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**Hepatitis C virus markers in infection by hepatitis C virus:
In the era of directly acting antivirals**

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Abstract

About 130-170 million people are infected with the hepatitis C virus (HCV) worldwide and more than 350000 people die each year of HCV-related liver diseases. The combination of pegylated interferon (Peg-IFN) and ribavirin (RBV) was recommended as the treatment of choice for chronic hepatitis C for nearly a decade. In 2011 the directly acting antivirals (DAA) HCV NS3/4A protease inhibitors, telaprevir and boceprevir, were approved to treat HCV-genotype-1 infection, each in triple combination with Peg-IFN and RBV. These treatments allowed higher rates of SVR than the double Peg-IFN + RBV, but the low tolerability and high pill burden of these triple regimes were responsible for reduced adherence and early treatment discontinuation. The second and third wave DAAs introduced in 2013-2014 enhanced the efficacy and tolerability of anti-HCV treatment. Consequently, the traditional indicators for disease management and predictors of treatment response should be revised in light of these new therapeutic options. This review article will focus on the use of the markers of HCV infection and replication, of laboratory and

instrumental data to define the stage of the disease and of predictors, if any, of response to therapy in the DAA era. The article is addressed particularly to physicians who have patients with hepatitis C in care in their everyday clinical practice.

Key words: Chronic hepatitis C; Hepatitis C virus replication; Directly acting antivirals; Staging; Hepatitis C virus infection

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Core tip: The second and third wave directly acting antivirals introduced in 2013-2014 enhanced the efficacy and tolerability of anti-hepatitis C virus (HCV) treatment. Consequently, the traditional indicators for disease management and predictors of treatment response should be revised in light of these new therapeutic options. This review article analyzes the modern use of the markers of HCV infection in: (1) the diagnosis of acute hepatitis C; (2) the diagnosis of chronic HCV infection; (3) the assessment of the severity of chronic hepatitis C; (4) the assessment of factors associated with response to anti-viral treatment; and (5) HCV-RNA kinetics and clearance as markers of remission.

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INTRODUCTION

The World Health Organization (WHO) estimates that 130-170 million people are infected with hepatitis C virus (HCV) worldwide and that more than 350000 people die each year of HCV-related liver diseases^[1]. Primary infection causes acute hepatitis C (AHC), which is asymptomatic in the majority of cases, but progresses to chronicity in about two-thirds of the cases and spontaneously remits in the remaining one-third^[2-7]. Patients with chronic hepatitis C (CHC) frequently show increasing severity of liver fibrosis over time, which leads to liver cirrhosis in nearly a quarter of cases. Hepatocellular carcinoma (HCC) develops in HCV-related liver cirrhosis with a yearly rate around 3%^[8-16].

The combination of pegylated interferon (Peg-IFN) and ribavirin (RBV) was recommended as the treatment of choice for CHC for nearly a decade^[17-22]. This treatment, although poorly tolerated, provided a sustained clearance of circulating HCV (sustained viral response - SVR) in half of the patients with CHC due to

HCV genotype 1 and in nearly 70% of those with HCV genotype 2 or 3. Several predictors of an unfavorable response to this treatment have been identified: viral (HCV genotype 1 or 4 and a slow decline in serum HCV RNA during treatment), host factors (male sex, older age), a co-pathology (insulin resistance, diabetes), Afro-American ethnicity, severe fibrosis and/or steatosis, high body mass index and interleukin (IL) 28-B non-CC genotype^[23]. In 2011 the directly acting antivirals (DAAs) NS3/4A protease inhibitors telaprevir and boceprevir were approved to treat HCV-genotype-1 infection, each in triple combination with Peg-IFN and RBV^[24-27]. These treatments allowed higher rates of SVR than the double Peg-IFN + RBV^[18,28-33], but the low tolerability and high pill burden of these triple regimes^[34] were responsible for reduced adherence and early treatment discontinuation. The second and third wave DAAs introduced in 2013-2014 enhanced the efficacy and tolerability of anti-HCV treatment^[35,36]. In fact the second and third generation DAAs afford SVR rates above 90%, regardless of HCV genotype, better tolerability and adherence used either in IFN-free regimens or in combination with interferon and ribavirin^[37-40]. Consequently, the traditional indicators for disease management and predictors of treatment response should be revised in light of these new therapeutic options.

