Writing Sample

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[*Excerpt from a needs assessment on the use of STAT-C inhibitors in management of HCV infection; May, 2011*]

ABSTRACT

The hepatitis C virus (HCV) is a bloodborne RNA virus that infects roughly 180 million people worldwide, including about 3.9 million Americans, with approximately 12, 000 deaths each year attributable to HCV infection. Most persons infected with HCV have chronic infection, defined as detectable HCV RNA in the blood for greater than 6 months, resulting in complications such cirrhosis, hepatocellular carcinoma (HCC), and the need for liver transplantation. Predicted increases in numbers of HCV diagnoses and associated medical costs underscore the fact that HCV infection is a national and global healthcare problem [NIH 2002; Milliman Inc. 2009]

Currently, the most reliable predictor of treatment response is HCV genotype. Six HCV genotypes are known, however genotype 1 predominates in the United States (70-75% of all HCV infections). This genotype is less responsive to current therapies, with a success rate of only 40-50%, and therefore has been a driver of efforts to identify new therapies with improved efficacy [Rodis 2007].

The current standard of care (SOC) for HCV infection is combination therapy including peginterferon (Peg-IFN; either Peg-IFN alfa-2a or Peg-IFN alfa-2b) and the anti-viral nucleoside analog ribavirin (RBV), given for up to 48 weeks depending upon viral genotype. These agents are not specific for HCV, and they are contraindicated in many patients. In addition, PegIFN/RBV combination therapy (PR) requires a long duration of treatment and carries high potential for adverse events and toxicity leading to non-adherence or even discontinuation of therapy. As well as being less effective for genotype 1 infection in general, the current SOC has been documented to be less effective in patients with advanced stage infection with cirrhosis, with HCC or undergoing liver transplantation, in African Americans, and in patients coinfected with HIV. There is great need and anticipation for novel therapies with reduced toxicity, shorter duration, and applicability to a larger number of HCV patients [Bruno 2011].

Novel treatment options are emerging as advances in understanding of HCV structure and virology converge with the push for improved therapies. Significant effort in the development of specifically targeted antiviral therapies for HCV (STAT-C) has led to clinical trials for several inhibitors of nonstructural HCV replication proteins. Two peptidomimetic NS3/NS4a serine protease inhibitors, boceprevir (BOC) and telaprevir (TVR), have completed phase III clinical

trials and are expected to gain approval from the United States Food and Drug Administration (US FDA) in 2011 [Lange 2010].

Results of phase III clinical trials with BOC in treatment-naïve (SPRINT-2) and previous treatment-failure (RESPOND-2) genotype 1 patients and of TVR in treatment-naïve (ADVANCE and ILLUMINATE, the latter of these evaluating reduced therapeutic duration of 24 weeks) and previous treatment-failure (REALIZE) genotype 1 HCV patients were recently reported. Both agents produced an increase in SVR in combination with PR, achieving up to 75%. There is also evidence that STAT-C agents may be effective for populations in which poor response rate with PR is typical. In the PROVE-1 trial testing TVR with PR, four times as many African American participants achieved SVR as with PR and placebo, and in the PROVE-3 trial, SVR was not negatively impacted by cirrhosis [Pawlotsky 2011; McHutchinson 2009; McHutchinson 2010].

BOC and TVR are metabolized by the cytochrome P450 system and have been shown to interact with CYP3A4/5, enzymes involved in metabolism of many of the drugs being used to treat comorbidities in HCV patients. The potential for drug-drug interactions, which can lower the effectiveness of antiviral agents, is therefore of concern. Although some studies have evaluated DDIs with novel STAT-C inhibitors, these drugs will likely reach clinical practice before more extensive testing of DDIs is complete.

Another concern regarding incorporation of these agents into clinical use is the high potential for anemia. Clinically relevant decreases in hemoglobin were observed in Phase III trials with BOC and TVR [Jensen 2011]. In some cases, anemia will be treatable by co-administration of erythropoietin; however, in cases where erythropoietin is contraindicated, clinicians must be aware of substantial problems associated with reduction of RBV or STAT-C inhibitor dose, namely reduction in SVR rate and possible selection of resistant HCV mutants [Jenson 2011; Pawlotsky 2011].

It is critical that clinicians managing HCV infected patients, including those who may not be specialized in infectious disease, be educated as to the current clinical trial data on optimization of SOC, emerging STAT-C agents and the potential for DDIs, and the management of anemia.

Practice Gap #1: Physicians are not always current with the latest data on how to optimize current HCV treatment protocols.

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