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RESEARCH ARTICLE

Implementation of a pharmaceutical care program for patients with hepatitis C treated with new direct-action antivirals

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Abstract

Background A pharmaceutical care program is necessary to improve the management of direct-acting antivirals in hepatitis C. *Objective* Describe health outcomes obtained with the implementation of a pharmaceutical care program in Hepatitis C patients treated with direct-acting antivirals. *Setting* This study was performed in a pharmacy department of a university hospital. *Methods* Retrospective study between 1st-April 2015 and 28st-February 2016. Hospital pharmacists implemented interventional measures for validation of antivirals prescriptions, detection of drug-interaction, adverse drug events, education and patient´s adherence to antiviral regimen. *Main outcome measure* Health and quality outcomes of the implementation of the pharmaceutical care program. *Results* A total 128 patients were enrolled. The overall sustained virologic response at week 12 post-treatment rate was 96.1% (95% CI 92.7–99.5). Adverse drug events occurred in 90.6% of the patients, and the majority were grade 1–2. Pharmacists made 334 pharmaceutical interventions. 35.5% of these interventions were aimed to resolve negative results of drugs. 80.9% of the negative results of drugs improved or were eliminated with the application of the measures proposed by the pharmacists ($p \leq 0.001$). Pharmacists carried out 175 preventive interventions to avoid negative results of drugs. 97.3% of these interventions were accepted and managed to prevent the appearance of negative results of drugs ($p = 0.453$). *Conclusion* The implementation of a pharmaceutical care program in patients with hepatitis C treated with direct-acting antivirals has improved the safety in the use of these drugs.

Keywords Antivirals · Chronic hepatitis C · Infectious diseases · Pharmaceutical care · Spain

Impacts on Practice

- Clinical pharmacists in Spain can have an important contribution to the safety of the treatment with direct acting antiviral agents in patients with Hepatitis C.
- Interventions suggested by clinical pharmacists about the treatment with direct acting antivirals in patients with Hepatitis C are often accepted by physicians (in almost 90% of the cases), especially suggestions around (potential) negative results of the drug use.

Introduction

Direct-acting antivirals (DAAs) have improved the management of hepatitis C virus (HCV) infection. These medications are high efficacy, well tolerated, and the course of treatment is normally 12 weeks [1]. These DAAs treatments offer sustained virologic response (SVR) above > 90% in most prevalent populations without the need of pegylated-interferon (Peg-INF) combination [2]. Due to its high efficacy and good tolerability, PegINF-free DAAs regimens have already become the new standard of care in several European countries such as Spain [3].

The access to DAAs into the clinical practice of hepatitis C has been fast. Therefore, there are still many uncertainties

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about its effectiveness and safety in specific populations of patients. On the other hand, the high cost of these treatments requires a careful selection of patients and treatment regimens [4]. These considerations highlight the need to implement pharmaceutical care programs (PCP) to patients with hepatitis C to optimize health outcomes and the resources for these treatments [5, 6].

In Spain, the hospital pharmacist is the last health professional to attend the patient before taking these medications, so the clinical pharmacist could play an important role in the management of these new therapies.

Aim of study

To describe the health results obtained with the implementation of a PCP aimed at patients with hepatitis C treated with DAA.

Ethics approval

This study received the approval from Institutional Review Committee of the hospital of the Universidad Complutense de Madrid (ethics approval number: 3373) and complied with the World Medical Association Declaration of Helsinki (2008 revision) and national standards.

Method

A retrospective study to collect the results of the implementation of a PCP aimed at outpatients with chronic hepatitis C who started treatment with AAD was performed. The study was conducted between 1st April 2015 and 28st February 2016 in the pharmacy department of a general primary university hospital by clinical pharmacists.

