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Inhaled Corticosteroids or Antileukotrienes for Asthma?

To the Editor: The editorial (1) that accompanied the report by Malmstrom and coworkers (2) states that "the antileukotrienes are a good first choice" for patients with mild persistent asthma. The results of the clinical trial seem to suggest otherwise.

In Malmstrom and colleagues' study, patients with chronic asthma were randomly assigned to receive montelukast, inhaled beclomethasone, or placebo (2). When one compares the results in patients receiving one of the active treatments, it is apparent that beclomethasone therapy resulted in 77% greater improvement in FEV_1 than montelukast, 64% greater improvement in morning peak expiratory flow rates, 51% greater improvement in daytime asthma symptoms, 40% less β-agonist use, and 54% fewer asthma attacks. There were also 41% fewer nocturnal awakenings per month among beclomethasone-treated patients.

Furthermore, the patient taking the antileukotriene drug would be required to pay more for a less effective medication. On the basis of the dosages used in this study, the average wholesale price for montelukast would be $311 more per year than beclomethasone, a 37% increase in annual cost (3). It seems doubtful that enhanced ease of administration with a pill outweighs this in the long run.

This study and others show that the inhaled corticosteroids are the most effective medications available for treatment of persistent asthma of all degrees of severity. They are typically free from clinically significant side effects when used properly. Although antileukotrienes may be considered by some to be a "good first choice" in patients with asthma who require more than as-needed short-acting β-agonist therapy, I propose that the inhaled corticosteroids are a better first choice.

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3. Red Book. Montvale, NJ: Medical Economics; 1999.

In response: Dr. Hampson suggests that inhaled corticosteroids are a better treatment for asthma than montelukast. Although he correctly points out that, in our study, the mean response of inhaled beclomethasone was larger for some end points, he neglects to mention the important aspect of our analysis: the response distribution. Mean values frequently provide less clinical information than a clear understanding of response distributions. For example, our report clearly demonstrates how these two therapies largely overlap in their response distributions for the FEV_1 end point. In addition, with regard to the clinically important outcome of the prevention of worsening asthma episodes (attacks), both therapies significantly differed from placebo and were not different from each other.

With a once-daily oral medication such as montelukast, greater real-world compliance may translate into even greater real-world effectiveness.

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Breast Symptoms in a Health Maintenance Organization

To the Editor: Barton and colleagues' study (1) illustrates the ill-conceived notion of placing increased emphasis on the primary care provider. Most initial visits prompted by breast symptoms were to internal medicine departments. The authors' study, however, didn't mention some components of the patient's history. Many well-known factors, such as regular performance of breast self-examination (2), obesity (3), breast density, ethnicity, and estrogen replacement therapy (4), were not described. We would be interested to know the number of patients for whom the physician and midlevel clinicians properly registered this information. Adequate follow-up of breast symptoms is very important in primary care practices, and the authors should be congratulated for their analysis.

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In response: Drs. Stefani and Cadore raise two interesting questions. We drew no conclusions regarding the appropriateness of patients presenting to internal medicine departments; our

finding that 71% of initial symptoms were brought to clinicians in internal medicine probably reflects a culture wherein the first contact is with an identified primary care provider; this is also seen in countries other than the United States (1). As we noted in our article, rates of presentation of breast symptoms did not differ by ethnic group, although presenting with a breast symptom was more likely in patients with a family history of breast cancer.

We agree that it would be interesting to know how clinicians document information on breast cancer risk factors. However, although the clinical factors (obesity, breast density, and estrogen replacement therapy) mentioned are known to be correlated with breast cancer risk in the general population, no data suggest that the presence or absence of these risk factors would modify the probability that a woman presenting with a symptom has breast cancer. Our study showed that any symptom significantly increased the likelihood that a woman had cancer over the baseline risk in the population; this suggests that all breast symptoms should be taken seriously.

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Olestra Snacks Compared with Regular Snacks

To the Editor: Sandler and colleagues (1) state that anecdotal reports of severe diarrhea and abdominal pain associated with ingestion of olestra have not been substantiated by controlled testing. In fact, several clinical trials have shown such effects.

