



Medical treatment of gastroesophageal reflux disease

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ABSTRACT

Proton pump inhibitors (PPIs) are the most effective agents in the first-line and maintenance treatment of gastroesophageal reflux disease. As the grade of esophagitis increases, an increase is also observed in the level of endoscopic response to PPIs. In the first-line therapy of patients with severe esophagitis (Los Angeles (LA) Grade C-D), administration of a standard dose of PPIs bid has been reported to be more beneficial than PPIs qd. While any intermittent and low dose-continuous treatment can be chosen for the maintenance therapy of patients with non-erosive reflux disease or mild esophagitis (LA Grade A-B), continuous use of a standard dose of PPIs is preferred in the maintenance therapy of patients with severe esophagitis (LA Grade C-D). In patients who use PPIs for a long time, the drug must be stopped by gradually decreasing the dose.

Keywords: Treatment, reflux, remission, on-demand, cessation

WHAT ARE THE AVAILABLE MEDICAL TREATMENT REGIMENS FOR GERD?

In the literature, most studies on the treatment of gastroesophageal reflux disease (GERD) examine the use of proton pump inhibitors (PPIs) at standard doses (1). The standard doses of PPIs are 40 mg for esomeprazole, 30 mg for lansoprazole, 20 mg for omeprazole, 40 mg for pantoprazole, and 20 mg for rabeprazole qd. The PPI dose for maintenance therapy is defined as a half-dose of PPIs. A high dose of PPIs is defined as a double dose of PPIs. In the literature, in addition to the standard doses of PPIs, there are studies regarding:

- Double doses of PPIs
- On-demand PPIs
- H₂ receptor blockers
- Intermittant PPIs
- Antacid-alginates
- Prokinetics
- Baclofen
- Sucralfate

There are several definitions of the use of PPIs for maintenance therapy:

- **Continuous treatment:** The use of therapy without stopping.
- **On-demand treatment:** The use of a standard/maintenance dose of a drug when a symptom occurs.
- **Intermittant treatment:** In cases with recurrent symptoms, a standard/maintenance dose of therapy is given for two to eight weeks, and the treatment regimen is re-initiated when symptoms recur.

FIRST-LINE MEDICAL TREATMENT OF GERD- IS THERE ANY DIFFERENCE BETWEEN THERAPIES?

The most commonly used medications for the first-line treatment of GERD are PPIs and histamine-2 receptor antagonists (H₂RAs). In the literature, there is sufficient evidence demonstrating that PPIs are superior to other drugs in the treatment of GERD. In the meta-analysis conducted by Sigterman et al. (1), in which 34 studies were analyzed, PPIs were found to be superior to placebos (RR: 0.71, CI: 0.65 to 0.78), H₂RAs (RR: 0.78, CI: 0.62 to 0.97), and prokinetics (RR: 0.72, CI: 0.56 to 0.92) in the treatment of heartburn in patients with non-erosive reflux disease. A

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similar analysis was more clearly documented in a group given empirical treatment without undergoing endoscopy (PPI vs. placebo: RR: 0.37 (CI: 0.32 to 0.44), PPI vs. H2RA: RR: 0.66 (CI: 0.60 to 0.73), PPI vs. prokinetic: RR: 0.53 (CI: 0.32 to 0.87)).

The relative therapeutic gain achieved by PPIs for regurgitation, which is another symptom of GERD, is apparently lower than the therapeutic gain for heartburn. In the systematic literature review performed by Kahrilas et al. (2), which examined 7 placebo-controlled trials, while the relative therapeutic gain obtained with PPIs was 17% for regurgitation, this rate was >20% less for heartburn. Similar findings were observed in studies comparing PPIs with prokinetics or H2RAs.

Contradictory results have been obtained from studies comparing the effectiveness of various PPIs in the treatment of GERD. In a meta-analysis examining 16 studies on GERD treatment, the therapy of esomeprazole 40 mg/day was demonstrated to be more effective than the therapy of omeprazole 20 mg/day for providing endoscopic remission (RR: 1.18, CI: 1.14 to 1.23) (3). However, in this meta-analysis, omeprazole 20 mg/day was used and esomeprazole, which is an enantiomer of omeprazole, was used at a dose of 40 mg/day. The authors have emphasized that omeprazole must be used at a dose of at least 40 mg/day for a proper comparison (3).

