Diagnosis of Celiac Disease Depends on Category

BY SUSAN BIRK

CHICAGO — When testing patients for celiac disease, physicians can no longer rely on a single paradigm for both overtly symptomatic patients and asymptomatic but genetically at-risk patients, according to Dr. Edwin Liu.

These two categories of patients require different approaches, said Dr. Liu, who spoke at a meeting on celiac disease sponsored by the American Gastroenterological Association.

Most symptomatic patients need only one antibody test, transglutaminase IgA (IgA-TGA) and an IgA antibody level to assess for celiac disease. But genetically at-risk patients may need multiple tests over time to screen for the presence of celiac autoimmunity and to determine if a biopsy is needed. Patients considered at risk for celiac disease include first-degree relatives of those with celiac disease or type 1 diabetes, and patients with type 1 diabetes.

The patient with classic symptoms and an abnormal TGA result usually can be biopsied immediately with a greater than 90% likelihood that intestinal lesions will be found, but TGA predicts disease in only about 75% of asymptomatic patients at genetic risk.

Patients with very elevated blood TGA levels are more likely to have more severe intestinal injury, so "in screening those at genetic risk, we have to understand our own lab tests well," Dr. Liu said in an interview. Therefore, in deciding when to perform a biopsy, physicians should interpret tests in a quantitative fashion. This interpretation should consider changes in TGA values over time, because a single positive result may not provide enough information to make a decision to proceed with biopsy.

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"In the case of a symptomatic person, [a single positive result] is probably okay, because you are looking for the presence or absence of disease. However, in the case of a person who's at risk for celiac disease, multiple tests over time may be needed due to the potential for disease. In addition, "we really need to understand what is a very high level," he said, "because higher TGA levels are more likely to lead to findings of intestinal lesions."

Complicating this diagnostic picture is the wide variability of currently available IgA-TGA assays, said Dr. Liu of the Barbara Davis Center for Childhood Diabetes and the section of gastroenterology, hepatology, and nutrition at the Children's Hospital and the University of Colorado at Denver. The definition of what constitutes a high TGA value differs depending on the laboratory and the assay used.

Asymptomatic individuals may need to be tested several times before deciding whether to proceed with biopsy. This is because a biopsy done too soon could produce normal histologic findings that suggest the absence of disease, but these normal findings do not necessarily rule out the possibility that disease will develop, Dr. Liu said.

He cited an example of the patient with type 1 diabetes who has an abnormal TGA and whose small intestinal biopsy is normal. The finding is not necessarily a "false positive" TGA level, but could be caused instead by the underlying biology of celiac disease. "If we biopsy patients too early they may not have had time to develop intestinal lesions," he said. "If we believe that the paradigm for most autoimmunity also applies to celiac disease—that autoantibodies precede the development of actual disease—then performing intestinal biopsy in the early stages of autoimmunity might lead to findings of normal histology."

Although some clinicians prefer to perform a biopsy at the first sign of abnormality on TGA because they do not want to miss a case of disease, Dr. Liu said the approach to diagnosis at his institution differs somewhat. "We don't want to biopsy more than once," he said, adding that this strategy is viable because "the kids we follow are in the medical system, so we can afford to be patient and try to determine the optimal time for biopsy" with serial serologic tests. ■

Early Eradication of *H. pylori* May Prevent Gastric Cancer

BY MARY ANN MOON

Among patients with peptic ulcer disease, early eradication of *Helicobacter pylori* protects against the development of gastric cancer, Dr. Chun-Ying Wu and colleagues.

In a retrospective cohort study of more than 80,000 patients throughout China who were hospitalized for peptic ulcer disease, those who received therapy to eradicate *H. pylori* soon after recovery showed a risk of gastric cancer similar to that in the general population. In contrast, patients who did not receive such therapy until years later had a higher risk of developing gastric cancer.

In animal models, a causal link between *H. pylori* infection and gastric cancer has been proved, with studies showing that *H. pylori* induces the cancer by first causing atrophic gastritis, intestinal metaplasia, and dysplasia.

However, the findings in human studies have been conflicting.