Procter & Gamble (the maker of olestra) conducted two 8-week studies indicating that daily consumption of 20 g of olestra (equivalent to 2.5 ounces of potato chips) increased rates of loose stools and diarrhea, fecal urgency, and flatulence. The Food and Drug Administration (FDA) concluded that those studies showed that olestra causes increased rates of severe symptoms (2). On the basis of those and other studies, the FDA requires a notice—"Olestra may cause abdominal cramping and loose stools"—on products containing olestra. Another Procter & Gamble study tested persons who thought they had previously reacted to olestra. That study confirmed that eating 20 g of olestra daily for several days can cause severe diarrhea (Klontz K. Personal communication to Thorsheim H. Food and Drug Administration, 26 December 1995). A study (underwritten by Unilever) found that daily consumption of olestra (mean, 24 g/d) increased "urgent calls to stool" and other symptoms (3).

Sandler and colleagues state that "clinically meaningful" symptoms are not associated with unregulated consumption of olestra. Still, in the highest decile of consumers, olestra doubled the incidence of more frequent bowel movements and loose stools. These persons had symptoms on 18% of person-days, compared with only 12% of days in the control group (the authors' Table 4). Olestra consumers missed some or all of their activities on 0.4% of days, compared with 0.2% in the controls.

The FDA has received more than 20 000 reports of gastrointestinal symptoms attributed to olestra, including hundreds from people who went to emergency departments or physicians' offices. Clinicians should be aware that olestra may cause severe gastrointestinal symptoms and should question patients about their consumption of foods containing olestra.

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Plasma Exchange for Hemolytic Crisis in Wilson Disease

To the Editor: Half of patients with Wilson disease, a disorder of copper metabolism with two mutant ATP7B genes (1), present with hepatic disturbance (2). Acute hepatic failure tends to be fulminant when it is associated with hemolysis (3); patients can survive for only days or weeks unless transplantation is performed (2). We describe a patient with Wilson disease whose hemolysis was treated with plasma exchange.

A 17-year-old boy was hospitalized because of fatigue. He was alert and slightly jaundiced. Laboratory findings included a hemoglobin level of 11.9 g/dL, an albumin level of 3.1 g/dL, an aspartate aminotransferase level of 135 U/L, an alanine aminotransferase level of 119 U/L, an alkaline phosphatase level of 212 U/L, a total bilirubin level of 60 μmol/L (3.5 mg/dL), and a prothrombin time of 32%. Results of tests for viral hepatitis were negative. Ultrasonography showed a coarse echogenic texture of the liver and slight ascites. Acute hepatic failure with less pronounced elevations of aminotransferase levels prompted us to consider Wilson disease. Kayser–Fleischer rings were detected on slit-lamp examination. The serum copper level was 72 μg/dL (normal range, 78 to 131 μg/dL), and the ceruloplasmin level was 8 mg/dL (normal range, 18 to 37 mg/dL). Free serum copper level, a reliable indicator of Wilson disease (4), was elevated at 61 μg/dL (normal range, 4 to 7 μg/dL). On the sixth day of hospitalization, the hemoglobin level and prothrombin time decreased to 8.8 g/dL and 22%, respectively, and unconjugated hyperbilirubinemia was seen (total bilirubin level, 154 μmol/L [9.0 mg/dL]; unconjugated bilirubin level, 82 μmol/L [4.8 mg/dL]). Plasma exchange was started on 3 consecutive days. Copper elimination was 2300 μg at the first plasma exchange, which resulted in a reduction in total bilirubin level (21 μmol/L [1.2 mg/dL]) at the completion of plasma exchange. One year later, prothrombin time returned to 70% and results of other laboratory tests were normal; D-penicillamine therapy was continued.

We treated acute hepatic failure related to Wilson disease at the beginning of hemolysis (caused by a flux of copper from hepatocytes); plasma exchange removed copper (5). Our report suggests that after rapid diagnosis of Wilson disease, liver transplantation can be avoided when hemolysis is controlled first with plasma exchange and thereafter with chelation therapy.

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