Patient inclusion criteria was the following: 18 years or older, confirmed HCV infection, and treated with DAAs [ombitasvir/paritaprevir/ritonavir (OTV/PTV/r), dasabuvir (DSV), sofosbuvir/ledipasvir (SOF/LDV), sofosbuvir (SOF), simeprevir (SMV), daclatasvir (DCV) or peginterferon-alfa (PegINF) with or without ribavirin (RBV)] according to the criteria for treatment defined in clinical practice guidelines and specific recommendations of Madrid Health Service for indication and selection of treatment.

The following variables were collected from the patient clinical record and the Pharmacy Department databases: age, sex, race, presence of comorbidities, concomitant treatment, HCV genotype, liver fibrosis stage, HCV viral load, DAAs regimen and duration. Also, adverse drugs events (ADEs) detected, drug-interactions found and it´s clinical relevance, adherence to antiviral therapy, pharmaceutical interventions (PIs) performed, degree of acceptance and results obtained with these interventions were collected, from the baseline until 12 weeks after completion of DAA treatment in all patients.

Measure of outcomes of the PCP

Effectiveness and safety of treatment with DAA

The effectiveness of treatment with DAAs was defined as the achievement of sustained virologic response at week 12 post-treatment (SVR12) (viral load HCV lower to 15 UI/mL at week 12 post-treatment). HCV-RNA levels were measured using the real-time transcriptase-kPCR assay versant HCV RNA 1.0 Assay (Siemens health care, Erlangen, Germany).

Virologic relapse was defined as a confirmed HCV-RNA level higher than 15 UI/mL between the end of treatment and 12 weeks after the last dose of the DAA in patients who completed treatment and had an HCV-RNA level lower than 15 UI/mL at the final visit during the treatment period.

A methodology for detection and grading of ADEs was implemented by the clinical pharmacists. At each visit to pharmacy department, pharmacists detected and monitored the occurrence of ADEs with the treatment. The pharmacists collected the number of discontinuations due to ADEs with DAAs. Also, the incidence and severity of ADEs related to these treatments. The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [7] was used to classify and determine the severity of the ADEs observed. The pharmacists proposed measures to reduce the toxicity of the DAAs in all patients who presented some ADE.

A protocol for the detection, classification and management of clinically relevant drug-drug interactions was designed. The pharmacists collected and analyzed the number of drug-drug interactions detected, their clinical relevance and the medications, over-the-counter medicine and herbal supplements involved. They also proposed measures to reduce or avoid the possible effects of the drug-interaction detected. For the detection and management of these interactions, the recommendations of the University of Liverpool (http://www.hep-druginteractions.org/) and Micromedex™ and Lexi-Comp® databases were followed.

Adherence to DAA treatment

The adherence to DAAs was assessed using two methods: pill counts (PC) and pharmacy dispensing record (PDR). The overall percentage of adherence for these methods was calculated by making the average percentage of adherence for each of the visits. A personalized program of patient education to improve adherence was implemented in all patients.

Measurement of pharmaceutical interventions carried out during the PCP

A methodology for the collected pharmaceutical interventions (PIs) was implemented. All the PIs were recorded. The PIs were documented and classified according to the classification proposed by the Pharmaceutical Research Group of the University of Granada (PRGUG) (Spain) [8]. This classification is based on the adjustment of drugs doses, the pharmacological strategy and the health education on pharmacotherapy and healthy life habits. The methodology proposed by the PRGUG has never been used to assess a pharmaceutical care program for patients with hepatitis C treated with DAA.

In addition, a specific system was designed to grade the impact and clinical relevance of each PIs in our hospital. The objective of the impact grade was to indicate the meaning of the intervention and its possible benefits on health outcomes of the patient and the sustainability of the health system. Table 1 summarizes the classification of the PIs used in this study. The specific impact grade system has been validated by our hospital pharmaceutical department for the patients enrolled in the study. No similar system is used for other patients in our hospital or in other hospital in Spain.

The parameters evaluated were the number of pharmaceutical interventions (PIs) performed and the degree of acceptance, the number of problems related to medication (PRMs) detected and avoided. And the amount of negative results of the drug (NRD) detected and resolved with the measures proposed by the pharmacists.

