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Editorial

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The hepatitis C virus NS5A inhibitor daclatasvir has a dual mode of action and leads to a new virus half-life estimate

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"We employed mathematical modeling to decipher the origin of the very rapid viral decline observed in the first hours following initiation of daclatasvir, a first-in-class NS5A inhibitor, where one dose of daclatasvir led to a 1000-fold decrease in viral levels within approximately 12 h."

Chronic infection with hepatitis C virus (HCV) affects approximately 160 million people worldwide [1] and is the leading cause of cirrhosis, liver cancer and liver transplantation [2]. Until 2011, the standard of care in the western world was weekly injections of pegylated-interferon (peg-IFN)-α and daily oral ribavirin (RBV), but viral eradication was achieved in less than 50% in treatment-naive HCV genotype 1 patients, the most prevalent genotype in western world [3].

Since the approval in 2011 of two protease inhibitors (PIs), telaprevir (TVR) and boceprevir, in combination with peg-IFN/RBV, the landscape of anti-HCV therapy has been rapidly changing. Dozens of direct antiviral agents targeting different stages of the viral lifecycle are currently in clinical development, holding the promise that a universal cure can be achieved. Although results from clinical trials, often obtained in small populations of highly selected patients, should be taken with caution, short, tolerable, pan-genotype and IFN-free regimens appear to be attainable within the next couple of years.

In this highly dynamical context, there has been an increasing appeal from the industry and academics to use viral kinetic mathematical modeling to anticipate, evaluate and rationalize the effectiveness of these new antiviral strategies [4]. This is particularly true in the case of agents that target proteins with complex or ill-defined functions, such as the HCV nonstructural protein 5A. In a recent paper published in *Proceedings of the National Academy of Sciences* [5], we employed mathematical modeling to decipher the origin of the very rapid viral decline observed in the first hours following initiation of daclatasvir (DCV), a first-in-class NS5A inhibitor, where one dose of DCV led to a 1000-fold decrease in viral levels within approximately 12 h [6].

Hepatitis C viral dynamics, virion half-life & drug antiviral effectiveness

One of the most important results of viral kinetic modeling was to introduce the idea that viral load level observed in a patient reflects the balance between the antagonist processes of production and clearance of the virus. By blocking viral production from infected cells, the initiation of antiviral treatment disrupts this equilibrium and the clearance of the virus is no longer efficiently compensated. Thus, the rate of viral decline observed early after treatment initiation can be used to calculate the virus half-life. This basic idea was used by Neumann *et al.* to fit the viral decline observed during interferon therapy and to estimate the antiviral effectiveness of interferon, as well as to obtain the original estimate of the HCV half-life of 2.7 h [7]. Importantly, if HCV is rapidly eliminated from the circulation, it implies that large quantities of the virus

KEYWORDS: daclatasvir • hepatitis C virus • multiscale model • NS5A inhibitor • viral kinetics

EXPERT REVIEWS

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