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EDITORIAL

New biomarkers for clinical management of hepatitis C virus infected patients

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Abstract

Hepatocellular carcinoma (HCC) is the third most frequent oncological cause of death worldwide, principally a consequence of hepatitis C virus (HCV) infection and its prognosis is mostly poor. For early identification and surveillance of HCV patients with liver disease progression, the availability of suitable diagnostic and prognostic biomarkers is still an unmet clinical need. Alfa-fetoprotein together with imaging techniques is commonly used, however its specificity and sensitivity are not satisfactory. Several clinical and serological data have been proposed to define the risk of disease progression in HCV infected patients and new biomarkers have been proposed, including post-transcriptionally modified molecules and genetic biomarkers. The present editorial article attempts to summarize the current knowledge on the new promising tools for effective early diagnosis of HCV-related liver disease progression and for the surveillance of HCC.

Key words: Hepatitis C virus infection; Biomarkers; Liver disease progression; Hepatocellular carcinoma

Core tip: Hepatitis C virus (HCV) infection is a major cause of cirrhosis and hepatocellular carcinoma (HCC), leading to liver failure and/or liver transplantation. The current knowledge on the new promising biomarkers, able to predict the progression of HCV-related liver disease and HCC, has been the focus of this editorial.

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INTRODUCTION

To date, the natural history of hepatitis C virus (HCV)

infection is still difficult to define because of the insidious onset of the disease and the absence or paucity of symptoms during the generally prolonged (20-40 years) chronic phase of the illness. Moreover, the methodologic differences used to study the clinical course of disease (prospective-retrospective cohort, community-based or cross-sectional studies), in addition to the different selected study populations (patients referring to specialist liver clinics or tertiary care centers, blood donors) or different phases of the disease, determine heterogeneous results in terms of rates of disease progression[1-6]. The ideal study to define the natural history of HCV infection would be to closely monitor a representative group of patients from the onset of the acute infection, refrain from treating their liver disease, and then monitor their untreated course to a liver disease end point and/or death, whether from liver disease or from other causes. Since such kind of study cannot be performed, reliance must be placed on surrogate markers of disease progression.

The long-term sequelae of HCV infection, include the transition from not perceivable acute to chronic hepatitis up to cirrhosis, which may progress to end-stage liver disease and/or to hepatocellular carcinoma (HCC), frequently leading to liver transplantation or death[7-11]. The recent Global Burden of Disease project estimated that in 2010, among 170 million people with chronic HCV, more than 30 million suffer from cirrhosis and the incidence of HCC is about 1-2 million new cases/year. The actual estimated incidence has been markedly decreased, and this is mainly attributable to the employment of a safe transfusion screening policy, which has markedly decreased the number of new infection. Several reports have identified that among persons with chronic hepatitis C (CHC), cirrhosis has developed in 20% and HCC in 1%-5%, approximately 20 years after disease onset. These data indicate that not all persons with CHC will develop cirrhosis or complications of the disease. The detection of specific markers, able to predict the progression of the disease, has been therefore the focus of this editorial.

HCV INFECTION MARKERS AND RISK OF LIVER DISEASE PROGRESSION

A long-lasting elevated necroinflammatory activity seems to play a crucial role in the progression of the liver disease, as supported by data from patients with persistently normal transaminase levels[12-14]. The biochemistry profile is indeed only partially indicative to predict the disease's progression and the clinical outcome might be modified by different variables and many factors, either virus-related, host-related and environmental associated.

The role of viral-dependent factors as viral load and genotype is still debated and controversial. Several studies have evaluated the relationship between serum concentration of HCV-RNA and liver disease severity with conflicting results. While some reports have demonstrated a positive correlation between HCV-RNA load and histopathological abnormalities[15-17], others have found no association with hepatic inflammation[18] or liver fibrosis[19,20]. These studies were conducted as cross-sectional design, resulting in limitations of casual temporality or including a particular type of person [*i.e.*, drug users coinfected with human immunodeficiency virus (HIV)], thus the generalization of the obtained results to the population in the community was limited[21].

