

Insights on New Paradigms in GI Treatment

An interview with James W. Freston, MD, PhD; President, American Gastroenterological Association



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AJMC: What is the prevalence of gastroesophageal reflux disease (GERD) in the United States? Can you comment on the nature and relative severity of the symptoms of this disease?

Dr. Freston: GERD is ubiquitous in the United States. For example, 40% to 44% of adults have heartburn; of these, 7% have heartburn every day and 2% have evidence of erosive esophagitis. This leaves only a small percentage of patients with heartburn who have esophageal lesions (esophagitis).

AJMC: What is the relationship between severity of patient symptoms and extent of disease (ie, degree of erosion in the esophagus)?

Dr. Freston: The severity of symptoms does not correlate with the severity of

esophageal lesions as seen on endoscopy, with one exception: in erosive disease, the healing of lesions is associated with the disappearance of symptoms. Thus, the correlation is with healing, not with severity of symptoms.

AJMC: What are the complications of esophagitis and how do they affect patient quality of life? What impact do they have on overall healthcare costs?

Dr. Freston: There are three complications of esophagitis, and all of them have a negative impact on quality of life: strictures, Barrett's esophagus (with and without adenocarcinoma), and rarely, bleeding from esophageal ulcers. Strictures cause dysphagia and require periodic dilation of the esophagus, which is uncomfortable. Barrett's esophagus requires periodic endoscopic surveillance to detect adenocarcinoma, which occurs in about 10% to 15% of these patients. The surveillance is uncomfortable and costly, and adenocarcinoma is a lethal disease with low cure rates unless detected very early. Bleeding from esophageal ulcers occurs rarely, but requires hospitalization, which definitely compromises quality of life.

Quality of life is affected in patients with GERD before complications occur. GERD is a chronic, relapsing condition patients will have for the rest of their lives and it requires long-term management with medications or surgery. Complications further worsen quality of life. GERD is a costly condition, mainly because it is so widespread and requires

lifelong management. In 1985 the direct and indirect costs associated with GERD totalled \$5 billion, and the figure may be double that amount in 1996. In 1995, \$1 billion was spent for over-the-counter medications for heartburn.

AJMC: Can you compare proton pump inhibitors (PPIs) and H2-receptors (H2RAs) as treatments for reflux disease in terms of gross healing rates, symptom relief, and safety? What about the pace of healing and its implications for quality of life?

Dr. Freston: PPIs are superior for healing and symptom relief. The healing rate with H2RAs in therapeutic doses (600 mg/day of ranitidine or its equivalent) is 12 weeks compared to 4 weeks for PPIs. PPIs cause healing in 30% to 45% more patients than H2RAs within 4 weeks. All studies to date show that symptoms are more completely relieved and relieved faster with PPIs than with H2RAs. Short-term direct comparisons of the two drugs show equivalent safety. The pace of both healing and symptom relief are substantially faster with PPIs—4 weeks versus 12 weeks with H2RAs—which has implications for quality of life. When patients feel sick, they want to get better quickly, and they do so with PPIs. Additionally, PPIs maintain healing better than H2RAs, which is likely to reduce complication rates and improve quality of life. Two studies show that once strictures are relieved by dilation, they are less likely to recur on PPIs versus H2RAs, which translates to fewer episodes of dysphagia, fewer dilations, and improved quality of life.

AJMC: What is the rationale for long-term maintenance therapy of esophagitis? What are the relative merits of the two classes of acid-suppressing agents in maintenance therapy?

Dr. Freston: Reflux esophagitis is a chronic, relapsing disorder that requires continuous management for most pa-

tients. The goals of maintenance therapy are to keep the esophageal mucosa healed and keep the patient symptom-free so the development of complications will be prevented. The relative merits of the two classes of drug have

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been assessed in head-to-head trials. PPIs have superior efficacy to that of H2RAs in maintaining mucosal healing and in keeping patients free of symptoms.

AJMC: Please address the historical PPI safety concerns knowing that these drugs are now approved for long-term use.

Dr. Freston: The historical concerns are related to serum gastrin elevation and its consequences, including gastric carcinoids. It is well known that hypergastrinemia causes gastric carcinoids in rats, but this has not proven to be a problem in humans. It appears to be related to unique features in rats that make them susceptible to developing carcinoids. In particular, rats have a high density of enterocromaffin cells (ECL) in the stomach which are uniquely sensitive to gastrin. Serial biopsies in humans during PPI therapy show no evidence of disturbance in ECL cells. For these reasons, the FDA removed the box warning regarding carcinoids when omeprazole was approved for chronic therapy. Lansoprazole has never had this box warning. In up to 15 years of experience with omeprazole and 7 years with lansoprazole, there has been no evidence of carcinoids. We have 20 to 40 years of clinical experience with patients who have undergone gastric vagotomy and have no evidence of gastric carcinoids. These people have hypergastrinemia to an even greater extent than those taking continuous PPI therapy.

