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HCV and DAAs in the Next 20 Years: The Hidden Plague of Few Patients

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Introduction

Hepatitis C virus (HCV) is globally spread and it has been estimated that 184 million people are chronically infected worldwide leading to severe liver disease, liver cancer, and death [1]. The better knowledge of the HCV replication cycle and the role of viral proteins leads to revolutionized treatment of chronic HCV infection, so it is possible supposing its eradication over the next 20-30 years [2]. The introduction of the highly potent direct-acting antivirals (DAAs) targeting the three no structural HCV proteins NS3, NS5A and NS5B, makes possible to treat different HCV genotypes (GT)-infected patients, providing short and well-tolerated all-oral regimens [2]. In addition, the recent possibility to combine two or more DAAs, according to HCV genotype and to drug resistance evaluation, offers several therapeutic solutions leadingto higher sustained viral response (SVR)[3], even in patientswith cirrhosis and prior treatment failure, until now considered as difficult to treat [4,5]. In addition, SVR after DAAs treatment is associated with a significantly lower mortality and HCC rates incidence.The recent possibility to combinesofosbuvir with voxilaprevir and velpatasvirleads to SVR in 95% of multi-genotypic infected patients and also seems to overcome the problem of the drug resistance in DAAs failures, extending treatment to 12 weeks, placing as a major step towards HCV eradication [6]. However, effective treatment is not enough and a population difficult to treat,after treatment failure, remains a challenge for the viral eradication at global level.The success rate with DAAs treatment is strictly related to both parasite and host unique characteristics and is highly influenced by additional factors, including treatment success rate, duration, cost, and side effects [3].

Patient characteristics affecting change of cure include age, body mass index, ethnicity, genetic factors such as polymorphisms near the Interferon Lambda 3 (IFNL3) gene,stage of fibrosis, cirrhotic status, HCC presence, failure to past regimens [7,8]. It is more complex considering viral factors because the intrinsic HCV variability and its subdivision in several different genotypes and subtypes [3,9]. Because of the high replication rate and the lack of proofreading activity of viral NS5B polymerase, HCV is naturally susceptible to develop mutations during replication cycles. Therefore, even within the same host, HCV exists as a population of slightly different viral variants (differing by 1-5% in nucleotide sequence) known as "quasispecies" [9]. The quasispecies nature allows a rapid adaptability to a changeable environment, inducing the evolution of escape strategies to selective forces, such as immune system and DAAs [10,11]. All these factors in addition tothe intrinsic drug characteristics (i.e. low potency, low genetic barrier to resistance) can cooperate to a partial viral suppression during DAA-treatment, leading to the selection and/or development of viral strains harboring resistance-associated substitutions (RASs) and ultimately causing treatment failure [3,10,11]. HCV treatment can be affected by both natural and acquired drug resistance, two scenarios with different implications and impacts on drug efficacy. The development of highly resistant viral strains after DAAs-failure (often harboring more than one RASs, in more than 1 drug-target gene) can significantly impact the choice and the efficacy of a second-, or third-line treatment strategy. On the contrary, the role of natural resistance is still controversial due to the high SVR rates and, to date, it is relevant only for selected NS3-protease inhibitors and NS5A inhibitors in selected HCV genotypes and clinical setting [10,11].

In addition, the existence of mutations thatindividuallyare mildly or not associated to resistance but in clusters are able to reduce SVR rate, makes difficult the interpretation of genotype-specific resistance profile. These mutations may intensify resistance profiles if associated with major mutations, or may generate new, genotype-specific, resistance patterns. With the advent of multi DAAs-combined regimen, the new concept of "pattern-RASs"can also be extended to the contemporary presence of particular major RASs in more than one gene [3]. Although this cross-resistance phenomenon in naïve patients is less common (1.04%) [12,13], recent studies reported significant frequency of double-multiclass resistance in patients failing DAA-combinations regimens [14] andalso a reduced efficacy of retreatment in DAA-experienced patients [3,15]. In conclusion, however this plague seems to be destined to disappear in the next years, it is due to consider the slice of patients difficult to treat failing also the newest regimens. Until now, just multigenotipic and not pangenotipic solution are available, so DAAs regimens increase the effectiveness and reduces (but not eliminate) the risk of RASs development. In this regard, Food Drug Administration, European Medicine Agency and international guidelines, continuously updated,endorse the importance of correct genotyping and RASs tests in DAAs-treatment failure patients [7,8]. In addition, considering HCV infection related diseases, such as metabolic disorders or HCC onset, and its implication in epigenetic modulation, it is necessary investigate more on virus mechanism and hypothesize more and more personalized therapies.

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