This review article will focus on the use of the markers of HCV infection and replication, of laboratory and instrumental data to define the stage of the disease and of predictors, if any, of response to therapy in the DAA era (Table 1). The article is addressed particularly to physicians who have patients with hepatitis C in care in their everyday clinical practice.

HCV MARKERS IN AHC

In its symptomatic form AHC is characterized by nausea, malaise, abdominal pain, jaundice and by the typical biochemical abnormalities^[41-43]. The HCV etiology is usually established on the basis of a documented seroconversion to anti-HCV and/or HCV-RNA positivity during the natural course of the illness^[19,39,44,45], but it is impossible to establish for patients first observed when seroconversion has already occurred. In addition, AHC remains frequently undiagnosed because asymptomatic in the majority of the cases^[41]. Despite its typically mild clinical course, AHC progresses to chronicity in nearly 70% of the cases. Treatment with a 3- or 6-mo course of Peg-IFN has been shown to be effective in eradicating acute HCV infection in most cases, but to date no standardized treatment schedule has been defined. Delaying the treatment to 8-12 wk after the beginning of the illness allows the identification of cases that resolve spontaneously and does not compromise the efficacy. The use of IFN-free treatment regimens for AHC patients awaits assessment.

Table 1 Viral and host markers useful for the management or treatment of chronic hepatitis C

	Roles in the Peg-IFN era	Roles in the DAA era
Anti-HCV assay	Diagnosis/screening	Diagnosis/screening
HCV-RNA assay	Diagnosis/active replication Pre-treatment predictor of response to antiviral treatments Monitoring antiviral treatment Assessment of response to treatment	Diagnosis/active replication Assessment of response to treatment
HCV genotype	Pre-treatment predictor of response to antiviral treatments	Choosing the most appropriate DAA regimen
HCV Q80K polymorphism	None	Selecting patients with HCV-genotype 1a for the simeprevir plus Peg-IFN regimen
Markers of liver fibrosis (liver biopsy/non-invasive methods)	Staging of liver disease Pre-treatment predictors of response to antiviral treatments	Staging of liver disease Selecting the patients with urgency for DAA-based treatment
IL-28B polymorphism	Pre-treatment predictor of response to antiviral treatments	Pre-treatment predictor of response only in Peg-IFN-based regimens
ITPA polymorphism	Pre-treatment predictive factor of hemolytic anemia during ribavirin-based regimen	Indicator of risk/benefit of using ribavirin in a DAA-based regimen

Peg-IFN: Pegylated interferon; DAAs: Directly acting antivirals; HCV: Hepatitis C virus; IL: Interleukin.

New strategies for an early diagnosis of AHC have been investigated^[46,47]. In addition, attempts have been made to distinguish this clinical form from an acute exacerbation of CHC, a clinical event characterized by a substantial increase in serum alanine aminotransferase (ALT) levels above the previous values in patients with CHC^[6,7,48-50]. A combined use in serial serum samples of the rise in the anti-HCV titers and of the changes in antibody positivity in a recombinant immunoblot assay was found to be of some use by Lu *et al.*^[46]. Araujo *et al.*^[47], using a flow-cytometric microsphere immunoassay to measure anti-HCV IgG reactivity to the core NS3, NS4 and NS5 HCV recombinant proteins, correctly classified serum samples of AHC and CHC with a cross-validation of 90.8% for the AHC group and 97.2% for the CHC group. The role of anti-HCV IgG avidity and anti-HCV IgM titers to diagnose AHC have been extensively investigated^[5,51-54]. A successful attempt to distinguish between AHC and a reactivation of CHC was made by Sagnelli *et al.*^[41] by carrying out a serial determination of anti-HCV IgM at two or three checking points within the third week from the disease onset. In another study by the same group, Coppola *et al.*^[5] successfully explored the distinction between AHC and a reactivation of CHC using the avidity of anti-HCV IgG to diagnose AHC. When both methods (anti-HCV IgM titer and anti-HCV IgG avidity) were applied to serial serum samples obtained during the illness, the distinction between the two clinical forms reached a level of sensitivity and specificity approaching 95%. The IgG avidity assay showed the highest efficacy during the initial two weeks of the illness and the IgM titer assay during the subsequent two weeks^[53].

