The HCV NS5B Nucleoside and Non-Nucleoside Inhibitors

Fernando E. Membreno, MD, MSc, Eric J. Lawitz, MD, CPI*

KEYWORDS

• Hepatitis C virus • NS5B nucleoside inhibitors
• Non-nucleoside inhibitors • Polymerase inhibitors

In the world, approximately 130 to 170 million people are chronically infected with hepatitis C virus (HCV) and it is estimated that more than 350,000 people die from this infection each year.[1] Since its discovery in 1989, there has been a slow evolution of therapies for this disease, which currently are still marked by marginal effectiveness and significant toxicities. For approximately 20 years there have not been had any major breakthroughs in the development of therapies except for the addition of ribavirin (RVB) and the pegylation of interferon alfa, which have boosted genotype 1 (GT-1) sustained viral response (SVR) rates to a disappointing 40% to 41%.[2] The inability to cure this virus has led to the accumulation of nonresponder patients who are at continued risk of progressive liver disease, liver decompensation, and consequently liver transplantation.

A new era of direct-acting antivirals (DAAs) is beginning. Unlike the current standard of care (SOC) therapy, pegylated interferon (PegIFN) and RBV, these new molecules target specific sites that disrupt the function of viral proteases and polymerases that are vital for the virus life cycle. During the past 10 years, a profound understanding of the molecular structure of HCV, which is an enveloped, single-stranded-RNA virus that encodes a polyprotein of approximately 3300 amino acids that lead to the formation of 4 structural proteins (core, E1, E2, and p7) and 6 nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B), has been acquired.[3] This polypeptide chain is proteolytically processed by host proteases to release proteins involved in packaging of progeny virions and viral proteases cleave the rest of the polyprotein. This article focuses on the NS5B, the RNA-dependent RNA polymerase that is essential for viral replication.[4] After the structure of the NS5B polymerase was solved in 1999, laboratory developments in biochemical enzymatic assays and cell-based HCV replicon systems[5] built a framework for an explosion of new molecules targeting various sites of the HCV polymerase.

Alamo Medical Research, 621 Camden Street, San Antonio, TX 78215, USA
* Corresponding author.
E-mail address: lawitz@alamomedicalresearch.com

Clin Liver Dis 15 (2011) 611–626
doi:10.1016/j.cld.2011.05.003 **liver.theclinics.com**
1089-3261/11/$ – see front matter

Similar to other viral polymerases, NS5B has a right-hand motif consisting of a thumb domain and a finger domain, both encircling the active site located within the palm domain.[6] The active site includes a highly conserved GDD motif,[6,7] less prone to mutations. The NS5B inhibitors are classified into nucleoside/nucleotide inhibitors (NIs) and non-nucleoside inhibitors (NNIs).[8–10] The NIs mimic natural polymerase substrates and bind to the NS5B active site, causing chain termination and/or an increased number of errors when incorporated into a growing RNA chain. They tend to have similar efficacy across all HCV genotypes, because the NS5B's active site is well conserved among genotypes.[11] NNIs bind to 1 of the 4, less conserved, allosteric sites inhibiting important conformational changes in the polyprotein replication complex necessary for the catalytic efficiency of the enzyme's active site.[4] In contrast to NIs, these molecules have shown a restricted spectrum of activity against the various HCV genotypes. So far, NNIs have targeted 4 main allosteric sites in the NS5B polymerase, thumb domains 1 and 2 and palm domains 1 and 2 (depicted in **Fig. 1**).[11] Because there are 5 targets of antivirals in this class (4 allosteric and 1 active), it is likely that combinations of agents with different targets in this class would be complementary to each other. Both intraclass and interclass combinations are expected in the future.

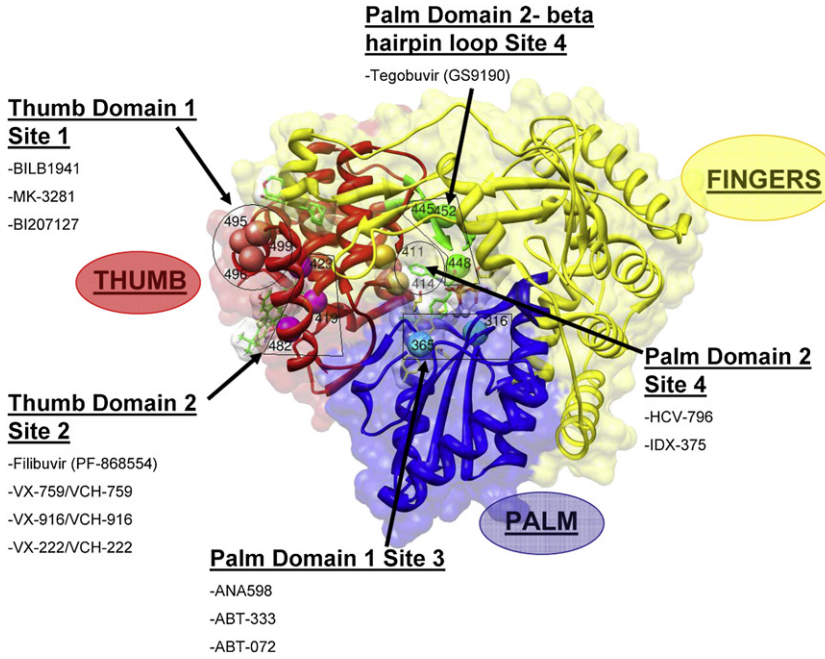

Fig. 1. Binding sites for non-nucleoside HCV NS5B polymerase inhibitors. The palm, fingers, and thumb domains are colored blue, yellow, and red respectively. Mutations in different regions have a different color: salmon for residues P495, P496, V499 in thumb domain 1; magenta for L419, M423, I482 in thumb domain 2; gold for N411, M414 in palm domain 1; cyan for C316, S365 in palm domain 2; and green for C445, Y448, Y452 in the β-hairpin loop. (*Adapted from* Delang L, Coelmont L, Neyts J. Antiviral therapy for hepatitis C virus: beyond the standard of care. Viruses 2010;2:826–66.)