Review

The role of core antigen detection in management of hepatitis C: a critical review

Katja Seme, Mario Poljak, Dunja Z. Babić, Tina Močilnik, Adriana Vince

Medical Faculty, Institute of Microbiology and Immunology, Zaloška 4, 1000 Ljubljana, Slovenia
Dr. Fran Miklošević University Hospital for Infectious Diseases, Mirogojska 8, 10000 Zagreb, Croatia

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Abstract

Several assays in research format and two commercial assays for the detection of hepatitis C virus (HCV) core protein or HCV core antigen have been developed in recent years. In order to elucidate the role and significance of HCV core antigen detection in the diagnosis and management of hepatitis C, we reviewed 56 studies published in peer-reviewed journals until September 2004. Evaluations in transfusion settings showed that the HCV core antigen assay detects HCV infection, similarly as nucleic acid techniques (NAT), between 40 and 50 days earlier than the current third generation HCV antibody screening assays. HCV core antigen levels closely track HCV RNA dynamics, and allow clinical monitoring of a patient’s therapy, independently of HCV genotype; however, mainly in the samples with HCV RNA levels above 20,000 IU/ml. Considering the lower sensitivity of HCV core antigen detection in comparison to NAT, the HCV core antigen assay is not practical for the determination of the end of treatment response and sustained viral response, but could be useful for the determination of early viral response in the pegylated interferon-alpha and ribavirin treated patients infected with HCV genotype 1. The HCV core antigen detection is a viable tool for study of hepatitis C pathogenesis. The HCV core antigen can be used as a marker of HCV replication in anti-HCV positive individuals in the areas of the world that cannot afford NAT and/or in the settings that are not equipped or competent to perform HCV RNA testing. Because the manufacturer of HCV core antigen assays recently stopped an 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.

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1. Introduction

Virological tests for the diagnosis and management of hepatitis C virus (HCV) infection included, until recently, screening enzyme immunoassays (EIAs) and confirmatory immunoblot assays for the detection of anti-HCV antibodies, qualitative and quantitative nucleic acid techniques (NAT) for the detection of HCV RNA and methods for the determination of HCV genotype. Since the discovery of HCV in 1989, several changes have been introduced in the diagnostic procedure of hepatitis C, the most recent after National Institutes of Health Consensus Development Conference: Management of Hepatitis C in June 2002 (National Institutes of Health, 2002).

Thus, at present, virological diagnosis of hepatitis C usually begins with the detection of anti-HCV antibodies using screening ELISA. The anti-HCV antibodies can be detected 7–8 weeks after infection and usually persist for life. A negative anti-HCV EIA result is sufficient to exclude chronic HCV infection in immunocompetent subjects, while EIAs can be negative in small proportion of hemodialysis and profoundly immunodeficient patients despite ongoing HCV replication (Pawlotsky, 2003). Given the high sensitivity and specificity of current anti-HCV EIAs, immunoblot tests, which have been used in the past as confirmatory anti-HCV assays, are now considered no longer useful (Pawlotsky, 2002, 2004).

In case of anti-HCV EIA positivity, each individual should be rather tested by a qualitative NAT with a lower limit of detection of at least 50 IU of HCV RNA/ml. Qualitative NAT is, namely, the key diagnostic method for distinguishing the individuals who have resolved HCV infection (HCV RNA negative) from the patients with active/ongoing HCV infection (HCV RNA positive) (Pawlotsky, 2004). However, there are at least four clinical situations when the screening for HCV infection cannot rely only on serology, but should also include a sensitive qualitative NAT. These are acute hepatitis C, diagnosis of HCV infection after occupational exposure, in babies born to HCV-infected mothers, and in immunocompromised patients (Pawlotsky, 2004). When antiviral therapy is considered in chronic hepatitis C patients, the HCV genotype has to be determined first. The indication and duration of antiviral treatment namely depends mainly on the HCV genotype. Additionally, quantitative HCV RNA testing before and after 12 weeks of treatment (referred to as early viral response) is used to monitor and to predict success of pegylated interferon-alpha and ribavirin treatment of the patients infected with genotype 1 (Kessler et al., 2002; Pawlotsky, 2002, 2004).

