Research Article

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Evaluation of HCV-Core Antigen in Diagnosis of Chronic Hepatitis C Patients under Direct-Acting Antiviral Treatment

Doğrudan Etkili Antiviral Tedavi Kullanan Kronik Hepatit C Hastalarının Tanısında HCV Çekirdek Antijeninin Değerlendirilmesi

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ABSTRACT

Objectives: Recently, with the use of direct-acting antivirals (DAA) for treating chronic hepatitis C (CHC), the success rate has exceeded 90%. The implementation of these strong therapies has reduced the role of monitoring therapy with hepatitis C virus (HCV)-RNA tests. The current study compares the HCV-core antigen test (HCV-Ag) with HCV-RNA in terms of correlation, effectiveness and cost in patients who started DAA and to evaluate the usability of HCV-Ag as a routine laboratory test.

Materials and Methods: This study includes 76 patients with CHC. Patients with positive HCV-RNA, over 18 years old and who will initiate DAA are included. HCV-Ag level was studied in all samples by using ARCHITECT core antigen measurement Abbott method. HCV-RNA and anti-HCV levels compared with HCV-Ag levels.

Results: Of the 76 patients, 44 (57%) were males, 48 (63%) were treatment experienced and 21 (27%) were cirrhotic. All patients were started with DAAs. When compared before and after treatment, HCV-RNA level, HCV-Ag level was found to be significantly different ($p<0.001$). Before treatment, HCV-RNA and HCV-Ag levels were found to be positive correlations (correlation coefficient: 0.419).

Conclusion: The use of DAAs in HCV therapy has eliminated the need for response-guided therapy. It has been demonstrated in the study that HCV-Ag measurement is very successful and cost effective in detecting viremic patients and evaluating virological response, which are the two most important factors in the management of CHC.

Keywords: Hepatitis C virus, correlation, viral load, hepatitis C antibodies

ÖZ

Amaç: Son yıllarda kronik hepatit C (KHC) tedavisinde doğrudan etkili antivirallerin (DEA) kullanılmasıyla başarı oranı %90'ı geçmiştir. Bu güçlü tedavilerin uygulanması, tedavinin hepatit C virüs (HCV)-RNA testleri ile izlenmesinin rolünü azaltmıştır. Bu çalışmanın amacı, DEA başlanan hastalarda HCV çekirdek antijen testi (HCV-Ag) ile HCV-RNA'yı korelasyon, etkinlik ve maliyet açısından karşılaştırmak ve HCV-Ag'nin rutin laboratuvar testi olarak kullanılabilirliğini değerlendirmektir.

Gereç ve Yöntemler: Çalışmamıza 76 KHC hastası dahil edilmiştir. HCV-RNA pozitif olan, 18 yaş üstü ve DEA başlanacak olan hastalar dahil edilmiştir. ARCHITECT-Abbott yöntemi kullanılarak tüm örneklerde HCV-Ag düzeyi çalışıldı. HCV-Ag seviyeleri ile RNA ve anti-HCV seviyeleri ile karşılaştırıldı.

Bulgular: Yetmiş altı hastanın 44'ü (%57) erkek, 48'i (%63) önceden tedavi görmüş ve 21'i (%27) sirotikti. Tüm hastalara DEA başlandı. Tedavi öncesi ve sonrası karşılaştırıldığında, HCV-RNA düzeyi, HCV-Ag düzeyi anlamlı olarak farklı bulundu ($p<0,001$). Tedavi öncesi HCV-RNA ve HCV-Ag seviyeleri arasında pozitif korelasyon (korelasyon katsayısı: 0,419) saptandı.

Sonuç: HCV tedavisinde DEA'larin kullanılması tedavi yanıtının değerlendirilmesinde HCV-RNA takibi yapılmasının önemini azaltmıştır. KHC yönetiminde en önemli iki faktör olan viremik hastaları saptamada ve virolojik yanıtı değerlendirmede HCV-Ag ölçümünün oldukça başarılı ve maliyet etkin olduğu çalışmamızda gösterilmiştir.