Data analysis

Demographic, clinical characteristics, effectiveness and safety results are presented as number (percentage) and median (interquartile range), as appropriate. To assess the relationship between the resolution or prevention of the NRD and the grade of acceptance of the PI made, the Chi square test was used. Outcomes were analyzed based on all patients who received at least one dose of the DAA. Data was analyzed using IBM SPSS Statistics program version 19 (Armonk, New York).

Results

A total of 128 patients were enrolled in the study and received at least one dose of DAA. Baseline demographic and clinical characteristics in the overall population are

Table 1 Classification of the PIs used in this study and code of impact and significance

Classification of the PIs	
A. PI directed to intervene on the quantity of drug	A.1. Modify the dose (Adjust the amount of drug that is administered at once)
	A.2. Modify the dosage (change in the frequency and / or duration of the treatment)
	A.3. Modify the dosage schedule (redistribution of the amount of medication)
B. PI directed to intervene on the pharmacological strategy	B.1. Add a drug (substitute a drug with another of different composition or different dosage form or route of administration)
	B.2. Suspend a drug
	B.3. Substitute a medication (replace one medication with another of different composition or different pharmaceutical form or route of administration)
C. PI directed to intervene on the education of the patient	C.1. Form of use and administration of the medication (education in the instructions and precautions for the correct use and administration of medications)
	C.2. Reinforce the importance of adherence to treatment (modify skills with respect to treatment, to reduce voluntary non-compliance)
	C.3. Educate in non-pharmacological measures. (hygienic-dietetic measures that favor the achievement of therapeutic objectives)
Measures of the results of pharmaceutical care provided	
PI impact code	
Impact on patient health outcomes	
Effectiveness	Interventions that allow a greater utility of the drug in the patient to achieve the objectives set, including those that affect the improvement of the care circuits
Security	PI that allow to reduce the risk in the use of the drug in the patient
Impact on sustainability of the Health System	
Sustainability	Interventions that allow a greater use of resources, save direct or indirect costs, improve efficiency, etc

Classification of IPs adapted from the DADER methodology of the Pharmaceutical Research Group of the University of Granada (Spain)

Table 2 Baseline demographic and clinical characteristics of HCV-infected patients and DAA prescription profile

Total patient included	N = 128
Demographic data	
Median age, years (IQR)	55 (14)
Male sex	81 (63.3%)
Ethnicity	
White/Caucasian	128 (100%)
Clinical characteristics and comorbidities	
HCV genotype	
1 unspecified	3 (2.3%)
1a	23 (18%)
1b	85 (66.4%)
3	6 (4.7%)
4	11 (8.6%)
Hepatic fibrosis stage	
Non-cirrhosis	71 (55.5%)
Cirrhosis	57 (44.5%)
Presence of comorbidities	100 (78.1%)
Psychiatric disorders	26 (20.3%)
Heart failure	8 (6.3%)
Arterial hypertension	44 (34.4%)
Diabetes	21 (16.5%)
HIV coinfection	9 (7.0%)
VHB coinfection	2 (1.6%)
Other	58 (45.3%)
History of recreational substance abuse	66 (51.6%)
Any history of addiction to parenteral drugs	38 (29.7%)
Any history of alcohol abuse	34 (26.6%)
Treatment characteristics	
Prior HCV treatment	
Treatment-naïve	81 (63.3%)
Prior treatment with peginterferon plus ribavirin	47 (36.7%)
Prior treatment with boceprevir/telaprevir	10 (7.8%)
DAA prescription profile	
Treatment selection	
OTV/PTV/r+DSV	64 (50.0%)
SOF/LDV	45 (35.2%)
SOF+DCV	4 (3.1%)
OTV/PTV/r	3 (2.3%)
SOF+SMV	4 (3.1%)
Other	8 (6.25%)
Addition of ribavirin (RBV)	53 (41.4%)
Treatment duration	
8 weeks	2 (1.6%)
12 weeks	99 (77.3%)
24 weeks	27 (21.1%)

