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RESEARCH ARTICLE

Measure of adherence to direct-acting antivirals as a predictor of the effectiveness of hepatitis C treatment

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Abstract

Background Adherence to direct-acting antivirals could be a predictor response to these treatments in hepatitis C. *Objective* To assess the ability of three methods of measuring adherence to direct-acting antivirals [pill counts, pharmacy dispensing record and Simplified Medication Adherence Questionnaire (SMAQ)] as predictors of their effectiveness. *Setting* Study conducted by the pharmacy department of the hospital. Methods: A retrospective study was performed. Patients ≥ 18 years with hepatitis C that started and completed treatment with direct-acting antivirals between the 1st-April-2015 and 28st-February-2016 were enrolled. To evaluate the predictive ability to obtain a response to treatment, Chi squared test, Mann–Whitney-U test and ROC-curves were used. *Main outcome measure* Adherence to antivirals was assessed by three methods and response to treatment, which was defined as obtaining a viral load of hepatitis C virus ≤ 15UI/ml at week 12 after the end of treatment. *Results* 128 patients were enrolled. The overall average adherence obtained with SMAQ (99.09%) was similar to the pill counts (96.40%, $p = 0.043$) and pharmacy dispensing record (91.10%, $p = 0.02$). There was no correlation between the percentage of patients considered as adherent by SMAQ (99.09%) and the achievement of response to treatment (96.40%, $p = 0.999$). The ROC-curve obtained for the pill count method shows a global area under the curve of 0.53. For pharmacy dispensing record method, patients with an adherence ≤ 66.66% have a high probability of not achieving response (sensitivity and specificity of 79.00% and 100.00%, respectively). *Conclusions* Pharmacy dispensing record is shown as the best indicator of adherence to predict therapeutic failure in our study.

Keywords Adherence · Antivirals · Chronic hepatitis C · Infectious diseases · Spain

Impact on Practice

- The Simplified Medication Adherence Questionnaire and the pill count method are not sensitive enough to predict effectiveness of the treatment with direct acting antivirals.
- The pharmacy dispensing record method seems a good indicator of adherence to predict therapeutic failure with treatments with direct acting antiviral agents in hepatitis C.

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Introduction

Direct-acting antivirals (DAAs) have revolutionized the management of hepatitis C virus (HCV) infection. These medications are highly effective, well tolerated, and the course of treatment is normally 12 weeks [1, 2]. Although DAAs treatments offer sustained virologic response (SVR) above > 90%, their efficacy is highly dependent on medication adherence [3, 4].

Because of the clinical importance of adherence, it should be closely monitored in clinical routine in patients receiving treatment with DAAs [5]. Unfortunately, measurement of medication adherence is not widely implemented in HCV care, and there are few evidence-based methods of measuring the adherence to HCV medications. To date, the majority of published studies measuring adherence to HCV antivirals have focused on medication dispensing data in the pharmacy records (PDR), pill counts (PC) [6, 7], Visual Analog Scale (VAS) [8] or medication possession ratio [3]. There is no consensus on an optimal procedure for measuring adherence to HCV treatment in clinical practice and the level of adherence needed for treatment success with DAAs in hepatitis C.

The Simplified Medication Adherence Questionnaire (SMAQ) is a short and simple tool based on questions posed directly to the patients regarding their medication-taking habits. The SMAQ was originally validated for the measurement of adherence in human immunodeficiency virus (HIV) patients with antiretroviral treatment [9]. The advantages of this method of measurement include its simplicity, agility and viability of use, because it does not require technologies and qualified personnel in its implementation. In contrast to the Morisky-Green questionnaire [10], the SMAQ questionnaire also allows a semiquantitative evaluation of the patient´s medication adherence [5].

Aim of study

Our objectives were to compare the results of adherence to DAAs in hepatitis C obtained with three different methods of adherence measurement (SMAQ, pharmacy dispensing recors (PDR) and pill count (PC)) and evaluate the potential of these three methods to predict the effectiveness of the treatments.

Ethics approval

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

Method

Study design, population and data collection

A retrospective and observational study was performed. All patients who had received treatment with a DAA and complied the inclusion criteria of the study were enrolled. The study was carried out by the pharmacy department of the Hospital Universitario del Henares, a general, primary university hospital in Madrid, Spain.

