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Management of Chronic Hepatitis C Virus Infection: Residual Critical Issues after the DAA Revolution

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Editorial

Until a few years ago, double therapy with Pegylated Interferon (PEG-IFN) and Ribavirin (RBV) was the miliary stone in the treatment of chronic Hepatitis C Virus (HCV) infection [1,2], then followed by triple therapy with PEG-IFN plus RBV plus a first-generation protease inhibitor (boceprevir or telaprevir) limitedly to genotype [3]. The above therapeutic regimens were penalized by some negative characteristics, mainly an efficacy-in terms of Sustained Virological Response (SVR) – varying from 40% to 80%, and the frequent emergence of even severe adverse events. So, the recent availability of the new Direct-Acting Antivirals (DAAs) has revolutionized the approach to patients with chronic HCV infection in virtue of a lot of advantages: a) SVR generally higher than 90% for virtually all patients; b) ease of administration summed up in one to four pills per day, if RBV association is not required; c) shortened duration of therapy, varying from eight to 24 weeks; d) substantial absence of severe adverse events, whereas frequent secondary reactions (fatigue, headache, muscle pain, and others) are generally mild and transient [4]. About the latter aspect, I remember my curious experience with some patients, who asked me whether I was giving them a DAA or a placebo, having previously suffered the heavy effects of IFN-based therapies!

However, some critical issues are still present even in the DAA era. First, the DAAs' efficacy is not 100%, and some treatment failures emerge. Indeed, Resistance-Associated Substitutions (RASs) in NS3 protease and NS5A regions can confer high-level resistance to protease and NS5A inhibitors, respectively, whereas sofosbuvir has the highest barrier to resistance and, therefore, remains the backbone of retreatment, with or without ribavirin, in patients who failed a DAA-based regimen [5,6]. The triple association of sofosbuvir plus velpatasvir plus voxilaprevir has been approved last summer in both the Unites States (US) and Europe for retreatment of DAA failures, and other associations are already (glecaprevir plus pibrentasvir) or will be soon (grazoprevir plus ruzasvir plus uprifosbuvir) available [7-9].

Second, DAAs can cause Drug-Drug Interactions (DDIs) in a relevant number of patients with co-therapies and, consequently, either result in lower efficacy or increase the risk of drug toxicity. Proton Pump Inhibitors (PPIs) and lipid-lowering medications (statins) are two examples of hyper-prescribed drug classes that can interact with DAAs and diminish their efficacy (PPIs) or cause significant toxicity such as muscle damage (statins) [10]. This is in particular true in the case of old age or multiple co-morbidities, therefore physicians should be aware of the potential DDIs and carefully evaluate patients' co-medications before initiating a DAA-based therapy. As for me I use the well-done and free-of-charge website of the University of Liverpool (https://www.hep-druginteractions.org), established in 2010 by members of the Department of Pharmacology.

Third, some clinical experience has recently suggested that the HCV clearance obtained with the DAAs could be associated with the de novo emergence or, much more frequently, the recurrence of Hepatocellular Carcinoma (HCC), maybe in virtue of immunological changes due to the faster viral elimination [11] than seen with IFN-based therapies, which were known to reduce the risk of HCC after SVR [12]. On the other part, a recently published Veterans Affairs system revision conducted on a large cohort of both IFN- and DAA-based treatments has evidenced no significant differences in HCC risk between the two therapies [13], so reducing concern and fear and outlining the importance of DAA use and benefits.

Last but not least, in many countries stakeholders and clinicians must face up to affordability of DAA treatments and sustainability of health systems. When approved in the US and introduced into clinical practice in late 2013, the initial cost of 12-week treatment with sofosbuvir alone was US$84,000, namely US$1,000 per pill per day, so the substantial budget impact caused coverage restriction, reimbursement delay and cost and discount negotiation in both high- and

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low/medium-income countries [14]. In my country, the Italian government authority (AIFA) initially gave DAA therapies only for patients with severe fibrosis/cirrhosis or with at-risk conditions (liver transplantation, severe extra-hepatic manifestations). Consequently, a lot of patients with only absent-to-moderate fibrosis (six patients of mine included) got the DAAs abroad, in particular in India, Pakistan, or Egypt, where the price of a 12-week course of sofosbuvir was less than US$1,000. Nowadays in Italy, after almost three years of coverage restriction and price negotiation, virtually all patients have access to DAAs, even in virtue of a significant lowering of their cost (approximately €5,000-50,000 per 12-week treatment).

In summary, the critical issues still present in the management of chronic HCV infection must not pass into the background the great progress made since the availability of DAAs, as we can now cure the vast majority of patients, stop the disease progression towards cirrhosis and HCC, and, as a consequence, reduce morbidity, mortality, and economic costs.

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