

Drug Class Review on Proton Pump Inhibitors

Update #5: Preliminary Scan Report #2

June 2008

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update Report

July 2006 (searches through November 2005)

Date of Last Scan

June 2007

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of different PPIs in patients with symptoms of GERD?
 - a. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse in patients with symptoms of GERD?
 - b. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in healing esophagitis, reducing symptoms, and preventing relapse of GERD?

2. What is the comparative effectiveness of different proton pump inhibitors in patients with peptic ulcer and NSAID-induced ulcer?
 - a. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with duodenal ulcer?
 - b. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with duodenal ulcer?
 - c. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with gastric ulcer?
 - d. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with gastric ulcer?
 - e. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with NSAID-induced ulcer?
 - f. In comparisons of PPIs and misoprostol or H2-RAs, what is the comparative effectiveness of different PPIs in reducing symptoms and improving endoscopic healing in patients with NSAID-induced ulcer?
 - g. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in preventing NSAID-induced ulcer?
 - h. In comparisons of PPIs and other drugs or placebo, what is the comparative effectiveness of different PPIs in preventing NSAID-induced ulcer?
 - i. In head-to-head comparisons, what is the comparative effectiveness of different PPIs in improving eradication rates in patients with *Helicobacter pylori*?
 - j. In comparisons of PPIs and H2-RAs, what is the comparative effectiveness of different PPIs in improving eradication rates in patients with *Helicobacter pylori*?
3. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different PPIs in

patients being treated for symptoms of gastroesophageal reflux, peptic ulcer, and NSAID-induced ulcer?

4. Are there subgroups of patients based on demographics, other medications, or co-morbidities (including patients with nasogastric tubes, or who cannot swallow solid oral medications) for which one medication or preparation is more effective or associated with fewer adverse effects?

Inclusion Criteria

Populations

Patients with symptoms of gastroesophageal reflux, peptic ulcer, or NSAID- induced ulcer.

Interventions

- Omeprazole (Prilosec[®], Prilosec OTC[®])
- Omeprazole/sodium bicarbonate (Zegerid[®])
- Lansoprazole (Prevacid[®])
- Pantoprazole (Protonix[®])
- Rabeprazole (Aciphex[®])
- Esomeprazole (Nexium[®])

Effectiveness outcomes

- Symptoms
- Endoscopic healing
- Eradication rates
- Functional outcomes
- Quality of life

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Specific adverse effects or withdrawals due to specific adverse events (e.g., diarrhea)

Study designs

1. For effectiveness, study is a randomized controlled trial in an outpatient setting and treatment period is at least 4 weeks duration.
2. For safety, study is a controlled clinical trial or observational study.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from June 2007 2005 through June Week 3 2008, using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/index-eng.php>) web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 136 citations. Of those, there are 18 potentially relevant new trials (see Appendix):

12 head-to-head trials

- Esomeprazole vs pantoprazole for treatment of GERD (4 trials)
- Lansoprazole vs omeprazole vs rabeprazole for Helicobacter pylori eradication (2 trials)
- 1 trial each:
 - Lansoprazole vs rabeprazole for treatment of GERD
 - Esomeprazole vs rabeprazole for Helicobacter pylori eradication
 - Omeprazole vs pantoprazole vs rabeprazole for Helicobacter pylori eradication
 - Esomeprazole vs omeprazole vs pantoprazole vs rabeprazole for Helicobacter pylori eradication
 - Omeprazole vs esomeprazole for ulcer
 - Omeprazole vs rabeprazole for ulcer

4 trials in children or adolescents

- 3 placebo-controlled trials for treatment of GERD
- 1 placebo-controlled trial for Helicobacter pylori eradication

2 placebo-controlled or active control trials

- Esomeprazole vs ranitidine for healing of NSAID-induced ulcer
- Esomeprazole vs placebo for maintenance treatment of NSAID-induced ulcer

Trials identified in previous scan

8 head-to-head trials

- Esomeprazole vs omeprazole for short-term treatment of GERD (2 trials)
- Esomeprazole vs pantoprazole for short-term treatment of GERD
- Esomeprazole vs pantoprazole for maintenance treatment of GERD (2 trials)
- Esomeprazole vs lansoprazole for maintenance treatment of GERD
- Rabeprazole vs omeprazole for peptic ulcer
- Lansoprazole vs omeprazole for Helicobacter pylori eradication

6 trials in children or adolescents

- 5 trials of lansoprazole, pantoprazole, or esomeprazole for short-term treatment of GERD
- 1 trial of omeprazole for helicobacter pylori eradication

6 placebo-controlled or active control trials

- Lansoprazole vs placebo for maintenance treatment of GERD
- Pantoprazole vs placebo for maintenance treatment of GERD
- 2 trials of PPI vs surgical treatment for GERD with 7-year followup
- 2 trials of esomeprazole vs placebo for prevention of NSAID-induced ulcer

New Drugs

A new drug, AZD0865, is in development by AstraZeneca. The drug is described as a proton pump selective, potassium-competitive acid blocker. Two trials comparing this drug to esomeprazole in patients with erosive and nonerosive esophagitis were identified.

