Qualitative Application of COBAS AMPLICOR HCV Test Version 2.0 Assays in Patients with Chronic Hepatitis C Virus Infection and Comparison of Clinical Performance with Version 1.0

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The objective of this research was to investigate the clinical performance of COBAS AMPLICOR hepatitis C virus (HCV) test version 2.0 Assays (CA V2.0). Eight serial samples with standard HCV ribonucleic acid (RNA) concentration and 10 times serial dilution of the 500 IU/mL samples were tested in triplicate by CA V2.0 (the limit of detection was 50 IU/mL). HCV RNA was investigated with CA V2.0 in 220 specimens from 100 chronic hepatitis C (CHC) patients, 60 chronic hepatitis B patients, and 60 healthy blood donors. The sensitivity was 99% and the specificity was 98.3%. Sera of 84 naïve CHC patients receiving standard interferon plus ribavirin for 24 weeks were tested by CA V2.0 and CA V1.0 at weeks 2, 4 and 8. The positive detection rates of CA V2.0 were significantly higher than CA V1.0 at week 2 (60.7% *vs.* 51.2%; $p < 0.01$) and week 8 (27.4% *vs.* 21.4%; $p < 0.05$). At weeks 2, 4 and 8, the positive predictive values were 90.91%, 83.02% and 78.69% with CA V2.0, and 90.24%, 82.14% and 72.73% with CA V1.0. The negative predictive values were 58.82%, 77.42% and 86.96% with CA V2.0, and 67.44%, 82.14% and 83.33% with CA V1.0. However, there was no significant difference between CA V2.0 and CA V1.0 for predicting sustained virologic response.

Key Words: hepatitis C virus, hepatitis C virus RNA, interferon therapy, qualitative hepatitis C virus RNA assay

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Chronic hepatitis C (CHC) infection is a major health problem worldwide. The global prevalence is estimated to be 3%, ranging from 0.1% to 12% in different countries [1,2]. It is estimated that there are 170 million hepatitis C virus (HCV) carriers in the world. The incidence of new symptomatic infections has been

estimated to be 1–3 cases per 100,000 persons annually [1]. Because the majority of cases are asymptomatic, the actual incidence of new infections is obviously much higher.

The enzyme immunoassays (EIAs) that detect antibodies to HCV cannot differentiate between active and resolved infection. Qualitative HCV RNA assays detect viral genomes and therefore can both confirm the presence of active infection and demonstrate its presence 4–6 weeks before antibody seroconversion takes place [3]. The application of polymerase chain reaction (PCR) methods for identification of the HCV RNA thus provides important data relating to diagnosis, monitoring, and treatment of HCV infection. Moreover, recent studies have shown that treatment strategies were mainly determined or tailored by HCV RNA measurements before and/or during treatment [4,5]. Therefore, qualitative HCV RNA assays have become an essential tool for both the diagnosis and monitoring of HCV infection.

HCV RNA can usually be detected in the patient's serum within 10–14 days after infection [3]. In clinical practice, qualitative HCV RNA assay offers the desired sensitivity and specificity for detecting and confirming the presence of active infection and for documenting the response after antiviral treatment. The detection of HCV RNA by reverse transcription–polymerase chain reaction (RT–PCR) has been widely developed with standard ready-to-use assays such as the AMPLICOR HCV test. This test was successfully automated by using an integrated PCR system based on COBAS AMPLICOR technology that fully automates all steps of PCR amplification and detection. Developed and manufactured by Roche Diagnostics System, the COBAS AMPLICOR HCV RNA assay version 1.0 (CA V1.0; Roche Diagnostic Systems, Branchburg, NJ, USA) is available worldwide. Recently, a new version (version 2.0) of the COBAS AMPLICOR HCV RNA assay (CA V2.0; Roche Diagnostic Systems) has been developed and marketed.

In this study, we aimed to evaluate the clinical performance of these two versions of COBAS AMPLICOR HCV RNA assays in terms of sensitivity, specificity, and reproducibility. We also attempted to compare the performance characteristics for the prediction of sustained virologic response (SVR) between these two versions among CHC patients receiving standard interferon (IFN) and ribavirin combination therapy.

