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Current dilemmas in hepatitis virus C management. What should we do after achieving sustained virologic response?

Dilemas actuales en el seguimiento de la infección por el virus de la hepatitis C. ¿Qué debemos hacer tras conseguir una respuesta viral sostenida?

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Introduction

Since its characterization in 1989, hepatitis C virus (HCV) chronic infection has been a leading cause of liver-related morbidity and mortality. In the year 2015, the World Health Organization estimated that 71 million people were infected with HCV. Furthermore, in 2016 approximately 400,000 individuals with HCV infection died due to complications of cirrhosis or hepatocellular carcinoma (HCC).[1] This data offers insights of the magnitude of the problem. In the last decades, physicians treating liver conditions have witnessed an unequivocal historic breakthrough. The advent of direct-acting antiviral agents (DAAs), enabling highly effective interferon-free regimens, has fundamentally transformed the landscape. While tolerance or efficacy issues are part of the past, new challenges emerge when managing patients with sustained virologic response (SVR) after DAAs treatment. Relevant questions regarding how to evaluate the risk of HCC or how to non-invasively stage liver fibrosis after SVR have not been yet properly answered. In the present manuscript we seek to explore the Top 5 current dilemmas frequently faced in HCV clinics (Fig. 1).

Dilemma n°1: is liver fibrosis reversible after achieving SVR?

Answer: Yes, although the stage of fibrosis (F) when HCV is diagnosed directly influences the degree of achievable fibrosis regression.

Commentary: *In vitro* studies have proven that viral eradication is associated with a lower production of profibrotic cytokines and consequently inactivation of hepatic stellate cells. Hepatocyte repopulation and microvascular remodeling processes also take place after viral clearance.[2] These changes are more pronounced in earlier stages of fibrosis defining a non-returning point after which, despite

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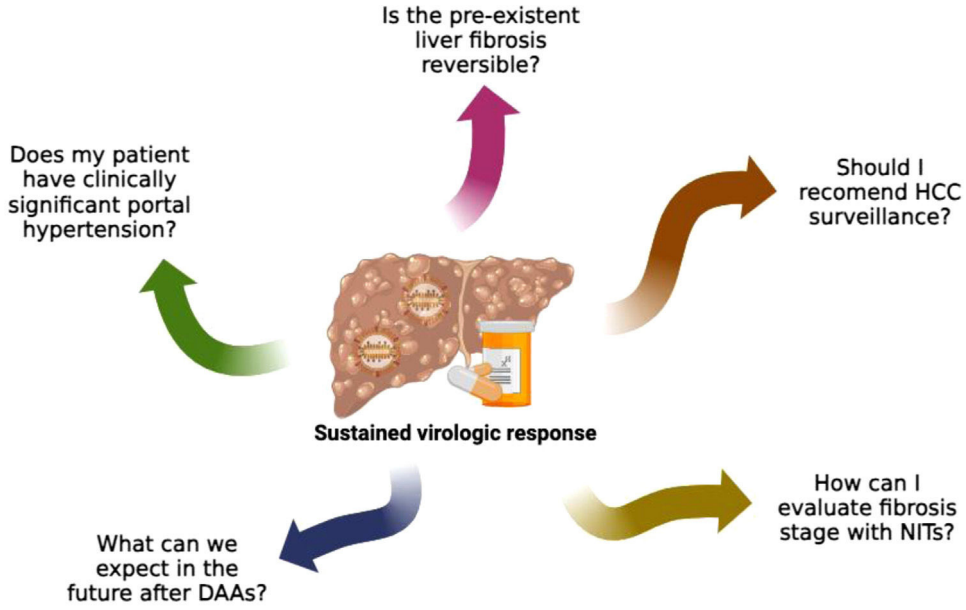

Figure 1 The 5 dilemmas in the treatment of hepatitis C in the era of direct-acting antivirals.

HCV eradication, the pre-existing alterations perpetuate the inflammation cascade and fibrosis progression. In this line, an Italian study that compared paired pre- and post-treatment liver biopsies from 38 HCV-infected patients showed that 61% had at least a one-stage reduction on the METAVIR scale after treatment, with a mean follow-up period of 61 months. All patients who maintained the same fibrosis stage after treatment showed macronodular cirrhosis in the first biopsy. Despite the lack of regression in fibrosis stage, up to 89% of patients showed a decrease in collagen content, indicating the beneficial effects of HCV clearance even in patients with advanced fibrosis.[3] Hence, there is no doubt that HCV elimination can lead to fibrosis regression although the degree of improvement consistently adheres to ''*the sooner, the better*'' rule.

Dilemma n°2: can we evaluate with non-invasive tests (NITs) the stage of liver fibrosis before and after treatment?

Answer: Currently there are not optimal NITs for evaluating liver fibrosis before and after HCV treatment. The sensitivity for predicting advanced fibrosis after SVR with the commonly used cutoff values is markedly reduced in this scenario.

Commentary: Adequate evaluation of liver fibrosis with NITs after achieving SVR remains one of the most controversial topics in this matter. The costs and risks of a liver biopsy hinders the possibility of using systematic histological evaluation after treatment. In the last decades, liver stiffness measurement (LSM) by transient elastography (TE) has emerged as the most used NIT for liver fibrosis in this scenario. As seen in the study by Badia-Aranda et al., pre-treatment LSM is markedly influenced by liver necrosis and inflammation which explains the rapid TE decrease seen within the first weeks of treatment.[4] Therefore, while a low pre-treatment-TE value reliably rules out advanced fibrosis, in patients with high baseline-LSM an overestimation of the existing fibrosis is plausible. In the case of patients with SVR, a relevant dissociation between liver biopsies and post-treatment LSM has been repeatedly reported highlighting the limitations of TE in assessing liver fibrosis after HCV clearance. In this regard, an Italian study including patients with cirrhosis biopsied 5 years after SVR showed that 72% of patients still had advanced fibrosis despite having a LSM < 12 kPa.[5] This reduced sensitivity for advanced fibrosis (as low as 61% in the aforementioned study) has been attributed to liver remodeling and fibrosis reabsorption phenomena.[5] The existent literature in this scenario with other NITs such as serum composite markers (APRI, Fib-4, ELF) and other devices measuring liver stiffness (pSWE, MRE) is scarce. Additionally, these methods may be equally influenced by the same factors as TE. These limitations have been recently addressed in the EASL clinical practice guidelines, concluding that larger studies with longer follow-up are necessary to establish the role of NITs after viral clearance.[6]

Dilemma n°3: which patients should be kept in HCC surveillance programs after SVR?