The diagnosis of AHC remains important even in the DAA era, since, although not yet assessed, it seems reasonable that all or nearly all patients with AHC can be cured with a short DAA-based regimen.

HCV MARKERS IN CHC

Diagnosis of chronic HCV infection

The diagnosis of CHC is based on the detection of serum anti-HCV and HCV RNA, elevated serum values of aminotransferases for at least six months and necroinflammation and fibrosis in liver tissue^[8,19,39]. Screening to detect anti-HCV in serum is indicated for persons with a history of intravenous drug use, or sharing paraphernalia for intranasal drug use, acupuncture, body piercing or tattooing, persons who received blood, blood products or solid organs before 1992, hemodialysis patients, children born of HCV-infected mothers, patients with hepatitis B virus (HBV) infection and those with human immunodeficiency virus (HIV) infection^[19,55-61]. Anti-HCV-positive subjects should be tested for serum HCV RNA, the confirmatory test of an ongoing HCV infection^[62-65].

Anti-HCV can be detected by an enzyme-linked immunosorbent assay, three generations of which have been developed since 1989. The first generation assay, incorporating the recombinant c100-3 epitope from the NS4 region was used until 1992, when it was replaced with the second generation assay incorporating the epitopes c22-3 and c33c from the HCV core and NS3 regions, respectively. The third generation assay used at present contains reconfigured core and NS3 antigens and a newly incorporated antigen from the NS5 region^[62,66,67], is more sensitive than the previous assays and has a diagnostic specificity of over 99%^[62]. However, the third generation enzyme immunoassays can, albeit rarely, yield false-negative results in immunocompromised patients and in those undergoing hemodialysis^[19].

More recently an assay for a rapid detection of anti-HCV in fingerstick capillary blood, venipuncture whole blood or saliva has been developed^[68]. This assay, easy

to perform and time-saving, has a good sensitivity and specificity and is particularly indicated for screening large populations.

The recombinant immunoblot assay, used in the past as a confirmatory assay of HCV infection, has not been recommended since 2013^[69]. Subjects found to be anti-HCV-positive at screening should be tested for HCV RNA, the serum marker of HCV replication and current infection. Real-time PCR technologies can quantify HCV RNA during the exponential phase of amplification, with great sensitivity and a broad linear dynamic range (about 10 to 108 IU/mL). The majority of the commercial HCV RNA assays used by the clinical laboratories are based on the WHO international standard for HCV-RNA nucleic acid technology^[70] and have an excellent specificity (98%-99%)^[19].

Testing for HCV RNA should be considered for all anti-HCV-positive subjects and among the anti-HCV-negative for immunocompromised patients and for individuals exposed to HCV in the past 6 mo.

Concluding on this point, the high rate of SVR obtained by the DAA-based treatments is a further stimulus to screen all subjects exposed to HCV infection using a sensitive, specific, easy-to-perform and time-saving assay.

