EDITORIAL
What is the best first choice treatment option for *Helicobacter pylori?*

Helikobakter pilori tedavisinde ilk tercih edilecek rejim ne olmalıdır?

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Treatment of *Helicobacter pylori* (*H. pylori*) is still a big challenge because of antibiotic resistance and low patient's compliance. The Maastricht II consensus report suggested proton pump inhibitors (PPIs) or ranitidine bismuth citrate (RBC) based triple regimen with clarithromycin and amoxicillin or metronidazole as a first-line therapy (1). Quadruple therapy which consisted of bismuth and PPI-based triple therapy has also been suggested as an additional first choice treatment option in the Maastricht III consensus report (2). The strong inhibition of gastric acid secretion with PPIs and positive results on patient's symptoms made the PPI-based approach "treatment of choice" for many clinicians. However, some recent studies from different countries report eradication rates lower than 80% with PPI-based triple protocols, mostly related with clarithromycin resistance (3-5). These results have required the search for alternative ways to effectively treat *H. pylori* infection in situations where PPI-based treatment had failed.

Sezgin et al investigated the effectivity of two treatment options on 82 patients with *H. pylori* infection in a recently published article in the Turk J Gastroenterol (6). They randomly assigned the patients into two study groups. The first group of patients was given RBC, 2x400 mg, metronidazole, 3x500mg and tetracycline, 2x1000mg for 14 days (RMT group) and the second group was given pantoprazole 2x40mg, bismuth subcitrate 4x300mg, amoxicillin 2x1000 mg and clarithromycin 2x500 mg for 14 days (PBAC group). They checked for eradication rate four weeks after the completion of the treatment. All of the patients completed their protocol and the compliance rate was 100%. The eradication rate was 61.9% in the RMT group and 55% in the PBAC group with a 58.5% of total eradication success.

In this study, the first group of patients was given a common treatment protocol which was also suggested in the Maastricht II consensus report; the second group was given a quadruple regimen which was also suggested in the Maastricht III consensus report. Thus, this study, at the same time, was a comparison of two treatment options which was suggested in consensus reports (1, 2). However, both regimens used in this study achieved disappointing results on *H. pylori* eradication. The causes for the eradication failure are not clear from the results of the study. As a major limitation, the authors did not simultaneously study the antibiotic resistance for *H. pylori*. As suggested by the authors, high clarithromycin and metronidazole resistance in our country might be an important cause for the eradication failure. They also suggested that the study groups which mostly consisted of patients with non-ulcer dyspepsia might be another reason for low eradication rate. Interestingly, compliance to treatment was excellent in this study and had no negative effect on eradication failure (6).

Most clinicians would agree that the best treatment option for *H. pylori* eradication should be effective (at least more than 80% success rate), safe and simple. Unfortunately, it is more difficult today to reach these goals. The low efficacy of many antibiotics against to *H. pylori* and the increasing problem of antibiotic resistance especially in developing countries makes eradication even more difficult. Eradication rate with popular regimens are associated with lower eradication rates than in previously reported studies. A randomized controlled study by our research group found that compared with 1996, when a 7-day course of the combination of omeprazole, clarithromycin, and amoxicillin at standard doses was associated with a 88% rate of *H. pylori* eradication, the rate of eradication with the same protocol was 69.4% in 1999 (7, 8). In 2004, our group combined the same antibiotics with lansoprazole and pantoprazole for 14 rather than 7 days, with an eradication rate that remained at 69.0% (9). Because of the increasing

concern about the efficacy of this popular and first line eradication regimen on *H. pylori*, we assessed in a recent epidemiological analysis all eradication trials which were conducted in the last 10 years in our country (10).

In this analysis, the mean rate of *H. pylori* eradication with a PPI, clarithromycin, and amoxicillin regimen was investigated from trials performed in Turkey from 1996 to 2005. It also investigated the relationship between eradication rates and the duration of treatment, choice of PPI, and indication for treatment. Articles concerning *H. pylori* eradication in Turkey that were published in peer-reviewed national and international journals were identified through searches of MEDLINE and the Turkish Medical Index. Abstracts from the Turkish Gastroenterology Congress from 1996 through 2005 were searched manually. Open-label trials, controlled trials, treatment arms, and case series that included a triple-therapy regimen consisting of standard doses of any PPI with clarithromycin 500 mg BID and amoxicillin 1 g BID for 7 to 14 days were selected for analysis. Of 138 trials or treatment arms identified, 94 met the criteria for inclusion (3637 subjects). The 'per protocol' pooled eradication rate was 68.8%. Pooled eradication rates for each year from 1996 through 2005 were 79.4%, 83.7%, 81.8%, 81.8%, 75.1%, 61.3%, 65.6%, 65.1%, 55.3%, and 61.1%, respectively. A marked decrease in the eradication was noted after the year 2000. Eradication rates were not affected by the duration of treatment, choice of PPI, or indication for treatment (dyspepsia or peptic ulcer). According to the results of this study, rates of eradication with the triple-therapy regimen decreased sharply in Turkey over the 10-year period. The study clearly showed that this regimen for *H. pylori* eradication was no more effective in our population. We thought that reassessment of effectivity for this common and first line eradication regimen was also needed in other countries.

Our study group also investigated the success of bismuth-based eradication regimens for the first line eradication of *H. pylori* in a recent study (11). A total of 300 consecutive *H. pylori* positive patients with non-ulcer dyspepsia were randomized into three different regimens including standard doses of RBC and two antibiotics for 14 days (RBC+amoxicillin+tetracycline, RBC+amoxicillin+clarithromycin and RBC+ metronidazole+tetracycline). The overall 'intention to treat' and 'per protocol' *H. pylori* eradication rates in all subjects were 57.6% and % 63, respectively, without any significant differences among the groups. Our results were similar to the study by Sezgin et al with respect to low eradication rates of RBC based triple therapies.

