

Direct Acting Antivirals (DAAs) Against
Hepatitis C Virus Infection: Excellent
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Editorial

Infection with Hepatitis C Virus (HCV) is the major cause of chronic and persistent hepatitis, liver cirrhosis, and Hepatocellular Carcinoma (HCC) and accordingly main reason for liver transplantation needs. In fact, only a small fraction (20%-30%) of the infected people resolve from the acute phase of HCV infection while majority develop the chronic state which may finally end up with adverse liver diseases (cirrhosis and HCC). Around 170 Million individuals are infected with HCV and at least 350,000 people die each year from this infection while there is no approved vaccine available against this threatening infection to date [1,2].

HCV contains an RNA genome encoding for three structural (core, E1, E2) and seven nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). Structural proteins, core and envelope proteins (E1 and E2), make the nucleocapsid and virion particles. The P7 protein might act like calcium ion channel and NS2 plays role as a transmembrane protein needed for NS2/3 auto protease activity. NS3 shows protease and NTPase/ and NS4A acts as a cofactor for this protease activity while NS4B and NS5A are needed for viral replication. Finally, NS5B is an error-prone RNA-dependent RNA polymerase (an RNA polymerase with lack of a proof-reading activity) which induces high rate of mutation and thus extensive HCV genetic diversity (7 major genotypes and around 70 subtypes). In fact, High sequence divergence level of HCV among its seven major genotypes and induction of antibody and CTL escape mutants by emergence of quasispecies in the course of infection (HCV evasion from humeral and cellular immune responses) are among main obstacles for HCV vaccine development and therapy. HCV genotypes are not distributed evenly in different geographical areas of the world. While genotypes 1 to 3 are more common in most regions, genotypes 1, 2, 4 and 5 are prevalent in Africa and genotype 3 and 6 in India and Southeast Asia, respectively [1-4].

Before 2011, the only curing strategy (standard therapy) for HCV infection was consisted of the combination of pegylated interferon α (peg-IFN) with Ribavirin (RBV) for 24 or 48 weeks. However this treatment was only successful in fractions of patients depending on the HCV genotype (less efficient for genotypes 1 and 4). In addition, occurrence of severe side effects like: leukopenia, thrombocytopenia, flu-like symptoms and depression as well as contraindication of peg-IFN and/or RBV in many patients had limited its application. However, advances in understanding HCV replication mechanisms and identification of its main targets (NS3/4A, NS5B and NS5A) in last decade led to the invention of direct-acting anti-viral agents (DAAs) against the main viral replication targets, as highly efficient new therapies to cure chronic HCV infection. In 2011, first HCV NS3 protease inhibitors, boceprevir (BOC, VICTRELIS[®]) or telaprevir (TLV, INCIVEK[®], INCIVO[®]) were introduced for a combination, triple therapy with peg-IFN and RBV. With a same period of therapy (24 to 48 weeks), this new treatment reached cured rates around 75% in treatment-naive patients infected with HCV genotypes 1 (that otherwise fairly reached to 50% with peg-IFN/RBV therapy). However, addition of extra severe side effects and dosing burden beside extra costs, limited their applications [2,5].

Fortunately, starting from 2013, invention of other excellent DAAs like: Sofosbuvir (a nucleotide NS5B polymerase inhibitor), Simeprevir (a NS3/4a protease inhibitor), Daclatasvir (a non-structural NS5A protein inhibitor), dasabuvir (a non-nucleoside NS5B polymerase inhibitor) and administration of targeted combination of different DAAs, for the first time provided interferon and/or RBV free therapy regimens with high Sustained Viral responses (SVR) up to 100%, shorter treatment periods and less toxicity and side effects. Accordingly, in coming years, it is expected that additional DAAs in various combinations could be approved for even more efficient and safer therapy of chronic HCV infection which might decrease the number of liver cirrhosis, HCC and HCV induced deaths in the next decade (at least in many developed and rich countries) [5,6].

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It is important to note however, that almost all reports concerning excellent benefits of DAAs are based on results of clinical trials and information provided by pharmaceutical related agencies and case-control or cohort studies with small number of patients and/or select groups in last 2-3 years. Therefore, it might be too early to conclude everything before availability of enough clinical reports on SVR, potential side effects, interactions with other drugs, or use in special populations and patients. In addition, it should be noted that, although DAAs are considered as an excellent therapy for chronic HCV infection and their invention is a landmark in HCV history but their efficiency is limited in several aspects. In fact, there is a huge misunderstanding for their therapeutic effects among both patients and even some professional physicians. DAAs are not a treatment for an already HCV-induced cirrhotic liver or HCC but might prevent HCV-induced cirrhosis or HCC by curing chronic HCV infection before induction of severe liver damages by long-term viral infection. This means early diagnosis and treatment. However, unfortunately most of the patients are not aware about their infection (due to mild symptoms) before extensive liver damages and lack of population based screening programs (except in a few developed countries) should also restrict the proper and on time therapeutic intervention of DAAs. Other difficulties encountered with application of DAAs are: high cost of these drugs (which almost completely restrict their applications in few rich countries) and their limited therapeutic efficiency in some genotypes (like HCV genotype 3). In addition, increasing number of reports on viral resistance cases through so-called resistance-associated amino acid variants (RAVs) [7] as well as possibility of reinfection after complete treatment might be further challenges on their versatile application.

Therefore, although recent invention of DAAs revolutionized the therapeutic approaches for chronic HCV infection but due to reasons mentioned above they should not be considered as a miracle to cure severe liver damages induced by HCV and a termination for global HCV infection.

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