%,[14] contrary to patients with acute HCV infection without HIV-co-infection.[15] In the present study, viral recurrence in HIV/HCV-coinfected patients was not the consequence of reinfection, as re-emergence of plasma HCV viremia fulfilled relapse definition criteria and was more frequent among HIV/HCV-coinfected patients treated with SL8 than among those receiving SL12. The higher recurrence among patients with HIV remains a question, whether is a consequence of immune suppression or of the presence of other concomitant factors.[16]

The present study results could be applied in the management of SOF/LDV in daily clinical practice. If response in HIV/HCV-coinfected patients has to be ensured, SL12 regimen should be selected, in order to minimize the relapses. However, given that relapses to 8-weeks SOF/LDV regimen could be easily retreated, this is an option that could be considered in HIV/HCV-coinfected patients in specific scenarios. For example, SL8 therapy could be cost-effective and could result in better population outcomes, even with lower rates of SVR,[17] under a constrained budget. The savings stemmed from this regimen would allow treating 30% more patients, with potentially fewer visits. This could be a way to optimize resources, especially in resource-limited countries, and to promote the access to treatment between patients with a lower economic status or lower health coverage by insurance in countries without universal health care coverage.

This study has the limitations associated with its own design as an uncontrolled and observational retrospective study. However, potential bias involving the clinician selection of SL8 or SL12 regimens was minimized because patients receiving SL12 were required to fulfill the criteria for SL8. These criteria include some determinants of response as cirrhosis, HCV viral load or treatment experience. In spite of this, there were some differences in baseline characteristics between HIV/HCV-coinfected individuals treated with SL8 and SL12. In fact, HIV/HCV-coinfected patients treated with SL8 had significantly lower baseline HCV RNA and liver stiffness, and higher CD4 cell counts than those treated with a SL12 regimen. The distribution of G1 subtype was also different between SL8 and SL12, with a higher proportion of subtype 1b among those receiving SL8. All these may be favorable features that should have led to better response rates among HIV/HCV-coinfected individuals receiving SL8 compared to those treated for 12 weeks. However, even with these differences, among HIV/HCV-coinfected patients, the relapse rates were higher for SL8 than for SL12. This finding clearly indicates a lower virologic efficacy of SL8 in HIV/HCV coinfection. Phylogenetic assessment was carried out in four of the eight of the patients who failed to respond. Although it is unlikely that a plasma HCV re-emergence at week 4 post-treatment was a re-infection, provided that re-infection risk factors are absent, this possibility cannot completely be excluded. To the best of our knowledge, this is the study that included the largest HIV/HCV-coinfected patients group, treated with SL8. Besides it has been conducted within the same clinical units that treat HCV-monoinfected patients, so the differences in treatment responses are not attributable to different clinical management.

SL8 therapy is a safe and effective regimen that could be considered as a first line treatment in HIV/HCV-coinfected patients under specific conditions. Thus, it could allow shorter duration of treatment, with lower economic costs associated to drugs and monitoring. The ambitious aim of HCV worldwide elimination can only be achieved with effective and significantly less expensive regimens. SL8 could result in the ability to treat more individuals and, consequently, aid in the path to HCV elimination.

Funding

This study was partly supported by the projects "PI15/01607" and "PI16/01443", funded by Instituto de Salud Carlos III, integrated in the national I+D+i 2013-2016 and co-funded by European Union (ERDF/ESF, "Investing in your future") and by the Grupo para el Estudio de las Hepatitis Víricas (GEHEP) (grant GEHEP 001 2017). J.M. is the recipient of a grant from the Servicio Andaluz de Salud de la Junta de Andalucía (grant number B-0037). J.A.P. is recipient of an intensification grant from the Instituto de Salud Carlos III (grant number Programa-I3SNS). This work has been partially funded by the Spanish AIDS Research Network RD16/0025/0010 and RD16/0025/0034 - ISCIII – FEDER.

Conflict of interest

ACG has received lecture fees from Gilead. JM has been an investigator in clinical trials supported by Bristol-Myers Squibb, Gilead and Merck Sharp & Dome. He has received lectures fees from Gilead, Bristol-Myers Squibb, and Merck Sharp & Dome, and consulting fees from Bristol Myers-Squibb, Gilead, and Merck Sharp & Dome. JAP reports having received consulting fees from Bristol-Myers Squibb, Abbvie, Gilead, Merck Sharp & Dome, and Janssen Cilag. He has received research support from Bristol-Myers Squibb, Abbvie and Gilead and has received lecture fees from Abbvie, Bristol-Myers Squibb, Janssen Cilag, and Gilead. RP has received lectura fees and consulting fees from ViiV Healthcare, Gilead Sciences, Merk Sharp and Dohme, Janssen-Cilag. FV has received lecture fees from Gilead and MSD. DM has received lectures fees from ViiV Healthcare, MSD, Gilead and Janssen. She has received consulting fees from ViiV Healthcare and has been an investigator in clinical trials supported by GlaxoSmtihKline. RG has received lecture fees from Abbvie, Gilead, MSD and Janssen. He has received consulting fees from Abbvie and Janssen. The remaining authors report no conflict of interest.