Anahtar Kelimeler: Hepatit C virüs, korelasyon, viral yük, hepatit C antikorları

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Introduction

Hepatitis C virus (HCV) infection is a blood-borne disease that affected approximately 185 million people worldwide (1). It has been estimated that HCV accounts for 27% of cirrhosis and 25% of hepatocellular carcinoma (HCC) worldwide (2). In Turkey, the prevalence of anti-HCV positivity was found to be 1% and prevalence increased after 50 years of age most of them unaware of their infection (3). In 2030, it is estimated that approximately 80,000 people may have cirrhosis, 3,770 people may have HCC related to HCV, and 3,420 people will be lost due to HCV infection (4).

The diagnosis of hepatitis C infection is made by detection of HCV-RNA by molecular methods after detection of anti-HCV antibodies by ELISA. HCV-core antigen testing is a convenient, inexpensive alternative, as it is correlated with HCV-RNA, in resource-restricted locations or when the HCV-RNA test is not available. HCV-core antigen tests have been introduced to supplement anti-HCV tests or HCV quantitative real time polymerase chain reaction (qRT-PCR) analyses over the last decade (5,6). This chemiluminescent microparticle immunoassay uses microparticles coated with anti-HCV monoclonal antibodies for the detection of HCV-Ag by capturing. The first in-house HCV-core antigen assays that were shown to have insufficient performance for clinical application mainly due to their low sensitivity were developed in Japan in the early 1990s. Over the years, researchers from Abbott Laboratories (North Chicago, IL) have recently developed the ARCHITECT HCV-Ag method which is used in this study. Despite all the advantages mentioned in the literature the manufacturer of HCV-core antigen assays recently stopped active marketing of these assays in several countries. It will, unfortunately, and probably, never be possible to determine the actual potential and usefulness of HCV-core antigen testing in the management of hepatitis C (7).

The diagnosis and treatment of HCV infection have improved a lot over the years. Over finally, well-tolerated and effective treatments with oral antivirals inhibiting HCV non-structural viral proteins involved in viral replication have been marketed this last decade, allowing the cure of all infected subjects (8). The main goal of chronic hepatitis C (CHC) treatment is to reduce the risk of developing HCC, the morbidity, and mortality associated with this disease, and the need for liver transplantation by the sustained virological response (SVR), which is defined as the inability to detect HCV-RNA in the blood 12 or 24 weeks after treatment is completed (9). The ratio of SVR is over 90% with these direct-acting antivirals (DAA). With these advances in HCV treatment, it would be beneficial to simplify the diagnosis and increase the screening to provide more patients access to new treatments. According to the European Association for the Study of the Liver (EASL) guideline, two main factors in the management of CHC; to detect basal viral load before treatment and to see that viral load becomes negative after treatment. In resource-limited environments where a nuclear acid test (NAT) is not available, using an HCV-c-Ag test to confirm viremia is recommended (10).

The purpose of this study; to compare the HCV-core antigen test with HCV-RNA, which is studied in the patient before and after the treatment of patients using DAA, and to evaluate the usability of core antigen measurement as a routine laboratory test.

Materials and Methods

Seventy-six patients with chronic HCV infection who applied to infectious diseases outpatient were included in this study. Patients were diagnosed with CHC according to the EASL guidelines. The presence of HCV-RNA above the threshold value was used for establishing the diagnosis of HCV. The anti-HCV positivity longer than 6 months was used as the criterion for chronicity (11). All patients were HCV-RNA positive, over 18 years old, and who would start treatment with DAA. Patients used sofosbuvir/ledipasvir (SOF/LDV), ritonavir boosted paritaprevir-ombitasvir-dasabuvir (PrOD), telaprevir (TEL) and bocepravir (BOC) as DAA regimen. Patients with acute hepatitis C and under 18 years of age have been excluded from the study. The demographic, clinical, and virological variables of the patients were obtained by scanning from the hospital electronic data system. Whether patients had cirrhosis or not was obtained from imaging records or biopsy reports. ISHAK Modified Histological Activity index (HAI) scoring system was used for the pathological diagnosis of cirrhosis. HCV treatment was initiated according to guides and our the Health Practice Communiqué (12,13).

