Hybrid Tx for *H. pylori* Achieved Superior Results

BY CAROLINE HELWICK

FROM THE ANNUAL DIGESTIVE DISEASE WEEK

NEW ORLEANS — For *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, according to Dr. Ping-I. Hsu.

"Worldwide, the eradication rate with standard triple therapy is less than 80% in intention-to-treat analyses," Dr. Hsu of Kaohsiung (Taiwan) Veterans General Hospital said at the meeting. 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 e-pub June 4, 2010), both of which are grade B results, he noted.

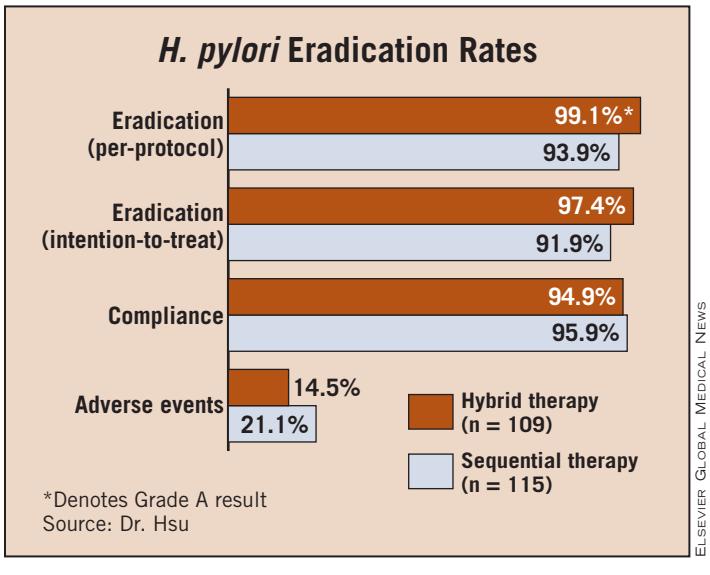
The specific aim of the current study was to investigate whether either extending the duration of sequential therapy to 14 days or a 14-day hybrid regimen that combined sequential and concomitant approaches might increase the eradication rate to at least 95% (grade A) in per-protocol analysis. Subjects 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.

The eradication rate was better after hybrid therapy than after standard sequential therapy.

DR. HSU

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.



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

"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%.

When patients are resistant to both clarithromycin and metronidazole, 10-day sequential therapy carries only a 33% cure rate, and 14-day sequential therapy has a 75% cure rare; however, with hybrid therapy, amoxicillin administration is prolonged out to 14 days, which can result in a 100% cure rate, he reported.

AstraZeneca provided the study medications, but was not otherwise involved in the study. ■

Flexible Approach Advised for Constipation-Predominant IBS

BY CAROLINE HELWICK

EXPERT ANALYSIS FROM DIGESTIVE DISEASE WEEK

NEW ORLEANS — When patients with constipation-predominant irritable bowel syndrome do not respond to standard treatments, good communication is essential for defining the multiple factors likely to be causing symptoms, Dr. Lin Chang said.

"Use 'brain' and 'gut' signs to help guide centrally versus peripherally acting therapy," advised Dr. Chang, of the Center for Neurobiology of Stress at the University of California, Los Angeles.

The standard treatment, fiber, may not be sufficient for C-IBS because the dose may be insufficient, the side effects intolerable, or the patient's symptoms too severe or not responsive to fiber. Some patients may have dyssynergic defecation, which will not be helped with fiber.

Dr. Chang defined key areas in managing C-IBS:

► **Establish a good provider/patient relationship.**

First, determine the reason for the current visit. For example, is it worsening pain, lack of treatment response, or concern about cancer? Next, assess the severity of gastrointestinal and non-GI symptoms and any stress-related or comorbid psychological symptoms. Finally, conduct a patient-centered interview to determine whether the patient understands the illness. This is an opportunity for patient education and involvement of the patient in treatment decisions.

Dr. Chang said she incorporates her own form of counseling in sessions with severe symptoms, especially when there is a strong emotional component, but she does not hesitate to refer patients for psychological treatment. Frequent follow-up is important for moderately and severely affected patients.

'Use "brain" and "gut" signs to help guide centrally versus peripherally acting therapy.'

DR. CHANG

► **Rely on evidence-based pharmacotherapy.**

The use of fiber and polyethylene glycol laxatives have only grade 2C recommendations in specialty guidelines since they improve constipation but have little to no effect on pain, which is key in IBS.

Lubiprostone and antidepressants, on the other hand, improve global symptoms and pain. Lubiprostone activates chloride channel-2, increases liquidity in the intestinal lumen, and improves stool consistency. These two approaches carry a grade 1B recommendation. While tegaserod improves global symptoms, bloating, stool frequency, stool consistency, and pain in some patients, the risk/benefit ratio is not favorable and therefore it has a grade 2A recommendation.

Probiotics can also help, as there is a physiological basis for their benefit. At least for *Bifidobacterium infantis*, clinical trials have shown positive results.

► **Consider psychological treatment.**

GI distress is multifactorial. It affects, and is affected by, emotions such as visceral and general anxiety, depression, devitalization, and somatization, and by cognitive factors, including locus of control, catastrophizing, anticipatory concerns, embarrassment, and stigma.

Tricyclic antidepressants are effective in some patients, especially patients with enhanced sensory perception, according to nine randomized controlled trials. Dr. Chang said she favors desipramine, since it has fewer anticholinergic effects, and starts with a low dose and titrates slowly. Selective serotonin receptor inhibitors (SSRIs) have also shown efficacy in at least five trials, though the study populations were smaller. She considers them when psychological symptoms seem to be driving the IBS symptoms or there is a coexistent somatic pain syndrome. SSRIs may be better for somatic than for visceral pain, and their effects can be additive with tricyclics.

► **Anticipate new treatments.**

Emerging therapies include linaclotide, a chloride channel activator that boosts intestinal fluid secretion, and prucalopride, a 5-HT4 agonist.

At DDW, investigators presented the phase III results for linaclotide. In two nearly identical 12-week trials involving 1,272 patients, linaclotide significantly increased the percentage of patients having at least three complete spontaneous bowel movements (CSBMs) per week, and increased the weekly CSBM count by at least one from baseline. Response rates were 21.3% and 19.4% for high-dose linaclotide in the two studies, compared with 6.0% and 3.3% for placebo, reported Dr. Anthony Lembo of Beth Israel Deaconess Medical Center, Boston.

In patients with chronic constipation, prucalopride has also been shown to significantly increase CSBMs, versus placebo (N. Engl. J. Med. 2008;358:2344-54).

Finally, Dr. Chang reminded clinicians that patients who are refractory to all treatments may have dyssynergic defecation. Biofeedback has been shown to significantly improve constipation in these patients, according to a study in which 80% responded to biofeedback versus 20% to laxatives (Gastroenterology 2006;130:657-64). ■

Disclosures: *Dr. Chang has received consulting fees from Albireo, GlaxoSmithKline, McNeil Pharmaceuticals, Ocera Therapeutics, Prometheus Laboratories, Rose Pharmaceuticals, Salix Pharmaceuticals, and Takeda Pharmaceutical Co., as well as salary and grant/research support from Prometheus, Rose, and Takeda.*