Since NAT is labour intensive, prone to environmental contamination, and particularly expensive, efforts have been made over the past several years to identify a test that could successfully supplement or eventually replace NAT in the management of hepatitis C (Alter, 2002; Mondelli, 2004). Similarly to some other viral pathogens, a detection of circulating viral proteins or antigens instead of viral nucleic acids was the initial logical approach. Among the potential candidate HCV proteins, the viral nucleoprotein or core protein has attracted the attention of researchers because it is a structural HCV protein and its sequence is highly conserved across HCV genotypes (Simmonds, 1999; Mondelli, 2004).

Several assays in research format and two commercial assays for the detection of HCV core antigen have been developed in recent years. Although, as evident from many evaluations, these assays showed the potential for diagnostic applications, their arrival to “hepatitis C scene” was accompanied by various reactions ranging from uncritical enthusiasm to complete ignorance (Alter, 2002; Diment and Calmann, 2002; Mondelli, 2004). To the best of our knowledge, no systematic review concerning the HCV core antigen assays has been published in peer-reviewed journals. Thus, here we reviewed all studies regarding the HCV core antigen detection published to date and tried to elucidate critically its role and significance in the diagnosis and management of hepatitis C. For this review, we searched PubMed, Current Contents (Clinical Medicine and Life Sciences Editions), and ISI Web of Science using the search terms HCV, hepatitis C, core, antigen and trak-C without any search limits. The search was carried out in April 2004 and repeated in September 2004. From the described search, 56 papers published in peer-reviewed journals were selected and evaluated in the present review. No abstracts or proceedings of the symposia and congresses as well as commercially sponsored educational materials were included, but, when appropriate, the results of our research group were presented.
2. HCV core protein

The core protein is a highly conserved HCV protein of 191 amino acids with a molecular mass of 21 kDa (Tsutsumi et al., 1994; Forns and Bukh, 1999). During the translation of the HCV polyprotein, the nascent polypeptide is first targeted to the host endoplasmic reticulum membrane. The cleavage of the polyprotein by the host signal peptidase yields the immature form of the core protein which contains the E1 signal sequence at its C-terminus. This signal peptide is processed further by a host signal peptide peptidase, thereby yielding the mature core protein (McLauchlan et al., 2002; Penin et al., 2004). Most of the core protein is found in the cytoplasm, where it is bound to endoplasmic reticulum membranes or located at the surface of lipid droplets (Hope and McLauchlan, 2000; Maillard et al., 2001). In addition, a small proportion of the core protein may also be found in the nucleus of an infected cell (Penin et al., 2004).

The role of HCV core protein has been reviewed recently in several articles (McLauchlan, 2000; Lai and Ware, 2000; Kato, 2001; Penin et al., 2004). Briefly, it seems that the core protein interacts with cell membranes or lipids and/or envelop glycoproteins is important for a correct HCV particle morphogenesis. In addition to its role in the nucleocapsid formation, the HCV core protein may also modulate the gene transcription, cell proliferation, cell death, and cell signaling, interfere with lipid metabolism, and suppress host immune responses. However, most of these findings are controversial, and further research is required to elucidate the exact role of core protein (Penin et al., 2004).

3. Development of HCV core antigen assays

3.1. In-house HCV core antigen assays

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 early 1990s (Takahashi et al., 1992a, 1992b; Moriya et al., 1994). Improved HCV core antigen assays were therefore developed soon afterwards also in Japan (Tanaka et al., 1995, 1996; Kashiwakuma et al., 1996). These improved HCV core antigen assays were simple protein-capture fluorescence enzyme immunoassays in a microtiter plate-based test format, utilizing two monoclonal antibodies: a 5F11 antibody to capture the core antigen and a β-1,2-galactosidase conjugated 5E3 antibody with different epitope reactivity to detect the bound antigen. The major disadvantage of these improved assays was a complicated specimen pretreatment protocol.

