Importance of genetics in the age of direct acting antivirals against the Hepatitis C virus

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Hepatitis C virus (HCV) is one of the main causes of chronic liver disease, cirrhosis, hepatocarcinoma, liver transplantation and liver death [1].

Nearly 70 million people worldwide are chronically infected with HCV, many of them are unaware of their infection [1,2]. The natural history of Chronic Hepatitis C (CHC) is highly variable, in some cases having a relatively benign behavior, while in others it has a fast progression to hepatic cirrhosis and hepatocellular carcinoma (HCC). Current treatment with direct-acting antivirals (DAAs) with very high efficacy (greater than 95%) has changed the natural history of HCV liver disease drastically. Despite the short time that these antiviral drugs have been used, they have shown a decrease in the appearance of cirrhosis and its complications, development of HCC, need for liver transplantation and mortality in patients who get virus elimination [3]. Additionally, they have also shown significant economic savings. On the other hand, HCV chronic liver disease can be associated with extrahepatic manifestations that also improve with viral eradication [4-6].

The Human Genome Project, initiated in 1990, achieved a draft of the genetic map in 2001 and was an important advance in the understanding of the genetic mechanisms of diseases [7]. The impact of genetic factors on the natural history of CHC and its implication in the response to treatment, has been an object of great scientific interest and many studies [8,9]. The study of genetic polymorphisms has led to multiple investigations often with relevant results [10].

In the last few years, single-nucleotide polymorphisms (SNPs) of the IL28B gene were extensively studied. A significant influence of certain IL28B SNPs was described both in the response to antiviral treatment [11-14] and in the evolution of acute hepatitis C [15,16]. This discovery was of great importance at a time that antivirals were less effective and had significant adverse effects. In this context, the determination of IL28B SNPs was very useful to predict the possible response to treatment. Although at present this SNP has lost much of its importance [17], others can be very useful in the management of HCV liver disease [18].

Recently, our group found an association of certain SNPs of genes related to immune system and inflammation mediators, with the severity of HCV liver disease and its progression. Thus, polymorphisms of CXCL9-11 were associated with the stage of fibrosis measured by transient elastography. On the one hand, heterozygosis (CXCL9 rs10336 AG, CXCL10 rs3921 CG and CXCL11 rs4619915 AG) seemed to be a protective factor; while homozygosis for the minor allele (CXCL9 rs10336 AA, CXCL10 rs3921 CC and CXCL11 rs4619915 AA) was a risk factor for liver fibrosis [19].

In addition, IL7RA polymorphisms were also associated with changes in transient elastography values and progression in fibrosis stages in patients infected with HCV, especially the IL7RA allele rs6897932 T that was associated with an increased risk of liver fibrosis progression and cirrhosis. IL7RA rs987106 showed a weaker association with the progression of liver disease while IL7RA rs3194051 did not [20].

Therefore, although current DAAs have been a transcendental change in treatment of HCV liver diseases, modifying substantially their natural history; genetic polymorphisms can be a very important tool in the management of HCV liver disease [21] and will be probably a key factor in the evolution of patients once the sustained viral response with antiviral treatment has been achieved.

References


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