Before the treatment started, informed consent was obtained from the patients, and blood was taken into a 1 tube EDTA hemogram tube, centrifugation (5K rpm in 10 min) was performed as soon as they were received and their plasma was separated. At the end of the treatment, plasma of the same patients was obtained. Patients' plasma samples were stored at -80 °C until required for testing. Then, HCV-Ag level was studied in all samples by using the ARCHITECT core antigen measurement Abbott method (Denka Seiken Co., Tokyo, Japan) HCV-RNA and anti-HCV levels before and after treatment, which were routinely studied in our hospital, were obtained using the hospital data system and compared with HCV-Ag levels. The lower detection limit for the HCV-RNA and HCV-Ag levels was 15 IU/mL and 3 fmol/L, respectively. In addition, the HCV genotype was detected using type-specific RT-PCR. Patients with HCV-RNA negative or below the lower limit of measurement at 12 weeks post-treatment were identified as providing SVR.

Ethical approval for the study was received from Kocaeli University Faculty of Medicine Ethics Committee (approval number: 2018/212, date: 11.7.2018).

Statistical Analysis

Statistical evaluation was done with IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program. Compatibility with normal distribution was evaluated with the Kolmogorov-Smirnov test. Continuous variables were given as mean ± standard deviation and median (25^{th}-75^{th} percentile), and categorical variables were given as frequency (percent). The pre-treatment and post-treatment comparisons were determined by the Wilcoxon-Signed Ranks test since normal distribution assumption was not provided. Relationships between categorical variables were evaluated by chi-square analysis. Spearman correlation analysis was used to analyze the relationships between continuous variables. For statistical significance $p<0.05$ was considered sufficient.

Results

For this study, a total of 76 patients treated with DAAs in the Kocaeli University, Infectious Diseases Outpatient Clinic during the year 2017 were included. Of the 76 patients; 44 (58%) were males and 32 (42%) were females. The average age was 56.97±13.56. It was determined that 46 of the patient's liver biopsy was performed. Nineteen patients were treatment - experienced, and 11 of them were chronic kidney failure. Patients with fibrosis 3 and above as a result of the biopsy were considered cirrhosis. Totally 21 patients had cirrhosis. Of these patients, 17 patients were accepted as cirrhosis as a result of the biopsy, 2 patients with liver imaging, 2 patients with fibroscan fibrosis score 4. The most common genotype in our patients was GT-1b (45, 59%). When the underlying diseases of the patients were evaluated, it was observed that 11 patients, 7 of whom underwent hemodialysis, had chronic kidney failure and eight patients had type 2 diabetes mellitus. There was also a history of liver transplantation in one patient and kidney in one patient. Five of the patients (6.6%) were coinfected with the hepatitis B virus (HBV), and their current HBV-DNA levels were negative. The demographic features are shown in Table 1.

Based on the guidelines, all patients started DAA treatment. Twenty-five patients were treatment-experienced. The most common DAAs for these patients were TEL (35%), SOF + LDV (27%), and BOC (25%) which were pan-genotypic. Treatments initiated to patients are summarized in Table 2.

When compared before and after treatment, HCV-RNA level, HCV-Ag level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alpha-fetoprotein (AFP) parameters were found to be significantly different ($p<0.001$). However, there was no significant decrease in anti-HCV titer after treatment. A comparison of the laboratory parameters of the patients before and after the treatment is shown in Table 3.

