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Hepatitis C core antigen: Diagnosis and monitoring of patients infected with hepatitis C virus

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ABSTRACT

Introduction: New efficient strategies are needed for the assessment of active hepatitis C virus (HCV) infection. The aim of this study was to evaluate the ability of HCV core antigen (HCV-cAg) as a marker of active HCV infection in newly diagnosed patients, for treatment monitoring, and for the detection of therapeutic failure.

Materials and methods: A prospective study was conducted at a regional reference hospital in Spain. HCV-cAg and viral load (RNA-HCV) were tested in plasma or serum samples from three patient groups: new diagnosis, treatment monitoring, and treatment failure. The treatment monitoring group was tested at the beginning of treatment, at 4 weeks post-initiation, at the end of treatment, and at 12 weeks post-treatment completion. The Architect HCV core antigen assay was performed for HCV-cAg testing, and viral load was quantified with the Cobas 6800 system.

Results: A total of 303 samples from 124 patients were analyzed. Excellent correlation was seen between HCV-cAg and HCV-RNA ($R^2 = 0.932$). The optimal cut-off value was 3 fmol/l in the receiver operating characteristics curve analysis, and the area under the curve was 0.987 (95% confidence interval 0.972–1.000). HCV-cAg sensitivity and specificity were 97% and 95%, respectively. Most diverging results were observed in the treatment follow-up group.

Conclusions: HCV-cAg demonstrated good sensitivity and specificity as a marker for active HCV infection, new diagnosis, detection of antiviral therapeutic failure, and treatment monitoring.

Introduction

The global prevalence of people with hepatitis C virus (HCV) antibodies (anti-HCV-positive) is estimated to be 115 million, and 80 million of them have an active infection (anti-HCV-positive and HCV-RNA-positive) (WHO, 2016; Gower et al., 2014). Most HCV-infected individuals remain asymptomatic for decades and only 25% of them achieve spontaneous viral clearance, while 75% develop chronic infection (Forman and Valsamakis, 2015; Ray and Thomas, 2015). Around 10–20% of chronically infected patients develop liver cirrhosis or hepatocellular carcinoma (Ponziani et al., 2017). Despite improvements in diagnosis and screening, the morbidity and mortality due to chronic HCV infection remain high (Lozano et al., 2012; GBD Mortality and Causes of Death Collaborators, 2015; Razavi et al., 2014).

In recent years, the availability of direct-acting antiviral (DAA) therapies with very high effectiveness in the clearance of HCV infection has improved the prognosis of these patients (Hu and Cui, 2016; Kuo et al., 2012). In this new scenario, priorities arise for the detection of active HCV infections in the population, treatment monitoring, and the detection of therapeutic failures.

The diagnosis of HCV infection commonly involves a two-stage procedure. Antibody screening (anti-HCV) is performed first, followed by the determination of the viral load (VL: HCV-RNA), which allows the differentiation between active and past infection (WHO, 2016; Kuo et al., 2012; Ghany et al., 2009; Centers for Disease Control and Prevention, 2013a; Centers for Disease Control and Prevention, 2013b; Alados-Arboledas et al., 2017). In recent years, a new technique for the detection of the HCV core antigen

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(HCV-cAg) in blood or plasma samples has been commercialized. HCV-cAg is a highly conserved and antigenic protein of the internal capsid (Hu and Cui, 2016; Kuo et al., 2012; Alados-Arboledas et al., 2017).This structural protein is released and can be detected early, well before the antibodies against the virus, and throughout the complete course of the infection (Freiman, 2016). HCV-cAg has been described as an active marker of infection, thus being an alternative to HCV-RNA, with A1 evidence grading by the European Association for the Study of the Liver (Ross et al., 2010; Ottiger et al., 2013; Chevaliez et al., 2014; European Association for the Study of the Liver, 2018). The newly described assay (Architect HCV core antigen, Abbott Diagnostics, Wiesbaden, Germany) uses the same platform employed in anti-HCV antibody determination, contributing to the simplification of the diagnosis of active HCV infection to a single step (Alados-Arboledas et al., 2017; Tillmann, 2014). Studies on the use of HCV-cAg in routine laboratory tests for completing the diagnosis of anti-HCV-positive cases and for patient follow-up and treatment monitoring have been conducted (Hu and Cui, 2016; Kuo et al., 2012; Alados-Arboledas et al., 2017; Freiman, 2016; Kesli et al., 2011; Miedouge et al., 2010). However, prospective comparison of the two techniques in different clinical situations in real-life scenarios are needed.