Some publications have shown that esomeprazole is superior to other PPIs in cases of severe erosive esophagitis. In the systematic literature review conducted by Edwards et al. (4), in which 12 studies were analyzed, among PPIs (esomeprazole 40 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day, rabeprazole 20 mg/day), only esomeprazole 40 mg/day was found to be superior to omeprazole 20 mg/day in terms of endoscopic remission in the 4th week (RR: 1.84, CI: 1.5 to 2.2) and in the 8th week (RR: 1.91, CI: 1.13 to 2.88) following the beginning of treatment. However, it should also be considered in these studies that while esomeprazole was used at a dose of 40 mg/day, the dose of omeprazole was 20 mg/day. In another meta-analysis of 10 studies, a 5% relative increase was observed in the healing of erosive esophagitis with esomeprazole (CI: 1.02 to 1.08) compared to other PPIs at the end of the 8th week. Another important result of this meta-analysis was that the effects of esomeprazole became more evident as the stage of esophagitis increased (while the NNT (number needed to treat) was 50 for Los Angeles (LA) Grade A Esophagitis, it was 8 for LA Grade D) (5).

Although some studies show that esomeprazole is superior to other PPIs in the treatment of erosive esophagitis, a similar result has not been found for cases of non-erosive reflux disease. Armstrong et al. (6) compared more than 400 patients using esomeprazole 40 mg/day and omeprazole 20 mg/day in their study; they found no difference between the groups at the end of the 4th week in terms of heartburn healing.

Conflicting results have been obtained in studies comparing the efficiencies of the same PPI at different doses. In the studies on pantoprazole, a dose of 40 mg/day was found to be superior to a dose of 20 mg/day, while a dose of 80 mg/day was found to be more effective than doses of 40 mg/day and 20 mg/day (7,8). Richter et al. (7) compared 173 patients using pantoprazole 40 mg/day with 174 patients using pantoprazole 20 mg/day. They obtained higher rates of endoscopic and symptomatic remission in the group receiving pantoprazole 40 mg/day at the end of the 4th and 8th weeks. Moreover, in a recent study, higher symptomatic remission rates were found in patients with erosive esophagitis who received an 80 mg/day dose of pantoprazole at the end of the 4th and 8th weeks, compared to those who received a 40 mg/day dose of pantoprazole (8).

RECOMMENDATIONS

- The most effective medication group for the first-line treatment of GERD is PPIs (Level of evidence: 1a).
- PPIs are more effective in the treatment of erosive esophagitis than in the treatment of heartburn (Level of evidence: 1a).
- With PPIs, the rate of relieving is higher in heartburn than in regurgitation (Level of evidence: 1a).
- As the grade of esophagitis increases, the endoscopic response rate to PPIs also increases (Level of evidence: 1a).
- In severe esophagitis (LA grade C-D), esomeprazole is more effective than other PPIs (Level of evidence: 1a).
- In patients with severe esophagitis (LA grade C-D), standard doses of PPIs must be given twice a day for first-line treatment (Level of evidence: 5).
- H2 receptor blockers are superior to placebo but not as effective as PPIs (Level of evidence: 1a).
- There are insufficient data on therapies other than PPI and H2 receptor blockers (Level of evidence: 5).

HOW SHOULD MAINTENANCE TREATMENT BE PERFORMED FOR GERD?

Gastroesophageal reflux disease is a chronic disease that causes a serious decrease in quality of life and can present with relapses (9). The symptoms of GERD rapidly re-occur following cessation of treatment; therefore, planning an appropriate maintenance treatment for GERD is highly important (10). Randomized-controlled studies have demonstrated that the most effective drugs for the maintenance treatment of GERD are PPIs. In a meta-analysis by Donnellan et al. (11), which was conducted in 2004 and published in the Cochrane database, it was revealed that the use of PPIs in the maintenance treatment of GERD both at the maintenance dose and the standard dose significantly decreased the risks of endoscopic and symptomatic relapses compared to placebos and H2RAs.

Contradictory results have been obtained in studies comparing the efficiencies of PPIs in the maintenance treatment of GERD.