Assessment of the severity of CHC

The severity of CHC is variable among patients and over time in single patients. In most cases the disease shows a benign indolent course, but in some cases there is a rapid progression to liver cirrhosis, hepatocellular carcinoma and to an end-stage liver disease^[8]. Liver cirrhosis is found in approximately 20% of patients with HCV-related chronic liver disease, associated in its advanced stages with life-threatening complications such as ascites, esophageal varice hemorrhage and liver failure. Hepatocellular carcinoma (HCC) occurs mostly in cirrhotic patients at a rate of 3%-5% per year^[8].

The extent of liver necroinflammation and the degree of fibrosis in liver biopsy are considered reliable predictors of disease progression^[71]. Several other investigators considered the stage of fibrosis detected in liver biopsy as a key point for the clinical management of CHC^[72].

Although the liver histology is still considered the gold standard to assess the stage of liver fibrosis, because of the sides effects of liver biopsy^[73-79] several surrogate non-invasive methods have been introduced. The measurement of liver stiffness by transient elastography offers an accredited method for the assessment of liver fibrosis^[80]. This technique involves the use of a transducer on the end of an ultrasound probe that transmits 50 MHz pressure waves through the liver tissue. The velocity of the resulting "shear wave" is measured by ultrasound. The shear-wave velocity correlates with liver stiffness, thus providing an estimate of liver fibrosis^[81,82]. Tsochatzis

et al.^[82] performed a meta-analysis including 40 studies on numerous patients with chronic hepatitis of various etiologies (HBV, HCV, alcohol and other etiologic agents) and showed that transient elastography had a pooled sensitivity and specificity in diagnosing liver cirrhosis of 83% and 89%, respectively.

The ultrasound assay is another well-established non-invasive method to diagnose liver cirrhosis. The transition to cirrhosis is documented by the development of the characteristic coarse or nodular patterns in the liver parenchyma, hepatomegaly and caudate lobe hypertrophy^[83]. Ultrasound can also detect the development of portal hypertension by measuring the portal vein diameter, velocity of flow and flow reversal, ascites and splenomegaly^[84], but the sensitivity of ultrasound in assessing liver fibrosis is low.

There is no single surrogate test able to predict reliably the progression to cirrhosis in each single patient. However, high serum ALT levels have been associated with a higher risk of fibrosis progression^[85-87], which, instead, is an uncommon event in patients with persistently normal serum ALT^[88-91].

Several other non-invasive surrogate biomarkers or a combination of biomarkers may be of some help in assessing liver fibrosis, such as platelet count, INR index, aspartate aminotransferase (AST) serum levels and albumin serum concentration. One well-known combination of biomarkers that has been extensively validated in CHC^[92,93] and in non-alcoholic fatty liver disease^[94] is the so-called APRI test, an acronym for AST-platelet ratio index^[95]. Also of some interest is the Fibrotest (Fibrosure in the United States), which includes five biomarkers and 2 clinical parameters^[96]: α -2 macroglobulin, haptoglobin, total bilirubin, apolipoprotein-A, γ -glutamyl transferase, age and gender. Using a patented formula, a numerical value from 0.0 to 1.0 is obtained, a score correlated with the METAVIR fibrosis score in chronic hepatitis of different etiologies^[92,97,98]. Combining the ALT serum value with the panel of biomarkers included in the Fibrotest, a new surrogate method to measure liver fibrosis was obtained, named Actitest and validated to diagnose liver cirrhosis in CHC patients^[99]. FIB4 is a biomarker panel using age, AST, ALT and platelet count^[100] validated in HIV/HCV co-infected^[101] and HCV-monoinfected patients^[102].

Concluding on this point, the assessment of liver fibrosis is still essential, even in the DAA era, since it allows the high-cost DAA treatment to be applied on the basis of the severity of liver damage and of the presumed speed of disease progression.