The aim of this prospective study was to evaluate the ability of HCV-cAg as a marker of active HCV infection in diagnosis, treatment monitoring, and the detection of therapeutic failures.

Materials and methods

This prospective study included a sample of patients attending a regional reference hospital in Spain between September 2016 and December 2017, for whom VL quantification was required. For these patients, HCV-cAg determination was performed in parallel. Three groups of patients or clinical situations were considered. (1) Monitoring of treatment group: plasma VL and HCV-cAg were tested at the beginning of the treatment with DAA (baseline), at 4 weeks of treatment, at the end of treatment (8, 12, 16, or 24 weeks, according to the duration of treatment), and at 12 weeks post-treatment to assess sustained virological response (SVR) (Figure 1). (2) New diagnosis group: VL and HCV-cAg were tested in serum and/or plasma samples in patients with new positive anti-HCV determination to distinguish between active and past infection. (3) Treatment failure group: VL and HCV-cAg were tested in serum and/or plasma samples at the time therapeutic failure of DAA was suspected due to no response, breakthrough, relapse, or reinfection.

Clinical, demographic, and epidemiological variables were extracted from the database of the Navarre Health Service. VL testing was performed by RT-PCR using the Cobas 6800 system (Roche Diagnostics, Mannheim, Germany), with a linear range of between 15 and 10^8 IU/ml. The detection and quantification of HCV-cAg was performed by chemiluminescence immunoassay (CLIA) in an Architect system (Architect HCV core antigen; Abbott Diagnostics, Wiesbaden, Germany), with a linear range of between 0 and 20 000 fmol/l. For the detection of anti-HCV antibodies, the Architect (Architect HCV anti-Ab; Abbott Diagnostics, Wiesbaden, Germany) and Liaison (DiaSorin, Saluggia, VC, Italy) systems were used, and/or confirmed with INNO-LIA (Innogenetics, Fujirebio, Gent, Belgium). Viral genotype and subtype data were determined by reverse hybridization assay Versant HCV Genotype 2.0 (LiPA; Siemens Healthcare Diagnostics, Tarrytown, NY, USA).

For statistical analysis, two categories of VL results were created: negative (VL $\leq$ 15 IU/ml) and positive (VL > 15 IU/ml). For HCV-cAg, the categorization was done as follows: negative (HCV-cAg <3 fmol/l), indeterminate (3 $\leq$ HCV-cAg $\leq$ 10 fmol/l), and positive (HCV-cAg >10 fmol/l).

Different receiver operating characteristics (ROC) curves were calculated for the HCV-cAg technique (total population per group of patients, and based on the infecting genotype) using VL quantification as the gold standard. HCV-cAg sensitivity and specificity values were determined for the cut-off points of the proposed ROC curves. Correlation between the two techniques was estimated using regression lines and the Pearson coefficient (R^2) for the HCV-cAg ($\log_{10}$ HCV-cAg) and VL ($\log_{10}$ HCV-RNA) transformed values. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Five hundred and seven patients (507 treatments) initiated DAA therapy during the study period, with 70 (13.8%) of these patients prospectively included in the treatment monitoring group (with HCV-cAg and VL). The new diagnosis group comprised 40 out of 91 (44%) patients with new positive anti-HCV antibody detection. The treatment failure group included 14 patients with therapeutic failure to DAAs. A total of 124 patients were included in the study.

Most patients were male (72%) and the mean age was 52.4 (standard deviation 10.4) years; 18.2% of the patients were HIV co-infected. The principal genotype was GT1 (37.5% GT1a and 22.5% GT1b) (Table 1).

The results of 303 determinations of HCV-cAg and VL for the 124 study subjects were compared (Table 2).

Among the 40 patients with a new HCV diagnosis, 38 (95%) had an active infection (VL-positive) and 36 (90%) had positive HCV-cAg. Two subjects had discordant results. One was a false-negative for HCV-cAg (2.88 fmol/l) in a patient with a low VL (726 IU/ml). The patient was diagnosed with acute cholestatic hepatitis in remission with anti-HCV positive. In a later control determination, VL and HCV-cAg were negative, which was diagnosed as spontaneous resolution. The second case was a patient with a low VL (4240 IU/ml) and indeterminate HCV-cAg (5.18 fmol/l). At the following visit, VL was 19 700 IU/ml. HCV-cAg could not be determined due to technical issues.