Regardless from the evidence that genotype 1b was reported to be more associated with the development of HCC than genotype 2[22] and with a poor outcome of disease[22-24], no data are available, so far, for other HCV genotypes. It should be noted that most of the studies were cross-sectional or included patients enrolled in clinical trials[25-29]. In a prospective study, Martinot-Peignoux *et al*[25], followed 163 patients with liver cirrhosis for seventeen years and reported that HCV genoptype 1b was a major risk factor for HCC development. This genotype was confirmed to have three times higher risk of liver tumor development, compared with patients infected with other genotypes[26]. Within the community based study REVEAL-HCV study cohort, that recruited 1095 subjects seropositive for antibodies against HCV followed for fifteen years, the multivariate analysis selected serum HCV-RNA, alanine aminotransferase (ALT) levels and HCV genotype as independent risk predictors of HCC. These seromarkers have been proposed as pretreatment markers in clinical decision to classify high-risk patients who need particular clinical care[30].

The presence of other viral coinfections (*i.e.*, HIV, HBV) speeds up the clinical course of the disease with a negative impact on the natural history of HCV[31,32]. The progression to cirrhosis is higher in HCV-HIV coinfected patients[33,34] and is associated to other complications, such as hematologic disorders[35], kidney disease[36], cardiovascular disease[37] and neurologic abnormalities[38]. In addition, the coinfection with HBV determines a more severe liver injury in terms of progression of fibrosis, liver cirrhosis and hepatic decompensation[39,40].

Among the host-related factors, age at infection, male gender and heavy alcohol intake seem to influence the outcome of CHC[41-43]. Freeman *et al*[44], using an ecologic analysis to estimate relative risk of cirrhosis progression across four study methodologies, have found an association between male sex (RR = 1.08) with heavy alcohol consumption (RR = 1.61) and elevated serum ALT levels (RR = 1.23) with higher histological activity index.

In the last few years, another important aspect, represented by the presence of comorbidities, was shown to impact on the evolution of chronic HCV infection. Hepatic steatosis, obesity and insulin resistance must be considered important determinants of liver disease progression, although the relationship between these metabolic factors and clinical outcomes is still complicated. In a long-term peginterferon treatment (HALT-C study) the modifiable risk factors for liver

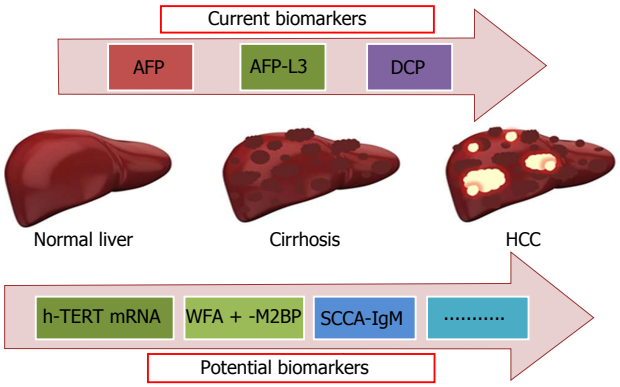

Figure 1 Current and newly proposed biomarkers of liver disease progression and hepatocellular carcinoma development. AFP: α-fetoprotein; AFP-L3: *Lens culinaris* agglutinin A (LCA) - reactive fraction of α-AFP; DCP: Des-γ-carboxyprothrombin; h-TERTmRNA: Human telomerase reverse trascriptase mRNA; WFA + M2BP: *Wisteria floribunda* agglutinin-positive human Mac-2-binding protein; SCCA-IgM: Squamous cell carcinoma antigen-immunoglobulin M; HCC: Hepatocellular carcinoma.

disease progression were studied, and insulin resistance was found strongly associated with clinical outcomes[45]. Similar results were found in a large scale community-based study in which an association between diabetes and HCC was observed[46]. However, the association between HCV infection and the development of diabetes remains controversial[47,48].