All patients included in our study had a post-treatment response. Subsequently, 73 patients (96.1%) were provided with SVR, and 3 patients (3.9%) had positive HCV-RNA at the 12th week after treatment. It was determined that all patients who did not provide SVR received a TEL regimen. Relationship between cirrhosis and SVR or cirrhosis and age, no significant difference was found respectively ($p=0.567$, $p=0.566$).

In addition, pretreatment HCV-RNA, HCV-Ag, and anti-HCV values were compared and a significant relationship was found between HCV-Ag and HCV-RNA ($p<0.001$) (Table 4). There was no significant relationship between anti-HCV and other parameters. Also, it was observed that the patients had a positive correlation with HCV-RNA and HCV-Ag levels before treatment (Spearman correlation coefficient: $r=0.419$) (Figure 1).

Discussion

The amount of HCV-core antigen in the blood correlates with the level of HCV-RNA, so it is also a test that can be used to demonstrate HCV replication and detect infected individuals (14,15,16,17,18,19,20,21). Studies evaluating the accuracy of these tests, the most studied analyzes (Abbott ARCHITECT HCV-Ag test and Ortho HCV-Ag ELISA) detected HCV viremia at approximately 93% and 99%, respectively (22). Chevaliez et al. (21) demonstrated in the SAPPHIRE I study that the level of HCV-Ag is a good option for detecting patients with viremia and evaluating their response to treatment. Similarly, in our study, it is seen that the HCV-Ag test can be used safely instead of HCV-RNA in the diagnosis and monitoring of treatment success of HCV-infected patients. Kesli et al. (23) reported a high correlation coefficient of 0.864 when comparing HCV-c-Ag levels with HCV-RNA levels. Also, Ergünay et al. (24) found a correlation coefficient of 0.937 between these parameters. Similarly, in this study the correlation coefficient of the two tests was found 0.419 ($p<0.001$) (Figure 1). For this reason, HCV-Ag can also be used as a new serological marker in diagnosis and follow-up. In the 2016 update of the EASL guideline, core antigen level measurement is now recommended as an alternative test in the diagnosis of acute and CHC (25). The results of our study may be useful feedback for the treatment and diagnosis guidelines.

Abbott ARCHITECT HCV-Ag detection is based on a two-stage microparticle-based chemoluminescent analysis. This test provides to determine the HCV-core antigen and anti-HCV in human serum and plasma in 60 minutes (26,27). The HCV-Ag is more durable because of its protein structure but nucleic acid amplification tests are sensitive to environmental contamination. Unlike NAT tests, which require qualified personnel, HCV-Ag measurement can be applied in most laboratories due to its simple methodology (28). Usually, when a patient is infected with HCV, first HCV-RNA is detected in the blood while the core antigen can be detected after 1-2 days. It may seem rational to use in screening of risk groups (intravenous drug addicts, hemodialysis patients, human immunodeficiency virus coinfected patients, and other immunosuppressive patients). Also, it is recommended to use for screening in the blood bank (29). As of the time of the study, in terms of cost, the HCV-Ag measurement per kit is $8, while the PCR method is $25. So HCV-Ag method especially can be used in lower-income countries. The lower detection limit is 3 fmol/L and it was able to detect patients with HCV-RNA levels between 500 IU

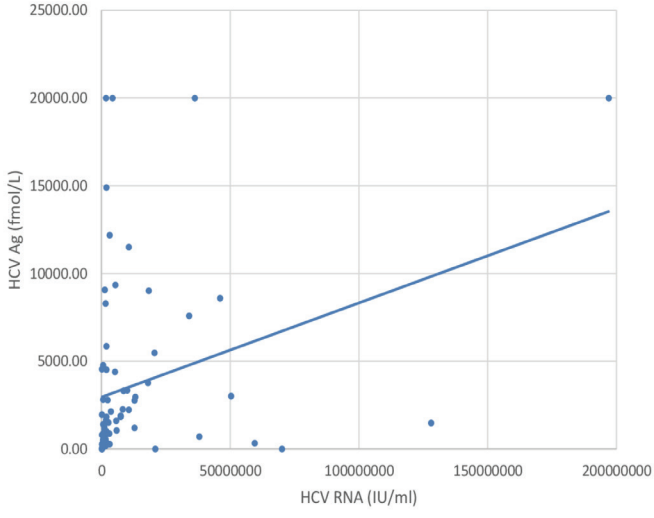

Figure 1. Spearman correlation dynamic between HCV-RNA and HCV-Ag parameters
HCV: Hepatitis C virus

