

## Managed Care Issues in the Treatment of Gastroesophageal Reflux Disease

Based on a presentation by Kenneth R. DeVault, MD

### *Presentation Summary*

The impact that reflux disease has on patients' quality of life is reviewed and some of the managed care issues surrounding treatment, including the step-up/step-down philosophy and a comparison of available proton pump inhibitor (PPI) agents, are explored. PPIs are first-line pharmacotherapy for treating reflux disease. They have shown superior efficacy compared with previously recommended agents. Whereas PPI therapy has some limitations, it offers substantial benefits in terms of clinical and quality-of-life factors.

**G**astroesophageal reflux disease (GERD) does not have to cause severe mucosal disease (esophagitis) to impair quality of life. Considering that many meals for GERD patients are ruined by reflux symptoms, such as heartburn, it is not surprising that this disease has a significant impact on quality of life. In studies measuring quality of life, GERD patients with symptoms had statistically significant lower quality-of-life scores compared with patients without symptoms.<sup>1</sup> In addition, GERD patients had significantly lower quality-of-life scores than people with diabetes or hypertension. The only disease where quality-of-life scores were worse was clinical depression.<sup>2,3</sup>

Clinicians have the opportunity to affect their patients' quality of life. GERD symptoms are treatable in

most patients, and even managing milder symptoms may have a significant impact on the patient's well-being. For example, treating heartburn symptoms can have a significant impact on patients' health-related quality of life.

A study examining patients with nonerosive GERD who were treated with omeprazole, a proton pump inhibitor (PPI), indicated that PPI therapy produced a statistically significant improvement in Psychological General Well-Being Index scores in GERD patients compared with those receiving placebo.<sup>4</sup> Another study indicated that patients who do not experience complete resolution of symptoms experience a declining quality of life that can continue for weeks, months, or years.<sup>5</sup> Thus, the goal for clinicians is to restore a patient's

quality of life by eliminating GERD symptoms.

### Acid Suppression and the Treatment of Reflux

Originally, antacids were the treatment of choice—essentially the only

treatment option—for GERD patients. They provided prompt but temporary relief, but in most placebo-controlled trials there was no statistical improvement with antacids versus placebo. Proton pump inhibitors (PPIs) are effective in treating mild reflux symptoms. In the 1970s and into the 1980s, the advent of histamine-2 receptor antagonists (H<sub>2</sub>RAs) revolutionized the treatment of all forms of acid disease. They relieved symptoms (particularly milder symptoms) in 40% to 60% of patients. The development of PPIs in the 1980s resulted in more effective therapy than that afforded by the H<sub>2</sub>RAs, especially in more severe cases of GERD. Some interpatient and inpatient variability has been observed that may result in some patients who do not respond to PPI therapy.<sup>6-9</sup>

In 1995, the American College of Gastroenterology published guidelines for the diagnosis and treatment of GERD. This review of the world literature suggested that a symptomatic response could be expected in approximately 25% of patients on placebo, 50% to 60% of patients taking H<sub>2</sub>RAs, and 80% of patients taking PPIs. These findings are similar to those that analyzed healing of esophagitis.<sup>10</sup> It is important to note that in the 1970s and 1980s, when H<sub>2</sub>RAs were considered the state-of-the-art therapy, the goals of therapy were primarily an improvement in symptoms, but symptomatic response did not necessarily mean the resolution of symptoms.

**Table 1.** Step-Up/Step-Down Therapy for GERD Patients

<b>Step-Up Therapy</b>	
First 6 Weeks:	All patients receive suggested lifestyle changes and OTC therapy
Second 6 Weeks:	All patients receive suggested lifestyle changes and OTC therapy; patients who are not controlled receive H <sub>2</sub> RAs
Third 6 Weeks:	All patients receive suggested lifestyle changes and OTC therapy; patients who are not controlled on H <sub>2</sub> RAs receive PPIs
<b>Step-Down Therapy</b>	
First 6 Weeks:	All patients are treated with a PPI
Second 6 Weeks:	All patients are stepped down to H <sub>2</sub> RAs; patients who fail are placed on PPIs again
Third 6 Weeks:	Patients who fail the step down to H <sub>2</sub> RAs stay on PPIs. All patients who are on H <sub>2</sub> RAs are stepped down; those with breakthrough symptoms step back up to H <sub>2</sub> RAs

GERD = gastroesophageal reflux disease; H<sub>2</sub>RAs = histamine-2 receptor antagonists; OTC = over the counter; PPI = proton pump inhibitor.

**Table 2.** The Los Angeles Grade Scale for Endoscopic Assessment of Esophagitis

Grade A:	Very small mucosal breaks
Grade B:	More substantial erosion with at least 1 mucosal break greater than 5 mm, but the mucosal breaks are not continuous between folds
Grade C:	Deeper breaks, which may be continuous between 2 folds but are not circumferential. Seventy-five percent of the esophagus is not involved, but there are scattered mucosal breaks that become confluent
Grade D:	Mucosal breaks involving at least 75% of esophageal circumference

Source: Adapted from reference 12.