Clinical applicability of the improved in-house HCV core antigen assays was proven in several evaluations. Oriio et al. (1996) evaluated the relation between the serum HCV core antigen level, HCV RNA level as determined by branched DNA assay Quantiplex HCV RNA 1.0 (Chiron, Emeryville, CA), and HCV genotype in the patients with chronic HCV infection. Their study showed that fluorescence enzyme immunoassay is a sensitive assay for detection of the serum HCV core antigen and may have a role as a predictor of the subsequent response to interferon therapy. Kobayashi et al. (1998) showed that the assay was useful in the early diagnosis of an acute hepatitis C. Dickson et al. (1999) demonstrated that HCV core antigen level reflected a HCV viremia and might have clinical implications in the liver transplanted patients with HCV recurrence. Komatsu and Tanksaki (1999) compared an improved in-house HCV core antigen assay with the in-house PCR and used it successfully for the quantification of the HCV core antigen in patients with chronic hepatitis C. Kawan et al. (2002) evaluated recently the clinical relevance of the in-house core antigen assay in comparison with Cobas Amplicor HCV Monitor 2.0 (Roche Diagnostics, Branchburg, NJ) and Amplicor HCV Monitor 1.0 (Roche Diagnostics) in therapy-naïve patients with chronic hepatitis C. They showed that the sensitivity of the HCV core antigen assay was lower than that of the Cobas Amplicor HCV Monitor 2.0; however, the HCV core antigen levels correlated well with the HCV RNA levels.

3.2. Commercial HCV core antigen assays

The studies described earlier, which showed that it was possible to detect the HCV core antigen in the peripheral blood of HCV-infected patients, led to the commercialisation of HCV core antigen assay. The first generation of commercial HCV core antigen assay, referred to as HCV Core Antigen ELISA Test System (Ortho Clinical Diagnostics, Raritan, NJ), was a qualitative microwell-plate format ELISA which utilized 5F11 and 5E3 monoclonal antibodies for the capturing and detection of core antigen, respectively. The first generation assay unfortunately detected HCV core antigen only in the anti-HCV negative phase of HCV infection or the so-called "free HCV core antigen" (Fig. 1). Inability to detect the HCV core antigen in the presence of anti-HCV antibodies, which was the major disadvantage of the first generation of commercial HCV core antigen assay, led to the development of the second generation assay referred to as Total HCV Core Antigen ELISA Test System or test-C assay (Ortho Clinical Diagnostics). The most important improvements of a second generation of commercial HCV core antigen assay were: (i) incorporation of a short and simple sample pretreatment procedure that enables dissociation of the core antigen–anti-core antibodies complex, (ii) usage of four monoclonal antibodies: two capture monoclonal antibodies (C11-3 and C11-7) and two horseshadish peroxidase-conjugated monoclonal antibodies (C11-10 and C11-14) for the detection of the bound HCV core antigen, and (iii) quantitative determination of the HCV core antigen (Aoyagi et al., 1999; Tanaka et al., 2000). Improvements introduced in the second generation of commercial HCV core antigen assay enabled the quantitative detection of the HCV core antigen not only during the pre-seroconversion period, but most importantly, also in the
presence of anti-HCV antibodies (Fig. 1). Studies that evaluated analytical performance of the second generation of commercial HCV core antigen assay showed a good test performance, with intra- and interassay coefficient variations ranging from 1.0% to 33.2% and 6.0% to 26.7%, respectively (Kurtz et al., 2001; Bourvier-Alias et al., 2002; Haas et al., 2004).

