

## **Updated AASLD HCV Guideline Aims To Simplify Use of DAAs More Data Needed To Fill Gaps in Understanding**

by Christina Frangou

The American Association for the Study of Liver Diseases (AASLD) recently published an updated practice guideline on the treatment of chronic infection with hepatitis C virus (HCV) genotype 1 (Ghany MG et al. *Hepatology* 2011;54:1433-1444).

The guideline, authored by members of the AASLD practice guideline committee, was issued in response to the development of new direct-acting antivirals (DAAs) and the identification of several single nucleotide polymorphisms associated with spontaneous and treatment-induced clearance of HCV infection. The report makes 18 recommendations for clinicians who are considering using the new DAAs to treat patients with HCV. The two currently approved DAAs have complex prescribing rules, including outlines for response-guided therapy and unusual stopping rules, and many clinicians question how and when the agents are best used.

“We have entered into a very different treatment paradigm. I’d suggest that everyone read the guideline from the AASLD. It’s a very good overview of where we are today,” said David R. Nelson, MD, a study author and professor of medicine, Division of Gastroenterology, Hepatology and Nutrition at the University of Florida College of Medicine, in Jacksonville, during a presentation at The Liver Meeting last year.

The authors outline the current state of evidence regarding treatment with boceprevir and telaprevir, and provide some guidance on much-debated issues such as treatment of patients with cirrhosis and the role of interleukin-28B (IL28B) testing.

The guidelines are “very important and very helpful,” said Michal R. Charlton, MD, professor of medicine and head of the hepatobiliary section at Mayo Clinic, in Rochester, Minn. “The guidelines provide a lens through which clinicians can look to see the optimal approach to managing patients with HCV infection.”

### Inside the Recommendations

According to the authors of the report, the DAAs, in combination with peginterferon alfa and ribavirin, are now the “optimal therapy” for treating HCV genotype 1 chronic infection. Both therapies must be given with peginterferon and ribavirin, which limits selection of resistant variants and improves antiviral response. Furthermore, boceprevir and telaprevir should not be used to treat patients infected with HCV genotype 2 or 3.

The authors reiterated the FDA recommendation that treatment-naive patients with cirrhosis treated with either boceprevir or telaprevir in combination with interferon and ribavirin should receive therapy for 48 weeks instead of on a response-guided basis. However, the authors added that this recommendation is “based on limited data and requires further study.”

The report also specifies that the stopping rules differ for telaprevir and boceprevir in treatment-naive patients. Treatment with telaprevir, peginterferon alfa and ribavirin should be stopped if the HCV RNA level is greater than 1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24. Treatment with boceprevir, peginterferon and ribavirin should be stopped if the HCV RNA level is

greater than 100 IU/mL at treatment week 12 or detectable at treatment week 24. For both therapies, the evidence for the discontinuation rules is considered Class 2a, meaning the weight of evidence is in favor of the usefulness of this rule, but there is limited evidence.

Patients who previously received and failed therapy with interferon and ribavirin remain a conundrum with regard to starting DAA therapy. Studies have shown that patients' response to triple therapy regimens in both boceprevir and telaprevir trials was strongly influenced by the outcome of their earlier treatment with peginterferon and ribavirin. The decision to re-treat patients should depend on their previous response to peginterferon and ribavirin and on reasons why they may have failed, such as inadequate drug dosing or side-effect management, the report said. The authors call on physicians to review old treatment records to document previous treatment response.

This updated document is the first to clarify treatment for patients who fail DAA therapy. The authors say that patients who do not have a virologic response, who experience virologic breakthrough or who relapse on one protease inhibitor (PI) should not be retreated with the other PI.

Although the evidence is limited, the AASLD did make some recommendations for managing treatment-experienced patients. The AASLD suggests retreatment with boceprevir or telaprevir, together with peginterferon alfa and weight-based ribavirin, "be considered" for patients who had a virologic relapse or who were partial responders after a previous course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin.

"Relapsers and partial responder patients can expect relatively high sustained virologic response rates to retreatment with a PI-containing triple regimen and should be considered candidates for retreatment," the authors wrote.

For previously null responders, telaprevir may be considered but boceprevir cannot be recommended, the committee found. This finding differs from the FDA label, which indicates that boceprevir can be used in null responders. Null responders were excluded from Phase III trials of boceprevir (Poordad F et al. *N Engl J Med* 2011;364:1195-1206).

"Given the lack of definitive information for Phase III data, caution is advised in the use of [boceprevir] in null responders until further supportive evidence becomes available," according to the AASLD.

Additionally, the decision to re-treat a null responder with telaprevir should be individualized, particularly in patients with cirrhosis, because less than one-third of null responder patients in the telaprevir trial achieved a sustained virologic response (SVR). Moreover, the authors caution that a majority of null responders developed resistance to DAAs.

"Any potential benefit from treating nonresponders must be weighed against the risk for development of antiviral resistance and for serious side effects, and the high cost of therapy," the report said.

The AASLD acknowledged uncertainty about the benefit of the lead-in strategy required for treatment with boceprevir. Theoretically, the lead-in may improve efficacy by lowering HCV RNA levels, thus reducing the rate of viral breakthrough when the PI is introduced. The authors noted, however, that poor responders during the lead-in period can still achieve SVR.

“Thus, a poor response during the lead-in phase should not be used to deny patients access to PI therapy,” the authors said. Patients who develop anemia on PI therapy should be managed by reducing the ribavirin dose, they added.

The report also specified that IL28B genotype is a significant treatment predictor of response to therapy, but data are insufficient to determine whether IL28B testing can be used to recommend either interferon and ribavirin alone or a triple therapy with a PI.

“Consideration should be given to ordering the test when it is likely to influence either the physician’s or patient’s decision to initiate therapy,” the authors said.

Telaprevir and boceprevir are not recommended for use in children and adolescents younger than 18 years because safety and efficacy has not been established in this group.

Additionally, the guidelines do not address several important questions about DAAs, Dr. Charlton said. The report, for example, does not provide detailed and practical information about drug–drug interactions, managing HIV/HCV co-infection and managing side effects, he said.

“Perhaps the highest-impact omission, which was unavoidable, is whether in light of the spectacular report of efficacy and tolerability of PSI-7977 in combination with ribavirin without interferon, patients with early stages of liver disease should be treated at all with boceprevir or telaprevir,” he said. “In our practice, we are already beginning to advise many patients to wait. ... A strong case could be made for waiting for the results of the Phase III interferon-free studies.”

The committee cautions that the guidelines are “based on data that are presently limited” and the recommendations may need revision as additional data become available.

“There is a paucity of information for many of the subgroups with the greatest unmet need for treatment (e.g., patients co-infected with HIV and HCV, with decompensated cirrhosis and after liver transplantation),” the committee said.

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Dr. Nelson receives research support from Bayer/Onyx, Bristol-Myers Squibb, Genentech/Roche, Gilead, Merck, Pharmasset, Tibotec and Vertex Pharmaceuticals; he serves on the advisory boards of Bayer/Onyx, Genentech/Roche, Gilead, Merck, Pharmasset and Tibotec; and he is a consultant for Vertex Pharmaceuticals. Dr. Charlton receives research support from Bristol-Myers Squibb, Genentech/Roche, Merck and Vertex Pharmaceuticals; he is a consultant for Bristol-Myers Squibb, Genentech/Roche Gilead, Merck and Vertex Pharmaceuticals.