Materials and Methods

Validation test and detection limit test

For reliability test, eight validation nucleic acid panels with standard HCV RNA concentration (NAP-HCV 000; 0 IU/mL, and NAP-HCV 001-007; 50, 500, 5,000, 50,000, 200,000, 500,000, and 2,000,000 IU/mL; AcroMetrix, USA) were processed in triplicate with CA V2.0 (24 tests were performed).

To confirm the limit of detection, NAP-HCV 002 (500 IU/mL) was used for serial dilution in ratios of 1:10; 1:100; 1:1,000; and 1:10,000 (from 50 IU/mL to 0.05 IU/mL). All diluted specimens were tested in triplicate three times (total nine tests in each concentration) with CA V2.0 assay.

Sensitivity and specificity tests

The presence of HCV RNA was investigated with CA V2.0 in 220 specimens consecutively collected from 100 CHC patients, 60 chronic hepatitis B (CHB) patients, and 60 healthy blood donors. Serum samples from enrolled individuals were collected on SST Vacutainer (Becton-Dickinson, Meylan, France), centrifuged, aliquoted, stored at –30°C within 90 minute of collection, and tested with the assay within a period of 3 months. Eligibility criteria for CHC patients were defined as: anti-HCV (EIA 3.0; Abbott, North Chicago, IL, USA) positivity; consecutive serum alanine aminotransferase levels more than 1.5 times above the upper normal limit for more than 6 months; chronic hepatitis proven by liver histopathology; negative for HBsAg (enzyme-linked immunosorbent assay [ELISA]; Abbott); and patients without concomitant potential causes of chronic hepatitis other than HCV infection, such as alcoholism, drug-induced scenarios, autoimmune hepatitis, primary biliary cirrhosis, Wilson's disease, α-antitrypsin deficiency, etc. Healthy blood donors were defined as follows: (1) negative for anti-HCV (EIA 3.0) and HBsAg (ELISA); (2) normal liver function test; and (3) no history of drug abuse, transfusion, hepatitis, and of percutaneous risks such as tattooing, dental procedures, or any operation within 1 year. The sensitivity and specificity of CA V2.0 assay was determined directly from the comparison of the results with the biological standards.

Clinical performance

Sera of 84 naïve CHC patients receiving combination therapy with high dose conventional IFN (6 MU

subcutaneously three times weekly) plus oral ribavirin (1,000–1,200 mg daily) for 24 weeks were analyzed for HCV RNA retrospectively. SVR was defined as clearance of serum HCV RNA at the end of treatment and throughout the 24-week follow-up period.

Blood samples were collected at weeks 2, 4 and 8 after initiation of combination therapy. Each sample was processed in parallel for HCV RNA with both CA V2.0 and CA V1.0.

Undetectable HCV RNA was used as a prediction of SVR in CHC patients. In our study, the prognostic values for combination therapy in these 84 patients were analyzed in parallel with both CA V2.0 assay and CA V1.0 assay at weeks 2, 4 and 8. Negative HCV RNA test results were used as a positive prediction of SVR, and positive RNA test results indicated a negative prediction of SVR.

Statistical analyses

The discrepancy between these measures for CA V2.0 and CA V1.0 were analyzed with χ^2 tests for non-independent sample proportions (McNemar's test). A p value <0.05 was considered statistically significant.

Results

Validation tests and detection limit tests

A total of 24 tests were performed with CA V2.0 for the validation test (triplicate for eight panel members with standard HCV RNA concentration; NAP-HCV 000-007). Only NAP-HCV 000 (0 IU/mL) showed negative results in the triplicate test and all the other panel members showed positive results with CA V2.0.

