FLASHBACK TO 2012

2007-**10-Year Anniversary**-2017

It's a whole new biosimilar world. In the April 2012 issue of *GI & Hepatology News* (*GIHN*) there was a small article on the issued Food and Drug Administration guidance on how to develop biosimilars. A biosimilar molecule must be structurally similar to the reference or originator product with the expectation that the safety and efficacy will be the same. The European Medicines Agency (EMA) established a legal framework for approving biologics in the European Union in 2003 and guidelines for approval in 2005 to 2006 with the first biosimilar approved in 2006 (somatropin [Omnitrope]).

The first monoclonal antibody biosimilar approved by the EMA was CT-P13 (infliximab-dyyb) in June 2013. There are now over 23 biosimilars approved for use in Europe. In 2012 there were no biosimilars on the market in the United States. This past year (2016) has been the year of the biosimilar with two of the four approved compounds used in inflammatory bowel disease – Inflectra (infliximab-dyyb, Hospira) April 2016 and Amjevita (adalimumab-atto, Amgen) September 2016 appearing.

The launch of these biosimilars raises a whole new series of questions. First and foremost for gastroenterologists – are the biosimilars truly similar in patients with inflammatory bowel disease? Adalimumab-atto was approved on the basis of two phase III studies in psoriasis and in rheumatoid arthritis and infliximab-dyyb was approved on the basis of studies in rheumatoid arthritis and ankylosing spondylitis. Other questions arise: 1. Can a patient who is doing well on the originator be safely switched to the biosimilar? 2. Can we use the same assays for drug monitoring? 3. Will use of biosimilars lead to a lower cost structure for patients and hospitals? 4. What are the regulations and guidelines for interchangeability? (*GIHN* March 2017). In the United States, development of biosimilars was slow to start but we expect to see an explosion in development of these agents in gastroenterology as the patents expire on the biologics currently in use.

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FROM THE AGA JOURNALS

Start probiotics within 2 days of antibiotics to prevent *Clostridium difficile* infection, study suggests

BY AMY KARON
Frontline Medical News

Starting probiotics within 2 days of the first antibiotic dose could cut the risk of *Clostridium difficile* infection among hospitalized adults by more than 50%, according to the results of a systemic review and metaregression analysis.

The protective effect waned when patients delayed starting probiotics, reported Nicole T. Shen, MD, of Cornell University, New York, and her associates. The study appears in the June issue of Gastroenterology (doi: 10.1053/j.gastro.2017.02.003). "Given the magnitude of benefit and the low cost of probiotics, the decision is likely to be highly cost effective," they added.

Systematic reviews support the use of probiotics for preventing *Clostridium difficile* infection (CDI), but guidelines do not reflect these findings. To help guide clinical practice, the reviewers searched MEDLINE, EMBASE, the International Journal of Probiotics and Prebiotics, and the Cochrane Library databases for randomized controlled trials of probiotics and CDI among hospitalized adults taking antibiotics. This search yielded 19 published studies of 6,261 patients. Two reviewers separately extracted data from these studies and examined quality of evidence and risk of bias.

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"Given the magnitude of benefit and the low cost of probiotics, the decision is likely to be highly cost effective." Importantly, probiotics were significantly effective against CDI only when started within 2 days of antibiotic initiation.

A total of 54 patients in the probiotic cohort (1.6%) developed CDI, compared with 115 controls (3.9%), a statistically significant difference (*P* less than .001). In regression analysis, the probiotic group was about 58% less likely to develop CDI than controls (hazard ratio, 0.42; 95% confidence interval, 0.30-0.57; *P* less than .001). Importantly, probiotics were significantly effective against CDI only when started within 2 days of antibiotic initiation (relative risk, 0.32; 95% CI, 0.22-0.48), not when started within 3-7 days (RR, 0.70, 95% CI, 0.40-1.23). The difference between these estimated risk ratios was statistically significant (*P* = .02).

In 18 of the 19 studies, patients received probiotics within 3 days of starting antibiotics, while patients in the remaining study could start probiotics any time within 7 days of antibiotic initiation. "Not only was [this] study unusual with respect to probiotic timing, it was also much larger than all other studies, and its results were statistically insignificant," the reviewers wrote. Metaregression analyses of all studies and of all but the outlier study linked delaying probiotics with a decrease in efficacy against CDI, with *P* values of .04 and .09, respectively. Those findings "suggest that the decrement in efficacy with delay in starting probiotics is not sensitive to inclusion of a single large 'outlier' study," the reviewers emphasized. "In fact, inclusion only dampens the magnitude of the decrement in efficacy, although it is still clinically important and statistically significant."

The trials included 12 probiotic formulas containing Lactobacillus, *Saccharomyces*, *Bifidobacterium*, and *Streptococcus*, either alone or in combination. Probiotics were not associated with adverse effects in the trials. Quality of evidence was generally high, but seven trials had missing data on the primary outcome. Furthermore, two studies lacked a placebo group, and lead authors of two studies disclosed ties to the probiotic manufacturers that provided funding.

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