New Indications

No new indications were identified for any of the included drugs.

New Safety Alerts

The following information about omeprazole (Prilosec[®]), omeprazole + sodium bicarbonate (Zegerid[®]), and esomeprazole (Nexium[®]) was issued by the FDA:

8/9/2007: FDA issued an early communication about the ongoing review of new safety data for the proton pump inhibitors, Prilosec and Nexium. The new safety data was from two small long-term clinical studies in patients with severe gastroesophageal reflux disease (GERD). In both studies, patients were randomly assigned to receive treatment with a drug (either omeprazole or esomeprazole) or to have surgery to control their GERD. The results from the study of Prilosec and analyses from an ongoing study of Nexium raised concerns that long-term use of Prilosec or Nexium may have increased the risk of heart attacks, heart failure, and heart-related sudden death in those patients taking either one of the drugs compared to patients who received surgery. After reviewing these and other data submitted by the company, FDA's preliminary conclusion at this time, is that collectively, these data do not suggest an increased risk of heart problems for patients treated with omeprazole or esomeprazole. Healthcare providers should not change their prescribing practices and patients should not change their use of these products at this time.

UPDATE 12/11/2007: FDA informed healthcare professionals of the issuance of the Agency's follow-up communication regarding its review of safety data for the drugs omeprazole and esomeprazole that raised concerns about a potential increased risk of heart problems for patients treated with these drugs. The Agency conducted a comprehensive review of the data from two studies that were submitted to FDA. FDA continues to believe that long-term use of omeprazole or esomeprazole is not likely to be associated with an increased risk of heart problems and recommends that healthcare providers continue to prescribe and patients continue to use these products in the manner described in the labeling for the two products. See the "Update of Safety Review" for information regarding the two studies that were reviewed.

APPENDIX. Potentially Relevant New Trials

Head-to-head trials (N=12)

Ando, T., T. Ishikawa, et al. (2008). "Endoscopic analysis of gastric ulcer after one week's treatment with omeprazole and rabeprazole in relation to CYP2C19 genotype." Digestive Diseases & Sciences **53**(4): 933-7.

In Japanese healthy CYP2C19 extensive metabolizers, rabeprazole 10 mg shows a faster onset of action and stronger inhibition of acid secretion than does omeprazole 20 mg on the first 3 days of administration. We evaluated gastric ulcer improvement after 1 week's treatment with rabeprazole or omeprazole in relation to CYP2C19 polymorphism. A 6-mm rubber disc was placed temporarily at the side of the ulcer for measurement of the ulcer area. The improvement ratios of ulcer area in homozygous extensive metabolizers (homoEMs), heterozygous extensive metabolizers (heteroEMs) and poor metabolizers (PMs) treated with rabeprazole 10 mg were 60.8, 65.0 and 55.3%, respectively, and these values are not significantly different. Corresponding values with omeprazole 20 mg were 46.3, 61.7 and 63.2%, respectively, and the value of homoEMs was significantly smaller than that of heteroEMs. The improvement ratios with rabeprazole in homoEMs and heteroEMs were significantly greater than that with omeprazole in homoEMs.

Bardhan, K. D., A. Achim, et al. (2007). "A clinical trial comparing pantoprazole and esomeprazole to explore the concept of achieving 'complete remission' in gastro-oesophageal reflux disease." Alimentary Pharmacology & Therapeutics **25**(12): 1461-9.

BACKGROUND AND AIM: The outcome of gastro-oesophageal reflux disease treatment is traditionally assessed by measuring endoscopically confirmed healing and symptom relief separately. Both terms together, indicating complete remission, are intuitively a more realistic clinical endpoint but are assessed less often. **AIM:** To explore this concept, we formally compared the efficacy of the proton pump inhibitors (PPIs) pantoprazole and esomeprazole using rates of complete remission judged against rates of healing and symptom relief separately. **METHODS:** Five hundred and eighty-two patients with erosive gastro-oesophageal reflux disease were randomized to treatment for 4, 8, or 12 weeks with either pantoprazole or esomeprazole 40 mg daily. Symptom relief was assessed with the validated ReQuesttrade mark-GI subscale. **RESULTS:** Approximately 75% of patients were free of symptoms or had no oesophageal lesions after 4 weeks' treatment, rising to about 93% and 96%, respectively, at 12 weeks. Complete remission rates were, however, lower at these time points; approximately 60% and about 90%, respectively. Both PPIs had similar efficacy. **CONCLUSIONS:** Endoscopically confirmed healing and symptom relief assessed separately over-estimated the benefits of both drugs. In contrast, complete remission indicates that patients may be treated inadequately when given the standard 4- to 8-week treatment. We suggest that complete remission is a more reliable and clinically relevant endpoint of treatment.

