Aspirin May Prevent Cancer in Lynch Syndrome

BY PATRICE WENDLING

BERLIN — The perseverance of researchers has led to the preliminary finding that aspirin helps prevent cancers in Lynch syndrome, a genetic condition that accounts for about 5% of all colon cancers.

A daily 600-mg dose of aspirin reduces the cancer burden in this high-risk group by about half, with the effect becoming apparent after about 3 years, Dr. John Burn said at a joint congress of the European Cancer Organization and European Society for Medical Oncology.

This preliminary finding is surprising, given that a report last year of the main trial results showed no difference in the number of colonic adenomas, after a mean of 29 months, between those taking aspirin and those taking 30 g of the resistant maize starch Novelose and placebo (N. Engl. J. Med. 2008;359:2567-78).

"The results were profoundly disappointing," Dr. Burn said of the original trial. "There was absolutely no effect. If anything, the aspirin group had slightly more adenomas."

The results were, however, in line with a series of randomized trials that have not found a convincing benefit with aspirin use. The difference with the current analysis is that follow-up extended up to 10 years after randomization, and it focused directly on cancers rather than on using adenomas as a surrogate for cancer prevention, said Dr. Burn, head of the Institute of Human Genetics at Newcastle University, Newcastle upon Tyne, England.

"We are working hard to fill in some of the missing data," Dr. Burn said in an interview. "We can then begin to explore making treatment of Lynch syndrome a new official indication for aspirin."

The follow-up analysis almost didn't happen: The original negative results dashed two attempts to secure funding for it, the study manager retired, and the statistician went on maternity leave. Dr. Burn and his coinvestigators D. Timothy Bishop, Ph.D., of Leeds (England) University and John Mathers, Ph.D., of Newcastle University pressed on, buoyed by a systematic review of the original cardiovascular trials showing that regular use of at least 300 mg of aspirin reduced the incidence of colorectal cancer, but only after a latency of about 10 years (Lancet 2007;369:1603-13).

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A daily 600-mg dose of aspirin reduces the cancer burden by about half in these high-risk patients.

With the help of a visiting fellow, the team tracked down and analyzed 711 of the original 937 patients for whom follow-up extended beyond the end of the trial.

An analysis of the still-blinded data revealed 17 colorectal cancers in the aspirin group vs. 29 in the placebo group, Dr. Burn reported. The difference between the aspirin and placebo groups did not achieve statistical significance ($P = .08$), but did so when the two groups were compared at least 24 months after randomization ($P = .03$). Six patients among a small group randomized to the starch limb also developed colorectal cancers.

The number of endometrial cancers was significantly reduced, with only 5 occurring in the aspirin group and 13 in the placebo group ($P = .05$). There was no impact of aspirin on breast (seven vs. five cases), ovarian (five vs. three), or pancreatic (two vs. two) cancers.

The benefit of aspirin was most obvious in those who used it for more than 2 years, and was seen about 3 years after randomization when most or all patients would have discontinued their aspirin, Dr. Burn said. "The effect takes 3 years to begin, but persists for 5 more years," he said at a press briefing held during the meeting.

Surprisingly, the study did not demonstrate an effect of aspirin on adenoma formation, despite the decrease in cancers. Of the 100 participants with adenomas who were identified during long-term follow-up, 48% were in the aspirin group and 52% were in the placebo group.

Dr. Burn said that these data are still preliminary, and hypothesized that salicylate could induce apoptosis in aberrant stem cells, much as it does in plants as a defense against infection. Thus, adenomas may still form in patients on aspirin, but the reduced number of aberrant stem cells makes them less likely to progress to cancer.

The regular use of aspirin reduced cardiovascular events, but did not significantly increase bleeding events. This is likely because the cohort was relatively young (mean age, 45 years), said Dr. Burn, who noted that 600 mg is actually a subanalgesic dose.

The investigators are keen to initiate a large-scale, dose-inferiority study to determine if similar levels of protection can be achieved with a lower dose.

"We need large-scale international collaboration, but it can be done," Dr. Burn said. "If we can reduce the hereditary cancer burden with an over-the-counter cheap drug, the long-term benefits will be wonderful."

The initial CAPP2 (Colorectal Adenoma/Carcinoma Prevention Programme 2) trial was funded by multiple sources, including Bayer Pharmaceuticals, which provided administrative support for the follow-up analysis. The authors reported no conflicts of interest. ■

Genetic Risks Influence Diagnostic Strategy in Celiac Disease

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 noted in an interview.

Therefore, in deciding when a biopsy is needed, 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.

"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 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. Until universal testing and reporting standards are developed, specialists "must become familiar with their particular assay's performance in the screening-identified population. They need to understand how their test behaves in order to optimize the way they make decisions about biopsying."

Dr. Liu acknowledged, however, that "every hospital uses a different lab, and there are so many different assays out there. If we understood the behavior of each assay, then we would understand the best time to do biopsies on these patients," but physicians can't realistically be expected to know the dynamics of all these tests, he said.

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 intestine 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. He noted that the risks of waiting to diagnose celiac disease in the absence of symptoms are not known, "but it also hasn't been soundly established whether there are any benefits to treating these patients early, before there are any symptoms."

Dr. Liu and his colleagues at the University of Colorado have been conducting autoantibody workshops and are working with the Centers for Disease Control and Prevention to develop standards for IgA-TGA tests and reporting mechanisms. "Assay dynamics and quality can be very different. We need to standardize the assays to make them easier for physicians to interpret," he said. ■