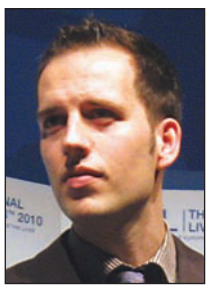
Strategies Aim to Optimize Hepatitis B Therapy

BY BRUCE JANCIN

FROM THE ANNUAL INTERNATIONAL LIVER CONGRESS

VIENNA — With no new blockbuster drug on the horizon for chronic hepatitis B, researchers are focusing on ways to boost the effectiveness of pegylated interferon, the current standard treatment for hepatitis B.

Two such novel strategies were introduced at the meeting, which was sponsored by the European Association for the Study of the Liver. One involves stopping pegylated interferon 12 weeks into the side-effect–heavy therapy in patients who are extremely unlikely to benefit from continuing for the standard 48 weeks.



The other method entails doubling treatment duration to 96 weeks.

Both of these strategies were developed specifically to boost the therapeutic yield in patients with hepatitis B e antigen–negative chronic hepatitis B, an infection that is more difficult to clear than hepatitis B e antigen–positive disease.

Dr. Vincent Rijckborst of Erasmus University, Rotterdam, the Netherlands, presented an international multicenter randomized double-blind study involving 107 antigen-negative patients who completed 48 weeks of once-weekly therapy with 180 mcg of pegylated interferon alpha-2a (Pegasys) plus either placebo or 1,000-1,200 mg/day of ribavirin.

Twenty-two percent of both groups had a sustained response at 24 weeks' follow-up after completing treatment. The goal of this retrospective analysis of serial hepatitis B surface antigen (HBsAg) and HBV DNA levels was to find the earliest possible point in treatment to identify who is most and least likely to sustain a response to pegylated interferon. Sustained responders exhibited a greater degree of HBsAg decline.

A sustained response was best predicted by HBsAg decline at week 12, along with a 2-log drop in HBV DNA.

DR. RIJCKBORST

The best prediction of sustained response came from a combination of an HBsAg decline at week 12, along with a 2-log or greater drop in HBV DNA level at that time. Twenty-seven percent of the study population met those requirements, and they had a 39% sustained response rate.

At the other extreme, 20% of patients had neither a 2-log decrease in HBV DNA nor a decline in HBsAg level at 12 weeks, and that group had a sustained response rate of 0%, establishing what Dr. Rijckborst called "a solid stopping rule."

"These patients should be advised to discontinue therapy," he said.

"On the other hand, patients with both declines had a 39% chance of sustained response, so those patients really should be encouraged to complete the treatment phase," he said.

Patients with a week-12 decline in one of the two measures had an intermediate sustained response rate of 24%-25%.

"We think the HBsAg decline reflects the decline in cDNA levels and the immunologic effects of [pegylated interferon], while the decline in HBV DNA levels appears to reflect the drug's direct antiviral effect," Dr. Rijckborst said.

In a second study, Dr. Pietro Lampertico of the University of Milan reported on 103 patients with hepatitis B e antigen–negative disease who were randomized in an open-label, multicenter study to 48 weeks or 96 weeks of pegylated interferon alpha-2a therapy.

The 96-week course resulted in a significantly higher sustained response rate 1 year after completing treatment, with 29% of patients demonstrating a sustained drop in HBV DNA to below 2,000 IU/mL, as compared with 12% of those treated for 48 weeks.

Moreover, 6% of patients in the prolonged treatment arm experienced HBsAg clearance. None did on the standard regimen, noted Dr. Lampertico.

The prolonged pegylated interferon therapy didn't bring any increase in safety issues. That's because most treatment-related adverse events happened in the first 6 months of the study. Roughly 80% of patients had one or more adverse events, one-quarter of subjects required a dose reduction, and 15% withdrew from participation because of side effects.

Ninety-six weeks of pegylated interferon yielded a higher sustained response rate than did 48 weeks.

DR. LAMPERTICO

In reply to an audience member's question whether he thinks it's reasonable to routinely use 96 weeks of pegylated interferon in hepatitis B e antigen–negative patients, given that only 6% cleared HBsAg, Dr. Lampertico said he does not.

"My point is that we really have to change our approach to pegylated interferon in these patients," he said. "We have to try to identify those patients who do not benefit from this monotherapy."

He added that he likes the 12-week stopping rule Dr. Rijckborst and his coworkers developed.

"The next step will be to try to develop a second stopping rule at 24 weeks so only a select subgroup of patients goes on for 2 years," said Dr. Lampertico, a gastroenterologist.