Assessment of factors associated with the response to anti-viral treatment

In the DAA era, HCV genotypes and subtypes remain cornerstones in the management of chronic HCV infection, since the rate of response and the consequent duration of treatment differ for the various

genotypes and subtypes^[103]. In fact, considering patients with HCV genotype 1 or 4, whether therapy-naïve or -experienced, the combination of sofosbuvir and simeprevir (\pm ribavirin in non-responders to previous treatment) is the regimen of choice for subjects with METAVIR fibrosis scores 3 or 4, whereas for patients with fibrosis 0-2, optimal results were obtained with the combination of Peg-IFN, ribavirin and simeprevir^[39,40]. Sofosbuvir plus ribavirin has been demonstrated to be an optimal combination for patients with HCV-genotype 2 or 3, whether therapy-naïve or -experienced, and the combination sofosbuvir plus daclatasvir for patients with HCV genotype 3^[39,40]. In addition, in the simeprevir plus Peg-IFN-based regimen, it is essential to distinguish between patients with HCV sub-genotype 1a and 1b, since subtype 1a at times showed a Q80K substitution in the NS3 protease sequence, thus entailing a higher rate of treatment failure^[39,40]. Currently, HCV genotyping can be performed by direct DNA sequencing by a bi-directional sequence where genotype and subtype characterization is determined by two fluorescently labeled DNA primers or by a commercial line probe assay^[103].

In the DAA era, the detection of HCV viral load at baseline is now of no value in the treatment choice, since the anti-viral potency of these drugs controls even the highest level of HCV replication. The use of this test to monitor treated patients during the follow-up in order to detect possible reactivation seems good clinical practice.

The impact of staging in choosing a treatment schedule has decreased in proportion to the increase in the antiviral potency of the DAAs. In fact, the treatment regimens based on the third-wave DAAs achieve HCV eradication in almost all patients, regardless of the presence of liver cirrhosis^[39,40].

The polymorphisms in the *IL28B* gene have been strongly associated with the spontaneous clearance of acute HCV infection and with the response to Peg-IFN and RBV combination therapy^[104-107]. Their predictive value was more evident in difficult-to-treat HCV-genotype 1 and genotype 4 patients than in those with HCV-genotype 2 or 3 infection^[108]. The distribution of *IL28B* polymorphisms varies among different populations, accounting, at least in part, for the ethnic and racial differences in the response to Peg-IFN plus RBV^[107], the CC genotype being a predictor of a favorable response. At present, IL-28 genotyping has no predictive role in the high-efficacy DAA-based regimens^[39,40], but might be of some value in settings where a Peg-IFN-based regimen might still be used.

Hemolytic anemia is a common side effect of RBV-based therapy that, although reversible and dose-related, induced a RBV dose reduction or premature treatment withdrawal in more than 15% of the cases^[109,110]. Fellay *et al.*^[111] identified two variants (rs1127354 and rs7270101) in the *ITPA* gene that

were functionally responsible for ITPA deficiency and correlated with the risk of RBV-induced anemia in European and American populations. The rs1127354 variant was associated with protection against anemia in other investigations^[112-115]. The single nucleotide polymorphism (SNP) ITPA has never been associated with the treatment outcome^[111-115], and in the DAA era it can be used only to evaluate the risk/benefit of adding ribavirin in some DAA-based regimens for patients with a lower rate of SVR, such as cirrhotics or previous non-responders.

Concluding on this point, DAA treatment eradicates HCV infection in nearly all treated patients, greatly reducing the clinical importance of markers previously used to predict the response to therapy. In fact, the HCV load and the degree of fibrosis do not predict the response to DAA therapy, and the polymorphisms in the *IL28B* gene may be useful only for patients with a METAVIR score F0-F2 treated with Peg-IFN, ribavirin and simeprevir, and the two SNPs in the *ITPA* gene only for those receiving a DAA plus ribavirin.

Instead, the determination of HCV genotype and subtype is of clinical value even in the DAA era, mandatory to choose the type and duration of therapy.

HCV-RNA kinetics and clearance as markers of remission

HCV-RNA clearance persisting 6 mo after therapy (SVR) remains a marker of the eradication of chronic HCV infection also in the DAA era.

