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A randomized prospective trial comparing results of different therapeutic regimens in the treatment of duodenal ulcer and Helicobacter pylori infection

Duodenum ülserinin ve Helicobacter pylori infeksiyonunun tedavisinde değişik tedavi sonuçlarını karşılaştıran randomize ve prospektif bir çalışma

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ÖZET: *Helicobacter pylori, duodenal ülser gelişmesinde majör bir faktör olarak düşünülmektedir. İyileşmiş duodenal ülserin uzun süreli remisyonu H. pylori eradikasyonu ile açıkça ilişkilidir. Fakat H. pylori'nin eradikasyonu zordur ve başarılı bir tedavi, iki veya daha fazla antimikrobial ilacın ilavesini gerektirir. Bu çalışmanın amacı, duodenal ülserin ve H. pylori infeksiyonunun tedavisinde değişik tedavi rejimlerini karşılaştırmaktır. Duodenal ülserli 125 hasta çalışmaya alındı. Her hastanın korpus, antrum ve bulbusundan çok sayıda endoskopik biyopsiler elde edildi. Biyopsi kesitleri, mukozal inflamasyonu ve H. pylori' yi göstermek için sırasıyla hematoxylin-eosin ve Warthin-Starry ile boyandı. Hastalar beş değişik tedavi rejiminden birini alacak şekilde randomize edidi; (1) famotidine, (2) omeprazole ve amoxicillin (OA), (3) bismuth (480 mg/g, 1 ay), metronidazole ve amoxicillin (DMA), (4) omeprazole ve clarithromycin (OC), (5) omeprazole, amoxicillin ve clarithromycin (OAC). (omeprazole 40 mg/g, amoxicillin 2 g/g, clarithromycin 1 g/g dozunda ve 15 gün süreyle verildi.) Tedavi bitiminde, iki ve altı ay sonra incelemeler tekrarlandı. DMA (%76) ve OAC (%81) gruplarında ülser iyileşme oranları daha yüksekti (p<0.001). H. pylori eradikasyonu DMA (53%), OC (55%) ve OAC (62%) gruplarında benzerdi (p>0.05). En düşük eradikasyon oranı (%21) OA grubundaki hastalarda görüldü. Asit sekresyonunun famotidinle devamlı supresyonu, düşük iyileşme (%47) ve yüksek nüks (%50) oranları nedeniyle başarısızdı.*

Anahtar Kelimeler: **Dudenal ülser, Helicobacter pylori, tedavi**

SUMMARY: *Helicobacter pylori is presently considered a major factor predisposing to the development of duodenal ulceration. Long-term remission of duodenal ulcer after initial healing is closely related to eradication of H. pylori. But, H. pylori is difficult to eradicate, and successful treatment requires the concurrent administration of two or more antimicrobial drugs. The aim of this study is to compare different therapeutic regimens in the treatment of duodenal ulcer and H. pylori infection. 125 patients with duodenal ulcer were studied. Multiple endoscopic biopsies were obtained from the corpus, antrum and the duodenal bulb of each patient. Sections of biopsy tissue were stained with hematoxylen-eosin and Warthin-Starry to examine for mucosal inflammation and H. pylori, respectively. The patients were randomized to receive one of the five different therapeutic regimens; (1) famotidine, (2) omeprazole plus amoxicillin (OA), (3) bismuth (De-Nol, 480 mg/d, 1 month), metronidazole and amoxicillin (DMA), (4) omeprazole plus clarithromycin (OC), (5) omeprazole, amoxicillin and clarithromycin (OAC).(omeprazole 40 mg/d, amoxicillin 2 g/d, and clarithromycin 1 g/d were given for two weeks.) Investigations were repeated at the end of treatment, after two and six months. Rates of ulcer healing were higher in the DMA (76%) and OAC (81%) groups than others (p<0.001). Eradication of H. pylori was similar in DMA (53%), OC (55%) and OAC (62%) groups (p > 0.05). The patients in OA group had the lowest eradication rate (21%). Continuous suppression of acid secretion with famotidine was not successful, because of low healing (47%) and high relapse (50%) rates of duodenal ulcer.*

Key Words: **Duodenal ulcer, Helicobacter pylori, treatment**

THE recognition of gastritis due to Helicobacter pylori as a factor of major importance has revolutionized the therapeutic approach to peptic ulcer disease (1). The recurrence of ulcers can be more effectively prevented by a single course of antimicrobial treatment that eradicates H. pylori infection than by the continuous suppression of acid secretion. Rates of recurrence in patients whose initial ulcers healed during conventional antisecretory therapy range from 60 to 100 percent per year, but ulcers recur in less than 15 percent of patients in whom the organism has been eradicated by antibacterial treatment (2, 3). This concept received important support when a recent Consensus Deve-

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lopment Conference of the National Institutes of Health (NIH) recommended that all patients with ulcers who are also infected with H. pylori receive antimicrobial therapy (4).