Choi, H. S., D. I. Park, et al. (2007). "Double-dose, new-generation proton pump inhibitors do not improve *Helicobacter pylori* eradication rate." *Helicobacter* **12**(6): 638-42.

BACKGROUND: Up to present, omeprazole plus two antibiotics are used for *Helicobacter pylori* eradication therapy. Few studies have compared double-dose new-generation, proton pump inhibitors (PPI) with omeprazole. Therefore, we conducted a randomized, prospective study to evaluate differences in *H. pylori* eradication rates by PPI type. **MATERIAL AND METHODS:** Between January 2006 and December 2006, 576 consecutive patients with proven *H. pylori* infection were enrolled prospectively. Four different PPIs (omeprazole 20 mg b.i.d. (old generation), or pantoprazole 40 mg b.i.d., rabeprazole 20 mg b.i.d., or esomeprazole 40 mg b.i.d. (new generation)) were added to clarithromycin (500 mg b.i.d.) and amoxicillin (1 g b.i.d.) for 1 week. **RESULTS:** By intention-to-treat analysis, no difference was found between the eradication rates of these four PPIs: 64.9% (omeprazole, n = 148), 69.3% (pantoprazole, n = 140), 69.3% (rabeprazole, n = 140), and 72.9% (esomeprazole, n = 148). When eradication rates were analyzed according to whether patients had an ulcer or not on a per-protocol basis, no difference was found between the eradication rates of the four PPIs. However, side-effects were more common in the esomeprazole-based triple therapy group than in the other groups ($p < .05$). **CONCLUSIONS:** No convincing evidence was obtained that double-dose new-generation PPIs have better *H. pylori* eradication rates and tolerability than omeprazole.

Glatzel, D., M. Abdel-Qader, et al. (2007). "Pantoprazole 40 mg is as effective as esomeprazole 40 mg to relieve symptoms of gastroesophageal reflux disease after 4 weeks of treatment and superior regarding the prevention of symptomatic relapse." *Digestion* **75 Suppl 1**: 69-78.

BACKGROUND/AIM: Little is known about the symptom course during and after treatment of gastroesophageal reflux disease (GERD). Here we address this question in patients with erosive GERD treated with pantoprazole or esomeprazole 40 mg once daily using the validated reflux questionnaire ReQuest. **METHODS:** Of 585 patients enrolled, 561 (intention-to-treat; ITT) patients with endoscopically confirmed GERD grades A-D (Los Angeles Classification) were randomized. To assess the GERD symptomatology, the patients completed the ReQuest daily, and analysis was done prior to (7 days), during (28 days), and after treatment (7 days). The mean scores (last 3 treatment days) of the subscale ReQuest(TM)-GI (gastrointestinal complaints) were compared between both groups. After the end of treatment, the number of symptom episodes and the rate of relapses were calculated. **RESULTS:** Noninferiority of pantoprazole versus esomeprazole during treatment was shown (mean ReQuest-GI score). During the posttreatment period, the proportion of patients experiencing a symptomatic relapse (51 vs. 61%, $p = 0.0216$, ITT) and the number of symptom episodes (0.56 vs. 0.74, $p = 0.0095$, ITT) were significantly lower on pantoprazole than on esomeprazole. **CONCLUSIONS:** Pantoprazole 40 mg was at least as effective as esomeprazole 40 mg for relieving GERD symptoms. During the posttreatment phase, patients on pantoprazole had a significantly lower risk to relapse and experienced significantly fewer symptom episodes. Copyright 2007 S. Karger AG, Basel.

Kawai, T., K. Kawakami, et al. (2007). "Efficacy of low-dose proton pump inhibitor (PPI) in the eradication of *Helicobacter pylori* following combination PPI/AC therapy in Japan." Hepato-Gastroenterology **54**(74): 649-54.