A Japanese commercial variety of HCV core antigen assay referred as Lumispot EIKEN HCV Antigen Assay (Eiken Chemical, Tokyo, Japan) has been automated recently using the Lumispot LS-2000 automated analyzer. Saito et al. (2003) showed that the automated assay had good reproducibility and a favorable dynamic range.

Researchers from Abbott Laboratories (North Chicago, IL) have recently developed two different assays, the microparticle-based chemoluminescent assay for the detection of HCV core antigen in human serum and plasma (Muerhoff et al., 2002) and the assay for simultaneous detection of HCV core antigen and anti-HCV in the human sera and plasma (Shah et al., 2003). Both assays can be performed on a high-throughput fully automated chemoluminescent analyzer. To our knowledge, besides Abbott publications, no “independent” evaluation of both assays has been published to date in peer-reviewed journals.

4. Potential applications for HCV core antigen testing

4.1. Hepatitis C screening in transfusion settings

The introduction of NAT testing of blood donors for HCV has been a recent measure adopted by blood transfusion organizations in some European countries and elsewhere to further increase the safety of blood and blood products. Detection of HCV RNA by NAT permits the identification of acutely infected donors before their seroconversion for antibody to HCV, who would have been missed by current serological tests (Simmonds et al., 2002).

Several research groups have tried to find out whether it is possible to replace NAT with the HCV core antigen detection for screening of blood donations. In eight retrospective evaluations of the first generation of Ortho HCV core antigen assay, published in peer-reviewed journals, the sensitivity of the assay was mainly evaluated on commercial and non-commercial seroconversion panels and the specificity on blood donor samples (Peterson et al., 2000; Courouce et al., 2000; Icardi et al., 2001; Lee et al., 2001; Piccoli et al., 2001; Widell et al., 2002; Grant et al., 2002; Nubling et al., 2002). In addition to retrospective evaluations, four prospective evaluations of this assay in transfusion settings have been performed to date. In prospective evaluations, either the HCV core antigen assay or NAT were used as first-line screening method followed by testing of reactive/positive samples by a second-line method (NAT or HCV core antigen assay). Thus, Lee et al. (2001) screened 9133 volunteer USA blood donors by the HCV core antigen assay, retested all antigen positive samples by NAT, and detected two putative window-phase donations. In contrast, Brojer et al. (2001) tested 144,000 Polish blood donor specimens by polymerase chain reaction (PCR) using the 48 mini-pool screening strategy and retested all PCR positive specimens by the HCV core antigen assay. They also detected two putative window-phase donations. After this positive experience, the feasibility of HCV core antigen testing for the routine screening of Polish blood donors has been evaluated by Letowska et al. (2004). In this second Polish evaluation, a total of 133,279 blood donor samples were screened by the HCV core antigen assay and all repeatedly reactive samples by PCR. Six window-phase donations were identified. As a consequence of both studies, a mandatory testing of every blood and plasma donation for HCV core antigen was recommended in Poland as of January 2002 (Letowska et al., 2004). A single window-phase donation was detected in the prospective study by Sanz et al. (2002), where 29,468 specimens obtained from Spanish blood donors were screened by the HCV core antigen assay.

Fig. 1. The kinetics of HCV markers during hepatitis C virus infection.
and positive samples retested by PCR. All 11 window-phase donations found in four prospective evaluations performed on total of 314,880 blood donor samples were detected using both the HCV core antigen assay and NAT. The results of 12 prospective and retrospective published evaluations of the Ortho HCV core antigen assay in transfusion settings can be summarised as follows: (i) the HCV core antigen assay detects HCV infection between 40 and 50 days earlier than the current third generation HCV antibody screening assays, (ii) its clinical sensitivity is similar to NAT (mean differential 1–2 days), (iii) its overall sensitivity versus NAT is 94–97%, (iv) its specificity in low risk populations is 99.5–99.9%, and (v) no difference in the ability to detect different HCV genotypes was recognized.