Major advances in genetics during the last decade allow the identification of specific markers associated with viral response and consequently with HCV infection outcomes. Among them, *IL28B* gene variants (*rs12979860* and *rs8099917*) have been strongly associated with favourable response to standard antiviral treatment in patients with CHC[49-51]. These treatment response findings were confirmed by many studies in different populations such as HCV-1 patients[52-57] and reproduced in several meta-analyses[58-60]. Therefore, both host and virus factors are important determinants of liver diseases outcome.

NEW BIOMARKERS OF LIVER DISEASE PROGRESSION AND HCC DEVELOPMENT

The most relevant consequence of HCV infection is HCC development[61]. This primary liver tumor is the third leading cause of cancer deaths worldwide, with an incidence in United States more than doubled in the past 25 years[62]. Screening strategies for detection of early HCC have relied primarily on radiologic imaging[63,64] and serum biomarkers[65]. Over the past two decades, considerable number of studies have been published in order to identify suitable biomarkers, however the results are frequently contradictory. For this reason, tumor marker levels are not included in the screening recommendations of international guidelines[66,67]. In this setting, α-fetoprotein (AFP) is the most commonly used biomarker, but its sensitivity and specificity in detecting HCC is poor. AFP levels are often increased in patients with cirrhosis without HCC[68,69] and the positive rate of AFP in HCC is about 60%, making it a diagnostic limitation.

Other tumor biomarkers have been proposed to complement or replace AFP in HCC detection. In clinical practice, *Lens culinaris* agglutinin A - reactive fraction of α-AFP (α-AFP-L3), a glycoform of AFP[70,71], and des-γ-carboxyprothrombin (DCP), an abnormal prothrombin molecule generated by the absence of vitamin K responsible of an insufficient post-traslational carboxylation of the prothrombin precursor in malignant cells[72,73] have been used. These biomarkers represent independent tumor proteins and, as reported in several studies, they may be complementary in the detection of HCC[74-76]. Few prospective studies have been addressed to evaluate the usefulness of these new biomarkers in terms of prognosis. Sterling *et al*[77], in an ancillary study of the prospective HALT-C trial including 855 patients, demonstrated that mild-moderate elevation of total AFP and DCP, but not AFP-L3 occurs in patients with CHC and advanced fibrosis in absence of HCC. However, marked increase of these biomarkers were uncommon in subjects without HCC, although several factors other than HCC, such as gender, age, race and the presence of more advanced liver disease, could be responsible for these increased values. Since sensitivity, specificity and predictive values of these biomarkers were low, the authors concluded that they are poor predictors of HCC development. More recently, the usefulness of these three biomarkers as diagnostic tool for HCC[78] and as predictors of outcome in patients with HCC has been reviewed. The combination of these biomarkers resulted to provide a good predictive ability of survival after diagnosis and when considered at time of diagnosis, together with serum albumin and birilubin levels, they could be used for HCC staging and to predict HCC prognosis[79].

Among the new class of genetic biomarkers, reflecting the presence of circulating HCC cells, serum h-TERT mRNA detection showed higher sensitivity and specificity compared with AFP-mRNA in HCC patients (90% and 85% *vs* 69% and 50%, respectively) and a close correlation with tumor size and number also in early tumor stage[80]. Circulating h-TERT mRNA was indeed detectable in small size tumors, indicating that h-TERT mRNA was up-regulated during rapid proliferation of the tumor, at the early phase of oncogenesis-dedifferentiation.