BACKGROUND/AIMS: In Japan, eradication regimens consisting of a proton pump inhibitor (PPI) + amoxicillin (AMPC) + clarithromycin (CAM) (PPI/AC) for 1 week have been conducted. In the present study, we assessed the eradication rates following treatment with low doses of various PPIs. **METHODOLOGY:** 135 patients were divided randomly into one of three 7-day regimens: (i) omeprazole (OPZ) 20 mg/day + AMPC 1500 mg/day + CAM 600 mg/day (OAC); (ii) lansoprazole (LPZ) 30 mg + AMPC 1500 mg/day + CAM 600 mg/day (LAC); and (iii) rabeprazole (RPZ) 10mg/day + AMPC 1500 mg/ day + CAM 600 mg/day (RAC). The genetic polymorphism of CYP2C19 was also examined. **RESULTS:** The eradication rates according to the treatment regimen were as follows: 69.9% (31/45) for OAC, 62.2% (28/45) for LAC, and 71.1% (32/45) for RPZ. No significant differences were found among the regimens. Moreover, eradication rates, according to CYP2C19 phenotype (homozygous extensive metabolizer (EM), heterozygous EM, and poor metabolizer) were: 68.6% (35/51), 77.4% (41/53), and 82.4% (14/17), respectively. **CONCLUSIONS:** In PPI/AC therapy, the eradication rate for each low-dose PPI was 60-70%, which is low. Based on previous reports, it is considered that doses greater than 40 mg/day OPZ, 60 mg/day LPZ, and 20 mg/day RPZ are required.

Kumar, R., V. R. Tandon, et al. (2007). "Comparative study of proton pump inhibitors for triple therapy in *H. pylori* eradication." Indian Journal of Gastroenterology **26**(2): 100-1.

Lu, M., V. Malladi, et al. (2007). "Failures in a proton pump inhibitor therapeutic substitution program: lessons learned." Digestive Diseases & Sciences **52**(10): 2813-20.

The pathogenesis of patient dissatisfaction following involuntary therapeutic substitutions involving proton pump inhibitors (PPIs) is poorly understood. The aim of this study was to describe the patient population experiencing therapeutic failure and investigate whether failure was related to individual differences in response to the different PPIs. Treatment failures in a lansoprazole-rabeprazole therapeutic substitution program were compared to switch successes. A subgroup was randomized in a double-blind, double-dummy, crossover study to four 2-week periods of lansoprazole-rabeprazole-lansoprazole-rabeprazole or vice versa. Measures included overall rating of gastrointestinal reflux disease (GERD) symptoms for the past week as well as the frequency and distress scales of the GERD Symptom Assessment Scale. One hundred fifteen nonresponders were compared with 54 successful responders. Nonresponders consisted primarily of patients with GERD (74%, vs. 44% of responders; $P = 0.005$) who had undergone upper gastrointestinal endoscopy (50%, vs. 31% of responders; $P = 0.02$). Twelve patients completed the randomized treatment study. The interrater kappa coefficient for responder status was estimated to be 0.80 for lansoprazole and 0.21 for rabeprazole. The majority of PPI nonresponders had a clinical diagnosis of GERD and were receiving ≥ 40 mg of rabeprazole daily. This pilot study provides new

insights into the design of subsequent studies of nonresponders in PPI therapeutic substitution programs.

Monnikes, H., B. Pfaffenberger, et al. (2007). "Novel measurement of rapid treatment success with ReQuest: first and sustained symptom relief as outcome parameters in patients with endoscopy-negative GERD receiving 20 mg pantoprazole or 20 mg esomeprazole." Digestion 75 Suppl 1: 62-8.

BACKGROUND/AIMS: A prime concern for gastroesophageal reflux disease (GERD) patients is fast symptom control. Sparse valid information is available on the rapidity of the effect of proton pump inhibitors in providing symptom relief. The new reflux questionnaire ReQuest is validated for daily assessment of changes in GERD symptoms. Therefore, this study investigated the efficacy of 20 mg pantoprazole and 20 mg esomeprazole with regard to the time to symptom relief in patients with endoscopy-negative GERD (enGERD) using ReQuest. **METHODS:** 529 patients were treated with pantoprazole or esomeprazole over 4 weeks. ReQuest symptom scores were assessed daily. The mean and median times to first and sustained symptom relief were determined. **RESULTS:** Median time to first symptom relief was 2 days for both drugs (intention-to-treat population). The median time to sustained symptom relief was 3 days shorter with pantoprazole (10.0 vs. 13.0 days). The Hodges-Lehmann estimator for the difference in time to reach first and sustained symptom relief between both groups was 0.00 days. For both variables the one-sided 95% CI (Moses) was [0.00; infinity], documenting no significant differences between the treatment groups. **CONCLUSIONS:** The rapidity of symptom control can be evaluated by clinically significant parameters using ReQuest. Pantoprazole and esomeprazole are equally effective in the time to first and sustained symptom relief. Copyright 2007 S. Karger AG, Basel.