"And we really need to study combination therapies."

The trial was supported by Novartis. Dr. Rijckborst's study was sponsored by the Rotterdam Foundation for Liver and Gastrointestinal Research. He reported having no relevant financial interests. Dr. Lampertico's study was sponsored by Roche, where he is a consultant. ■

Hybrid Therapy for *H. pylori* Achieved Superior Eradication

BY CAROLINE HELWICK

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — For eradication of *Helicobacter pylori* infection, a 14-day hybrid therapy that combines sequential and concomitant drug treatments improved the eradication rate, compared with 14-day standard sequential therapy, investigators reported.

"Worldwide, the eradication rate with standard triple therapy is less than 80% in intention-to-treat analyses," said Dr. Ping-I. Hsu of Kaohsiung (Taiwan) Veterans General Hospital, who presented the findings. Standard triple therapy includes a proton pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole.

"The ideal antimicrobial therapy would have an eradication rate of at least 95% by per-protocol analysis," which would earn it a grade A score, he said.

In a recent assessment of 15 trials, mean eradication rates were 93% with sequential therapy and less than 95% with concomitant therapy (Gut 2010 June 4 [doi: 10.1136/gut.2009.192757]), both of which are grade B results, he noted.

"We questioned whether prolonging the treatment duration of sequential therapy or continuing the amoxicillin throughout the treatment course might increase the eradication rate," he said. The specific aim of the study was to investigate whether either extending the duration of sequential therapy to 14 days or a 14-day hybrid regimen that combined sequential and concomitant approaches might increase the eradication rate to at least 95% (grade A) in per-protocol analysis. Subjects had *H. pylori* infection proven by at least two positive results for the urease test, histology, and urea breath test.

The study was done as two separate pilot studies where 240 patients were randomized to the sequential therapy group, which included esomeprazole 40 mg b.i.d. plus amoxicillin 1 g b.i.d. (EA) for 7 days followed by esomeprazole, clarithromycin 500 mg b.i.d., and metronidazole 500 mg b.i.d. for 7 days, or to hybrid therapy, which included EA for 7 days followed by EA plus clarithromycin and metronidazole for 7 days. Patients were followed to week 8, when they underwent endoscopy with urease testing and histology, or urea breath test.

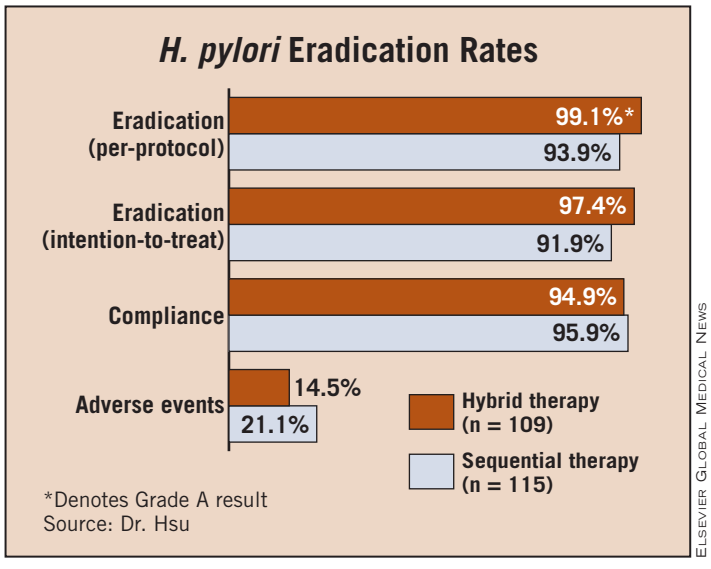
After excluding patients who had lack of compliance or incomplete follow-up, the final analyses included 115 in the sequential (control) group and 109 in the hybrid therapy group. The groups were similar demographically except for a higher proportion of metronidazole-susceptible patients in the sequential group.

In both the intention-to-treat and per-protocol analysis, the outcomes were superior after hybrid therapy, Dr. Hsu reported (see chart).

"The study also showed that simply prolonging the treatment duration of sequential therapy does not achieve a grade A result," Dr. Hsu pointed out, since a rate of 93% can be achieved with just 10 days of sequential therapy (Clin. Gastroenterol. Hepatol. 2010;8:36-41).

In a univariate analysis of clinical and bacterial factors associated with efficacy, no factors analyzed affected efficacy in the hybrid arm, but the presence of resistant strains reduced the eradication rate in the control arm to 88%.

The investigators received the medications from AstraZeneca, which was otherwise not involved in the planning, analysis, or writing of the paper. ■



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