H. pylori is difficult to eradicate, and successful treatment requires the concurrent administration of two or more antimicrobial drugs (5-7). Therapy with bismuth, metranidazole, and tetracycline or amoxicillin results in high eradication rates (89% and 84%), especially with organisms sensitive to metranidazole, and is the current treatment of choice because of its cost and efficacy (6-7). Second-choice regimens consist of combinations of two antimicrobial drugs -metranidazole, amoxicillin, or clarithromycin- with an antisecretory agent, preferably an H^+/ K^+-ATPase antagonist such as omeprazole. The combination of a single antimicrobial drug (especially amoxicillin) with omeprazole is less efficacious and cannot be recommended. Thus, a combination of omeprazole, amoxicillin, and clarithromycin resulted in the eradication rate of more than 90 percent, as compared with a rate of less than 30 percent for the combination of amoxicillin and omeprazole alone (8).

It is difficult to state with assurance which regimen for the eradication of H. pylori is clinically optimal, although it is clear that eradication rates of 80 to 90 percent are achievable with some regimens, including triple therapy (6, 7, 9). No regimen has yet been approved by the Food and Drug Administration for the treatment of H. pylori. Most studies of therapeutic regimens have involved only small numbers of patients; were not controlled, randomized, or blinded; and failed to use intention-to-treat analysis. Also, the dosage, timing and duration of drug administration varied greatly, making direct comparisons difficult.

The aim of this study is to compare five different therapeutic regimens in the treatment of duodenal ulcer and H. pylori infection.

MATERIAL AND METHODS

Patient selection: 125 patients who had duodenal ulcer diagnosed at endoscopy were selected for the follow-up study. Neither systemic illness nor use of antimicrobial agents since last month was present in the patients. 44 percent of patients were heavy smoker and 15.20 percent of patients were receiving NSAID. NSAID use was stopped, but smoking not.

The five treatment regimens were: 1) Famotidine, 40 mg/d for one month, and than 20 mg/ d for 6 months, 2) Omeprazole 40 mg/d plus amoxicillin 2g/d (OA group), 3) Bismuth (De-Nol 480 mg/d, for 1 month), metranidazole 1.5 g/d and amoxicillin 2 g/d (DMA group), 4) Omeprazole 40 mg/d plus clarithromycin 1 g/d (OC group), 5) Omeprazole 40 mg/d, amoxicillin 2 g/d and clarithromycin 1 g/d (OAC group). Omeprazole, amoxicillin and clarithromycin were given for two weeks. H. pylori (-) patients received only H2 receptor antagonist -famotidine. The patients in whom the cure of duodenal ulcer could not be achieved received another therapeutic regimen.

Endoscopy and biopsies: The endoscopic examinations were carried out by the same endoscopist using an Olympus GIF XQ 200 video-endoscope. The forceps were cleaned in 2% gluteraldehyde and water between examinations. The follow-up endoscopy was performed at the end of treatment, after two and six months. Ulcer healing (UH) was diagnosed with demonstration of scar of ulcer. Relapse of duodenal ulcer (RU) was diagnosed with activation of healed duodenal ulcer. Multiple endoscopic biopsies were obtained from the gastric corpus, antrum and the duodenal bulb of each patient.

Histopathology: All specimens were immediately fixed in formalin and processed for light microscopy. The sections were stained with hematoxylen-eosin and Warthin-Starry to examine for mucosal inflammation and H. pylori, respectively. Clearance (Cl) was assessed at the end of treatment (10) and eradication (Er) was assessed 4-8 week after the end of treatment (11). Relapse of H. pylori (RHp) was defined as the presence of H. pylori in patients whom H. pylori was eradicated.