In the therapeutic failure group, 100% of the determinations were positive for both techniques.

In the treatment monitoring group, all patients (100%) were positive for VL and HCV-cAg at the beginning of treatment. At the end of the follow-up, all patients except two had achieved SVR, as per VL determinations. Regarding HCV-cAg, all patients except three (two positive and one indeterminate) achieved SVR. Two

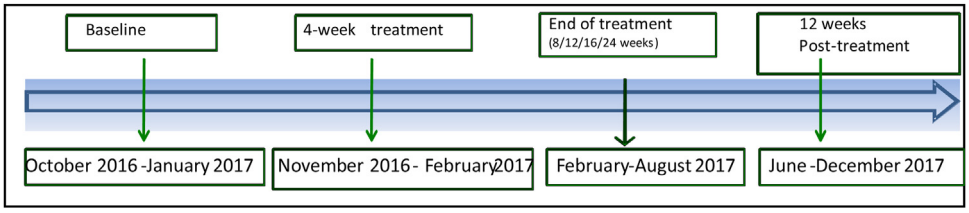

Figure 1. Flowchart of patients included in the study.

Table 1
Clinical and demographic characteristics of the study population by group.

Variable	Total ($N = 124$) *n* (%)	Treatment monitoring ($n = 70$) *n* (%)	New diagnosis ($n = 40$) *n* (%)	Treatment failure ($n = 14$) *n* (%)
Age (years)				
Mean (SD)	52.4 (10.5)	51.2 (8.4)	51.9 (14.5)	51.1 (5.9)
Sex				
Male	87 (70.2)	50 (71.4)	24 (60)	13 (92.8)
Female	37 (29.8)	20 28.6)	16 (40)	1 (7.2)
Group				
Treatment	70 (56.5)	70 (100)	0	0
Screening	40 (32.3)	0	40 (100)	0
Failure	14 (11.3)	0	0	14 (100)
HIV co-infection				
No	99 (79.8)	49 (70)	39 (97.5)	14 (100)
Yes	22 (18.2)	21 (30)	1 (2.5)	0
Genotype				
1a	45 (37.2)	26 (37.1)	12 (32.5)	7 (50)
1b	27 (22.3)	14 (20)	11 (29.7)	2 (14.3)
2	7 (5.8)	6 (8.6)	1 (2.7)	0
3	30 (24.8)	13 (18.6)	13 (35.1)	4 (28.6)
4	12 (9.9)	11 (15.7)	0	1 (7.1)

Table 2
HCV-cAg and HCV-RNA in the study population.

	Total ($n = 303$[a])		New diagnosis ($n = 40$)		Treatment failure ($n = 14$)		Treatment monitoring ($n = 70$)							
							Baseline		4 weeks		End of treatment		12 weeks post-treatment	
	VL		VL		VL		VL		VL		VL		VL	
	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos	Neg	Pos
HCV-cAg														
Negative	166	4	2	1	0	0	0	0	39[b]	3	62[c]	0	63[d]	0
Indeterminate	5	2	0	1	0	0	0	0	2	1	2	0	1	0
Positive	3	123	0	36	0	14	0	69[e]	1	2	2	0	0	2

HCV-cAg, hepatitis C virus core antigen; VL, viral load; Neg, negative; Pos, positive.
[a]Total of 305 determinations with VL and HCV-cAg values; three cases with VL values but without HCV-cAg values.
[b]Twenty-one patients were not assessed for treatment monitoring at 4 weeks post-initiation.
[c]One HCV-cAg is missing due to an error by the technician; three patients were not assessed for follow-up at the end of the treatment.
[d]One HCV-cAg is missing due to an insufficient sample; no follow-up sample after 12 weeks post-termination of the study was received for two patients.
[e]One HCV-cAg is missing due to an insufficient sample for the technical procedure.

patients who relapsed after ending their treatment had positive VL and HCV-cAg post-treatment.