AJMC: Recent interest in the long-term safety of PPIs has centered not so much on elevated gastric carcinoids, but on chronic gastritis in the H. pylori-positive patient who may need to be treated long-term for esophagitis. Can you comment on the various elements inherent in this debate and/or give some insight to others who may have concerns about atrophic gastritis in the setting of chronic acid inhibition?

Dr. Freston: We know that *H. pylori* gastritis progresses to gastric atrophy in some patients. Progression from atrophy to adenocarcinoma via intestinal metaplasia and dysplasia is postulated in patients with gastric carcinoma. Inhibition of acid secretion by H2-blockers, proton pump inhibitors, or vagotomy intensifies

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the inflammatory response to *H. pylori* infection. A recent study showed that more *H. pylori*-infected patients with reflux esophagitis progress to gastric atrophy when treated for up to 5 years with omeprazole than did *H. pylori*-infected patients treated with a fundoplication.¹

This report raises the question of whether all patients on chronic acid suppression should be tested and treated for *H. pylori* infection. Before recommending such a course, limitations of the Kuipers study should be acknowledged. The two groups were treated in two different countries and their mean age differed significantly. Since gastric atrophy is an age-related phenomenon, it is possible that the difference in gastric atrophy between the two groups could be due, at least partially, to the age difference. Thus I am uncomfortable with the recommendation to test and treat all patients at this time. There are, however, some cost-effective steps that can be undertaken pending further informa-

tion. We advocate a once in a lifetime endoscopy for patients with chronic GERD. This endoscopy can now include a rapid urease test which will add less than \$10 to the endoscopy. Those who are positive can undergo *H. pylori* eradication by adding two antibiotics to the PPI for one week. This clearly is not an urgent situation, given that patients with vagotomy and even those with pernicious anemia do not have an increased incidence of gastric adenocarcinoma.

AJMC: What are the therapeutic choices available to the clinician for management of duodenal ulcer (DU) and gastric ulcer (GU) disease and what are the relative merits of each?

Dr. Freston: Clinicians have the choice of healing ulcers by using antisecretory therapy (PPIs and H2RAs) or cytoprotective agents like sucralfate, both of which are effective. On the other hand, one can heal the ulcer and cure the underlying disease by eradicating *H. pylori* with antibiotics, which is far more cost-effective than the first approach. If left untreated, 75% of ulcers will recur within approximately 1 year. Eradication of *H. pylori* reduces the incidence of recurrence to 2% to 3% per year. If H2RAs are used to heal the ulcer and for maintenance, the recurrence rate rises to 25%. If PPIs are used for healing and maintenance, the recurrence rate is lower than that obtained with H2RAs, but higher than that obtained with eradication of *H. pylori*. There is no question that the preferred treatment of duodenal or gastric ulcer patients infected with *H. pylori* is to eradicate the organism, not just to heal the ulcer with antisecretory therapy or cytoprotective agents.

AJMC: In terms of peptic ulcer disease, what are the economic implications of testing, treating, and eradicating H. pylori?

Dr. Freston: All economic analyses show the most cost-effective approach is

to test and eradicate *H. pylori* rather than treat with antisecretory agents alone and then have a recurrence or to maintain patients on PPIs or H2RAs. The economic implications of eradication are considerable compared to intermittent or chronic therapy with antisecretory agents. Obviously, eradication is also cheaper than curative surgery.

AJMC: *With regard to H. pylori eradication, what regimens are emerging as the most viable in terms of efficacy, compliance, safety, and cost?*

Dr. Freston: There are three major groups of therapies for peptic ulcers: triple antibiotics, called bismuth-based triple therapy; PPI plus two antibiotics, called PPI-based triple therapy; and a PPI or H2RA plus one antibiotic, referred to as dual therapy. Both types of triple therapy have 90% eradication rates, while dual therapy has eradication rates ranging from 55% to 80%, depending on which antibiotic is used. Rates are higher with clarithromycin and lower with amoxicillin.

Compliance is problematic for bismuth-based triple therapy because the treatment entails taking 16 to 21 tablets a day divided into four doses for 2 weeks. We know that increased complexity of a regimen is associated with decreased compliance. Therefore, PPI-based triple therapy for shorter periods and dual therapy will have better compliance than bismuth-based triple therapy.

The rate of adverse effects for bismuth-based triple therapy is anywhere from 30% to 50%. These are mostly annoying side effects rather than severe or life-threatening ones. The side effects of PPI-based therapy, whether triple or dual therapy, are uniformly lower.