In a recent study published by Lapreche et al. (2003), the ability of both generations of Ortho HCV core antigen assays to detect early phase of HCV infection were compared on 31 non-commercial seroconversion panels. The second generation assay was found more sensitive than the first generation assay and had a similar performance as NAT in the window period.

A recent case report pointed out that an individual HCV core antigen testing could not have been considered equivalent to the NAT screening in certain blood donations (Dow et al., 2004). Namely, during the routine NAT screening, one PCR positive/anti-HCV negative blood donation was identified among more than 106 Scottish blood donations. The index donation was both PCR and HCV core antigen positive. The subsequent samples obtained from the same donor demonstrated the loss of the first generation HCV core antigen assay reactivity and reduced activity in the second generation HCV core antigen assay unit after 69 days. The anti-HCV screening assays became positive on day 62. The HCV RNA levels fluctuated considerably during the follow-up period, being completely undetectable at the time-point around seroconversion. In our opinion, this report describes an unusual virological course of an acute HCV infection and cannot overshadow positive experiences with the HCV core antigen testing in transfusion settings shared by other researchers.

### 4.2 Hepatitis C screening in non-transfusion settings

NAT screening for the HCV infection outside the blood transfusion settings is still controversial and is not recommended by any current consensus guidelines (National Institutes of Health, 2002). However, it is performed periodically or routinely in certain populations (e.g., intravenous drug users, patients on hemodialysis, HIV-infected individuals) in some centers.

To our knowledge, no single published study evaluated the HCV core antigen testing as a screening method for the HCV infection outside the blood transfusion settings. Thus, we have recently retrospectively evaluated the usefulness of the first generation of Ortho HCV core antigen assay for such purpose. Between May 1996 and March 2002, 12,621 serum samples were tested for anti-HCV in our laboratory and, among them, 1,464 samples tested positive for anti-HCV. Fifty anti-HCV positive patients had a previous anti-HCV negative serum sample available. The interval between the last anti-HCV negative and the first anti-HCV reactive serum sample in individual patients was between 8 and 1353 days, where it is necessary to emphasize that these were mostly coincidental consecutive samples. Among 50 selected anti-HCV negative serum samples, 5 samples tested positive and 45 negative using both the HCV core antigen assay and Cobas Amplicor 2.0 (Roche Diagnostics), confirming the results obtained in blood transfusion settings.

### 4.3 HCV core antigen as a marker of HCV replication in anti-HCV positive, therapy-naive individuals

The presence of HCV RNA in the peripheral blood is the most reliable marker of HCV replication and thus represents a key diagnostic marker of active/ongoing HCV infection in anti-HCV positive individuals (Pawlotsky, 2002, 2004). Consequently, the detection of HCV replication in anti-HCV positive, therapy-naive individuals should also be the main application for the HCV core antigen testing. Surprisingly, in most published evaluations of the HCV core antigen assays, this was not a primary aim of a study, but rather a study byproduct. In addition, the published evaluations were mainly performed on the samples obtained from anti-HCV positive individuals during antiviral therapy and resulted in somewhat disappointing sensitivity of the HCV core antigen assays in comparison to NAT. To the best of our knowledge, five studies evaluated the usefulness of HCV core antigen as a marker of active/ongoing HCV infection in the therapy-naive patients (Cano et al., 2003; Krajden et al., 2004; Netski et al., 2004; Agha et al., 2004; Valkavi et al., 2004). They were performed on 114–348 HCV RNA positive samples and showed an 86.9–97.4% sensitivity of second generation of Ortho HCV core antigen assay in comparison to NAT. Most HCV RNA positive samples that tested negative for the HCV core antigen had a low viral load (mostly below 14,000 IU/ml). However, since the range of baseline HCV RNA levels in the therapy-naive patients is relatively narrow (between 50,000 and 5,000,000 IU/ml), the HCV core antigen testing, if used as a marker of active/ongoing HCV infection in anti-HCV positive individuals, may lack sensitivity only for a small portion of patients with lower baseline viral loads.