Most discordant results were from the follow-up at 4 weeks of treatment. These were mainly false-negatives or indeterminate for HCV-cAg, with VL values <31.5 IU/ml, or negative VL with indeterminate HCV-cAg (3.89 and 4.46 fmol/l); or they were false-positives close to the cut-off point (12.05 fmol/l).

At the 12-week post-treatment follow-up, all patients had concordant negative results, with one exception: this patient had a negative VL (SVR) and indeterminate HCV-cAg (9.24 fmol/l). In the following determination (after 48 weeks), VL and HCV-cAg were negative.

Of the 170 determinations with HCV-cAg below 3 fmol/l, four were positive for VL (false-negative HCV-cAg with VL < 726 IU/ml). Of the 126 with HCV-cAg over 10 fmol/l, VL was negative in three cases (false HCV-cAg-positive = 11.64–24.24 fmol/l). Finally, seven results were classified as indefinite as per the HCV-cAg (HCV-cAg >3 and ≤10); for two, the VL was positive (30.4 and 19700 IU/ml) and for five the VL was negative (Table 3). The area under the ROC curve including all samples tested was 0.987; thus, the determination of HCV-cAg can be defined as an excellent technique with high discriminatory power (Table 3, Figure 2).

When the cut-off point was established at <3 vs. ≥ 3, 2.6% false-positives and 1.3% false-negatives were obtained, with sensitivity of 97%. However, when the cut-off point was set at <10 vs. ≥ 10, 1.0% were false-positive, 2.3% were false-negative, and sensitivity was 95%. Both cut-off points ensured ≥95% sensitivity and specificity.

No relevant differences were detected in the comparison of sensitivity and specificity for cases co-infected with HIV by genotype; thus, the sensitivity and the specificity remained over 94–95% in all groups analyzed, with no statistically significant differences (**Supplementary Material**, Tables S2 and S3). For genotype 2 at cut-off point 10, and for genotype 4 at the different proposed cut-off points, HCV-cAg sensitivity values were 86%. This could be explained by the small sample size for these two genotypes (**Supplementary Material**, Table S3).

Figure 2 shows the regression line for HCV-cAg and VL, as well as the values for the correlation coefficient ($R^2 = 0.932$). No differences were observed according to genotype or HIV–HCV co-infection (**Supplementary Material**, Figure S2 and Table S4).

Discussion

The results of this study show the high differentiation ability of the HCV-cAg technique in the diagnosis, treatment monitoring, and assessment of therapeutic failure in HCV infection. Since the first description, many publications and studies have confirmed the ability of HCV-cAg as a marker of viral replication similar to HCV-RNA (Alados-Arboledas et al., 2017; Freiman, 2016;

Table 3
Area under the curve ROC curve for HCV-cAg based on the characteristics of the population and genotypes.

	Number[a]	ROC (95% CI)	HCV-RNA		HCV-cAg		
			Negative	Positive	Negative	Positive	Indefinite
Total	303 (91%)	0.987 (0.972, 1.000)	174	129	170	126	7
Group							
Treatment monitoring	249 (90%)	0.979 (0.954, 1.000)	172	77	167	76	6
New diagnosis	40 (100%)	1.00 (1.00, 1.00)	2	38	3	36	1
Treatment failure	14 (100%)	Incalculable[b]	0	14	0	14	0
HIV Co-infection							
No	218 (89%)	0.988 (0.972, 1.000)	114	104	110	102	6
Yes	82 (97%)	0.977 (0.928, 1.000)	60	22	60	21	1
Genotype							
1a	107 (87%)	0.988 (0.965, 1.000)	58	49	55	48	4
1b	62 (90%)	1.000 (1.000, 1.000)	34	28	31	30	1
2	20 (80%)	1.000 (1.000, 1.000)	13	7	13	7	0
3	66 (97%)	1.000 (1.000, 1.000)	37	29	36	28	2
4	44 (98%)	0.931 (0.826, 1.000)	30	14	32	12	0

ROC, receiver operating characteristics; HCV-cAg, hepatitis C virus core antigen; CI, confidence interval.
[a] Number of cases with HCV-RNA and HCV-cAg available in the sample.
[b] In the 'Treatment failure' group, there are no negative cases, thus it is not possible to calculate the ROC curve.