Cost is a more complex issue. For the regimen itself, bismuth-based triple therapy is the least expensive, PPI-based triple therapy is the most expensive, and dual therapy falls between the two. However, looking at cost only in terms of the regimens is misleading. If

compliance is decreased, efficacy is decreased, which leads to recurrence, increasing the cost. For example, if compliance drops to the point where a patient takes less than 60% of the pills for bismuth-based triple therapy, eradication drops to 69% instead of 90%. At least 20% of patients will have a recurrence and require additional therapy. If you factor in compliance, bismuth-based triple therapy is not the cheapest. The important concept here is that the most expensive therapy is the least effective therapy.

When looking at this issue, one should not take the short view, but rather consider a 1-year time frame at least, during which time the majority of patients will recur if left untreated. Looking at all costs over 1 year, probably the most effective regimen would be PPI-based triple therapy given for a 7- to 10-day course.

AJMC: *Many managed care institutions and integrated hospital networks are moving toward single PPI formularies. Review boards and physicians often ask about the differences between omeprazole and the newer PPI, lansoprazole. Please compare and contrast the two compounds in terms of pharmacology, performance in the clinic, and other related issues.*

Dr. Freston: Both PPIs have a similar chemical structure, so it is not surprising that their clinical performance is comparable. Far more similarities than differences exist between the two compounds. However, there are pharmacologic differences in bioavailability, which translate into differences in the ability to inhibit acid secretion. Lansoprazole is 85% bioavailable, and peak bioavailability is reached within 2 days of dosing, whereas omeprazole is about 40% bioavailable after 1 day of dosing, increasing to about 60% to 65% after 5 days of dosing. Correspondingly, acid inhibition reaches its peak after 1 day with lansoprazole and after 5 days with omeprazole.

The ability to heal ulcers and esophagitis is comparable for both drugs. Three head-to-head comparisons have demonstrated a pattern of earlier symptom relief with lansoprazole, presumably because of quicker and more complete acid inhibition due to earlier and higher bioavailability of the drug. Lansoprazole is about 25% more potent in inhibiting acid secretion than omeprazole. This is an advantage in the setting of GERD, because an increased degree of acid control is required to manage esophagitis compared to DU or GU.

Lansoprazole has more convenient dosing than omeprazole; it is available in a 30-mg dose used to treat esophagitis, and a 15-mg dose used to treat ulcers. Omeprazole is available in a 20-mg dose and will soon be available in a 10-mg dose, designed to allow incremental dosing.

There are also differences in drug interactions between the two PPIs. Theophylline is the only P450-dependent drug that interacts with lansoprazole. Concomitant use of these two drugs results in an 11% decrease in blood levels of theophylline, which is not clinically significant. Omeprazole, on the other hand, interacts with R-warfarin, phenytoin, and diazepam.

AJMC: Today, managed care influences the way many chronic conditions are treated. This influence is exercised through a variety of techniques including implementation of guidelines and disease management programs. Taking into consideration long-term outcomes, relative costs, and economic analyses, what recommendations can you make regarding choice of gastrointestinal agents within the managed care environment?

Dr. Freston: Let me repeat, the most expensive therapy is the least effective therapy. The goal of managed care is to

manage costs within a reasonable time frame, which would be 1 to 2 years. This means using the most effective agent to heal the disease quickly and completely and prevent relapses, which drive up the costs.

PPIs are superior to H2RAs in healing and preventing GERD and it has been clearly documented in the literature that PPIs are more cost-effective. Even over the short term, there are clear advantages with PPIs. You have to treat twice as long with H2RAs as with PPIs to heal ulcers. In the short-term treatment of esophagitis, you have to treat three times as long with H2RAs as with PPIs for the same results, and that is costly. One month of treatment with a PPI is far cheaper than 3 months of treatment with an H2RA.

Thus, every economic analysis shows that PPIs are more cost-effective than H2RAs for acid-related disorders. There is only one exception: if you can use generic cimetidine 100% of the time, you can save about \$40 per year per patient with GERD. This regimen requires more medicine and patients are likely to have more relapses, so even though it is cheaper, quality of life is compromised.

For ulcers, you can treat half as long with PPIs as with H2RAs. Long-term treatment is irrelevant if you eradicate *H. pylori*. My recommendations are as follows: eradicate *H. pylori* in all ulcer patients on H2RA maintenance. Eradicate *H. pylori* in any new ulcer patients. Use a PPI in patients with GERD. Quality of life is improved with this approach and it is more cost-effective.

... REFERENCES ...

1. Kuipers et al. *N Engl J Med* 1996;334:1018-1022.