For the limit of detection, each serially diluted sample was tested nine times with CA V2.0. Samples with HCV RNA concentration of 50 IU/mL were all positive. However, some negative results were obtained below 50 IU/mL (the detection rate of serial dilutions: 50 IU/mL, 100%; 5 IU/mL, 33.3%; 0.5 IU/mL, 33.3%; 0.05 IU/mL, 0%; respectively). Our results indicate the clinical sensitivity of CA V2.0, which is capable of detecting >50 IU/mL HCV RNA concentration in clinical specimens.

Sensitivity and specificity tests

A total of 220 tests were performed with CA V2.0 for sensitivity and specificity. Among the sera from 100 CHC patients, HCV RNA was detectable in 99 (99%) samples with CA V2.0. HCV RNA was detectable in 1 (1.7%) of 60 CHB patients, and in 1 (1.7%) of 60 healthy blood donor samples. The sensitivity and specificity of CA V2.0 assay was 99% and 98.3%, respectively.

Clinical performance: comparison between CA V2.0 and V1.0

Of the 84 naïve CHC patients receiving combination therapy with high dose conventional IFN (6 MU subcutaneously three times weekly) plus ribavirin, the SVR rate for HCV was 60.7%. At weeks 2, 4 and 8, HCV RNA was detectable with CA V1.0 in 43 (51.2%), 28 (33.3%), and 18 (21.4%) patients, respectively. On the other hand, HCV RNA was detectable with CA V2.0 in 51 (60.7%), 31 (36.9%), and 23 (27.4%) patients, respectively (Table 1; $p=0.0047$, 0.083, 0.025 at weeks 2, 4 and 8).

Table 1. Comparison of the sensitivity between CA V1.0 and CA V2.0 assays in HCV RNA detection amongst 84 naïve chronic hepatitis C patients receiving interferon plus ribavirin combination therapy*†

	CA V1.0					
	Week 2		Week 4		Week 8	
	Positive	Negative	Positive	Negative	Positive	Negative
CA V2.0						
Positive	43 (51.2%)	8 (9.5%)	28 (33.3%)	3 (3.6%)	18 (21.4%)	5 (6.0%)
Negative	0	33 (39.3%)	0	53 (63.1%)	0	61 (72.6%)
	$p=0.0047$		$p=0.083$		$p=0.025$	

*Comparison between CA V2.0 assay and CA V1.0 assay in sera of 84 naïve chronic hepatitis C patients receiving interferon (6 MU three times weekly) plus ribavirin for 24 weeks at weeks 2, 4 and 8 after initiation of combination therapy; †discrepancy between these two assays was analyzed with χ^2 for non-independent sample proportions (McNemar's test). CA = COBAS AMPLICOR; HCV RNA = hepatitis C virus ribonucleic acid.

Table 2. Comparison of the predictions of sustained virologic response (SVR) rate between CA V1.0 and CA V2.0*†

	CA V1.0						CA V2.0					
	Week 2		Week 4		Week 8		Week 2		Week 4		Week 8	
	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive
SVR‡												
Positive	37	14	46	5	48	3	30	21	44	7	48	3
Negative	4	29	10	23	18	15	3	30	9	24	13	20
PPV§ (%)	90.24		82.14		72.73		90.91		83.02		78.68	
NPV‖ (%)	67.44		82.14		83.33		58.82		77.42		86.96	

*Prognostic values for combination therapy in 84 chronic hepatitis C patients were analyzed in parallel with both CA V2.0 and CA V1.0 at weeks 2, 4, and 8; †positive (+) and negative (–) predictive values for CA V1.0 and CA V2.0 were analyzed using McNemar's test; ‡SVR is defined as clearance of serum HCV RNA at the end of treatment and throughout the 24-week follow-up period; §p values for PPV between CA V1.0 and CA V2.0 were 0.923 at week 2, 0.904 at week 4, and 0.435 at week 8; ‖p values for NPV between CA V1.0 and CA V2.0 were 0.389 at week 2, 0.653 at week 4, and 0.745 at week 8. CA = COBAS AMPLICOR; PPV = positive prediction value; NPV = negative prediction value; HCV RNA = hepatitis C virus ribonucleic acid.