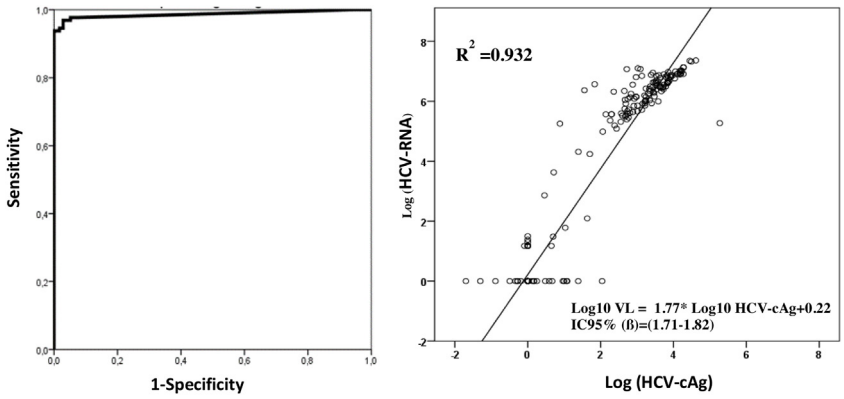

Figure 2. Receiver operating characteristics curve for HCV-cAg considering HCV-RNA as the gold standard, for all group of patients, and the regression line for $\log_{10}$ HCV-RNA vs. $\log_{10}$ HCV-cAg.

Ottiger et al., 2013; Chevaliez et al., 2014; Chevaliez et al., 2018; Alonso et al., 2018; Alonso et al., 2017). As described by Alados et al., for a test to replace HCV-RNA determination when studying HCV, it should be able to identify active infection and assess the response or follow-up of a patient under treatment (Alados-Arboledas et al., 2017).

The study results showed that with cut-off points at 3 and 10, and considering a gray zone in the interval between 3 and 10 (as suggested by the manufacturer), HCV-cAg determines 95.5% (123/129) of active infections (97.2% when only determinations at the time of diagnosis and before treatment initiation are considered) and 100% of therapeutic failures. These results are similar to those reported elsewhere (Alados-Arboledas et al., 2017; Freiman, 2016; Ottiger et al., 2013; Chevaliez et al., 2018; Alonso et al., 2018).

Most of the discrepancies between the techniques ($n = 11$) were observed in the treatment monitoring group, particularly at week 4 ($n = 7$). These discordant results are within the expected range, due to the lower sensitivity of the HCV-cAg technique, with an equivalence of around 3 fmol/l of HCV-cAg to 400–3000 IU/ml of HCV-RNA (Alados-Arboledas et al., 2017; Freiman, 2016; Ottiger et al., 2013; Chevaliez et al., 2014; Chevaliez et al., 2018; Alonso et al., 2018). All of these discrepancies achieved SVR at 12 weeks post-treatment, without implying the interruption of the therapy. Furthermore, as reported in previous studies, the lowest level of correlation between HCV-cAg and HCV-RNA occurs during the first weeks after treatment initiation (duration of therapy $\leq$4 weeks) (Alados-Arboledas et al., 2017; European Association for the Study of the Liver, 2018; Aghemo et al., 2016; Rockstroh et al., 2017). Even so, this does not imply that the use of HCV-cAg as a marker for monitoring the treatment in any of the cases is a relevant error or obstacle, because, during follow-up, a low but detectable VL at 4/8 weeks from treatment initiation does not indicate a lack of SVR to DAAs, thus there is no need to interrupt treatment (Alados-Arboledas et al., 2017; Freiman, 2016; Ottiger et al., 2013; Chevaliez et al., 2014; Chevaliez et al., 2018; Rockstroh et al., 2017; Sidharthan et al., 2015). VL determination at 4 weeks has been abandoned due to its low clinical impact. The most recent version of the European guidelines recommends VL determination at the beginning of treatment and when assessing SVR for evaluating the treatment response (European Association for the Study of the Liver, 2018). In this study, there was only one discrepant case regarding the assessment of SVR at 12 weeks post-treatment (indeterminate HCV-cAg and negative VL). In the subsequent patient determinations, there was global agreement between VL and HCV-cAg, which confirmed SVR. This is taken into account in the latest version of the guidelines, in which the recommendation is to determine SVR in the patient either at 12 weeks post-treatment by VL or at 24 weeks post-treatment when HCV-cAg is assessed (European Association for the Study of the Liver, 2018).