Patients were included in the study if they met the following inclusion criteria: 18 years or older, confirmed HCV infection, patients started and completed DAAs treatment between the 1st of April 2015 and 28st February 2016. The DAAs studied were: ombitasvir/paritaprevir/ritonavir (OTV/PTV/r), dasabuvir (DSV), sofosbuvir/ledipasvir (SOF/LDV), sofosbuvir (SOF), simeprevir (SMV), daclatasvir (DCV) with or without ribavirin (RBV) and combinations of SMV with RBV and peginterferon (PegINF) according to the criteria for treatment defined in clinical practice guidelines [11].

For the patients included in this study, the following data was collected from the clinical and pharmacy databases: demographic data (age, sex, HCV genotype, degree of liver fibrosis and comorbidity, previous treatments for hepatitis C and response), clinical evolution (plasma viral load HCV) and data referring to antiviral treatment (DAA regimen, dose, frequency, dates of dispensation and return, number of units dispensed and returned, and SMAQ results completed by patients). The data was collected from the beginning of treatment and up to 12 weeks post-treatment. The variables were registered and entered into the patient database (MS Excel® 2010).

Measure adherence

For our study we adopted the taxonomy established by the Medication Adherence Reporting Guideline (EMERGE) [12]. This guideline defines medication adherence as the process by which the patient takes his medication as prescribed and divides it into 3 interrelated phases: initiation, implementation, and persistence. Medication nonadherence can occur in any of these phases, such as late or incomplete initiation or noninitiation, suboptimal implementation of the dosing regimen or early discontinuation (non-persistence) [12].

In our study, non-adherence to treatment was analyzed in the phases of implementation and persistence in a global form. Adherence measurement methods used were: completion of the qualitative and quantitative SMAQ (Table 1), PC and PDR. These methods are described below:

Table 1 Simplified Medication Adherence Questionnaire (SMAQ) to the antiviral treatment against HCV

1. Taking medication for the treatment of hepatitis C can be difficult. Have you ever forgotten to take medication?
Yes
No
2. Did you always take the drugs at the indicated time?
Yes
No
3. Did you stop taking the drugs if you felt unwell during the treatment?
Yes
No
4. Did you forget to take the medication during the weekend?
Yes
No
5. In the last week, how many times did you not take any dose?
a) None
b) 1–2 times
c) 3–5 times
d) 6–10 times
e) More than 10 times
6. Since the last visit, how many full days did you not take the medication? Indicate number of days: _____

It is considered that a patient is non-adherent if he/she answers any of the questions of the SMAQ in the following way:
Question 1: Yes
Question 2: No
Question 3: Yes
Question 4: Yes
Question 5: c or d or e
Question 6: More than 2 days

The question 5 can be used to make a semiquantitative evaluation of the adherence. According to the option selected for this question (a, b, c, d or e), the questionnaire assigns a percentage of adherence as indicated below:
a) None. Equivalent to 100–95% adherence
b) 1–2 times. Equivalent to 85–94% adherence
c) 3–5 times. Equivalent to 65–84% adherence
d) 6–10 times. Equivalent to 30–64% adherence
e) More than 10 times. Less than 30% adherence

- The SMAQ is a short tool to measure the adherence of free access on the internet. However, authorization was requested for the use of the SMAQ questionnaire to its authors. It is based on questions addressed directly to patients about their habits in taking medications. The questionnaire consists of six questions that evaluates different aspects related to adherence to treatment such as routine, forgetting, adverse effects and quantification of omissions in the taking of drugs. The questionnaire considers the adherence as a dichotomous variable, and classifies the patient as non-adherent when the patient answers any of the questions in the sense of non-adherence. The question number five allows to quantify adherence to treatment in different ranges indicated in the Table 1, depending on the number of times that the patient has not taken the medication in the last week.

  The SMAQ was provided directly to patients by the staff pharmacist during the treatment every 4 weeks, coinciding with the patient's visit to the pharmacy to pich up the medication.