### Managed Care Issues in Reflux Therapy

In the era of managed care, cost is a consideration for any treatment, irrespective of the degree of efficacy and safety. However, cost is determined by many factors, including quality of life. For GERD patients, a common managed care philosophy can be described as step-up/step-down therapy, in which patients who

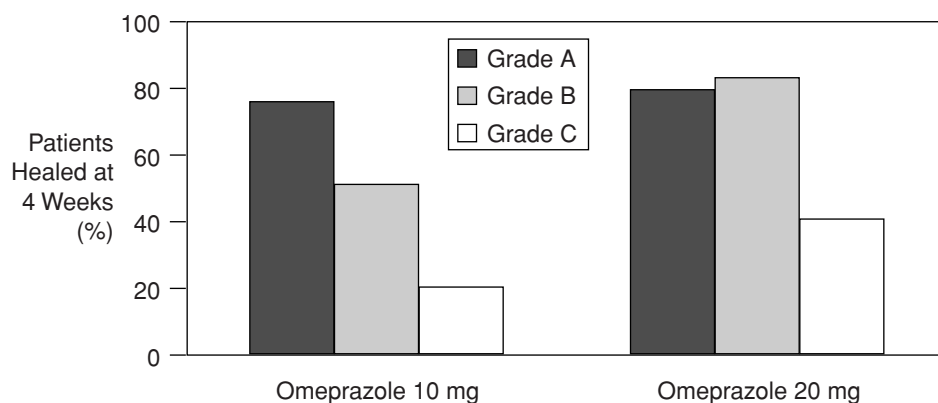
do not respond to initial treatment can step up to PPI therapy through increasingly effective and expensive therapy (Table 1). It is thought that patients who require step-up therapy to a PPI may not require a PPI for maintenance and therefore can be stepped down to a less expensive medication (eg, an H<sub>2</sub>RA) once the symptoms are treated. However, this reasoning is flawed, because if a patient fails a less effective therapy, he or she is not going to be maintained on that therapy if the most efficacious therapy available (a PPI) was required for symptom improvement.

Some plans request that high-dose H<sub>2</sub>RA therapy be tried before PPI therapy. However, a recent study showed that higher doses of H<sub>2</sub>RA therapy are not effective in patients who are poorly responsive to standard H<sub>2</sub>RA therapy. In that study, 285 patients were treated with ranitidine 150 mg bid for 6 weeks and remained symptomatic (ie, they continued to experience heartburn). Of these

patients, 271 were randomized to receive either the same dose or a higher dose (ie, 300 mg bid) for 8 weeks. The improvement with the higher dose was negligible; 45% of the patients in each treatment group experienced no more than mild heartburn. However, complete resolution was observed in less than 20% of patients in both treatment groups.<sup>11</sup>

The degree of esophagitis also affects treatment regimens. The Los Angeles classification system, which was proposed at the 10th World Congress of Gastroenterology in October 1994, is used to describe and classify the appearance of reflux esophagitis using 4 grade levels (Table 2). In a study to examine the reliability of this system, patients in each group were treated with either 10 or 20 mg of omeprazole. After 4 weeks, the results showed that patients with Grade A esophagitis showed healing with both treatment groups (Figure). For those with Grade B esophagitis, the higher dose offered better healing.

**Figure.** Endoscopic Assessment of Esophagitis: Correlation With PPI Response



Grade A, B, C are from the Los Angeles Classification System.

Source: Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: Clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45(2):172-180. Reprinted with permission from BMJ Publishing Group.

The more severe the grade of esophagitis (Grade C and D), the more difficult the disease was to heal, even with full-dose PPI therapy.<sup>12</sup>

In addition, more severe esophagitis results in a shorter time in remission when medication is stopped. Those with more severe disease (eg, grade C or D) will fail quickly if they are stepped down to H<sub>2</sub>RAs or are placed on half-dose PPI therapy after they are healed.<sup>12</sup> Therefore, severe erosive esophagitis requires higher-dose therapy and longer treatment times (probably lifelong).

### Comparing PPI Agents

There are now 4 PPIs available in the United States (omeprazole, lansoprazole, rabeprazole, and pantoprazole). No currently available PPI is clinically superior to any other. For example, a comparison of lansoprazole (15 and 30 mg) with omeprazole (20 mg) showed virtually no difference between lansoprazole 30 mg and omeprazole 20 mg in the percentage of patients who experienced healing of erosive esophagitis. Rates of symptom relief were also similar between these 2 treatment groups, although lansoprazole showed some superiority in nocturnal heartburn during the first few days of treatment. By the end of the treatment period, results in the 2 groups were equivalent. The lower dose of lansoprazole offered slightly lower healing rates and symptom relief, although these rates were significantly higher than for placebo.<sup>13</sup>

More recently, rabeprazole (20 mg) was compared with omeprazole (20 mg) to measure healing after 4 and 8 weeks of treatment in 202 patients with erosive esophagitis. At 4 weeks the healing rates were identical (81%), and at 8 weeks the healing rates were 92% and 94%, respectively, with no significant difference noted.<sup>14</sup>

Pantoprazole has recently been approved in the United States. In a European trial, pantoprazole (40 mg) was compared with omeprazole (20

mg) in 286 patients. At 4 weeks 78% and 74% of patients were completely healed in the pantoprazole and omeprazole groups, respectively. At 8 weeks the rates were 94% and 90%, respectively, with no significant difference between them.<sup>15</sup> Smaller studies comparing pantoprazole with lansoprazole showed equivalence in healing esophagitis and the symptomatic remission rate.

