

Introduction to a New Series



Melissa Palmer, Series Editor

When I began my career as a hepatologist at Mount Sinai Medical Center in 1988, the hepatitis C virus (HCV) was not yet identified and the liver disease associated with this unknown virus was called non-A non-B hepatitis (NANB). In 1989, Michael Houghton and a team of researchers at Chiron Corporation discovered this virus, now known as HCV. Treatment was initially approved in 1991, and consisted of 6 months of therapy with interferon—Intron A, manufactured by Schering Plough. Results were disappointing—a mere 6% of patients achieved a sustained virological response (SVR). The next major advance in treatment did not come until 1998—with the addition of ribavirin (RBV) to interferon. SVR rates rose to approximately 42%, as RBV was able to prevent virologic relapse after treatment termination in a substantial number of patients.

Phylogenetic analysis of nucleotide sequences from the gene encoding a non-structural protein (NS-5) revealed that HCV consisted of six major genotypes. The most common genotype worldwide—genotype 1 (G1), has proven to be the most difficult to eradicate. Thus, when the next major advance in HCV treatment occurred through pegylation (i.e., the pro-

longation of interferons, half-life by the addition of polyethylene glycol), while overall SVR rates increased, rates of viral eradication for genotype 1 remained around 42%.

We are now entering a new era of treatment for HCV. With the addition of a protease inhibitor—either telaprevir (*Incivek*, manufactured by Vertex) or boceprevir, (*Victrelis*, manufactured by Merck), to pegylated interferon (PIFN) plus RBV, SVR rates approach 79% in G1 patients. To say that this is a remarkable medical advance is truly an understatement. Triple combination therapy will be the new standard of care for patients with G1 chronic HCV. Furthermore, between 44–60% of treatment naïve patients will be capable of being cured in just 24–28 weeks.

Even though this milestone has been reached, the road ahead is not entirely smooth. Treatment paradigms will be complex, adverse events associated with triple therapy will be increased, and adherence to therapy will be more crucial than ever, as a lack thereof may give rise to the selection of protease inhibitor-resistant strains of HCV. Clinicians must familiarize themselves with an assortment of new terms, an understanding of which is crucial to optimal treatment duration, and improved treatment success. Table 1 (New Terminology for HCV) is included in this series intro-

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duction, as this list of terms is needed to understand the new standard of care.

It is my honor to present this important series dedicated to the new era of HCV treatment. The first article of this series reviews the hepatitis C virus structure and lifecycle, an important first step towards understanding how the new protease inhibitors work against HCV. This article will also address the key phase II and III trials of both telaprevir and boceprevir, which led to FDA approval. Future issues in this

series will address therapy for difficult-to-treat patients, such as those with cirrhosis, HIV/HCV coinfecting patients, null responders and African Americans. Other topics in this series will include IL28B testing, economic-issues associated with treatment, controversies in HCV treatment, and future treatments for HCV on the horizon—such as polymerase inhibitors, second-generation protease inhibitors, lambda interferon, and interferon/ribavirin-free regimens. ■

Table 1.
New Terminology for HCV

STAT-C: Specifically Targeted Antiviral Therapy for hepatitis C: drugs that interfere directly with HCV replication by targeting specific enzymes

DAA: Direct Acting Antiviral therapy against HCV: a term that has replaced STAT-C when referring to agents that interfere directly with the hepatitis C virus

RGT: Response-guided therapy: Adjustment of treatment duration according to rapid viral response (RVR) or extended rapid viral response (eRVR)

RVR: Rapid Virological Response: undetectable HCV RNA at week 4 of treatment

eRVR: Extended Rapid Viral Response: undetectable HCV RNA at *both* week 4 and week 12 of therapy

Virological Breakthrough: After initially achieving an undetectable HCVRNA level, HCV RNA becomes detectable before treatment is completed

PR: Partial responder: $>2 \log_{10}$ drop HCVRNA from baseline at week 12 but never achieving an undetectable HCVRNA throughout the course of therapy

NR: Null Responder: $<2 \log_{10}$ IU/mL reduction in serum HCV RNA from baseline at week 12 of treatment

SVR—Sustained Virological Response: Undetectable HCV RNA level 24 weeks after treatment discontinuation. Now accepted to be consistent with a “*cure*”

Treatment Naïve: received no prior therapy for HCV (including interferon or pegylated interferon monotherapy)

Relapser: undetectable HCV RNA at end of treatment, but HCV RNA detectable within 24 weeks of treatment follow-up

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