- PC: In every visit to the pharmacy department, the patient was asked to return the medication remaining since the last dispensation to the pharmacy service. Adherence was calculated with the following formula: [(number medication dispensed − number medication remaining)/(number medication dispensed)] × 100.
- PDR: Knowing the treatment regimen of each drug, the adherence was calculated according to the medication that the patient had withdrawn from the pharmacy department. The dispensing dates and units dispensed of the DAAs were collected from the database of pharmacy for each patient. With this information, the average adherence in the dispensing interval (AADI) was calculated (expressed as a percentage) [13]. AADI was defined as the proportion of days that a patient has sufficient medication to take all prescribed doses and was calculated with the following formula: (Number of days of medication dispensed/Number of days between dispensations) × 100.

For the PC and the PDR, the adherence was calculated for each of the drugs dispensed, and the average of all drugs was calculated in every visit. The overall percentage of adherence for these methods was calculated by adding up the average percentage of adherence for each of the visits.

Measure of health outcomes

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

Data analysis

Demographic, clinical characteristics and effectiveness results are presented as frequency expressed in percentage in qualitative variables and median and interquartile range (IQR) in quantitative variables. We used non-parametric test in all study because the distribution was not adjusted to normal distribution. Outcomes were analyzed based on all patients who received at least one dose of the DAA (intention to treat (ITT)).

We performed a bivariate analysis of adherence results of PC, PDR, SMAQ qualitative and quantitative with treatment effectiveness measured by SVR12. We evaluated the value of quantitative SMAQ, PC and PDR with the non-parametric Mann–Whitney U test. We evaluated the relationship between qualitative SMAQ and SVR12, with the Fisher exact-test.

We assessed the prediction capacity of treatment effectiveness (SVR12) of adherence measure of PC and PDR with Receiver Operating Characteristic (ROC) curve analysis, globally and with treatment duration. The area under curve (AUC) and their 95.0% confidence interval (95.0% CI) were calculated. In cases where AUC were higher that 0.6 (CI lower limit), we calculated the best cutoff based in their sensitivities and specificities. Sensitivity and specificity were calculated using ROC curve. The binary classifier is SVR12 and the values that we compared was SMAQ.

The SVR12 was used to analyze the psychometric properties (sensitivity and specificity) of the SMAQ questionnaire. Also, for the comparisons of the adherence results of the three different methods we used the non-parametric alternative of Pearson correlation, Spearman correlation.

In all test, the alpha and beta error assumed were 5.0% and 20.0% respectively. Data was analyzed using RStudio 1.1.546 (2009–2018 RStudio, Inc.).

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%)
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%)
Fibrosis stage	
Non-cirrhosis	71 (55.5%)
Cirrhosis	57 (44.5%)
Presence of comorbidities	100 (78.1%)
Psychiatric disorders	26 (20.3%)
HIV coinfection	9 (7.0%)
HBV coinfection	2 (1.6%)
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	
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	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

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 3 Adherence results obtained with PC and PDR methods and SMAQ qualitative and quantitative

	Total N = 128 (%)	8 W Treatment N = 2 (%)	12 W Treatment. N = 99 (%)	24 W Treatment. N = 27 (%)
Pill counts median (IQR)	100 (0)	100 (0)	100 (0)	100 (0)
Pharmacy dispensing record median (IQR)	100 (0)	100 (0)	100 (0)	100 (0)
SMAQ questionnaire				
Non-adherent patient N (%)	1 (0.8)	0	1 (1.0)	0
Adherent patient N (%)	110 (85.9)	2 (100)	92 (92.9)	16 (59.3)
Not performed N (%)	17 (13.3)	0	6 (6.1)	11 (40.7)
Quantitative SMAQ				
100–95%	107 (83.6)	2 (100)	90 (90.9)	15 (55.6)
94–85%	3 (2.3)	0	2 (2.0)	1 (3.7)
84–75%	0	0	0	0
74–65%	0	0	0	0
64–30%	1 (0.8)	0	1 (1.0)	0
< 30%	0	0	0	0

W Weeks, *IQR* interquartile range

Table 4 Spearman correlation between the three methods of adherence measure

	Pill counts	Pharmacy dispensing record	Quantitative SMAQ
Pill counts (PC)	1	0.19 $p = 0.835$	−0.18 $p = 0.059$
Pharmacy dispensing record (PDR)	0.19 $p = 0.835$	1	−0.30 $p = 0.002$
Quantitative SMAQ	−0.18 $p = 0.059$	−0.30 $p = 0.002$	1

shown in the Table 2. Most patients were non-cirrhotic, genotype 1b infection, and treatment-naïve to HCV. Overall, 7.0% patients were coinfected with 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%). The SMAQ questionnaire was carried out in 86.7% of the patients in the cohort.

