Digestive Disease Week (DDW) 2014

Interferon-Free Therapies Head for Approval in Hepatitis C on the Basis of Phase 3 Data

Chicago - There is increasing certainty that regulatory approval will come quickly to interferon-free (IFN-free) treatment regimens for hepatitis C virus (HCV). A series of studies presented at major meetings over the last few months, including the 2014 DDW, have associated the most effective therapies with sustained virologic response (SVR) rates exceeding 90%, even in patients with challenging HCV genotypes who have failed previous therapies.

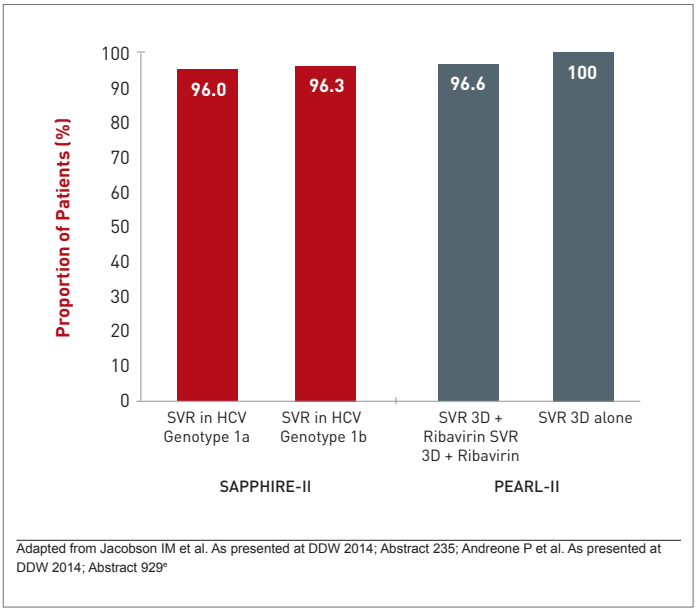
Relative to IFN, the efficacy of the newer agents is credited to their ability to block key enzymatic processes in HCV replication and survival. Results have been impressive. In two multinational studies in treatment-experienced patients presented at this year's DDW, a ritonavir-boosted ABT-450 combined with a second protease inhibitor, ABT-267, and the polymerase inhibitor ABT-333 achieved an SVR rate of 96% in genotype 1b patients whether or not it was combined with ribavirin. Rates with this regimen, known as 3D, have been even higher when patients are treatment-naïve.

"This combination is very effective but it is also well tolerated, so discontinuation rates are low, which is certainly contributing to these very high SVR rates," reported Dr. Ira M. Jacobson, who was the principal investigator of the SAPPHIRE-II trial. One of two studies presented in treatment-experienced patients with 3D, the double blind, randomized SAPPHIRE-II included 297 patients on active therapy and 97 patients on matching placebos. After 12 weeks, SVR rates were comparable for genotype 1a and 1b (96% and 96.7%, respectively).

A second open-label trial called PEARL-II was restricted to treatment-experienced non-cirrhotic genotype 1b patients. The 187 participants were randomized to 3D with or without ribavirin. At 12 weeks, the SVR rates were 96.6% for those receiving 3D with ribavirin and 100% for those treated with 3D alone. Both regimens were well tolerated and associated with low discontinuation rates, although the regimen without ribavirin was accompanied with lower laboratory abnormalities such as suppressed hemoglobin (Figure 1).

Other data with IFN-free regimens also show promise. In the ION-2 trial, which tested a combination of the polymerase inhibitor sofosbuvir with the protease inhibitor ledipasvir, 440 treatment-experienced patients were randomized to receive these two drugs alone or with ribavirin. This population was more mixed in regard to HCV genotypes than that of the SAPPHIRE-II and PEARL-II trials, but SVR rates again reached the 95% range with or without ribavirin, and the rate of serious adverse events was low.

FIGURE 1 I SAPPHIRE-II and PEARL-II: 3D SVR Rates in Treatment-Experienced Patients



Adapted from Jacobson IM et al. As presented at DDW 2014; Abstract 235; Andreone P et al. As presented at DDW 2014; Abstract 929[e]

There are several important implications from these studies. The first is that the new regimens appear to be capable of providing SVR rates that are comparable across genotypes. In the data presented at DDW, efficacy extended even to those with poor or null responses to the most aggressive IFN regimens previously available. Another is that treatment success from these highly-targeted therapies is unlikely to be compromised by serious adverse events. This "levels the playing field" for HCV patients, according to Dr. Jacobson.

"The data are very positive and suggest an important opportunity to reduce the risk of the long-term complications of HCV in most and perhaps all of those infected," he reported.●

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