Data are presented as n (%), unless otherwise indicated

IQR interquartile range, *HCV* hepatitis C virus, *HIV* Human immunodeficiency virus, *HBV* hepatitis B virus, *OTV* ombitasvir; *PTV/r* paritaprevir/ritonavir, *DSV* dasabuvir, *SOF* sofosbuvir, *LDV* ledipasvir, *DCV* daclatasvir, *SMV* simeprevir

Fig. 1 Sustained virologic response rate at week 12 post-treatment (SVR12) (ITT analysis). **a** SVR12 rate in patients according to prior HCV-treatment. **b** SVR12 rate according to HCV genotype. **c** SRV12 rate according to DAA regimen received. *OTV* ombitasvir, *PTV/r* paritaprevir/ritonavir, *DSV* dasabuvir, *SOF* sofosbuvir, *LDV* ledipasvir, *PegINF* peginterferon, *SMV* simeprevir, *RBV* ribavirin, *DCV* daclatasvir

shown in the Table 2. Most patients were non-cirrhotic (55.5%), genotype 1b infection (66.4%), and treatment-naïve to HCV (63.3%). Overall, 7.0% patients were coinfected with Human Immunodeficiency Virus (HIV) and a relevant number of patients had psychiatric disorder (20.3%). The most frequent DAA regimen was OTV/PTV/r+DSV (50.0%). The duration of treatment was 12 weeks in most patients (77.3%). In 41.4% of patients the ribavirin was added to the regimen.