The global SVR12 rate was 96.1% in the ITT analysis (CI 95%, 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).

In general, global adherence to DAAs was high for the three methods: SMAQ (99.1%), PC (96.4%) and PDR (91.1%). Adherence results obtained with SMAQ questionnaire for 8, 12 and 24 weeks of treatment were 100.0%, 98.9% and 100.0% respectively. Table 3 shows the results of adherence to the treatment obtained with the three methods of the 128 patients of the study. We only found a reverse weak correlation between quantitative SMAQ and PC and PDR (Table 4).

Table 5 shows bivariate analysis between the values of adherence obtained with the SMAQ questionnaire and the achievement of SVR12 with the antiviral treatment. The sensitivity and specificity of qualitative SMAQ is 99.0% (CI 95%, 94.9–99.8%) and 0.0% (CI 95%, 0.0–5.0%) respectively, and the sensitivity and specificity of SMAQ quantitative is 96.0% (CI 95%, 90.8–98.5%) and 0.0% (CI 95%, 0.0–5.0%) respectively.

The analyses of the ROC curves are shown in Fig. 1. The PDR globally cutoff is 66.6% of adherence with a sensitivity of 81.0% and specificity of 80.0%, and the PDR in 24 weeks treatment was also 66.6% with a sensitivity of 79.0% and specificity of 100.0%.

Discussion

Studies with the first generation DAAs, telaprevir or boceprevir, suggest that a high level of adherence is essential to achieve high rates of SVR and reduce the development of drugs resistance [14]. These results also seem to be confirmed with second generation DAAs [15].

The results obtained in our study show that the adherence to DAAs treatments was very high and comparable to other studies. Petersen et al. [6] found a high global adherence to DAA measured by three different methods [medication event monitoring system (MEMS) caps, PC and patient report]. In their study the percentages of adherence for PC method and patient report method were 98.2% and 99.3% respectively.

Table 5 Bivariate analysis of adherence measures obtained with the SMAQ questionnaire and the effectiveness of the treatment with DAAs

Qualitative and quantitative SMAQ results	Effectiveness of treatments with DAAs		
	SVR12 N = 123 (%)	No SVR12 N = 5 (%)	*p* value
Overall pill counts median (IQR)	100 (0)	100 (50)	0.696
8 weeks treatment	100 (0)	–	–
12 weeks treatment	100 (0)	100 (0)	0.710
24 weeks treatment	100 (0)	100 (0)	0.635
Overall PDR median (IQR)	100 (0)	66.6 (50)	0.002
8 weeks treatment	100 (0)	–	–
12 weeks treatment	100 (0)	83 (50)	0.519
24 weeks treatment	100 (0)	66.6 (50)	0.021
Overall qualitative SMAQ n (%)			
Patient adherent	106 (96.4%)	4 (3.6%)	0.999
Patient non-adherent	1 (100%)	–	
Overall quantitative SMAQ n (%)			
100–95% adherence	103 (96.3%)	4 (3.6%)	0.999
94–85% adherence	3 (100%)	–	
84–75% adherence	–	–	
74–65% adherence	1 (100%)	–	
64–30% adherence	–	–	
< 30% adherence	–	–	
Qualitative SMAQ 8 weeks treatment n (%)			
Patient adherent	2 (100%)	–	–
Patient non-adherent	–	–	
Quantitative SMAQ 8 weeks treatment n (%)			
100–95% adherence	2 (100%)	–	–
Result qualitative SMAQ patients treated for 12 weeks (n = 93)			
Patient adherent	90 (97.8%)	2 (2.2%)	0.999
Patient non-adherent	1 (100%)	–	
Result quantitative SMAQ patients treated for 12 weeks SMAQ (n = 93)			
100–95% adherence	88 (97.8%)	2 (2.2%)	0.999
94–85% adherence	2 (100%)	–	
84–75% adherence	–	–	
74–65% adherence	1 (100%)	–	
64–30% adherence	–	–	
< 30% adherence	–	–	
Result qualitative SMAQ patients treated for 24 weeks (n = 16)			
Patient adherent	14 (87.5%)	2 (13.3%)	0.999
Patient non-adherent	–	–	
Result quantitative SMAQ patients treated for 12 weeks SMAQ (n = 16)			
100–95% adherence	13 (86.7%)	2 (13.3%)	0.999
94–85% adherence	1 (100%)	–	
84–75% adherence	–	–	
74–65% adherence	–	–	
64–30% adherence	–	–	
< 30% adherence	–	–	