Murakami, K., T. Okimoto, et al. (2008). "Evaluation of three different proton pump inhibitors with amoxicillin and metronidazole in retreatment for *Helicobacter pylori* infection." Journal of Clinical Gastroenterology 42(2): 139-42.

GOALS: We compared the eradication results of retreatment of eradication with proton pump inhibitor (PPI) plus amoxicillin and metronidazole for patients with *Helicobacter pylori* infection not eradicated by initial treatment with PPI plus amoxicillin and clarithromycin. **BACKGROUND:** In Japan, the guideline proposes that the use of metronidazole in a triple therapy containing PPI, PPI plus amoxicillin and metronidazole is desirable in retreatment. However, there are no reports comparing various retreatment using different PPIs. **METHODS:** After initial treatment failure with a PPI plus amoxicillin and clarithromycin, 169 patients were randomized to a PPI (rabeprazole, lansoprazole, or omeprazole) plus amoxicillin and metronidazole given b.i.d. for 7 days. **RESULTS:** Pretreatment susceptibility testing showed a high level of clarithromycin resistance (78%). The over all eradication rates were similar with the 3 PPIs, 91.1% range 90.1 to 91.4 with intention-to-treat analysis. The presence of metronidazole resistance reduced the eradication rate by approximately 40% (from 96.6% to 57.1%, $P < 0.05$). **CONCLUSIONS:** In Japan, the combination of a PPI plus amoxicillin and metronidazole provide excellent eradication rates after initial treatment failure with

a PPI plus amoxicillin and clarithromycin. The results with metronidazole resistant strains are less satisfactory and pretreatment susceptibility testing may become needed if the prevalence of metronidazole resistant *H. pylori* increase.

Pilotto, A., M. Franceschi, et al. (2007). "Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients." World Journal of Gastroenterology **13**(33): 4467-72.

AIM: To compare efficacy and tolerability of four proton pump inhibitors (PPIs) commonly used in the short-term therapy of esophagitis in elderly patients. **METHODS:** A total of 320 patients over 65 years with endoscopically diagnosed esophagitis were randomly assigned to one of the following treatments for 8 wk: (1) omeprazole 20 mg/d; (2) lansoprazole 30 mg/d; (3) pantoprazole 40 mg/d, or (4) rabeprazole 20 mg/d. Major symptoms, compliance, and adverse events were recorded. After 8 wk, endoscopy and clinical evaluation were repeated. **RESULTS:** Per protocol and intention to treat healing rates of esophagitis were: omeprazole = 81.0% and 75.0%, lansoprazole = 90.7% ($P = 0.143$ vs omeprazole) and 85.0%, pantoprazole = 93.5% ($P = 0.04$ vs omeprazole) and 90.0% ($P = 0.02$ vs omeprazole), rabeprazole = 94.6% ($P = 0.02$ vs omeprazole) and 88.8% ($P = 0.04$ vs omeprazole). Dividing patients according to the grades of esophagitis, omeprazole was significantly less effective than the three other PPIs in healing grade 1 esophagitis (healing rates: 81.8% vs 100%, 100% and 100%, respectively, $P = 0.012$). Pantoprazole and rabeprazole (100%) were more effective vs omeprazole (89.6%, $P = 0.0001$) and lansoprazole (82.4%, $P = 0.0001$) in decreasing heartburn. Pantoprazole and rabeprazole (92.2% and 90.1%, respectively) were also more effective vs lansoprazole (75.0%, $P < 0.05$) in decreasing acid regurgitation. Finally, pantoprazole and rabeprazole (95.2% and 100%) were also more effective vs lansoprazole (82.6%, $P < 0.05$) in decreasing epigastric pain. **CONCLUSION:** In elderly patients, pantoprazole and rabeprazole were significantly more effective than omeprazole in healing esophagitis and than omeprazole or lansoprazole in improving symptoms. *H. pylori* infection did not influence the healing rates of esophagitis after a short-term treatment with PPI.

Subei, I. M., H. J. Cardona, et al. (2007). "One week of esomeprazole triple therapy vs 1 week of omeprazole triple therapy plus 3 weeks of omeprazole for duodenal ulcer healing in *Helicobacter pylori*-positive patients." Digestive Diseases & Sciences **52**(6): 1505-12.