Acknowledgments

Author contributions: J.M had full access and to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: J.M and J.A.P.

Acquisition, analysis, or interpretation of data: all authors.

Statistical analysis: A.C.G and J.M.

Drafting of the manuscript: A.C.G. and J.M.

Critical revision of the manuscript for important intellectual content: all authors.

Obtained funding: J.M, and J.A.P.

Study supervision: J.M.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.05.005.

References

1. World Health Organization. Global Hepatitis Programme. Global Hepatitis report, 2017. 68p. Available at: http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/. Accessed on 21 February 2018.
2. Gee LS. HCV management in resource-constrained countries. *Hepatol Int* 2017;**11**(3):245–54. doi:10.1007/s12072-017-9787-0.
3. UNAIDS. UNAIDS data 2017. http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf. Accessed on 21 February 2018.
4. Macías J, Berenguer J, Japón MA, Girón JA, Rivero A, López-Cortés LF, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. *Hepatology* 2009;**50**(4):1056–63. doi:10.1002/hep.23136.

5. Pineda JA, Romero-Gómez M, Díaz-García F, Girón-González JA, Montero JL, Torre-Cisneros J, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology* 2005;**41**(4):779–89. doi:10.1002/hep.20626.
6. Pineda JA, García-García JA, Aguilar-Guisado M, Ríos-Villegas MJ, Ruiz-Morales J, Rivero A, et al. Clinical progression of hepatitis C virus-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. *Hepatology* 2007;**46**(3):622–30. doi:10.1002/hep.21757.
7. Scott LJ. Ledipasvir/sofosbuvir: a review in chronic hepatitis C. *Drugs* 2018;**78**(2):245–56. doi:10.1007/s40265-018-0864-z.
8. AASLD/IDSA HCV Guidance Panel American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) recommendations for testing, managing, and treating adults infected with hepatitis C virus. *J Hepatol* 2015(62):932–54. doi:10.1002/hep.27950.
9. European Association for the Study of the Liver (EASL) EASL recommendations on treatment of hepatitis C 2018. *J Hepatol* 2018;**0**. doi:10.1016/j.jhep.2018.03.026.
10. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without Cirrhosis. *N Engl J Med* 2014;**370**(20):1879–88. doi:10.1056/NEJMoa1402355.
11. Lawitz E, Flamm S, Yang JC, Pang PS, Zhu Y, Svarovskaia E, et al. Retreatment of patients who failed 8 or 12 weeks of ledipasvir/sofosbuvir-based regimens with ledipasvir/sofosbuvir for 24 weeks. *J Hepatol* 2015;**62**:S192. doi:10.1016/S0168-8278(15)30012-X.
12. Ingiliz P, Christensen S, Kimhofer T, Hueppe D, Lutz T, Schewe K, et al. Sofosbuvir and Ledipasvir for 8 weeks for the treatment of chronic hepatitis C virus (HCV) infection in HCV-monoinfected and HIV-HCV-coinfected individuals: results from the German hepatitis C cohort (GECCO-01). *Clin Infect Dis* 2016;**63**(10):1320–4. doi:10.1093/cid/ciw567.
13. Buggisch P, Vermehren J, Mauss S, Günther R, Schott E, Pathil A, et al. Real-world effectiveness of 8-week treatment with ledipasvir/sofosbuvir in chronic hepatitis C. *J Hepatol* 2017;**68**(4):663–71. doi:10.1016/j.jhep.2017.11.009.
14. Rockstroh JK, Bhagani S, Hyland RH, Yun C, Dvory-Sobol H, Zheng W, et al. Ledipasvir–sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. *Lancet Gastroenterol Hepatol* 2017;**2**(5):347–53. doi:10.1016/S2468-1253(17)30003-1.
15. Deterding K, Cornberg M, Manns MP, Wedemeyer H, Weber K, Koch A, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. *Artic Lancet Infect Dis* 2017;**17**(17):215–22. Www.thelancet.com/infection. doi:10.1016/S1473-3099(16)30408-X.
16. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. *Clin Infect Dis* 2016;**62**(6):683–94. doi:10.1093/cid/civ948.
17. Morgan JR, Kim AY, Naggie S, Linas BP. The effect of shorter treatment regimens for hepatitis C on population health and under fixed budgets. *Open Forum Infect Dis* 2018;**5**(1) ofx267. doi:10.1093/ofid/ofx267.