In the study of Scholten et al. (12), in which 20 mg/day doses of pantoprazole and esomeprazole were compared in terms of their efficiencies for maintenance treatment, no difference was found with regard to the mean score of heartburn frequency and the mean number of tablets taken over 6 months. Similarly, in a study comparing more than 1200 cases, no difference was detected between the groups in terms of combined endoscopic and symptomatic remission rates after 6 months of maintenance treatment with 20 mg/day esomeprazole and pantoprazole (85% vs. 84%) (13). In the large population-based study of Labenz et al. (14), it was reported that the endoscopic remission rate was significantly higher in the esomeprazole group following 8 weeks of acute treatment in patients using esomeprazole and pantoprazole at 6-month maintenance doses (87.0% vs. 74.9%, $p < 0.0001$). In another study comparing esomeprazole 20 mg/day and lansoprazole 15 mg/day in maintenance treatment, both symptomatic remission rates (78% vs 71%, $p = 0.001$) and endoscopic remission rates (83% vs 74%, $p < 0.0001$) were detected to be higher in the esomeprazole group (15).

There are also conflicting results on the use of different doses of the same PPI in the maintenance treatment of GERD in the literature. In a study investigating the use of pantoprazole at doses of 40 mg/day, 20 mg/day, and 10 mg/day for 12 months, the endoscopic recurrence rate was reported to be lower in the group receiving the dose of 40 mg/day than in the groups receiving doses of 20 mg/day and 10 mg/day. Moreover, a lower endoscopic recurrence rate was found in the group receiving the dose of 20 mg/day than in the group receiving the dose of 10 mg/day (7). On the other hand, in the study of Scholten et al. (16), no difference was found between patients using pantoprazole at the standard dose and at the maintenance dose at the end of the 6th month in terms of the mean symptom load (2.7 vs. 2.9, $p > 0.05$). Similarly, at the end of the 6th month, there was no difference between patients receiving esomeprazole at the standard dose and at the maintenance dose with regard to symptomatic remission rates (17). On the other hand, in a study in which Caos et al. (18) compared the usage of rabeprazole 20 mg/day and rabeprazole 10 mg/day, endoscopic recurrence rates were found to be higher in the rabeprazole 10 mg/day group at the end of 5 years of medication therapy (11% vs. 23%, $p < 0.05$).

Some data indicate that continuous use of PPI in the maintenance treatment of GERD is superior to on-demand use of PPI for the prevention of both endoscopic recurrence and symptomatic recurrence (19,20). Sjöstedt et al. (19) randomized 477 patients, who had erosive esophagitis and who experienced remission with a therapy of esomeprazole 40 mg/day, as groups receiving continuous or on-demand esomeprazole at the maintenance dose. While the remission rate was found to be 81% in the continuous therapy group, this rate was 58% in the on-demand group at the end of the 6th month ($p < 0.0001$). In the study of Morgan et al. (20), 268 patients receiving continuous and on-demand rabeprazole 20 mg therapy during maintenance treatment were compared; it was revealed that the number of days

without experiencing heartburn was higher in the group given continuous treatment (90.3% vs. 64.8%, $p < 0.0001$). In the large population-based study of Pace et al. (21) (5256), improvement in the QoLRAD (quality of life in reflux and dyspepsia) questionnaire was reported to be higher in patients using continuous esomeprazole 20 mg/day for maintenance treatment than in those using on-demand esomeprazole 20 mg/day ($p < 0.0001$).

RECOMMENDATIONS

- The most effective medication group for the maintenance treatment of GERD is PPIs (Level of evidence: 1a).
- The standard dose is more effective than a low dose in maintenance treatment (Level of evidence: 1a).
- The maintenance dose must be continued with the lowest dose at which the patient remains asymptomatic (Level of evidence: 5).
- There are limited data regarding whether continuous treatment improves life quality and symptomatic recovery according to therapy (Level of evidence: 1b).
- In the maintenance treatment of GERD, H2 receptor blockers are superior to placebos but are not as effective as PPIs (Level of evidence: 1a).
- There are insufficient data on therapies other than PPIs and H2 receptor blockers.