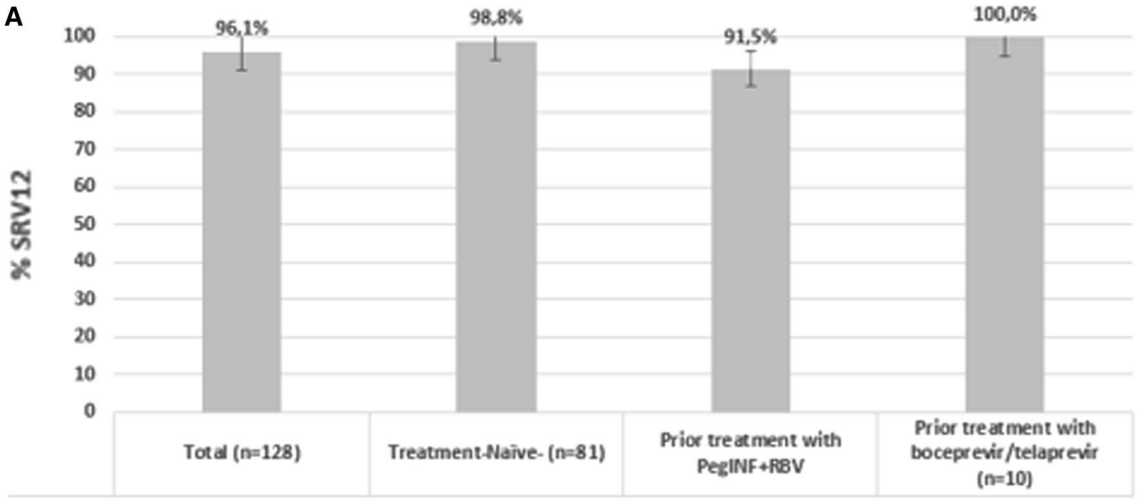
Effectiveness, adherence and safety

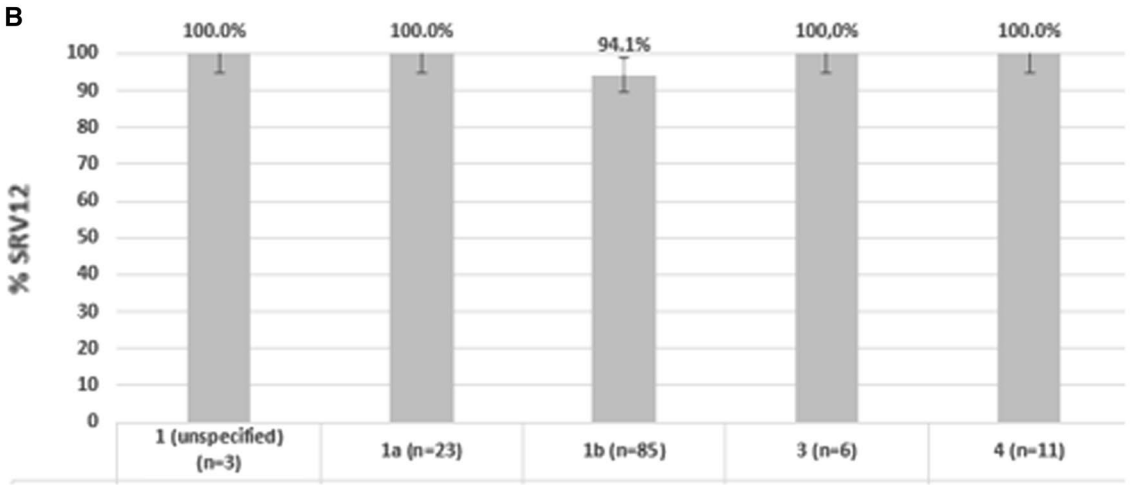
The global SVR12 rate was 96.1% in the intention to treat analysis (95% CI 92.7–99.5). SVR12 was 98.8% in naive patients, 91.5% in patients pretreated with RBV and PegINF combination, and 100.0% in patients previously treated with first generation DAA (boceprevir and telaprevir). Figure 1 shows the results of effectiveness observed in this study, according to genotype, degree of liver fibrosis and therapeutic regimen and duration.

The 2.3% of patients discontinued the antiviral treatment. In general, global adherence to DAAs was high by two methods of adherence measurement: PC (96.4%) and PDR (91.1%). Only 2 patients discontinued the treatment due to lack of adherence.

90.6% of patients presented some ADEs during treatment with DAAs. Table 3 shows the relationship of the most frequent ADEs observed during treatment with DAAs and its severity. No grade 4 ADEs was observed. No patient died during the treatment. In our cohort, only 1 patient (0.78%) under treatment with SMV/PegINF/RBV had to interrupt the treatment prematurely due to PegINF intolerance. Pharmacists performed 149 PIs to reduce or eliminate these NRDs.

Pharmacists identified 165 drug-drug interactions in 87 patients and they had to intervene in 43.6% of the cases. Ten contraindicated drug interactions were detected and avoided by the pharmacists. The therapeutic regimen that was most frequently involved in drug-drug interactions was OTV/PTV/r+DSV (48.5% of all interactions with DAAs), followed by SOF/LDV (32.7%). The highest risk of an interaction with the DAAs regimen was proton pump inhibitors (17.6%), antihypertensive agents (16.4%), medicinal herbs (10.9%) and lipid-lowering drugs (6.7%).


A
% SRV12
96,1%
98,8%
91,5%
100,0%
Total (n=128)
Treatment-Naïve- (n=81)
Prior treatment with PegINF+RBV
Prior treatment with boceprevir/telaprevir (n=10)


B
% SRV12
100.0%
100.0%
94.1%
100,0%
100.0%
1 (unspecified) (n=3)
1a (n=23)
1b (n=85)
3 (n=6)
4 (n=11)

