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Is Interferon-Free Treatment for HCV Possible?

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Editorial

Hepatitis C virus (HCV) was first discovered in the 1970s as the pathogen to cause non-A non-B hepatitis and HCV infection is the leading cause for liver transplantation and is associated with increased risk of liver fibrosis, cirrhosis and hepatocellular carcinoma [1]. With more than 185 million people having been infected with HCV world-wide, HCV infection remains a huge medical burden in most countries. Due to the limited efficacy and extensive side-effects of the standard combination therapy with pegylated interferon alpha (IFNα) and ribavirin, development of novel antivirals is urgently needed. Much progress has been made in the understanding of the HCV life cycle, including cell surface receptors that mediate virus entry, detailed mechanisms of HCV RNA replication, viral particle assembly and egress. In the meantime, HCV replicon system that allows efficient RNA replication without viral particle production and in vitro cell culture system (HCVcc) were successfully developed [2]. Coupled with the known crystal structures of HCV NS3/4A protease and RNA-dependent RNA polymerase (RdRp), these new advances make the development of new direct-acting antivirals (DAAs) for HCV possible [3].

Current Standard of Care (SOC) for the Treatment of HCV

Although there are numerous DAAs being developed in the preclinical and clinical stages, the current standard of care (SOC) for the treatment of chronic hepatitis C in most developing countries is the combination therapy with pegylated interferon alpha (PEG-IFNα) and ribavirin (RBV) [4]. With this combined treatment, sustained virological response (SVR) is achieved in 40–54% of patients infected with HCV genotype 1 and in 65–82% of patients infected with HCV genotypes 2 and 3 [5]. The efficacy of this IFN-based therapy is influenced by both viral and host factors, such as HCV RNA level at baseline, HCV genotypes, degree of liver fibrosis, and the host polymorphisms of the IL28B gene. Combination therapy with PEG-IFNα and RBV has a relatively low SVR in patients infected with HCV genotype 1 and is poorly tolerated with serious side-effects such as neutropenia, anemia, thrombocytopenia in some patients [6]. As interferon is expensive and daily injection is inconvenient, new therapy without IFN is urgently needed.

Development and clinical use of DAAs

Better understanding of the virus life-cycle, especially the solution of HCV protease and polymerase structures makes the development of direct-acting antivirals (DAAs) possible. The earliest two DAAs that were approved in Europe and the United States in 2011were inhibitors of NS3/4A protease: telaprevir and boceprevir. This leads to a new therapy for HCV genotype I-triple therapy (telaprevir or boceprevir in combination with pegIFN and RBV). It has been shown that this triple therapy is more effective than pegIFN and RBV combination regimen with a significant increase of SVR to 75% of patients chronically infected with HCV genotype1 [7]. Different groups of people respond to triple therapy very differently. This therapy fails to eradicate HCV infection in approximately 20%-30% of treatment-naive and 50%-60% of treatment-experienced patients [7]. As such, further development of more potent DAAs is needed.

Future directions of HCV treatment: Is IFN-free treatment possible?

Recent study indicates that if a drug has enough potency to shut down virus production, all-oral IFN-free DAA regimen could achieve high SVR rates. Development of these IFN-free therapies will benefit patients. In the therapy of PEG-INFa plus RBV, ribavirin has been shown to accelerate the second-phase decline and shorten the needed treatment duration. Recent findings suggest that this effect is not IFN-dependent and is obtained when ribavirin is combined with other potent DAAs. Therefore, ribavirin addition is likely to be useful to shorten treatment duration with future all-oral, IFN-free regimens.

A recent study indicated that a sustained virological response was achieved with oral DAA/RBV without IFN in a patient infected with genotype1b who underwent orthotopic liver transplantation, this means SVR of DAA without IFN can be achieved in low viral load and genotype1b infection [8]. This demonstrates that patients infected with particular genotypes may receive all oral IFN-free treatment although a lot of studies are needed in optimizing the combination.

Several IFN-free treatment projects were evaluated those years with the emergence of new DAAs. These studies provided valuable data support for the development of IFN-free treatment. The efficacy and safety of a 3-DAA-containing regimen plus ribavirin (RBV), including a protease inhibitor, NS5A inhibitor, and a non-nucleoside NS5B inhibitor was assessed in a clinical cohort of patients chronically infected with HCV genotype 1. This regimen was well tolerated and its antiviral efficacy is closely related to the dose of DAAs and IL28B genotypes. It was also reported that lower SVR rates in genotype 1a than genotype 1b was achieved [9]. Alisporivir (ALV) is an oral cyclophilin inhibitor that has potent anti-HCV activity, so alisporivir plus ribavirin without interferon treatment is predicted to achieve high SVR in patients with HCV genotype 2 and 3. Indeed 89% of those patients achieved SVR after only 24 weeks treatment [10]. Sofosbuvir is an oral nucleotide inhibitor of HCV polymerase with high barrier to resistance. Sofosbuvir combined with ribavirin for 12 weeks treatment achieved sustained virologic response in 100% of HCV genotype 2 or genotype

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3 infected patients. 12 weeks sofosbuvir plus RBV provided SVR in 84% of HCV genotype1 infected patients [11]. The cost-effectiveness analyses of all-oral IFN-free treatment showed that as SOC treatment for genotype 1 costs more and has a lower SVR, and IFN-free treatment was most cost-effective for genotype 1 infectors [12].

Conclusions

As we can see from this short editorial, several DAA combinations with or witout ribavirin have achieved high SVR with relatively good tolerance [13]. Although much work is still needed to be done, IFN-free oral pills that are effective for all HCV genotypes will be available in the future.

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