IQR interquartile range

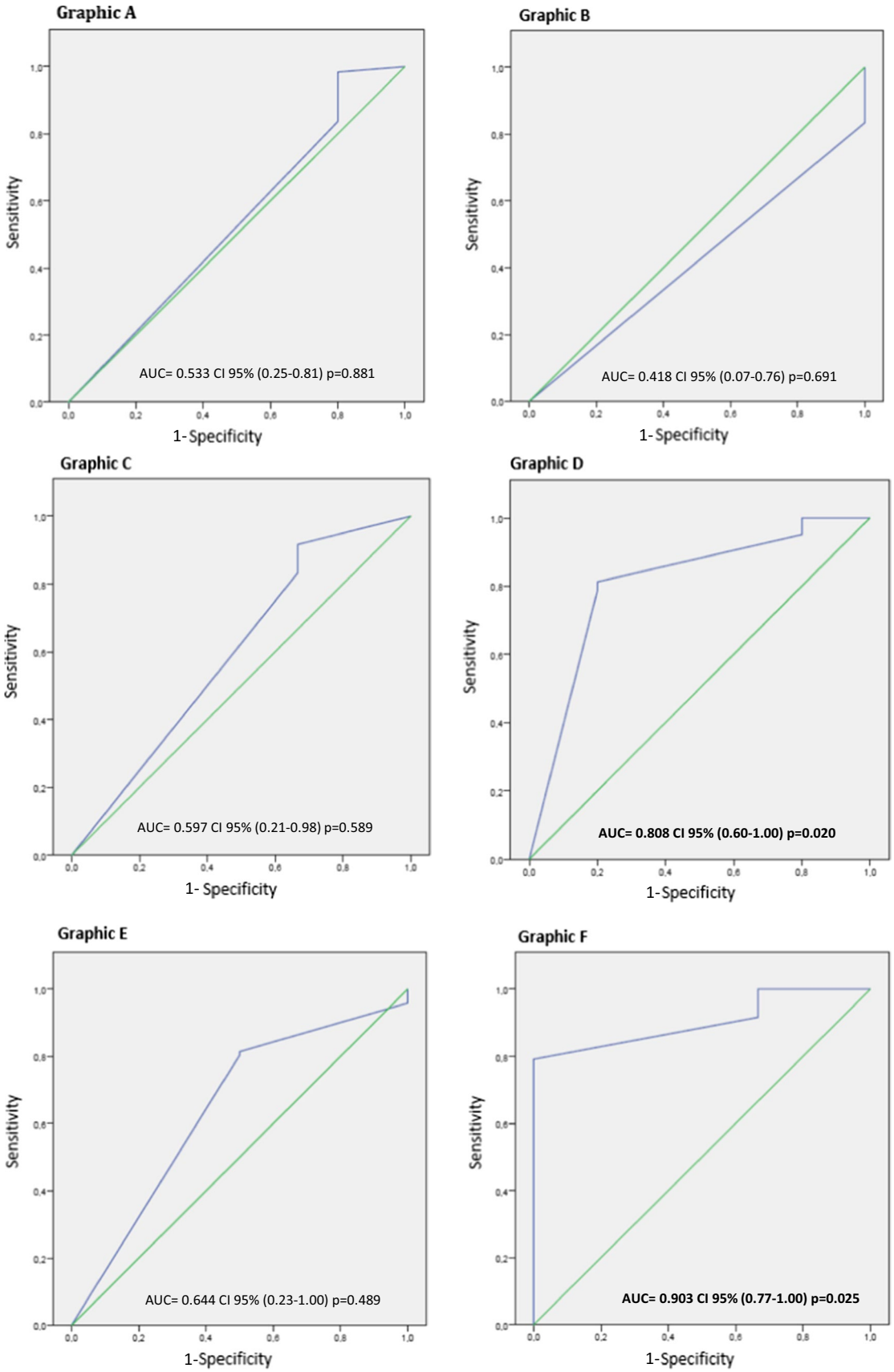
In our study, the overall results of adherence obtained for PC and SMAQ were similar, 99.1% and 96.4% respectively [6].