Overall, as shown in Table 2, the positive prediction values (PPV) for CA V2.0 and CA V1.0 were 90.91% (30/33) and 90.24% (37/41) at week 2, 83.02% (44/53) and 82.14% (46/56) at week 4, and 78.69% (48/61) and 72.73% (48/66) at week 8. The negative prediction values (NPV) for CA V2.0 and CA V1.0 were 58.82% (30/51) and 67.44% (29/43) at week 2, 77.42% (24/31) and 82.14% (23/28) at week 4, and 86.96% (20/23) and 83.33% (15/18) at week 8. There was no significant difference between CA V2.0 and V1.0 for the prediction of SVR in combination therapy.

Discussion

Despite the improvement achieved by third-generation EIA, seroconversion of anti-HCV would not be detected until 7 to 8 weeks in approximately 30% of patients after exposure [3]. Supplemental tests such as commonly used recombinant immunoblot assay (RIBA) are usually indicated to make a confirmation. RIBA is standardized and reproducible, but its clinical application is limited due to being time consuming and relatively expensive. Besides, in clinical practice, there will be some patients with normal liver function during long-term follow-up who will still test positive for RIBA. In contrast, HCV RNA can usually be detected in the patient's serum within 10–14 days after infection [3]. Therefore, in order to confirm the presence of active infection, it would be more efficient to use nucleic acid tests for circulating HCV RNA.

An ideal qualitative HCV RNA assay should be specific, accurate, reproducible, and standardized. Moreover, it should also be competent as a monitoring tool in diagnosis and treatment. To meet these practical requirements, two commercially available assays, the second generation branched DNA (bDNA) V2.0 assay (Quantiplex HCV RNA; Bayer Diagnostics) and the COBAS AMPLICOR HCV Monitor test (COBAS V2.0; Roche Diagnostic Systems) are widely used. The bDNA assay is convenient and has excellent reproducibility, but has a low rate of sensitivity. The COBAS AMPLICOR HCV monitor test, using competitive RT-PCR, has been semi-automated and modified to amplify all genotypes equally [6,7]. Our results demonstrated that the CA V2.0 showed good reliability in the triplicate validation test with standard HCV RNA panels. We also showed that samples containing

Table 3. Comparison between CA V1.0 and CA V2.0*

Assay	Method	Hands on time (hr)	Overall workload time	Limit of detection
COBAS AMPLICOR HCV 1.0 (CA V1.0)	Manual RT-PCR	~8	7 min/specimen	1,000 copies/mL
COBAS AMPLICOR HCV 2.0 (CA V2.0)	Automated RT-PCR	~2	5 min/specimen	50 IU/mL

*CA V2.0 offers some advantages over CA V1.0: CA V2.0 is approximately 10-fold more sensitive; CA V2.0 amplified all genotypes with similar efficiency, which improved sensitivity for non-1 genotypes HCV; by using the parallel-run feature of the instrument, the throughput can be increased to 3–4 runs per day.

>50 IU/mL of HCV RNA were positive (100%), and became negative below this level (0–33.3%). This verified the limit of detection of the COBAS AMPLICOR HCV assay version 2.0 to be 50 IU/mL. The limit of detection of the COBAS AMPLICOR HCV assay version 1.0 is 1,000 copies/mL [8–10]. Since an international unit is equivalent to approximately 0.93–3.1 copies as measured in the COBAS AMPLICOR HCV formats [11], CA V2.0 is approximately 10-fold more sensitive than CA V1.0 [6].

The competitive RT-PCR assay is highly sensitive but is associated with the risk of contamination. In some previous studies [8–10], CA V1.0 assay showed high sensitivity (94–100%) and specificity (98.0%). In our study, the results among CHC, CHB, and healthy blood donors were compared in terms of serology and clinical diagnosis. CA V2.0 assay showed good sensitivity (99%), specificity (98.3%), and had good reliability. It therefore appears to be a suitable system for the monitoring and diagnosis of HCV infection. Only one patient (who had a clinical diagnosis of CHC but a negative result with CA V2.0) probably had (1) a low level of circulating HCV RNA below the analytic sensitivity of CA V2.0 and (2) a PCR priming site mutation.