In this randomized, double-blind, multicenter study, *H. pylori*-positive patients with an active duodenal ulcer (DU) received esomeprazole, 20 mg twice daily (bid), or omeprazole, 20 mg bid, with amoxicillin, 1000 mg bid, and clarithromycin, 500 mg bid, for 1 week (EAC and OAC, respectively). Patients received an additional 3 weeks of either placebo or omeprazole, 20 mg once daily (od), in the EAC and OAC groups, respectively. The intent-to-treat population included 374 patients (EAC, 186; OAC, 188). Four-week DU healing rates were similar in the EAC+placebo and OAC+omeprazole groups: 74% and 76%, respectively. DU healing rates at 8 weeks were 87% for EAC+placebo and 88% for OAC+omeprazole. *H. pylori* eradication rates were 75% and 79% for EAC and OAC, respectively. Both regimens were well tolerated. A 1-week regimen of

esomeprazole-based H. pylori eradication triple therapy was as effective for DU healing and eradication of H. pylori as omeprazole-based triple therapy followed by an additional 3 weeks of monotherapy.

Wu, I. C., D.-C. Wu, et al. (2007). "Rabeprazole- versus esomeprazole-based eradication regimens for H. pylori infection." *Helicobacter* **12**(6): 633-7.

BACKGROUND: Different kinds of proton pump inhibitor-based triple therapies could result in different *Helicobacter pylori* eradication rates. **AIM:** The aims of this study were to compare the efficacy and safety of rabeprazole- and esomeprazole-based triple therapy in primary treatment of H. pylori infection in Taiwan.

PATIENTS AND METHODS: From June 2005 to March 2007, 420 H. pylori-infected patients were randomly assigned to receive a 7-day eradication therapy with either esomeprazole 40 mg daily (EAC group, n = 209) or rabeprazole 20 mg b.i.d. (RAC group, n = 211) in combination with amoxicillin 1 g b.i.d. and clarithromycin 500 mg b.i.d.. Follow-up endoscopy with biopsy was done 12-16 weeks after completion of eradication therapy. Those who refused endoscopic exams underwent (13)C-urea breath test to assess the treatment response.

RESULTS: Intention-to-treat analysis revealed that the eradication rate was 89.4% in the EAC group and 90.5% in RAC groups (p-value = .72). All of the subjects returned for assessment of compliance (100% in EAC group vs. 99.5% in RAC group, p-value = .32) and adverse events (3.83% in EAC group vs. 6.16% in RAC group, p-value = .27). Sixty (28.7%) and 37 (17.6%) patients in EAC and RAC group, respectively, refused endoscopy and underwent a (13)C-urea breath test to determine the treatment effect. **CONCLUSION:** In conclusion, rabeprazole- and esomeprazole-based primary therapies for H. pylori infection are comparable in efficacy and safety.

Trials in children or adolescents (N=4)

Boccia, G., F. Manguso, et al. (2007). "Maintenance therapy for erosive esophagitis in children after healing by omeprazole: is it advisable?[see comment]." *American Journal of Gastroenterology* **102**(6): 1291-7.

OBJECTIVES: To evaluate the efficacy of acid-suppressive maintenance therapy for gastroesophageal reflux disease (GERD) in children, after the healing of reflux esophagitis. **METHODS:** Forty-eight children (median age 105 months, range 32-170) with erosive reflux esophagitis were initially treated with omeprazole 1.4 mg/kg/day for 3 months. Patients in endoscopic remission were assigned in a randomized, blinded manner by means of a computer-generated list to three groups of 6-month maintenance treatment: group A (omeprazole at half the starting dose, once daily before breakfast), group B (ranitidine 10 mg/kg/day, divided in two doses), and group C (no treatment). Endoscopic, histological, and symptomatic scores were evaluated at: T0, enrollment; T1, assessment for remission at 3 months after enrollment (healing phase); T2, assessment for effective maintenance at 12 months after T0 (3 months after the completion of the maintenance phase). Relapse was defined as the recurrence of macroscopic esophageal lesions. After the completion of the maintenance phase, patients without macroscopic esophagitis

relapse were followed up for GERD symptoms for a further period of 30 months. RESULTS: Of 48 initially treated patients, 46 (94%) healed and entered the maintenance study. For all patients, in comparison to T0, the histological, endoscopic, and symptomatic scores were significantly reduced both at T1 and T2 ($P < 0.0001$, for each). No significant difference was found in these three scores, comparing group A, B, and C at T1 and T2. A relapse occurred in one patient only, who presented with macroscopic esophageal lesions at T2. Three months after the completion of the maintenance phase, 12 (26%) patients complained of symptoms sufficiently mild to discontinue GERD therapy, excluding the patient who showed macroscopic esophagitis relapse. Three of 44 (6.8%) patients reported very mild GERD symptoms within a period of 30 months after maintenance discontinuation. CONCLUSIONS: Our pediatric population showed a low rate of erosive esophagitis relapse and GERD symptom recurrence long term after healing with omeprazole, irrespective of the maintenance therapy.

Cadranel, S., P. Bontemps, et al. (2007). "Improvement of the eradication rate of *Helicobacter pylori* gastritis in children is by adjunction of omeprazole to a dual antibiotherapy." Acta Paediatrica **96**(1): 82-6.