International treatment guidelines^[116-118] identified some virological predictors of SVR to Peg-IFN + RBV treatment: a rapid virological response *i.e.*, HCV-RNA clearance after 1 mo of therapy, and an early virological response, *i.e.*, HCV-RNA clearance after 3 mo of therapy. Subsequently, a very early predictor of SVR to Peg-IFN + RBV was suggested^[119,120], *i.e.*, a decrease in the HCV load 2 d after the start of therapy. These predictors have been used to distinguish with good accuracy the patients with a good chance of achieving an SVR from those with a very low chance, who should discontinue treatment^[121].

Compared to Peg-IFN + RBV treatments, the DAA-based therapies are more effective and better tolerated, but more expensive. The HCV-RNA kinetics during DAA treatment have been investigated in a limited number of patients and for short periods. Simeprevir given alone achieved a median HCV-RNA reduction of 3.9- \log_{10} IU/mL over the first 3 d of treatment, independently of previous treatments and HCV genotype^[122]. The administration of a single dose of 100-mg daclatasvir generated a decline in the HCV load of nearly 2- \log_{10} in six hours and of 3.3- \log_{10} in 24 h^[123,124]. In addition, sofosbuvir obtained HCV-RNA clearance in 88%-94% of patients within the fourth week of treatment^[125]. These data suggest that the determination of the HCV-RNA kinetics is of limited value in predicting the SVR in the DAA-based

IFN-free treatments, since the majority of treated patients^[126] achieve this favorable outcome. Several studies assessed serum HCV RNA at weeks 2 and 4 of treatment^[37,127-129] and found that the persistence of HCV RNA in serum at these check-points is predictive of treatment failure^[130].

In Peg-IFN + RBV regimens, the normalization of serum aminotransferases has been used as a parameter to evaluate the biochemical response^[131], often associated with an SVR. In recent studies on DAA-based treatments, serum aminotransferases were no longer used to evaluate the response to treatment^[37,127-129], since, for reasons unrelated to HCV replication (presence of liver steatosis or consumption of alcohol or other drugs known to be hepatotoxic), they may remain elevated even in SVR patients. In addition, an increase in the aminotransferase serum values may occur in some patients during treatment, an event to be monitored carefully because therapy discontinuation may be necessary^[128]. At present, no other biochemical parameter has been associated with the SVR or with the need to discontinue therapy^[132].

Concluding on this point, monitoring the HCV-RNA kinetics during DAA treatment seems good clinical practice and may help to identify early on the patients with a lesser chance of eradicating HCV chronic infection. Due to the ability of HCV to replicate not only in hepatocytes, but also in lymphocytes and possibly in other cell subsets, a reactivation of HCV replication in patients who had achieved an SVR cannot be excluded, and monitoring the HCV-RNA kinetics during the post-treatment follow-up can identify these cases.

CONCLUSION

The eradication of HCV infection in nearly all patients treated with the second- or third-wave DAAs and a more extensive use of these treatments in the near future will significantly contribute to curbing the spread of HCV infection and to reducing its related morbidity and mortality. At present, there is a strong stimulus for an early diagnosis of AHC, which can almost certainly be cured with a short-term DAA-based regimen, and for screening subjects with a history of previous exposure to HCV. Because of the high efficacy of the DAA treatments, the majority of the predictors of response to therapy will become obsolete. In particular, the degree of liver fibrosis does not predict the response to DAA therapy and its determination remains essential only to assess the priority for the high-cost DAA treatments based on disease severity and progression. Instead, the determination of HCV genotype and subtype remain essential in order to choose the type and duration of DAA treatment.

Monitoring the HCV-RNA kinetics during DAA treatment and post-treatment follow-up seems good inexpensive clinical practice, useful for an early identification of patients with a lesser chance of HCV eradication and of those prone to reactivation.

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