ADVANCES IN HCV

Current Developments in the Management of Hepatitis C Virus Infection

Advances in Combination Regimens in the Management of HCV Infection



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G&H Can you summarize the advantages and pitfalls of peginterferon/ribavirin-based therapies in hepatitis C virus infection?

DJ Interferon was introduced as therapy in the early 1990s, and ribavirin was added in the late 1990s. Then, pegylated interferon plus ribavirin was introduced in the early 2000s. However, the regimen generated success rates of only 50% to 55% in patients infected with genotype 1 hepatitis C virus (HCV.) In addition, pegylated interferon plus ribavirin was associated with significant adverse effects that were mainly attributed to interferon, although ribavirin also contributed to adverse effects.

Research in molecular biology was undertaken to increase the cure rate. Different proteins of the HCV replication machinery were identified, and one of those proteins, the HCV protease enzyme, was investigated as a potential target to directly inhibit viral replication. Protease inhibitor therapy, without interferon and ribavirin, led to rapid development of resistance, so, clearly, the HCV protease inhibitor needed to be combined with some other therapy to prevent the emergence of resistant HCV variants. Combination pegylated interferon and ribavirin were, thus, used to prevent emergence of resistance while the protease inhibitor suppressed viral replication.

The treatment strategy for HCV genotype 1 infection since 2011 has been the use of a protease inhibitor plus pegylated interferon and ribavirin, in which the role of the pegylated interferon and ribavirin is, basically, to prevent the development of emergence of resistance, although it may somewhat enhance the efficacy of the protease inhibitor.

G&H Are there roles for pegylated interferon and ribavirin going forward with the number of new agents expected to come to market in the next 2 to 3 years?

DJ I think pegylated interferon probably has a relatively short shelf life—perhaps 1 more year—in terms of therapy for HCV infection. Ribavirin may have a different and unique role outside of its ability to be used with interferon, and some studies are using ribavirin in combination with direct-acting antiviral (DAA) agents in interferon-free regimens. In the future, the old standard of care will be supplanted by combinations of DAAs that target different areas of the virus replication machinery to prevent emergence of resistance.

G&H How are the newer and emerging DAAs improving on first-generation protease inhibitors?

DJ Telaprevir (Incivek, Vertex) and boceprevir (Victrelis, Merck) were unique and a huge advance when they were first introduced in 2011, but they brought additional adverse effects to the table and also were associated with a significant pill burden—up to 12 or more pills a day. The agents also needed to be taken with a high-fat meal. These first-generation protease inhibitor–based regimens gave way to more effective and convenient therapies that were very recently approved by the US Food and Drug Administration (FDA), the second-generation protease inhibitor simeprevir (Olysio, Janssen) and the nucleotide polymerase inhibitor sofosbuvir (Sovaldi, Gilead). These 2 agents are expected to take the place of telaprevir and boceprevir. Simeprevir has fewer adverse effects than first-generation protease inhibitors and has convenient, once-a-day dosing, but it does have some issues with the emergence of resistance, so it needs to be given in combination with other agents, which, right now, are pegylated interferon and ribavirin. In addition, some patients infected with genotype 1a HCV may have a preexisting mutation called Q80K, which can make simeprevir less effective. The Q80K mutation is not common in patients infected with genotype 1b HCV, so these patients generally achieve good viral suppression with simeprevir.

Sofosbuvir has broad efficacy against genotypes 1 through 6 HCV. It is FDA-approved for use in combination with pegylated interferon for genotype 1 HCV infection and in combination with ribavirin (interferon-free) for genotypes 2 and 3 HCV infection. Because sofosbuvir is a chain terminator and nucleotide polymerase inhibitor, resistance is not an issue; resistant HCV variants do not develop. A S282T mutation did develop in a very few patients treated in clinical trial settings, but the mutation is unfit, and its emergence did not seem to have a significant impact on therapeutic outcome. Thus, it is probably safe to assume that sofosbuvir is a compound that is relatively free of development of resistance, so it may be useful to combine it with some other agent to thwart emergence of resistance, such as was done in the COSMOS study, which combined sofosbuvir with simeprevir in an interferon-free regimen.