Dr. Wu of China Medical University in Taichung, Taiwan, and colleagues conducted a retrospective study comparing 54,576 patients who received timely treatment with 25,679 who, for unknown reasons, did not receive treatment to eradicate *H. pylori* until 1 or more years after an index hospitalization for peptic ulcer disease.

All the study subjects were initially hospitalized between 1997 and 2005 with a primary diagnosis of peptic ulcer, including gastric, duodenal, and nonspecific ulcer. Treatment to eradicate *H. pylori* included a proton pump inhibitor or H_2 receptor blocker, plus clarithromycin or metronidazole, plus amoxicillin or tetracycline, with or without the addition of bismuth. All the subjects were followed for 2-10 years, with an average of 7.5 years of follow-up.

In the "early-eradication group," the median interval between hospitalization for peptic ulcer disease and receipt of eradication therapy was 14 days. In contrast, in the "late-eradication group," the median interval was 1,053 days.

The cumulative incidence of gastric cancer in the early-intervention group was similar to that in the general Chinese population, but such incidence was significantly higher in the late-eradication group. Moreover, gastric cancer risk was higher still in late-eradication patients who were at high risk because of older age, male sex, or ulcer complications. "The result [indicates that there is a] stronger protective role of *H. pylori* eradication in high-risk populations," they said.

H. pylori eradication conveyed protection in all age groups, not just in young patients. "The highest protective effect was actually found in the 60-69 age group, with the second-highest protective effect in the 50-59 age group," the researchers said.

The researchers were unable to determine whether treatment to eradicate *H. pylori* was successful or not.

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Benefits of Thiopurines for IBD Outweigh Potential Risks

BY HEIDI SPLETE

Patients who receive thiopurines for inflammatory bowel disease are at increased risk for lymphoproliferative disorders, but the overall incidence is low and the benefits of treatment for IBD still outweigh the risks, according to data from more than 19,000 adults.

"We have shown that risk of lymphoproliferative disorders was five times higher in patients exposed to thiopurines than in those never exposed to the drugs," wrote Dr. Laurent Beaugerie of Saint Antoine Hospital, Paris, and colleagues in their report of the prospective, observational cohort study.

But the results also indicate absolute cumulative risks of lymphoproliferative disorders among patients who continue to take thiopurines at less than 1% in patients younger than 50 years, less than 3% in patients aged 50-65 years, and less than 6% in patients older than 65, the researchers said.

The team reviewed data from the CESAME (Cancers et Surrisque Associe aux Maladies Inflammatories Intestinales en France) study, which was designed to assess various risks of taking thiopurines for IBD. The study included 11,759 adults with Crohn's disease and 7,727 adults with ulcerative colitis or unclassified IBD (Lancet 2009 Oct. 18 [Epub doi:10.1016/S0140-6736(09)61302-7]).

At baseline, 5,867 patients were receiving thiopurines, 2,809 patients had discontinued thiopurines, and 10,810 patients had never received thiopurines. Patients were recruited into the study between May 2004 and June 2005, and the researchers followed them until Dec. 31, 2007, an average of 35 months.

During the study period, 114 (2%) of patients who were receiving thiopurines at baseline developed cancer, compared with 41 (1%) of patients who had discontinued the drugs and 134 (1%) of patients who had never taken them. A total of 22 patients were diagnosed with non-Hodgkin's lymphoma, and 1 patient was diagnosed with Hodgkin's lymphoma during 49,713 patient-years of follow-up.

Old age, being male, and longer disease duration were associated with an increased risk of lymphoproliferative disorders.

"Our hypothesis of a constant risk of lymphoproliferative disorder during thiopurine therapy is supported by three considerations," they said. First, the consistent dose of immunosuppressants in a post-transplant setting keeps the risk for lymphoma constant. Second, the same number of lymphomas was seen during the first and third years of the study. Finally, "the duration of previous thiopurine exposure was evenly distributed among the 23 patients who developed lymphoma."

Patients who discontinued therapy had more clinically active IBD but a lower risk of lymphoproliferative disorders compared with those receiving thiopurines. Dr. Beaugerie has received funding from UCB Pharma, Sanofi-Aventis, Abbott, and Ferring Pharmaceuticals. ■