The excellent correlation between the techniques (area under the ROC curve = 0.987; $R^2 = 0.932$) is in agreement with previous results (Kuo et al., 2012; Alados-Arboledas et al., 2017; Miedouge et al., 2010; Alonso et al., 2018; Alonso et al., 2017; Rockstroh et al., 2017). Thus, HCV-cAg can be considered as an alternative for VL

monitoring of HCV regardless of the genotype, confirming our hypothesis (Kuo et al., 2012; Alados-Arboledas et al., 2017; Tillmann, 2014; Alonso et al., 2017; Hadziyannins et al., 2013). This study showed the ability of the HCV-cAg technique for monitoring patients infected with HCV under treatment with new DAAs, the primary objective of this study.

Finally, there were two discrepancies in the screening group. A patient had negative HCV-cAg and a low VL (726 IU/ml), and in a later determination, VL and HCV-cAg were both negative (spontaneous resolution). A second patient presented a low VL (4240 IU/ml) and indeterminate HCV-cAg (5.18 fmol/l), and in the next determination, VL was 19 700 IU/ml. Unfortunately, it was not possible to determine HCV-cAg in the second sample, although the good correlation ($R^2 = 0.932$) between the techniques could let us assume a positive value for HCV-cAg, the same as the VL. Nevertheless, the recommendation in indeterminate HCV-cAg cases (3–10 fmol/l) is to repeat the determination and request a second sample to repeat HCV-cAg, and to perform a VL test depending on the result. Currently, low-level viremia mostly occurs in patients under treatment, and the detection of HCV-cAg at levels below the threshold of positivity in naïve patients is unusual (Alados-Arboledas et al., 2018). From this, it is possible to deduce the usefulness of HCV-cAg as a screening tool for the detection of new cases of active HCV infection. In agreement with this, the results of our study showed the good differentiation of the technique, as well as its adequacy to distinguish between active and past infection. This allows the diagnostic algorithm for HCV infection to be simplified to one step. A single sample may be sufficient to determine whether a patient has been in contact with the virus and if the infection has been resolved or is still active, and therefore whether the patient becomes a candidate for treatment and monitoring of the infection (Alados-Arboledas et al., 2017; Tillmann, 2014; Alonso et al., 2017; Wang et al., 2017).

In this study, we confirmed the ability of HCV-cAg as a marker of therapeutic failure. A possible explanation for this could be that in treatment failure cases, VL values are high and this would not interfere with the detection of the antigen, regardless of the genotype or whether the patient is co-infected with HIV.

The correlation between these two determinations (HCV-cAg and VL) may allow follow-up costs and DAA treatment to be reduced for patients diagnosed with HCV, as well as faster and easier results.

A limitation of this study is the small sample size for some of the subgroups considered. Despite this, we reproduced the results in patients co-infected with HIV as well as in the different groups. One of the advantages of this study is its prospective design in parallel with the follow-up of the included patients and the determinations in the various study groups. This allowed homogeneity in the preservation of the samples and ensured results were obtained under the same stability and storage conditions. Furthermore, the patient selection allowed us to perform a wider and more representative study regarding the epidemiological features of the study population. With respect to VL, the detection of HCV-cAg not only has less limitation in terms of samples, but also allows a continuous workflow without the need to accumulate samples in order to optimize resources.

Fast and immediate results, a reduction in the number of visits or steps to follow for the intention-to-treat population before contact with the specialist, and lower costs of the technique are some of the main advantages of HCV-cAg in comparison to VL (Tillmann, 2014). These advantages and the abilities shown in the monitoring of treatment with DAAs, as a marker of therapeutic adherence, for diagnosis of active HCV infection, and for the detection of therapeutic failure, make it a potentially useful tool for screening HCV in the population, for surveillance of high-risk populations (injection drug users, HIV-infected people, those with health risk behaviors), and for screening in organ and blood donors.

In conclusion, the hepatitis C virus core antigen demonstrated good sensitivity and specificity as a marker for the detection of active HCV infection in the diagnosis of new cases, for the detection of antiviral therapeutic failures, and for monitoring of the antiviral treatment.

Conflict of interest

The authors have declared that no competing interests exist.

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Ethical approval

The “evaluation of preventive and therapeutic interventions against hepatitis C virus infection” received a valuable report from the Clinical Ethics Committee of Navarra dated September 2, 2015. Project code: 2015/70.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.09.022.

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