Answer: Patients with cirrhosis undoubtedly benefit from HCC screening. In patients with uncertain stage of liver fibrosis after SVR, HCC surveillance should be decided on an individualized basis. Multivariant HCC risk stratification models can be useful in this scenario.

Commentary: The number of individuals who will be cured from HCV infection world-wide is expected to exceed 1 million per year for the next decade. Hence, an adequate selection of patients that will benefit from HCC surveillance is of key importance. Based on cost-effectiveness criteria, liver societies guidelines recommend HCC screening when

the annual risk exceeds 1.5%. The indiscriminate inclusion in screening programs comes at a cost both economically and in terms of the quality of life of patients. As seen in other liver diseases, fibrosis is the major risk factor for HCC development. Thus, all patients with cirrhosis or advanced fibrosis stages after SVR should be kept in HCC surveillance programs. The question arises when evaluating the need of HCC screening in patients with high LSM pre-treatment (possibly due to liver inflammation) with low TE values after SVR. In addition to hepatic fibrosis, other cofactors such as age, smoking, alcohol consumption and baseline alpha-fetoprotein (AFP) have been proven to be independent risk factors for HCC. This is the rationale behind the multivariant models aiming to predict the risk of HCC development. A recently published algorithm validated in a cohort of 1500 patients from several European countries uses age, TE, albumin, AFP and the existence of excessive alcohol consumption to identify a low-risk group of patients that could safely avoid HCC screening.[7] Similarly, in 2020 our group published a predictive-model based on non-invasive markers which also allowed for a low-risk of HCC group selection among patients with HCV advanced fibrosis.[8] Therefore, it is highly likely that in the upcoming years, dynamic multivariant models (maybe assisted by artificial intelligence) will be systematically used to identify patients with low risk of HCC development that could avoid periodic screening. Until then, a case-by-case approach is needed.

Dilemma n°4: how can I evaluate the existence of clinically significant portal hypertension after HCV cure?

Answer: Non-invasive criteria using TE and platelet count are useful to evaluate the existence of clinically significant portal hypertension (csPH) in patients with SVR.

Commentary: Since the publication of the PREDESCI study[9] and subsequently the Baveno VII recommendations,[10] identifying patients with csPH to assess the initiation of beta-blockers to prevent liver decompensation and increase survival has become of great importance. As proven by our group, among patients with HCV infection, viral clearance achieved with Interferon plus Ribavirin regimes is associated with portal hypertension amelioration when evaluated at the time of treatment conclusion.[11] This benefit has also been reported with DAA therapy when assessed 24 weeks after SVR.[12] More importantly, sustained improvement is observed over time, as demonstrated in a multicenter Spanish study in which out of 117 patients with csPH at week 24 after treatment, 55/117 (47%) exhibited a hepatic vein pressure gradient (HVPG) lower than 10 mmHg at week 96 after SVR. Likewise, the proportion of patients with HVPG > 16 mmHg (cutoff associated with poorer outcome) diminished from 41% to 15% in this period of time.[13] Considering that an HVPG of <10 mmHg after treatment eliminates the risk of liver decompensation, the availability of NITs that allow the identification of patients without csPH is of great interest. TE and platelet count (PLT) cutoffs have been validated for this purpose. In a recently published large-cohort study, post-treatment LSM < 12 kPa and PLT > 150 G/L had a 99.2% sensitivity to exclude csPH. Additionally, in a large validation cohort among patients meeting these criteria, the risk of decompensation in a 3-year follow-up was 0%. On the other hand, a post-treatment LSM > 25 kPa was highly specific (93.6%) for csPH.[14] Nevertheless, it should be noted that these algorithms have been validated in patients without other cofactors of liver disease, therefore an individualized risk assessment is always recommended before discharging the patient from portal hypertension surveillance.

Dilemma n°5: what can we expect in the future?

Answer: Given the high efficacy and tolerability of DAAs, global HCV eradication is feasible. Public-health multidisciplinary efforts are needed to achieve this ambitious objective.

Commentary: Since the use of Interferon in 90s decade until the approval of second generation multitarget DAAs in 2015, great advances have been witnessed in the area of HCV treatment, with current regimes achieving SVR rates as high as 96–100% regardless of the viral genotype. Thanks to the proficient execution of the 2015 Spanish National Strategic Plan, in only 5 years more than 143,000 patients with HCV infection have been treated with DAAs. These efforts have paved the way for a hitherto unthinkable idea: the elimination of HCV in Spain. HCV eradication comes with unmeasurable multidimensional benefits, including reduction in mortality, alleviation of the economic burden associated with the treatment of decompensated cirrhosis or HCC and benefits beyond the liver such as cognition and quality of life improvements.[15] As explained in the positioning document of the Spanish Association for the Study of the Liver (AEEH), HCV eradication is possible although efforts to allow for viral screening according to age and risk factors, one-step efficient diagnosis and clinical care circuits simplifications are still necessary.[16]

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