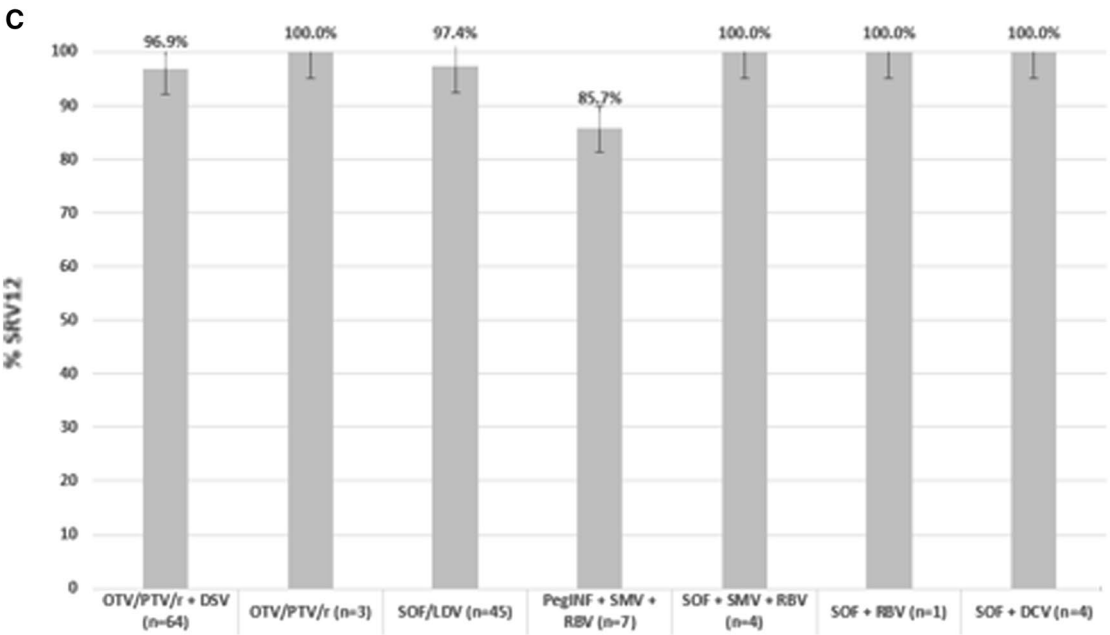

C
% SRV12
96.9%
100.0%
97.4%
85.7%
100.0%
100.0%
100.0%
OTV/PTV/r + DSV (n=64)
OTV/PTV/r (n=3)
SOF/LDV (n=45)
PegINF + SMV + RBV (n=7)
SOF + SMV + RBV (n=4)
SOF + RBV (n=1)
SOF + DCV (n=4)

Table 3 ADEs observed during treatment with DDAs

More frequent ADEs	Total (n, %)	ADEs grade 3 (n, %)
Fatigue	69 (53.9%)	5 (3.9%)
Asthenia	54 (42.2%)	7 (7.0%)
Dizziness	46 (35.9%)	2 (1.6%)
Headache	37 (28.9%)	0 (0.0%)
Hyperglycemia	22 (17.2%)	3 (2.3%)
Pruritus	16 (12.5%)	4 (3.1%)
Insomnia	15 (11.7%)	3 (2.3%)
General discomfort	15 (11.7%)	3 (2.3%)
Dyspepsia	13 (11.2%)	0 (0.0%)
Dry skin	13 (11.2%)	1 (0.8%)
Hyperbilirubinemia	12 (10.4%)	1 (0.8%)
Renal insufficiency	10 (7.8%)	0 (0.0%)
Diarrhea	9 (7.0%)	0 (0.0%)
Nausea	9 (7.0%)	0 (0.0%)
Flu-like symptoms	6 (4.7%)	0 (0.0%)
Hyperglycemia	5 (3.9%)	2 (1.6%)
Hair loss or weakness	3 (2.3%)	1 (0.8%)
Exanthema	3 (2.3%)	1 (0.8%)
Dermatitis	2 (1.6%)	1 (0.8%)
Weight loss	2 (1.6%)	1 (0.8%)