AIM: The possible improvement of efficacy and tolerability of a 7-day dual antibiotherapy amoxicillin-clarithromycin (AC) on the eradication of *Helicobacter pylori* (*H. pylori*) gastritis in children by the adjunction of omeprazole (OAC) was studied. METHODS: Forty-six children presenting with *H. pylori* gastritis, assessed at inclusion by endoscopy, *H. pylori* urease test, histology and/or culture were randomised to a twice-daily regimen of AC or OAC. A ¹³C-urease breath test was performed 4-6 weeks after the end of the treatment period to evaluate *H. pylori* eradication. RESULTS: A larger proportion of patients was *H. pylori* negative (69%) in the OAC regimen treatment 4-6 weeks after eradication treatment compared with those who received dual AC therapy (15%). A total of seven patients (three in the OAC and four in the AC group) reported adverse events (AEs). Only vomiting was reported in more than one patient (one in each treatment regimen) and only one AE was severe (urticaria: in the OAC group, but considered not related to treatment). CONCLUSION: A larger eradication rate of *H. pylori* was obtained in the triple OAC group than in the dual AC group. Both therapy regimens can be safely administered to children for 7 days.

Gold, B. D., T. Gunasekaran, et al. (2007). "Safety and symptom improvement with esomeprazole in adolescents with gastroesophageal reflux disease." Journal of Pediatric Gastroenterology & Nutrition **45**(5): 520-9.

OBJECTIVES: The primary objective was to assess the safety of esomeprazole 20 or 40 mg once daily in adolescents with clinically diagnosed gastroesophageal reflux disease (GERD). A secondary aim was to assess changes in GERD symptoms after esomeprazole therapy. PATIENTS AND METHODS: In this multicenter, randomized, double-blind study, adolescents ages 12 to 17 years inclusive received esomeprazole 20 or 40 mg once daily for 8 weeks. Adverse events and changes in clinical parameters (eg, physical examination, laboratory measurements) were evaluated to assess safety. Patients or their parents or guardians scored symptom

severity daily, and investigators scored overall GERD symptom severity every 2 weeks using a 4-point scale. **RESULTS:** In the 148 adolescents with safety data, treatment-related and non-treatment-related adverse events were reported by 75% and 78% of patients in the esomeprazole 20- and 40-mg groups, respectively. Twenty-two patients (14.9%) experienced adverse events that were considered related to treatment; the most common were headache (8%, 12/148), abdominal pain (3%, 4/148), nausea (2%, 3/148), and diarrhea (2%, 3/148). No serious adverse events or clinically important findings in other safety assessments were observed. At baseline, 68% (100/147) had heartburn, 63% (93/147) had epigastric pain, 57% (84/147) had acid regurgitation, and 15% (22/147) had vomiting symptoms. Symptom scores decreased significantly in both the esomeprazole 20-mg and 40-mg groups by the final study week ($P < 0.0001$). Investigators rated 63.1% (94/149) of the patients as having moderate or severe symptoms at baseline; at the final visit, this percentage decreased significantly to 9.3% (13/140; $P < .0001$). **CONCLUSIONS:** In adolescent patients with GERD, esomeprazole 20 or 40 mg daily for 8 weeks was well tolerated, and GERD-related symptoms were significantly reduced from baseline values in both groups.

Khoshoo, V. and P. Dhume (2008). "Clinical response to 2 dosing regimens of lansoprazole in infants with gastroesophageal reflux." Journal of Pediatric Gastroenterology & Nutrition **46**(3): 352-4.

Proton pump inhibitors such as lansoprazole are used in the treatment of gastroesophageal reflux disease (GERD), but dosing guidelines for infants have not been determined. The objective of this study was to assess the clinical efficacy of 2 dosing regimens of lansoprazole in infants with GERD using the revised infant gastroesophageal reflux questionnaire scores (I-GERQ-R). Thirty consecutive infants (3-7 months) with GERD, whose conditions were diagnosed by I-GERQ-R scores of $>$ or $=16$, were randomly assigned to receive 1 of 2 lansoprazole dosing regimens: 15 mg given once per day (group A) or approximately 7.5 mg given 2 times per day (group B). Matched infants in a control group were treated with an extensively hydrolyzed formula (group C). Daily I-GERQ-R scores were gathered, and the scores after 1 and 2 weeks of treatment were used for analysis. The mean pretreatment scores were similar in groups A, B, and C (26.6, 26.9, and 25.9, respectively). After treatment there was a similar drop in the mean scores in groups A and B (20.6 and 20.0, respectively), but not in group C (25.8). At the end of the first week of treatment, in group A, 5 of 15 infants (33%) had a significant reduction in their I-GERQ-R scores, whereas in group B, 10 of 15 infants (67%) had a significant reduction in their I-GERQ-R scores ($P < 0.05$). At the end of the second week of treatment, groups A and B had similar numbers of patients with significant improvement (60% and 67%), which was higher than in group C (3/15, 20%). Overall, there was no difference in the symptom response, as measured by I-GERQ-R scores, between 15 mg of lansoprazole given once per day and 7.5 mg given twice per day in infants with GERD, but the twice-daily regimen produced a faster symptom response. Both regimens were significantly better than treatment of infants with an extensively hydrolyzed formula.