In the last 10 years a large number of new molecules potentially clinically useful as markers of liver disease progression in HCV infected patients has been identified (Figure 1). One of them is *Wisteria floribunda* agglutinin-positive human Mac-2-binding protein (WFA + -M2BP), a liver fibrosis glycobiomarker with a unique fibrosis-related glyco-alteration. Using fully automated immunoassay Yamasaki *et al*[81]. tested serum samples of 707 patients infected with HCV and found increased serum WFA + -M2BP levels in parallel with the progression of liver fibrosis stage. In each distinctive

stage of fibrosis, the risk of HCC development was increased, according to elevation of WFA + -M2BP. The diagnostic performance of this protein, based on the AUROC values, was superior to that of AFP for predicting the development of HCC at 3, 5, and 7 years. The WFA + -M2BP values are proposed as noninvasive predictors of HCC development and could be considered a surrogate marker of liver fibrosis to be added to FibroScan tecnique.

Several studies have demonstrated in recent years that tumor released antigens can react with natural IgM class of immunoglobulins and form circulating immune complexes in different human tumors. The circulating immune complex composed of squamous cell carcinoma antigen (SCCA) linked with IgM (SCCA-IgM) has been recently discovered as a promising tool to identify patients with progressive liver disease in HCV infected patients. SCCA-IgM complexes were undetectable in the sera of healthy subjects, but the detection rates and the levels consistently increased with liver disease progression[82]. In another study, SCCA-IgM complexes were detectable in 33% of the patients with chronic hepatitis[83] and in this study a significant increase over time of the immune complex levels was observed in patients with significant increase of liver fibrosis within a time frame of four years, but not in those without histologic progression, suggesting that monitoring the immune complex over time allowed to identify patients at higher risk of cirrhosis progression. In agreement with these findings, significant decrease of the immune complex was observed in sera of patients with HCV infection and persistent virologic response to antiviral therapy[84,85]. The positivity of SCCA-IgM has been found correlated with histologic non-alcoholic steatohepatitis (NASH) in patients with CHC[86]. It is worth to note that NASH has been recognized as risk factor of liver disease worsening and of HCC development[87]. On the basis of these considerations, it is likely that patients with HCV infection and SCCA-IgM positivity present a more fibrogenic and tumorigenic liver condition that should be accurately monitored and therapeutically managed, if possible.

In line with these results, the behaviour profile of SCCA-IgM was different in patient with early HCV-related cirrhosis with or without HCC progression. In a longitudinal, retrospective study a progressive increase of this immune complex was described in the majority of the patients with histological diagnosis of cirrhosis C who developed HCC after at least one year from the end of the study, while the levels of this biomarker remained unchanged or decreased in the majority of the patients without evidence of HCC development during the same time interval. Conversely, the increase of AFP, which was chosen as reference biomarker, was not significantly different between the two groups. The diagnostic accuracy, measured as AUROC values, was higher for SCCA-IgM than for AFP and the former biomarker performed better to identify cirrhotic patients at higher risk of HCC development[88]. This behaviour was observed at least one year before clinical diagnosis of HCC, suggesting that this preclinical phase might become a suitable window to specifically address new potentially effective therapies. A multicenter study, performed in HCV infected patients with overt cirrhosis, started from an opposite approach and demonstrated that the SCCA-IgM value ≤ 200 AU/mL accurately identifies patients with low risk of HCC development in the subsequent year (sensitivity 75%, specificity 62%). On the basis of the obtained results the authors concluded that this biomarker might be utilized to tailor surveillance timing[89].

CONCLUSION

Identifying new factors that could influence clinical outcome of HCV infection is important in order to counsel individuals regarding prognosis and to facilitate decisions related to clinical management. This point is crucial mostly in the current scenarios of new antiviral treatments that include various direct acting antiviral drugs[90,91]. Given the high cost of treatment and the increased possibility of adverse events, identification of factors predicting sustained virological response to individualize HCV therapy in clinical decision-making is urgent. While prioritizing treatment to patients who are at risk of future problems seems the optimal solution to deliver most benefits at the lowest costs, the problem still lies in the identification of those patients who should be included in the target population[92]. In this context, the above new biomarkers might become useful tools, as part of personalized medicine, for the surveillance of HCV infected patients with chronic hepatitis and/or cirrhosis, in order to better define follow up timing and suitable therapeutic management of the patients at higher risk of liver disease worsening.

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