### 4.4 HCV core antigen level as a quantitative marker of HCV replication and monitoring of antiviral therapy

According to recent consensus guidelines, the main application for HCV RNA quantification is the assessment of early viral response (EVR) in pegylated interferon-alpha and ribavirin treated patients infected with HCV genotype 1 (National Institutes of Health, 2002). Namely, the patients who do not achieve EVR (defined as a minimum 2 log decrease in viral load during the first 12 weeks of treatment) have virtually no chance to achieve a sustained viral response,
and it is recommended that these patients stop the therapy (National Institutes of Health, 2002).

In the majority of samples studied to date, the HCV core antigen assay values closely tracked HCV RNA dynamics and allowed the monitoring of treatment (Bouvier-Alias et al., 2002; Cano et al., 2003; Cividini et al., 2003; Icardi et al., 2003; Lunel et al., 2003; Maynard et al., 2003; Zanetti et al., 2003; Netski et al., 2004; Agha et al., 2004; Krajden et al., 2004; Lorenzo et al., 2004). The HCV core antigen and HCV RNA concentrations in a given sample were significantly related in all studies published to date with Pearson’s correlation coefficient ranging from 0.614 to 0.920 (Bouvier-Alias et al., 2002; Cano et al., 2003; Icardi et al., 2003; Maynard et al., 2003; Zanetti et al., 2003; Netski et al., 2004; Krajden et al., 2004). In addition, the HCV core antigen and HCV RNA levels correlated well across all HCV genotypes. Discrepancies between the HCV core antigen and HCV RNA assay results were mostly limited to the samples with HCV RNA levels below 20,000 IU/ml (Bouvier-Alias et al., 2002; Zanetti et al., 2003; Cividini et al., 2003; Icardi et al., 2003; Lunel et al., 2003; Maynard et al., 2003; Zanetti et al., 2003; Netski et al., 2004). The correlation between the HCV core antigen levels measured by the second generation Ortho HCV core antigen assay and the HCV RNA levels measured by Roche Cobas Amplicor HCV Monitor 2.0 in 270 serum samples obtained from Slovenian patients with chronic hepatitis C, is shown in Fig. 2, and the examples of close monitoring of two Slovenian patients using both HCV diagnostic markers, in Figs. 3 and 4.

The second generation Ortho HCV core antigen assay has been used in monitoring the response to antiviral therapy in the patients who received various formulations of treatment, e.g. interferon-alpha monotherapy (Tanaka et al., 2000; Bouvier-Alias et al., 2002; Zanetti et al., 2003), interferon-alpha and ribavirin (Bouvier-Alias et al., 2002; Veillon et al., 2003; Lunel et al., 2003; Lorenzo et al., 2004; Soffredini et al., 2004), and pegylated interferon-alpha and ribavirin (Bouvier-Alias et al., 2002; Rebucci et al., 2003; Maynard et al., 2003; Buti et al., 2004; Pradat et al., 2004; Soffredini et al., 2004). According to the results of these studies and considering the lower sensitivity of HCV core antigen detection in comparison to the qualitative NAT, it seems that the second generation Ortho HCV core antigen assay is not practical for the determination of end of treatment response and sustained viral response, but could be useful for the determination of EVR. To the best of our knowledge, four research groups studied the usefulness of measuring EVR using the second generation Ortho HCV core antigen assay in genotype 1 patients treated with pegylated interferon-alpha and ribavirin standard therapy (Maynard et al., 2003; Buti et al., 2004; Pradat et al., 2004; Soffredini et al., 2004). The negativity of HCV core antigen at week 12 (referred to as HCV core antigen EVR) had 100% negative predictive value in all four studies in contrast to 80–100% negative predictive value of EVR determined by HCV RNA quantification. According to the obtained results, the HCV core antigen testing could be considered as a reliable alternative to NAT for an early prediction of virological non-response in the patients treated with pegylated interferon-alpha and ribavirin.