G&H What did the COSMOS study teach us about ribavirin-free regimens?

DJ As the DAAs become more and more potent—with the combinations of these different agents having cure rates in the high 90% range—the role of ribavirin becomes less clear. For one, we do not know the mechanism of action of ribavirin. It seems to have a number of different effects. In combination with pegylated interferon, it seemed to enhance response and prevent relapses after therapy was discontinued. As better regimens are developed, the role of ribavirin becomes more marginalized, and clinicians would probably like to be rid of ribavirin for 2 main reasons: 1) it can cause a mild anemia and 2) it has teratogenic properties, so precautions are needed in regard to use of ribavirin in patients who are of childbearing age, and these precautions must be followed not just during the course of therapy but for up to 6 months after the therapy is discontinued.

The COSMOS study demonstrated that the results with and without ribavirin were similar with the 2 new DAAs in combination. High cure rates—more than 90%—were seen in a broad range of patients infected with genotype 1 HCV regardless of whether ribavirin was included in the regimen.

G&H What are the prospects of this regimen being FDA-approved?

DJ Considering that the agents are manufactured by 2 different companies, it is unlikely that the regimen will be submitted for FDA approval. It will be up to payers to decide whether they will pay for use of this combination. Physicians can combine these agents, and some have already treated patients infected with genotype 1 HCV for whom combination simeprevir and sofosbuvir has been approved by their insurance companies. Regardless of labeling, feasible use of these agents in combination is in the lap of payers and authors of practice guidelines.

G&H What other combinations do you foresee being soon introduced to the clinical setting?

DJ Several agents look promising and effective. One is AbbVie's interferon-free triple combination of the protease inhibitor plus ritonavir ABT450/r, nonstructural (NS) 5A inhibitor ABT267, and nonnucleoside polymerase inhibitor ABT333 with or without ribavirin, which has shown very high cure rates in patients infected with genotype 1 HCV and even treatment-experienced, cirrhotic patients infected with genotype 1 HCV. The regimen is expected to be FDA-approved in late 2014 or early in the first quarter of 2015.

Gilead is also developing a coformulation of sofosbuvir plus their NS5A compound ledipasvir. Results of several recent trials have shown that this combination is also effective in difficult-to-treat patients. The regimen also will hopefully be FDA-approved in late 2014 or early 2015.

Other companies have agents and combinations of agents in the pipeline. Bristol-Myers Squibb is developing daclatasvir, which is a pangenotypic NS5A inhibitor. Boehringer Ingelheim has a protease inhibitor called faldaprevir, which will be used with pegylated interferon and ribavirin.

In addition to these agents, which will probably debut within the next 2 years, about 20 more compounds are in different stages of development. The future of management of HCV infection looks very bright, but once cure rates get into the high 90% range, what newer agents have to offer may be limited. The focus of newer therapies may be ease of use, shortened treatment duration, or cost. It will be interesting to see how the field evolves.

G&H How might the practice of HCV infection management change with the introduction of new, highly effective therapies?

DJ If the need for both pegylated interferon and ribavirin were dropped, the range of providers willing to treat HCV infection might expand. That is, if treat-

ment did not require use of an injectable drug, such as interferon, and did not require use of ribavirin with its adverse effects, even primary care physicians might be more likely to treat HCV-infected patients instead of referring them to specialists. Considering that so many persons with the virus have not been treated, as greater numbers of persons are screened and diagnosed, the specialist community may be overwhelmed and need the assistance of fellow physicians in other specialties to provide care to the HCV-infected community. Also, as treatment becomes easier to administer, perhaps even some practitioners will get involved in screening as well as treatment. As more people are screened, access to care will become an increasing point of focus.

Dr Jensen has no relevant conflicts of interest to disclose.

Suggested Reading

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