Telaprevir Combos Efficacious in Hepatitis C

BY MARY ANN MOON

FROM GASTROENTEROLOGY

In patients who have chronic hepatitis C, combining telaprevir with ribavirin and peginterferon alfa-2a or 2b yielded sustained virologic response rates of more than 80%, regardless of which type of interferon or which dosing regimen of telaprevir was used, Dr. Patrick Marcellin and his colleagues reported.

The researchers assessed the efficacy and safety of four different dosing approaches in a phase II, open-label clinical trial, which they described as "the first trial comparing the two licensed peginterferon alfa/ribavirin treatments in combination with the same protease inhibitor."

The study was conducted at 30 medical centers in Austria, Belgium, France, Germany, Italy, the Netherlands, and Spain, and included treatment-naive patients aged 18-65 years who had no cirrhosis, history of drug use, HIV coinfection, or any suspicion of alcohol use (Gastroenterology 2011;140:459-68.e1).

The 161 study subjects were randomly assigned to four treatment groups: 750 mg of telaprevir taken every 8 hours plus peginterferon alfa-2a and ribavirin; 750 mg of telaprevir taken every 8 hours plus peginterferon alfa-2b and ribavirin; 1,125 mg of telaprevir taken every 12 hours plus peginterferon alfa-2a and ribavirin; or 1,125 mg of telaprevir taken every 12 hours plus peginterferon alfa-2b and ribavirin, said Dr. Marcellin, who is with Beaujon Hospital, University of Paris, Clichy, France, and his associates.

Subjects who had undetectable plasma levels of hepatitis C virus (HCV) RNA at weeks 4-20 (109 patients) were scheduled to discontinue treatment at 24 weeks, while those who still had detectable HCV RNA (29 patients) were scheduled to continue for the standard 48 weeks of treatment. A total of 33 patients dropped out of the study before completing their assigned treatment.

The main efficacy end point was the percentage of patients who achieved a sustained virologic response, with levels of HCV RNA that were either undetectable or less than 25 IU/mL.

Overall, this percentage was not significantly different among the four treatment groups: 85% in group 1, 81% in group 2, 83% in group 3, and 82% in group 4.

Given the small number of patients in each treatment arm of this trial, different dosing regimens warrant further study in a larger clinical trial, Dr. Marcellin and his associates added.

This primary outcome also was not significantly different when the results were pooled for all patients taking telaprevir every 8 hours (83%) compared with all patients taking telaprevir every 12 hours (82%), as well as when the results were pooled for all patients taking peginterferon alfa-2a (84%) compared with all patients taking peginterferon alfa-2b (82%).

When the results were assessed according to duration of treatment, 96% of the patients who were treated for only 24 weeks achieved a sustained virologic response, as did 79% of those who received the standard 48-week course, the investigators said.

This strategy of guiding treatment duration according to each patient's virologic response at 4-20 weeks was clearly successful, allowing the majority of patients to cut their course of treatment by half without adversely affecting efficacy.

"This response-guided treatment duration strategy is currently being further explored in ongoing telaprevir phase III clinical trials in treatment-naive patients," Dr. Marcellin and his colleagues noted.

When the results were assessed according to completion of assigned treatment, 95% of the 128 patients who completed treatment achieved a sustained virologic response.

Both the every-8-hours and every-12-hours doses of telaprevir were equally effective at producing a sustained virologic response, and were equally tolerated by patients. There also were no significant differences between the two doses in relapse rates or in safety profiles. "Thus, it could be hypothesized that coadministration of telaprevir with standard therapy might allow for less frequent telaprevir dosing," the investigators said.

Similarly, both formulations of peginterferon were equally effective in this study, although the two agents have different pharmacokinetic properties and a recent meta-analysis suggested that peginterferon alfa-2a is slightly more effective. ■

VITALS

Major Finding: Of 161 treatment-naive patients, 109 had undetectable plasma levels of HCV RNA at weeks 4-20 and stopped treatment at 24 weeks (96% sustained virologic response), 29 patients with detectable HCV RNA continued the standard 48 weeks of treatment (79% sustained virologic response), and 33 patients dropped out.