Pretreatment HCV RNA measurements have been found to be one of the independent predictors of a sustained response after combination therapy with IFN and ribavirin [7,12]. Moreover, recent studies have shown that treatment strategies were mainly determined or tailored by HCV RNA measurements before and/or during treatment [4,5]. The early disappearance of serum HCV RNA during antiviral therapy has been found to be associated with a favorable long-term response [13–17]. Our data showed that CA V2.0 had better performance than CA V1.0 regarding clinical performance as well as validation panel. It has been shown that CA V2.0 rather than V1.0 could predict the outcome of IFN therapy in both serotype 1 and serotype 2 HCV [18]. However, CA V2.0 did not yield a higher predictive value of SVR to combination therapy with standard IFN and ribavirin in our study. This might suggest that COBAS AMPLICOR HCV RNA assays, both CA V1.0 and CA V2.0 (combination or isolation), are an ideal method for qualitative monitoring of treatment. Overall, as shown in Table 3, CA V2.0 offers several advantages over CA V1.0 [6,9,11]. Further studies in terms of quantitative measurements, especially during different stages of treatment, are needed to elucidate and compare their impacts on viral kinetics.

In conclusion, CA V2.0 showed good sensitivity and specificity and had good reliability in triplicate test. The lower limit of detection for CA V2.0 was 50 IU/mL. CA V2.0 is more sensitive than CA V1.0 in the detection of HCV RNA after the beginning of IFN plus ribavirin therapy for CHC patients. Both CA V2.0 and V1.0 showed that the viral load was an indicator of SVR. However, there is no significant difference between CA V2.0 and V1.0 for predicting SVR in combination therapy.

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第二代 C 型肝炎病毒 RNA 定性檢驗套組的臨床應用及與第一代檢驗套組於臨床應用之比較

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本研究是評估第二代 C 型肝炎病毒 RNA 定性檢驗套組 (COBAS AMPLICOR HCV test version 2.0 Assays [CA V2.0]) 的臨床應用。使用標準血清盤 (AcroMetrix、USA)，每盤有 8 支檢體都經過以 CA V2.0 重複三次檢測。將含 HCV RNA 500 IU/mL 之檢體稀釋後，經 CA V2.0 檢測三次。證實本套組的偵測下限在 HCV RNA 50 IU/mL。敏感度及專一度測試使用三組檢體：第一組慢性 C 型肝炎共 100 支，第二組為慢性 B 型肝炎共 60 支，第三組為健康之捐血者共 60 支，三組血清都以 CA V2.0 檢測。發現本套組的偵測敏感度為 99%；特異性為 98.3%。84 位慢性 C 型肝炎患者接受干擾素及 ribavirin 合併治療 24 週，開始治療後之第 2、4、8 週將 84 位患者之血清分別以第一代 (CA V1.0) 及第二代 (CA V2.0) C 型肝炎病毒 RNA 檢驗套組加以檢測。於第 2 及第 8 週，CA V2.0 之檢測率高於 CA V1.0 (60.7% *vs.* 51.2%，$p < 0.01$；27.4% *vs.* 21.4%，$p < 0.05$)。在對合併治療之持續反應率 (sustained virologic response [SVR]) 預測方面：第2、4、8 週 CA V2.0 之陽性預測值為 90.91%、83.02%、78.69%，CA V1.0 之陽性預測值為 90.24%、82.14%、72.73%。第 2、4、8 週 CA V2.0 之陰性預測值為 58.82%、77.42%、86.96%，CA V1.0 之陰性預測值為 67.44%、82.14%、83.33%。CA V2.0 和 CA V1.0 在預測合併治療之 SVR 上無顯著差異。

關鍵詞：C 型肝炎病毒，C 型肝炎病毒RNA，干擾素治療，RNA定性檢驗
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