Quality of the PCP

During the study period, the pharmacists attended 565 patient consultations and a total of 324 pharmacist interventions were made over 108 patients (2.53 interventions per patients), and 87.9% of these were accepted by doctors and/or patients. The antiviral regimen with the most interventions was OTV/PTV/r+DSV with ribavirin (37.3%), followed by SOF/LDV (22.5%) and OTV/PTV/r+DSV (18.2%). 35.5% of interventions were made to avoid problems related to the concomitant medication that patients were taking. 46.0% of the interventions were aimed to resolve NRDs and 54.0% had a preventive character to avoid NRDs. Table 4 summarizes the type of measures proposed by pharmacists to health professionals and patients to solve or prevent the detected PRM, as well as the number and proportion of patients on which these measures were implemented. 4.0% of PRMs detected by the pharmacists was a consequence of a medication error. Table 5 establishes the relationship between the type of intervention made by the pharmacists and the results on the patient's health obtained with the intervention. Statistical significance was found in the acceptance of the intervention and resolution of the NRD using the Chi square test ($p \leq 0.001$), but not for the prevention of the appearance of NRD ($p = 0.453$). According to the impact code implemented, 27.5% of the PIs performed had some impact about the effectiveness of the treatments, 83.3% about the safety of the DAAs and 6.2% about its efficiency.

Discussion

To date, there is little data on the results of the implantation of a PCP in HCV-infected patients treated with DAAs. Our study shows the implementation of a PCP directed to these patients coordinated by clinical pharmacists.

In our cohort, the SVR12 rate was 96.1%, confirming the high effectiveness of the DAA regimens shown in clinical trials. This result was maintained across the different genotypes and antiviral regimens. Only patients treated with the combination PegINF + RBV + SMV obtained a lower SVR12 (<90%). However, these results are also consistent with the clinical trials of this antiviral regimen [9, 10]. Compared with a similar study conducted by Chamorro-de-Vega [11], who evaluated the implementation of a PCP in 1070 patients, our overall effectiveness rate was slightly higher. These differences could be related to the lower proportion of patients with HIV-coinfection, decompensated cirrhosis and liver transplantation of our cohort, who generally respond worse to treatment with DAAs [12, 13].

In our study, the adherence to DAAs treatments was very high and comparable to other studies. Petersen et al. found a high global adherence to DAAs measured by three different methods [medication event monitoring system (MEMS) caps, pill counts (PC) and patient report] [14]. In their study,

Table 4 Measures to resolve or prevent detected PRMs proposed by pharmacists to physicians and/or patients and the number and percentage of patients in whom these measures were implemented

Type of measure proposed by the pharmacist to a doctor and / or patient	Number of patients in which the measure was proposed, n (%)
Modify the medication dose or dosage	85 (26.3%)
Modify the treatment schedule	20 (6.2%)
DAA a medication	79 (24.4%)
Remove a medication	49 (15.1%)
Replace a medication	13 (4.0%)
Educate the patient about how to use and administer the medication	77 (23.8%)
Educate the patient about the importance of adherence	38 (11.7%)
Educate the patient about non-pharmacological measures	171 (52.8%)

Table 5 Correlation between the type of intervention made by the pharmacists and the results obtained with the intervention

Pharmaceutical Interventions (PIs)	N	Percentage of total interventions
Total number of PIs	324	–
Preventive interventions	175	54%
Resolution interventions	149	46%
Negative results of the drug (NRD) resolutive PIs		
PIs accepted		
Resolution or improvement of the NRD	110	80.9%[a]
No resolution of the NRD	25	18.4%[a]
Unknown / not assessable	1	0.7%[a]
PIs not accepted		
Resolution or improvement of the NRD	3	23.1%[b]
No resolution of the NRD	10	76.9%[b]
Pharmaceutical interventions to solve NRD		
PIs accepted		
Prevention of the appearance of the NRD	145	97.3%[c]
No prevention of the appearance of the NRD	3	2.0%[c]
Unknown / Not assessable	1	0.7%[c]
PIs not accepted	18	90%[d]
Prevention of the appearance of the NRD	1	5.0%[d]
No prevention of the appearance of the NRD	1	5.0%[d]
Unknown / not assessable	1	5.0%[d]