and 3,000 IU/mL depending on HCV genotype (30,31). However, as in our study, most HCV patients have HCV-RNA levels well above these limits at the time of diagnosis. This may indicate that the probability of false-negative detection of HCV-Ag measurement is very low. Nevertheless, Freiman et al. (32) suggested HCV-RNA level detection to excluding false negativity since HCV-RNA low viremia may continue when HCV-Ag detection results in negativity.

In this study, the treatment of CHC with DAAs results in more than 90% SVR, regardless of genotype, cirrhosis, and previous treatment history. According to our findings, 96.1% SVR was observed and 3 patients who had relapsed after treatment were taking the TEL regimen. Şahin et al. (33) in a study in which retrospectively evaluated the results of 53 patients who received triple therapy based on TEL, the rate of SVR was found to be 58.5%. The application of these powerful therapies in recent years reduced the role of monitoring therapy with quantitative HCV-RNA tests (30). Also, to provide more patients access to new treatments, it will be useful to simplify the diagnosis of the disease and increase its screening. Anti-HCV is used for screening and in patients who are found positive, candidates for treatment are detected by PCR for HCV-RNA and HCV genotype. The HCV-Ag immunoassay is an adequate alternative to the two-stage diagnostic process (34). As in Table 3, HCV-Ag, which has a positive correlation with HCV-RNA, has 100% diagnostic power in our study. Of course, this may be due to the high viral load in all our patients at the time of diagnosis.

Table 1. Demographic characteristics of the study patients

Characteristics	Study group (n, %)
Patient	**76**
Gender	
Female	32 (42)
Male	44 (58)
Age	
≥65	52 (68)
<65	24 (32)
Treatment status	
Naive	28 (37)
Experienced	48 (63)
Cirrhosis	
Yes	21 (28)
No	55 (72)
HCV-RNA*, IU/mL	
≥1.0+E6	55 (72)
<1.0+E6	21 (28)
HCV genotype/subtype	
1a	13 (17)
1b	45 (59)
1 (untyped)	10 (13)
2	1 (1)
3	5 (7)
4	2 (3)
Comorbidity	
Chronic renal failure	11 (15)
Diabetes mellitus	8 (11)

*HCV-RNA load belonging to the before treatment status. HCV: Hepatitis C virus

All HCV genotypes are common in the world, genotypes 1, 2, and 3 were found to be 1b of the most dominant genotype according to studies performed in Turkey (68-94%) (35). Therefore, pan-genotypic SOF + LDV and TEL were used most frequently in our patients, followed by the PrOD regimen which was used in only genotype 1b. The influence of HCV genotype on cor antigen level and viral load is another point of interest. The majority of HCV genotypes in our study consisted of type 1 strains (types 1b and 1a, 76%). Therefore, the effect of HCV genotype variation can be considered as minimal in this study. When the parameters of the patients before and after the treatment were compared, ALT, AST, and AFP were significantly different. It is seen in the literature that the ALT level has improved significantly after treatment in most studies because the significant linear relationship has been between the degree of ALT elevation and the amount of liver injury based on the HAI score (36,37).

