Hepatitis C in the interferon-free era

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The in-depth study of the genetic structure of hepatitis C virus (HCV) has generated a better understanding of the viral life cycle and, subsequently, of the ideal targets for direct-acting antivirals (DAAs).

First generation DAAs were designed to act on enzymatic targets such as the NS3/NS4A protease complex, to add a direct mechanism of action to the long-standing standard of care that was considered to be pegylated interferon (pegIFN) plus ribavirin (RBV). A second enzymatic target –the NS5B RNA-dependent RNA polymerase– proved to be a valuable addition to protease inhibitors and opened the door to IFN-free regimens.

However, it has become increasingly clear that viral replication does not rely solely on enzymatic reactions, and that viral proteins play important roles in establishing infectivity, viral persistence, intra-cellular signaling, host cell gene expression, host cell apoptosis, and so on.

Phosphoprotein NS5A, although typically not considered to display direct enzymatic activity, constitutes an essential component of the HCV replicase and it has also been shown to “cross-talk” with most non-structural proteins (e.g., NS2, NS3, NS4A, NS4B, etc).

[AbbVie's recent press release](#) regarding the all-oral, IFN-free, 12-week triple DAA (3D) anti-HCV regimen revealed a “combination of three different mechanisms of action [that] interrupts the HCV replication process”, with 96% sustained virologic response at 12 weeks post-treatment (SVR12) – the new time point set for evaluating DAA treatment response.

The regimen contains a boosted protease inhibitor co-formulated with an NS5A inhibitor, and a non-nucleoside polymerase inhibitor, administered with or without RBV.

This is just one in a long line of good news regarding the changes in what is considered to be the future treatment of hepatitis C, with multiple companies investing in R&D to provide IFN-free anti-HCV regimens, with unprecedented high SVR rates and excellent tolerability.

To date, clinical trials in the field of HCV have been registered by companies such as AbbVie, Gilead Sciences, Janssen, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Vertex Pharmaceuticals Inc., to name only a few. Interim and final study results are eagerly expected, to better assess future treatment options for patients with chronic hepatitis C.

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