

NS5A inhibitors in the treatment of hepatitis C

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Summary

Hepatitis C virus infection is a major health problem worldwide and no vaccine has yet been developed against this virus. In addition, currently approved pharmacotherapies achieve suboptimal cure rates and have side effects that result in non-compliance and premature treatment discontinuation. Significant research has been devoted to developing direct-acting antiviral agents that inhibit key viral functions. In particular, several novel drug candidates that inhibit the viral non-structural protein 5A (NS5A) have been demonstrated to possess high potency, pan-genotypic activity, and a high barrier to resistance. Clinical trials using

combination therapies containing NS5A inhibitors have reported results that promise high cure rates and raise the possibility of developing interferon-free, all-oral regimens.

Abbreviations:

[HCV](#) (hepatitis C virus), [DAA](#) (direct acting antiviral), [NS](#) (nonstructural), [RdRp](#) (RNA-dependent RNA polymerase), [IFN](#) (interferon), [UTR](#) (untranslated region), [IRES](#) (internal ribosome entry site), [SVR](#) (sustained virological response), [RVR](#) (rapid virologic response), [cEVR](#) (complete early virologic response)

Keywords:

[Hepatitis C virus](#), [NS5A inhibitor](#), [Daclatasvir](#), [Resistance](#)

etc.....

Conclusions

Although blood screening and other preventive measures have reduced the incidence of HCV in some parts of the world, infection with this virus remains a significant worldwide health concern. The multiple genotypes of HCV, as well as rapid development of mutations, have complicated the development of effective drugs. Until recently, a non-specific antiviral combination, pegylated IFN- α and ribavirin, was the mainstay of HCV therapy. The approval of two NS3/4A protease inhibitors has allowed the addition of a DAA to this treatment regimen. Although the first-generation protease inhibitors, telaprevir and boceprevir, in combination with pegylated IFN- α and ribavirin, have improved treatment of chronic HCV genotype 1 infection, response rates remain suboptimal. In addition, many patients are unable to tolerate this therapy and, among those who can, adverse events associated with the drugs can compromise patient compliance and lead to premature treatment discontinuations. Thus, there has been a strong desire to develop all-oral, IFN-free therapies with high efficacy. The discovery of the multiple roles of the NS5A protein in viral replication has been paralleled by the development of specific NS5A inhibitors. Evidence gathered thus far indicates that these agents are potent and possess antiviral activity against multiple HCV genotypes with acceptable safety profiles. In addition, clinical trial data support the efficacy of NS5A inhibitors with and without pegylated IFN- α and ribavirin, suggesting an important role for these agents as a component of all-oral therapeutic regimens for the treatment of HCV.

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