Data Source: A multicenter, phase II, open-label study of telaprevir with ribavirin and peginterferon alfa-2a or 2b in treatment-naive patients aged 18-65 years with no cirrhosis, history of drug use, HIV coinfection, or any suspicion of alcohol use.

Disclosures: The trial was funded by Tibotec, a division of Janssen-Cilag, and by Vertex Pharmaceuticals. The authors reported ties to 18 pharmaceutical and biomedical technology companies.

Evidence for Infectious Disease Guidelines Often Is Weak

BY MARY ANN MOON

FROM ARCHIVES OF INTERNAL MEDICINE

More than half of the current recommendations in practice guidelines concerning infectious disease are based on evidence derived only from expert opinion or descriptive studies, according to Dr. Dong Heun Lee and Dr. Ole Vielemeyer of Drexel University, Philadelphia.

Only 14% of the 4,218 individual recommendations included in 41 Infectious Diseases Society of America (IDSA) guidelines published in 1994-2010 are based on the highest-quality, or level I, evidence, such as that from randomized controlled trials, Dr. Lee and Dr. Vielemeyer reported.

"Guidelines can only summarize the best available evidence, which often may be weak. Thus, even more than 50 years since the inception of evidence-based medicine, following guidelines cannot always be equated with practicing medicine that is founded on robust data," they noted.

"Physicians and policy makers should remain cautious when using current guidelines as the sole source guiding decisions in patient care."

The study authors assessed the quality of evidence underlying 41 of the 52 IDSA guidelines currently available, which cover a wide range of topics and use an IDSA evidence-grading system. About half of these 41 guidelines are new and half are updates of earlier guidelines.

In addition to the highest-quality (level I) evidence, the IDSA grading system designates evidence from well-designed, but nonrandomized clinical trials, from cohort studies, from case-controlled analytical studies, or "dramatic results from uncontrolled experiments" as intermediate-quality (level II) evidence. The lowest-quality (level III) evidence is that "from the opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees," the investigators said.

Dr. Lee and Dr. Vielemeyer identified 4,218 individual recommendations among the 41 guidelines that could be charted according to the strength of the recommendations and the quality of the evidence supporting them. Only 14% were supported by level I evidence, 31% by level II evidence, and 55% by level III evidence (Arch. Intern. Med. 2011;171:18-22).

For example, greater than 80% of the recommendations concerning blastomycosis, which were published in 2008, were based on level III evidence and did not have any level I support. The findings were the same for recommendations concerning sporotrichosis, which were published in 2007.

The investigators also assessed the extent to which the quality of evidence has improved over time by selecting five guidelines that had recently been updated and comparing them with their respective earlier versions. The updates did include evidence from more studies, as well as evidence from more recent studies, than did the earlier guidelines. "However, only two updated guidelines had a significant increase in the number of level I quality-of-evidence recommendations; most additional recommendations were supported by level II or III quality of evidence only," Dr. Lee and Dr. Vielemeyer said.

In addition, "we came across imprecisions on more than one occasion and for more than one guideline, including illogical, erroneous, or missing references for recommendations and their associated grades," they added.

These findings are particularly concerning because guidelines are used not only for decision making in clinical practice but also "as benchmarks in the appraisal of quality of care provision," they said.

"We believe that the current clinical practice guidelines released by the IDSA constitute a great and reliable source of information that should be used. However, in circumstances when patient outcome is less than desirable, or when colleagues use diagnostic or therapeutic choices not included in the recommendations, it is prudent to remember that many of the individual recommendations are not supported by solid evidence.

"In such cases, we encourage reviewing the primary literature and using one's clinical judgment rather than relying solely on recommendations," Dr. Lee and Dr. Vielemeyer concluded. ■

VITALS

Major Finding: Only 14% of 4,218 individual recommendations in 41 Infectious Diseases Society of America clinical practice guidelines are based on level I evidence such as that from randomized clinical trials, while more than half are based on level III evidence, such as that from expert opinion or descriptive studies.

Data Source: A review of 41 current IDSA clinical practice guidelines aimed at assessing the quality of evidence on which each recommendation is based.

Disclosures: Dr. Lee and Dr. Vielemeyer reported that they had no relevant financial disclosures.