The PPI esomeprazole 40 mg, which may be available in the near future, has also recently been compared with omeprazole 20 mg in a large, randomized study of nearly 2000 patients. As with the other studies, the healing of esophagitis at weeks 4 and 8 was the primary endpoint. At week 4 esomeprazole 40 mg was superior to omeprazole 20 mg. By week 8 the healing rate for omeprazole was almost 87%, whereas the healing rate with esomeprazole was 94%. This is the first study using a clinically significant endpoint that suggests a benefit of one PPI over another. However, it is not known whether the clinical gain will result in widespread use of this compound.<sup>16</sup>

### Summary

Reflux disease, even in milder forms, significantly affects the quality of life of patients. Although some may trivialize the significance of this impact, a lower quality of life affects other healthcare utilization and the productivity of the patients. In fact, quality of life with reflux disease is comparable to other diseases such as diabetes and hypertension.

PPI therapy is considered first line, although the step-up/step-down approach encourages the use of a PPI as a last resort after failure of lifestyle changes, over-the-counter therapy, and H<sub>2</sub>RA therapy. The rationale for stepping down patients after successful treatment with PPI therapy is not well founded. The current paradigm should be that whichever treatment is necessary to heal a reflux disease

patient is the treatment that will be needed to maintain the healing. For those with severe erosive esophagitis, the doses will need to be higher, and therapy will probably be lifelong.

... REFERENCES ...

1. Enck P, Dubois D, Marquis P. Quality of life in patients with upper gastrointestinal symptoms: Results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). *Scand J Gastroenterol Suppl* 1999;231:48-54.
2. Dimenas E. Methodological aspects of evaluation of quality of life in upper gastrointestinal diseases. *Scand J Gastroenterol Suppl* 1993;199:18-21.
3. Revicki DA, Wood M, Maton PN, Sorenson S. The impact of gastroesophageal reflux disease on health-related quality of life. *Am J Med* 1998;104:252-258.
4. Revicki DA, Crawley JA, Zodet MW, Levine DS, Joelsson BO. Complete resolution of heartburn symptoms and health-related quality of life in patients with gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 1999;13:1621-1630.
5. Havelund T, Lind T, Wiklund I, et al. Quality of life in patients with heartburn but without esophagitis: Effects of treatment with omeprazole. *Am J Gastroenterology* 1999;94:1782-1789.
6. Furman D, Mensh R, Winan G, et al. A double-blind trial comparing high dose liquid antacid to placebo and cimetidine in improving symptoms and objective parameters in gastroesophageal reflux. *Gastroenterology* 1982;82:A1062. Abstract.
7. Klinkenberg-Knol EC, Festen HP, Meuwissen SG. Pharmacological management of gastro-oesophageal reflux disease. *Drugs* 1995;49:695-710.
8. Tytgat GN, Nio CY. The medical therapy of reflux oesophagitis. *Baillieres Clin Gastroenterol* 1987;1:791-807.
9. Wolfe MM, Sachs G. Acid suppression: Optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 2000;118:S9-S31.
10. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastro-oesophageal reflux disease. Practice Parameters Committee of the American College of Gastroenterology. *Arch Intern Med* 1995;155:2165-2173.
11. Kahrilas PJ, Fennerty MB, Joelsson B. High- versus standard-dose ranitidine for control of heartburn in poorly responsive acid reflux disease: A prospective, controlled trial. *Am J Gastroenterol* 1999;94:92-97.
12. Lundell LR, Dent J, Bennett JR, et al. Endoscopic assessment of oesophagitis: Clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999;45:172-180.
13. Castell DO, Richter JE, Robinson M, Sontag SJ, Haber MM. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. The Lansoprazole Group. *Am J Gastroenterol* 1996;91:1749-1757.
14. Dekkers CP, Beker JA, Thjodleifsson B, Gabryelewicz A, Bell NE, Humphries TJ. Double-blind comparison of rabeprazole 20 mg vs. omeprazole 20 mg in the treatment of erosive or ulcerative gastro-oesophageal reflux disease. The European Rabeprazole Study Group. *Aliment Pharmacol Ther* 1999;13:49-57.
15. Mossner J, Holscher AH, Herz R, Schneider A. A double-blind study of pantoprazole and omeprazole in the treatment of reflux oesophagitis: A multicentre trial. *Aliment Pharmacol Ther* 1995;9:321-326.
16. Kahrilas PJ, Falk G, Whipple J, D'Amico D, Joelsson B. Comparison of esomeprazole, a novel PPI, vs omeprazole in GERD patients with erosive esophagitis. *Gastroenterology* 2000;118(suppl 2 Pt 1):A193. Abstract 1224.