NRD Negative results of the drug

[a]Expressed on the total of accepted PIs (N = 136)

[b]Expressed on the total of PIs not accepted (N = 13)

[c]Expressed on the total of accepted PIs (N = 149)

[d]Expressed on the total of PIs not accepted (N = 20)

the percentages of adherence for PC method and patient report method were 98.2% and 99.3% respectively. In our cohort, the overall adherence obtained for PC was similar (99.09%) [14]. Factors such as its short duration of treatment with DAA and its good tolerance could have contributed to these adherence results. However, monitoring the adherence to DAAs was a key aspect of the follow-up carried out by the pharmacists.

Drug-drug interactions was another of the most relevant aspects in the management of antiviral treatment carried out by pharmacists. The exhaustive and continuous review of the interactions between the DAAs and the other medication and herbal products that the patients were taking, allowed the early detection of a significant number of interactions. Compared with the results obtained by Chamorro-de-Vega et al [11], we detected 2.21% more interactions than these authors. The type of interactions most frequently detected was similar to those obtained by Höner et al [15]. These authors evaluated pharmacological interactions in a population of 261 patients treated with AAD and reported that antihypertensive drugs (61.2%), proton pump inhibitors (24.1%) and antidiuretics (36.1%) were the drugs that most interacted with antiviral treatment. In our cohort, we found a significant percentage of interactions between DAAs and medicinal herbs (10.9%). These data warn about the need to review all the possible interactions between the rest of drugs, medicinal supplements, medicinal herbs and antiviral treatment to avoid NRDs.

A significant percentage of patients (90.6%) had some ADEs with antiviral treatment. The majority of the ADEs were mild-moderate severity and coincident with those reported in the clinical trials [16–19]. Despite this, tolerance was better in our study than in regimens containing interferon and first generation DAAs (telaprevir and boceprevir) [20, 21]. Besides, the percentage of discontinuation by ADEs was lower than the ones reported by other researchers (0.78%) [22, 23]. Only one patient who was treated with a regimen that included PegINF, had to withdraw treatment prematurely. The pharmacists monitored the ADEs and proposed solutions to their elimination or reduction. In our study, 80.9% of the NRDs improved or were eliminated with the measures proposed by the pharmacists.

On the other hand, pharmacists carried out a large number of preventive interventions to avoid NRDs. 97.3% of these interventions were accepted and prevented the appearance of NRDs, although these results did not reach statistical significance. Pharmacists prevented a medication error in 4.0% of patients. In view of these data, it seems necessary to carry out controlled prospective studies that confirm these results.

The impact of PIs on the improvement of health outcomes in HCV patients was evaluated through a code designed specifically for this purpose. According to this code, the majority (83.3%) of the PIs carried out had some type of repercussion on the safety of these treatments, while only 27.5% and 6.2% respectively, had some repercussion on the effectiveness and efficiency of the DAAs. Our results cannot be compared with other studies, because no studies with a similar design in hepatitis C have been published to date. Only the study by Chamorro-de-Vega shows the remarkable efficiency results obtained in a similar population of patients with the implantation of a PCP. They determined that treatment modifications suggested by pharmacists to a more cost-effective DAA regimen led to cost saving of €91975 [11].

Our study presents several limitations such as the small sample size, single-center enrollment and retrospective character. Due to the characteristics of the population included, some of our results may not be generalizable to other infected-HVC populations as for example liver transplant patients. Another important limitation is the absence of a control group that would allow comparison of results.

Conclusion

In view of our results, the implementation of a PCP by clinical pharmacists in patients with HCV treated with DAAs could optimize the use of these treatments, improving the safety of these therapies.

Our results show that the clinical pharmacist could play an important role within the healthcare team. In order to confirm our findings, additional studies would be needed. The methodology of these studies should include prospective design, with a larger cohort of patients included and the existence of a control group to compare results.

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