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Editorial

# Treatment of Chronic Hepatitis C: An Overview

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Hepatitis C Virus infection (HCV) is an increasing public health concern with an estimated 184 million people infected worldwide and approximately 350.000 yearly deaths from HCV-related complications [1] and, until recently, its treatment has been far from ideal. Thus, the scientific advances in the field of HCV treatment have been progressing in leaps and bounds and, in fact, numerous new drugs were recently added to the anti-HCV regimens. During the past decade, Interferon (IFN)-based antiviral regimens were the only available therapeutic option for all patients with Chronic Hepatitis C (CHC) [2]. Indeed, such regimens had significant side effects that, in many cases, precluded the completion of the treatment course. Undoubtedly, understanding the steps of HCV life cycle has paved the way for the development of highly effective therapies that target the virus at different steps of this cycle in order to impede it from hepatocyte entry to assembly, replication and virion release.

Since December 2013, the regulatory authorities approved seven new anti-HCV molecules and since then the treatment landscape has been changed drastically. Sofosbuvir (SOF) was the first FDA-approved nucleotide analogue inhibitor of HCV RNA-dependent RNA polymerase in 2013 followed by Simeprevir (SMV) [NS3/4A protease inhibitor], Daclatasvir (DCV) [NS5A replication complex inhibitors], the combination of Ledipasvir (LDV) [NS5A replication complex inhibitor] plus SOF and most recently the combination of Ombitasvir (OBV) [NS5A inhibitor], the ritonavir-boosted protease inhibitor Paritaprevir (PTV), and the first non-nucleosidic polymerase inhibitor Dasabuvir (DSV). Of note, only SOF and DCV can be considered Directly Acting Antivirals (DAAs) with pan-genotypic activity [3-5], while all the remaining drugs can exert a genotype-specific activity [6-8]. Historically, Genotype 1 (Gt1) was considered difficult-to-treat. However, with these new DAAs, Gt3 is the new challenging genotype especially in cirrhotic patients who failed previous anti-HCV therapy [9]. Currently, few regimens are available for Gt3 CHC and they are all SOF-based ones. Fortunately, there are some ongoing trials that investigate LDV/SOF, PTV/ritonavir plus the investigational NS5A inhibitor (ABT-530), and the combination of ABT-530 plus ABT-493 for the treatment of such genotype (NCT02243293 and NCT02576314). Recently, the results of the four ASTRAL trials have been revealed. In ASTRAL-3, the new combination of SOF and Velpatasvir (investigational pan-genotypic NS5A inhibitor) was evaluated in Gt3 patients for 12 weeks with Sustained Virologic Response (SVR) rates of 95%. If approved, this combination would be the first all-oral, pan-genotypic, single tablet regimen for CHC [10].

There is no doubt that with the discovery of these new molecules, the rates of SVR have improved tremendously even in patients with cirrhosis. Yet, rates of SVR are still unsatisfactory in patients with decompensated cirrhosis. In the recent SOLAR-1 study [11], the investigators evaluated SOF/LDV combination in conjunction with Ribavirin (RBV) for 12 or 24 weeks in Gt1 and 4 patients that had or had not undergone liver transplantation including those with decompensated liver disease. Rates of SVR were 60%–75% among patients with severe hepatic impairment. Likewise, Saxena and colleagues have recently revealed that the SOF+SMV with or without RBV can cure up to 73% of patients with Child-Pugh score B/C versus 91% of Child-Pugh A [12]. The investigators of this study, however, would advise against the use of this combination in patients with hyperbilirubinemia or hepatic encephalopathy at baseline. Another challenge that might face the hepatologist is liver transplant recipients with recurrent CHC. Those patients are always on calcineurin inhibitors (CYP3A4 substrates) and, unfortunately, these drugs have potential drug-drug interactions with SMV and ritonavir-boosted PTV, OBV and DSV combination [6,8] that might require immunosuppressant dose adjustment. On the other hand, SOF and LDV/SOF combination [5,7] lack that clinically relevant drug–drug interactions with CYP3A4 substrates, hence, can be considered as preferable therapeutic choice in those patients.

Albeit these new DAAs seem very promising, special patient populations still have unmet needs and patients with severe renal impairment are no exception. Most DAAs are metabolized primarily via the liver and, theoretically, can be used in patients with severe renal disease except SOF that should not be administered to patients with an estimated Glomerular Filtration Rate (eGFR)<30mL/min/1.73m2 or with end-stage renal disease. Certainly, more data are warranted to conclusively

demonstrate the efficacy and safety profiles of these DAAs in that setting of patients.

Even though these new molecules have been hailed internationally as a breakthrough anti-HCV therapy, there is still a worldwide concern over the high cost of those drugs. A 12-week course of SOF, for instance, costs $84,000 in the US, €41,000 in France, £35,000 in the UK and €45,000 in Italy. Not to mention the double price when a patient needs to undergo a 24-week course. Clearly, the various assistance programs are not able to cover the whole cost for all patients and, in fact, some national health systems restrict the reimbursement of these new all-oral regimens for the following groups: patients with advanced fibrosis (Metavir≥F3), intereferon-incapable, patients with extrahepatic manifestations of HCV infection (e.g. cryoglobulinemic syndrome or non-Hodgkin lymphoma) or with solid organ transplant recipients and CHC, with Metavir≥2 [13]. As regards drug resistance, treatment failure of SMV plus SOF is associated with resistance to SMV and other HCV NS3/ 4A protease inhibitors such as PTV. Conversely, SOF resistance-associated variants are uncommon [14]. Another major point of interest, we should acknowledge the fact that those formerly-called "experimental" drugs have been almost always evaluated in a setting of patients with no other significant concomitant disease and only time and real-life data can demonstrate their efficacy and safety in patients with CHC along with other important system involvement. Indeed, more robust evidence from ongoing trials in patients with non- Gt1, decompensated cirrhosis and with end-stage renal disease are eagerly awaited.

To conclude, we are witnessing a revolution of Hepatits C treatment that is IFN, and sometimes, RBV-free. A whole new era in which the treatment paradigm went from daily injections to once-daily pills and from one-year course to as short as 12 or even 8 weeks with much improved safety profile and response rates that are approaching 100% in some cases. Simply, we are living today the future that we always dreamed of in the past, as once said by Physician Sir William Osler "the future is today".

## Conflict of Interest

Pietro Andreone declares the following potential conflict of interest:

1) Research support from Roche, MSD and Gilead Sciences

2) Advisory committees for Roche, MSD, Janssen Cilag, AbbVie, Boehringer Ingelheim, Gilead Sciences and BMS.

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