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The Near Future of HCV Treatment: Supplementary Treatments against Oxidative Stress will be still useful?

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Hepatitis C virus (HCV) is a member of the genus Hepacivirus of Flaviviridae family and its infection is a global health burden because it affects 3- 4 million patients each year while about 150 million peoples are worldwide chronically infected [1], this is due by the fact that more than 80% of HCV infected patients become chronic [2].

It is a positive single-stranded RNA virus that gives rise to a polyprotein from which have origins: the core protein (core) and the envelope glycoproteins 1 and 2 (E1 and E2, respectively), which are constituents of the HCV particles, p7 and nonstructural protein 2 (NS2), primarily involved in HCV assembly, NS3, NS4A, NS4B, NS5A and NS5B nonstructural proteins with important roles in the polyprotein processing and HCV replication [3]. HCV infection often causes severe liver diseases, including end stage liver diseases like cirrhosis and HCC [4]. Chronically infected patients are featured by metabolic derangements, inflammation and oxidative stress (OS) [5-7]. The latter, in particular, plays a main role also in metabolic alteration and inflammation. OS occurs when the equilibrium between pro-oxidant sources and anti-oxidant defenses is unbalanced and the reactive oxygen species (ROS) or reactive nitrogen species (RNS) is not adequately counteracted [8]. The pro-oxidant sources are multiple but, among them, mitochondria have a special place. Mitochondria, that are the power plant of cells, are the main source of ROS production due to aerobic respiration and their high metabolic activity [9]. Unfortunately, they are the also the main targets of reactive molecules that worsening the mitochondrial functionality give rise to a vicious circle able to prompt liver damages. Mitochondria are well known targets of the HCV proteins. They, in fact, interact with these organelles promoting their dysfunctions [10].

Few months ago, after a decade in which pegylated interferon (IFN)-α and ribavirin represented the gold standard in the HCV treatment, new therapeutic approach was approved. Two direct-acting antiviral (DAA) agents known to be NS3/NS4A protease inhibitors, telaprevir and boceprevir [11], are now used in combination with the old therapeutic approach, IFN-α plus ribavirin, the so called triple therapy. Triple therapy reaches a significant improvement of the sustained viral response (SVR) especially in HCV genotype 1 patients (63-75%) with a reduction in therapy length.

These data, although they are excellent, highlight that in about 30% of cases triple therapy does not get the desired results, thus supporting the idea that complementary treatments to antiviral therapy, like antioxidants targeted to mitochondria, mitoQ for instance [12], or avoiding mitochondrial dysfunctions, like alisporivir [13,14], could be really useful to HCV treatment. Although, up to now, only in some cases the supplementation of antioxidants have improved the outcome of antiviral treatments when used in combination to IFN [11].

Today the new therapeutic approaches provide DAAs of second generation, targeting also NS5B, and the use of IFN-free therapy, in order to reduce the intolerance to IFN and to expand the number of treatable patients [11].

A combined therapy performed using DAAs of second generation, like Daclatasvir (a HCV NS5A replication complex inhibitor) and Sofosbuvir (a nucleotide analogue HCV NS5B polymerase inhibitor), obtained impressive results in patients affected by HCV genotype 1, 2 and 3 with an overall high sustained viral response (SVR) that reach 90% or more, also in patients in which the previous therapeutic approach failed [15]. In light of these exciting results, some questions arise in my mind, if only less than 10% of patients are yet resistant to therapy, what will be the future of the studies proposing supplemental treatments against HCV, like antioxidant therapy?

Such approaches are still considered useful and practical?

The truth is that we cannot know yet. Probably, they may be useful in promoting the reduction of liver damage hence facilitating the response to antiviral therapy in patients more difficult, such as those with advanced fibrosis or cirrhosis [16].

What is certain is that the potential impact of the additional antioxidant therapies may suffer a drastic reduction, and, therefore, all studies aimed at understanding their real clinical impact.

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