Considering that 3.8% of hemodialysis patients have anti-HCV positivity in our country, it may be rational to use the HCV-Ag test in hemodialysis patients for screening. Miedouge et al. (38) scanned 2,752 hemodialysis patients who were seronegative with HCV-RNA and HCV-Ag and found that these two tests were correlated and that the HCV-Ag test had a diagnostic power of 99.2%. In our study, 7 chronic kidney failure patients, 7 of whom were on hemodialysis, were included and HCV-Ag and HCV-RNA were correlated. Due to anti-HCV is generally negative in patients in this population, tests that directly measure the virus particles are preferred (39). Therefore HCV-core ag assay is a good, cost-effective option.

Study Limitations

There was no correlation study in the time series and the study was retrospective.

Conclusion

HCV-Ag measurement is a very successful and cost-effective test in detecting pre-treatment viremic patients and to follow-up treatment in patients using DAA. For these reasons, it was concluded that HCV-Ag measurement may be a good alternative laboratory test that can be used routinely.

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Ethics

Ethics Committee Approval: Ethical approval for the study was received from Kocaeli University Faculty of Medicine Ethics Committee (approval number: 2018/212, date: 11.7.2018).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Table 2. Treatment regiments applied to patients based on previous treatment and cirrhosis

Treatment regiment	Treatment status	Non-cirrhotic, (n)	Cirrhotic, (n)	Total, (n)
PRoD	Naive	9	2	11
	Experienced	3	ND	3
SOF + LDV	Naive	8	3	11
	Experienced	3	8	11
PRoD + RBV	Naive	7	ND	7
	Experienced	ND	1	1
SOF + LDV + RBV	Naive	1	ND	1
	Experienced	1	ND	1
SOF + RBV	Naive	3	ND	3
	Experienced	ND	ND	ND
Pro + RBV	Naive	1	ND	1
	Experienced	ND	ND	ND
TEL	Naive	1	ND	1
	Experienced	10	4	14
BOC	Naive	1	ND	1
	Experienced	8	2	10

ProD: Ritonavir boosted paritaprevir-ombitasvir and dasabuvir, SOF + LDV: Sofosbuvir/ledipasvir, RBV: Ribavirin, TEL: Telprevir, BOC: Boceprevir, ND: Not determined

Table 3. Laboratory parameters of the patients before and after the treatment

Laboratory parameters	Before treatment [mean ± SD, median (IQR)]	End of treatment [mean ± SD, median (IQR)]	Significancy, p-value
Anti-HCV	15±7.02 15 (12.9-15.6)	14±2.32 14 (13.3-14.78)	0.140
HCV-RNA	1.2+E7 1.8+E8	ND	**<0.0001**
HCV-Ag	3,648±5,092 1627 (493-4,468)	0.07±0.31 ND	**<0.0001**
ALT	40±27.09 35 (21.5-50)	19±13.09 16 (11.75-21)	**<0.0001**
AST	40±33.3 34 (23-46)	22±14.2 20 (14.2-24)	**<0.0001**
INR	1±0.11 1 (0.9-1.05)	1±0.17 1 (0.9-1.08)	0.156
AFP	7±12.7 4 (2.8-6.3)	3±2.4 3 (1.8-4.08)	<0.001

SD: Standard deviation, per: Percentil, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio, AFP: Alfa feto protein, ND: Not determined

Table 4. Comparison of patients' HCV-RNA, HCV-Ag and anti-HCV values before treatment

Parameter	HCV-RNA		HCV-Ag		anti-HCV	
	Correlation coenffient	p-value	Correlation coenffient	p-value	Correlation coenffient	p-value
HCV-RNA	-	-	0.419	<0.001	0.029	0.805
HCV-Ag	0.419	<0.001	-	-	0.122	0.302
anti-HCV	0.029	0.805	0.122	0.302	-	-

HCV: Hepatitis C virus

Authorship Contributions

Concept: M.T.D., S.A., M.S., G.S.T., E.A., Design: S.A., Data Collection or Processing: S.A., M.T.D., Analysis or Interpretation: S.A., Literature Search: S.A., Writing: S.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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