All these results with many others confirm that we are facing significant problems for the eradication of *H. pylori*. None of the first line treatment options which were suggested in different guidelines obtain a satisfactory rate of eradication in recent studies of our population (5-11). What are the reasons for these poor results and what can we do as clinicians in our daily practice? Unfortunately, most of the clinical trials for *H. pylori* eradication did not study antibiotic resistance. So, they were unable to identify the potential role of antibiotic resistance as a cause of the poor results. But, most of these studies blamed antibiotic resistance, mainly for metronidazole and clarithromycin, based on other antibiotic resistance studies, for the low eradication rate of *H. pylori*, a logic we also share. The worldwide use of these antibiotics against both *H. pylori* and other bacterial infections increases the problem of *H. pylori* resistance. A Japanese antibiotic susceptibility study in 593 patients reported an increase in the rate of clarithromycin-resistant *H. pylori* from 7.0% in 1997-1998 to 15.2% in 1999-2000 (12). In central Italy, rates of primary and secondary clarithromycin-resistant *H. pylori* detected by the screening agar and agar dilution methods were 23.4% and 82.3%, respectively, during the years 1998-2002 (13). A Turkish study of 66 *H. pylori* isolates reported a significant increase in clarithromycin resistance from 16.7% in 1999 to 37.5% in 2001 (14). Another Turkish study reported a 20.5% rate of clarithromycin resistance in 78 *H. pylori* isolates (15). In a study of 187 patients, Kawabata et al reported respective eradication rates of 24% and 86% in clarithromycin-resistant and clarithromycin-sensitive strains of *H. pylori* with a PPI plus clarithromycin and amoxicillin regime (16). McMahon et al reported a 77% rate of treatment failure with the same protocol in patients infected with clarithromycin-resistant strains (17). In a multicenter, randomized, subgroup study, De Francesco et al found that this combination was associated with a 48% rate of *H. pylori* eradication in patients with the A2143 G point mutation for clarithromycin resistance (18). Tetracycline resistance in clinical isolates of *H. pylori*, which is associated with a nucleotide substitution in the 16S rRNA, is also well defined in recent studies (19, 20) and resistance rates up to 58% of Helicobacter isolates against tetracycline is reported in a study (21). High metronidazole

resistance against *H. pylori* is also well-known in our population (22).

Noncompliance to treatment, short therapy duration, smoking and advanced age are the other important factors affecting eradication success of *H. pylori* (23). It is difficult to explain poor eradication rates of current studies with noncompliance and short therapy duration since most of the regimens were given for two weeks and compliance rates were acceptable. A poor *H. pylori* eradication rate has been reported in patients with non-ulcer dyspepsia compared to patients with peptic ulcer (24). Sezgin et al also suggested that this might be one of the reasons for their low eradication rate. However, this is unlikely to be the case since we found similar erdication rates in patients with non-ulcer dyspepsia and ulcer disease (11).

What can we suggest to clinicians on the basis of current data? My first suggestion is that we should limit the eradication treatment for indications for which the benefit of treatment has been shown clearly to outweigh the risk of resistance development. In this context, patients with *H. pylori* positive gastric and duodenal ulcer, low-grade mucosa-associated lymphoid tissue lymphoma and first-degree relatives of gastric cancer patients should be given an eradication regimen. Although some guidelines and consensus reports suggest that all dyspeptic patients with *H. pylori* might be given an eradication treatment, there is currently not enough scientific data showing the benefit of treatment in these patients. Unfortunately, clinicians are mostly trying to eradicate *H. pylori* in this group of patients where the benefit of treatment is uncertain. The 'too easily' set indication for anti-H pylori therapy, together with the limited choice of antibiotics, must have contributed to the development of antibiotic resistance.

As an alternative to standard triple therapy, sequential therapy which consisted of a 5-day induction phase of a PPI and amoxicillin directly followed by a 5 or 7 day triple therapy of a PPI plus two different antibiotics has been promoted as a novel and highly effective first-line anti-*H. pylori* treatment in recent reports (25, 26). In a recent study of our group (unpublished data), the sequential treatment (pantoprazole and amoxicillin for 7 days, followed by pantoprazole, tetracycline and metronidazole for the next 7 days) achieved a better eradication rate in 150 patients than RBC-based triple regimens (80.1% vs. 63.5%, at 'per protocol' analyses). The superiority of this approach may be related to the usage of three different antibiotics in each patient instead of two. It would also have the advantages of using quadruple therapy as a first line approach without possibly increasing side effects but decreasing compliance related issues. Futhermore, the suppression of bacterial load with PPI and amoxicillin may improve the response to the subsequent short course of triple therapy. Indeed, Moshkowitz et al. have shown that a low bacterial load is associated with a higher eradication rate after triple therapy (27). This point was also the main reasoning for using sequential treatment in *H. pylori* eradication (25, 26).

The study of Sezgin et al published in a recent issue of the Turk J Gastroenterol did on the one hand not show an unexpected finding since similar results had been reported in the literature. On the other hand, they showed that the poor results can be extended to bismuth salts containing regimes. Based on current data, the difficulties of *H. pylori* eradication should be appreciated and at least until availability of more effective regimes eradication may be confined for only definite indications. The trials of sequential treatment may be one right path to pursue for treatment optimisation.

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