CESSATION OF THE TREATMENT IN PATIENTS WITH GERD

Optimal Cessation Time of Drugs in the Treatment of GERD

During our systematic literature review, no study comparing the effects of the duration of drug use in GERD treatment on the success of treatment and on endoscopic or symptomatic recurrence was found. However, in cases in which treatment was continued for at least six or more months after four or eight weeks of first-line treatment, both endoscopic and symptomatic remission rates were found to be higher than in the group not receiving treatment. In the study by Lind et al. (22), higher symptomatic remission rates were detected at the end of the 6th month in patients using 20 mg/day or 10 mg/day omeprazole during 6 months of maintenance treatment after first-line treatment compared to the placebo group (83%, 70%, and 56%, respectively). Similarly, higher symptomatic remission rates were found in cases using rabeprazole at the treatment dose for 6 months after first-line treatment than in the cases receiving placebo during maintenance treatment (86.7% vs. 74.9%, $p < 0.02$) (23). In the study of Caos et al. (18), after patients with erosive esophagitis underwent 8 weeks of rabeprazole 20 mg/day therapy, during maintenance treatment up to the 52 weeks, the rate of healing was significantly higher in patients receiving rabeprazole 20 mg/day (90%) and 10 mg/day (73%), than in the placebo group (29%) (respectively, $p < 0.01$ and $p = 0.04$).

In our systematic literature review, no evidence was found that increasing the duration of drug use from six months to one year decreased the endoscopic or symptomatic recurrence

rates (7,18,24). In the study by Richter et al. (7), after one-year maintenance treatment with pantoprazole at the standard dose, the endoscopic recurrence rate was found to be 22%. In contrast, in the study by Festen et al. (24), the endoscopic recurrence rate was found to be 32% after 1 year of treatment with omeprazole at the maintenance dose. These values are similar to endoscopic recurrence rates detected after six months of continuous maintenance treatment (14,15).

RECOMMENDATIONS

- In the literature, there is no study comparing the effects of the duration of drug use in the treatment of GERD on treatment success and on endoscopic or symptomatic recurrence (evaluation of recurrence rates after giving a drug for different maintenance periods and then ceasing it).
- There is no evidence that extending the duration of drug use for a year increases the success of treatment and decreases the endoscopic or symptomatic recurrence rate.
- The rates of endoscopic and symptomatic remission with medication after short-term first-line treatment at the standard dose were found to be significantly higher than with placebos (Level of evidence: 1b).
- PPIs are superior to H2 receptor blockers and placebos in maintenance treatment (Level of evidence: 1a).
- Maintenance treatment must be given according to the clinical and endoscopic findings of the patient.
- In the maintenance treatment of patients with non-erosive reflux disease (NERD) or mild esophagitis (LA Grade A-B), on-demand, intermittent, and low dose-continuous therapies can be chosen (Level of evidence: 5).
- In patients with severe esophagitis (LA Grade C-D), maintenance treatment must be given with PPIs at the standard dose, continuously (Level of evidence: 5).

HOW MUST THE DRUGS USED IN THE TREATMENT OF GERD BE STOPPED?

Rebound acid secretion might occur after long-term drug use in the treatment of GERD; therefore, the drug must be stopped gradually, not suddenly. Rapid relapse of symptoms and the necessity of maintenance treatment in a specific patient group has been observed with the cessation of PPIs and H2RAs used in the treatment of GERD (25,26). However, data with this clinical experience have been found conflicting in studies conducted on this subject. In the systematic literature review of Lødrup et al. (27), including studies examining healthy volunteers, rebound acid secretion was detected after the cessation of PPIs. However, a similar result was not found in three different studies that examined patients who suddenly stopped PPI therapy while using it for GERD. Contrary to Lodrup's systematic literature review, Hunfeld reported in his systematic literature review that no significant rebound acid secretion occurred with the sudden cessation of PPIs in healthy volunteers (28).

RECOMMENDATIONS

- There are contradictory results on the sudden increase in acid release and, accordingly, in symptoms after the cessation of long-term PPI therapy.
- Additionally, it is recommended that PPI therapy should be stopped by decreasing the dose gradually (5).

Conflict of Interest: No conflict of interest was declared by the authors.

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