The percentages of adherence obtained with the SMAQ questionnaire were similar to those obtained with the PC and PDR, although higher. Although the SMAQ questionnaire is widely implemented in the HIV population [16], we have not found studies that evaluate SMAQ as a clinical tool for measuring adherence in patients with hepatitis C treated with DAAs. Therefore, our study would be the first one to use the SMAQ as a prospective tool for measuring adherence during the treatment of HCV with DAAs. According to our experience, the SMAQ questionnaire was a method easy to apply in our group of patients. Unlike other methods, SMAQ allowed a quick and simple quantification of adherence evaluation in our patients.

However, the low failure rate to the treatment observed with the DAAs [17, 18] (4% in our study), makes it necessary to search for a very sensitive and specific measurement instrument that allows predicting SVR12 from the obtained adherence results. In this sense, and in line with our results, the SMAQ questionnaire is not a sufficiently specific method to predict the effectiveness of these treatments. In our study we observed that all patients considered non-adherent by the SMAQ obtained SVR12. In relation to these results, there are few published studies that evaluate the ability to precede the response to treatment with DAAs of different methods of adherence measurement [8, 18]. The study by Burton et al., although with important methodological limitations, seems to indicate that there could be some correlation between adherence to DAAs, measured by means of a visual analog scale (VAS), and the serum levels of the viral load of HCV [8].

In our study, the PDR method would be the best one to predict treatment failure. Patients with an adherence less than 66.6% as measured by this method have a high probability of not achieving SVR12. The sensitivity and specificity for this cut-off point are 79.0% and 100.0% respectively. The high impact on health outcomes of patients and the associated high cost of these treatments, highlight the need to conduct future multicenter studies with a larger cohort to confirm this cut-off point (66.6%).

On the other hand, the results of PC method show that this method would not be an accurate predictor of treatment success. Although this method could be more sensitive than PDR method, is highly dependent on the behavior of the patients that could impact the final result [19]. With this


Graphic A
Sensitivity
1-Specificity
AUC= 0.533 CI 95% (0.25-0.81) p=0.881
Graphic B
Sensitivity
1-Specificity
AUC= 0.418 CI 95% (0.07-0.76) p=0.691
Graphic C
Sensitivity
1- Specificity
AUC= 0.597 CI 95% (0.21-0.98) p=0.589
Graphic D
Sensitivity
1-Specificity
AUC= 0.808 CI 95% (0.60-1.00) p=0.020
Graphic E
Sensitivity
1-Specificity
AUC= 0.644 CI 95% (0.23-1.00) p=0.489
Graphic F
Sensitivity
1-Specificity
AUC= 0.903 CI 95% (0.77-1.00) p=0.025

◂**Fig. 1** ROC curves of PC and PDR and SVR12. **a** ROC curve analysis Global PC and SVR12; **b** ROC curve analysis PC and SVR12 for 12 weeks treatment; **c** ROC curve analysis PC and SVR12 for 24 weeks treatment; **d** ROC curve analysis Global PDR and SVR12; **e** ROC curve analysis PDR and SVR12 for 12 weeks treatment. **f** ROC curve analysis PDR and SVR12 for 24 weeks treatment

method, the patient could not return the remaining medication and be included as adherent.

The limitations to our study include the small sample size and single-center enrollment. Due to the characteristics of the population included, our results may not be generalizable to other infected HCV populations as for example HIV coinfected, or liver transplant patients. In our cohort, there is a considerable percentage of patients with RBV and with a duration of treatment of 24 weeks. These may not be consistent with the current available agents and their treatment guidelines. Besides, other variables that can affect the adherence results have not been taken into account, for example: severe liver disease, psychiatric disorders, drug abuse or prior HCV treatment [20]. Other limitation is that the SMAQ questionnaire is not validated in Hepatitis C patients.

In order to confirm our findings, additional studies would be needed. The methodology for these studies should include factors with documented influence on adherence (severity of the disease, treatment regime, and individual patient factors) and a higher cohort of patients.

Conclusion

Of the three methods evaluated, our results show that the PDR method performs best to predict the effectiveness of the treatments with direct acting antiviral agents in hepatitis C.

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