4.5. Study of hepatitis C pathogenesis

Despite intensive research, pathogenesis of hepatitis C is still indistinct. One of possible reasons for such situation is that, until recently, only precise methods for the detection of HCV RNA have been available. With the development of
accurate commercially available assays for the quantitative measurement of HCV core protein, further improvement in our knowledge concerning pathogenesis of hepatitis C can be expected.

The first important question addressed by several studies was a quantitative relation between the HCV RNA and HCV core antigen. Thus, Bouvier-Alias et al. (2002) first showed that 1 pg of HCV core antigen is equivalent to approximately 8000 IU of HCV RNA. Similarly, Schuttler et al. (2004) showed that the HCV core antigen concentrations measured in 197 serum samples corresponded to an average ratio of 7900 IU of HCV RNA/pg of core antigen, but the variability of this ratio exceeded largely the variability of the two assays, ranging from 50 to 20,000 IU/pg. In addition, they proposed that HCV should contain approximately 43,000 IU of RNA/pg core antigen. Their data support the possible existence of HCV RNA-free but core antigen-containing structures, either secreted by the infected cell or generated by in vivo degradation. They also hypothesized that the excess of HCV viral core antigen could function as a decoy for the immune system. It was finally concluded that HCV core antigen assay seemed to detect, in addition to complete virions, RNA-free core protein structures and that the variable ratio of HCV RNA and core protein was not mainly due to standard deviations of quantification, but could have been an additional parameter for the treatment follow-up and state of viral replication (Schuttler et al., 2004).

The possible association between the HCV core antigen and HCV RNA quantification with regards to the change in liver histology over time in the untreated HCV-infected patients was studied by Lagging et al. (2002). No association was found between the HCV RNA or core antigen levels and...
Thus, Nakamura et al. (2001) showed that the HCV RNA levels decrease rapidly during the first 24 h of the incubation at 25°C. Similarly, in series of experiments, Tanaka et al. (2003) demonstrated that the HCV core antigen levels are reproducible and stable even after the incubation of serum for 7 days, whereas the HCV RNA levels decrease rapidly during the first 24 h of the incubation at 25°C.

5. Conclusions

In the present review, we summarized the results of 56 papers evaluating different aspects of HCV core antigen testing. Since we could not identify any major negative experiences and insufficiency of HCV core antigen assays, except their lower sensitivity in comparison to NAT, we are convinced that the HCV core antigen testing could be successfully used in management of hepatitis C in some indications traditionally reserved for NAT.

Despite the fact that a good analytical performance of the HCV core antigen assays, as summarized in our review, has been repeatedly proven in several studies and that the assays were relatively aggressively marketed, HCV core antigen assays surprisingly bypassed a majority of potential customers and, consequently, recently almost disappeared from the main world diagnostic markets. Beside the traditional “positive conservatisms” present in the majority of diagnostic laboratories, we strongly believe, as recently proposed by J.-M. Pawlotsky at the International Conference on the Management of Patients with Viral Hepatitis, Paris, 10–11 September 2004, that an important reason for unsuccessful enthronement of the HCV core antigen testing in the management of hepatitis C is a too narrow marketing strategy of HCV core antigen assays rather than an analytical imperfection of current HCV core antigen assays. We deem that the manufacturer of HCV core antigen assays marketed these assays too straightforwardly as a self-sufficient substitution to NAT instead of marketing them as a useful low-priced supplementary or alternative assay to NAT. Since the manufacturer, as already mentioned, recently stopped an active marketing of the HCV core antigen assays in Western European countries, USA and Japan, 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.

References


stage of fibrosis, progression of fibrosis, necro-inflammatory grade, steatosis, HCV genotype, alanine aminotransferase level, or alcohol consumption.