Placebo-controlled or active control trials (N=2)

Goldstein, J. L., J. F. Johanson, et al. (2007). "Clinical trial: healing of NSAID-associated gastric ulcers in patients continuing NSAID therapy - a randomized study comparing ranitidine with esomeprazole." Alimentary Pharmacology & Therapeutics **26**(8): 1101-11.

BACKGROUND: The use of non-steroidal anti-inflammatory drugs (NSAID) is associated with an increased risk of gastric ulcer (GU) development. **METHODS:** This multicentre, randomized, double-blind, parallel-group trial compared endoscopic healing rates at 4 and 8 weeks after treatment with oral esomeprazole 40 or 20 mg once daily, or ranitidine 150 mg twice daily, in patients with 1 baseline GU \geq 5 mm but no GUs or duodenal ulcers >25 mm in diameter who received continued cyclooxygenase-2-selective or non-selective NSAID therapies. The primary outcome was the percentage of patients in each treatment group who had no GUs at week 8. **RESULTS:** Four hundred and forty patients were randomized to treatment. At week 8, GU healing rates (95% CI) with esomeprazole 40 mg, esomeprazole 20 mg and ranitidine were 85.7 (79.8-91.7)%, 84.8 (78.8-90.8)% and 76.3 (69.2-83.3)%, respectively; between-group differences were not statistically significant. Week-4 GU healing rates were 70.7 (62.9-78.4)% and 72.5 (65.0-79.9)% with esomeprazole 40 and 20 mg, respectively, and were significantly higher ($P < 0.01$ for both doses) than those with ranitidine [55.4 (47.1-63.7)%]. **CONCLUSION:** In patients who require continued NSAID therapy, GU healing rates at 8 weeks numerically favoured esomeprazole but were not significantly different from ranitidine.

Hawkey, C. J., N. J. Talley, et al. (2007). "Maintenance treatment with esomeprazole following initial relief of non-steroidal anti-inflammatory drug-associated upper gastrointestinal symptoms: the NASA2 and SPACE2 studies." Arthritis Research & Therapy **9**(1): R17.

Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 (COX-2) inhibitors, cause upper gastrointestinal (GI) symptoms that are relieved by treatment with esomeprazole. We assessed esomeprazole for maintaining long-term relief of such symptoms. Six hundred and ten patients with a chronic condition requiring anti-inflammatory therapy who achieved relief of NSAID-associated symptoms of pain, discomfort, or burning in the upper abdomen during two previous studies were enrolled and randomly assigned into two identical, multicentre, parallel-group, placebo-controlled studies of esomeprazole 20 mg or 40 mg treatment (NASA2 [Nexium Anti-inflammatory Symptom Amelioration] and SPACE2 [Symptom Prevention by Acid Control with Esomeprazole] studies; ClinicalTrials.gov identifiers NCT00241514 and NCT00241553, respectively) performed at various rheumatology, gastroenterology, and primary care clinics. Four hundred and twenty-six patients completed the 6-month treatment period. The primary measure was the proportion of patients with relapse of upper GI symptoms, recorded in daily diary cards, after 6 months. Relapse was defined as moderate-to-severe upper GI symptoms (a score of more than or equal to 3 on a 7-grade scale) for 3 days or more in any 7-day period. Esomeprazole was significantly more effective than placebo in maintaining relief of upper GI symptoms throughout 6

months of treatment. Life-table estimates (95% confidence intervals) of the proportion of patients with relapse at 6 months (pooled population) were placebo, 39.1% (32.2% to 46.0%); esomeprazole 20 mg, 29.3% (22.3% to 36.2%) ($p = 0.006$ versus placebo); and esomeprazole 40 mg, 26.1% (19.4% to 32.9%) ($p = 0.001$ versus placebo). Patients on either non-selective NSAIDs or selective COX-2 inhibitors appeared to benefit. The frequency of adverse events was similar in the three groups. Esomeprazole maintains relief of NSAID-associated upper GI symptoms in patients taking continuous NSAIDs, including selective COX-2 inhibitors.