RESULTS

Male/ female ratio was 74/ 51, and mean age was 37.75 ± 11.35 years) No severe side effects were seen. Only a few patients had mild diarrhea and noise. H. pylori infection related with gastritis was found in 83.20% of the patients. Rates of ulcer healing, clearance and eradication of H. pylori, relapses of duodenal ulcer and H. pylori infection were shown in Table 1.

As seen on Table 1, rates of ulcer healing were higher in the DMA (76%) and OAC (81%) groups than others ($p<0.001$). There was no significant difference between these two groups. Eradication of H. pylori was similar in DMA (53%), OC (55%), and OAC (62%) groups. The patients in OA group had

Table 1. Ulcer healings, clearance and eradication of H. pylori, relapses of duodenal ulcer and H. pylori infection.

	End of treat.(%)			*2. Month (%)*				*6. Month (%)*			
Groups	n	U.H.	Cl.	n	U.H.	Er.	n	U.H.	Er.	R.U.	R.Hp.
Famotidine	19	74	0	17	47	0	6	33	0	50	0
OA	36	67	53	42	40	21	7	57	29	29	29
DMA	35	63	71	55	76	53	14	71	79	23	9
OC	8	50	75	20	35	55	8	50	62	14	29
OAC				16	81	62	2	100	100	0	0

H: Ulcer healing, Cl: Clearance, Er: Eradication.
R.U: Relapse of duodenal ulcer, R.Hp: Relapse of H. pylori

the lowest eradication rate (21%). The difference was significant ($p < 0.001$). The results found at 6th month were not enough for a successful statistical evaluation. Continuous suppression of acid secretion with famotidine was not successful because of low healing (47%) and high relapse (50%) rates of duodenal ulcer.

DISCUSSION

Antimicrobial therapy against H. pylori is indicated for all patients with documented peptic ulcer disease who have evidence of the infection. H. pylori is inherently resistant to only a few antimicrobial drugs (e.g., vancomycin, nalidixic acid, trimethoprim, and sulfonamides), but it readily becomes resistant to metranidazole and, to a lesser extent, clarithromycin, if either agent is given alone (12, 13). It does not become resistant to luminally active agents such as bismuth, tetracycline, and amoxicillin. Luminal acidity influences the effectiveness of some drugs against H. pylori. Raising the gastric pH from 3.5 to 5.5 increases the in vitro effectiveness of amoxicillin and erythromycin more than 10-fold (14). This increased activity at higher pH values may explain the effectiveness of regimens that combine potent inhibition of gastric-acid secretion with an antimicrobial drug that is pH-sensitive, although the precise pH in the gastric microenviroment occupied by H. pylori is not known.

In our study we found low eradication rates for all therapeutic regimens in opposite to available studies (7, 8). Also, we found no difference between DMA, OC, and OAC groups ($p > 0.05$).

One reason of our low eradication rates may be frequent use of both metranidazole and clarithromycin for other reasons. This is important, because the resistance of H. pylori to metranidazole and clarithromycin has a substantial effect on the success of regimens involving these drugs (13, 14). Factors unrelated to the drug regimens themselves also may influence our eradication rates. Patient compliance is one such factor; the failure to take at least 80 percent of the prescribed doses of antimicrobial drugs leads to their decreased efficacy (15, 16). This is a special problem in triple-therapy regimens that involve taking multiple drugs three or four times a day and that have troublesome side effects in 20 to 30 percent of patients. Older age, smoking, and a greater severity of gastric mucosal inflammation may also result in lower rates of eradication (15, 16). 44 percent of our patients were heavy smoker and smoking may be responsible for low eradication rates in our study.

In OA group, the eradication rate was 21%. This finding is similar with other studies (8). Therefore, we can say again that the combination of amoxicillin with omeprazole is less efficacious and cannot be recommended. In OC group, our eradication rate is similar to another study from Turkey in that study eradication rate was 53% with this combination (17).

Ozmen and Johnson (18) recently reported a small pilot study that included 13 H.pylori-positive patients, treated with lansoprazole 30 mg bid plus clarithromycin 500 mg bid plus metranidazole 400 mg bid for 1 week. The authers obtained an impressive eradicaion rate of 100%. Although these results appear very interesting, eradication was assessed with 13C-UBT 4-6 week after the end of treatment in that study. We think that this time is too short to prove real eradication, because at that time the 13C-UBT could not effectively point out a low bacterial load (19).

None of the drug regimens currently used to treat H. pylori eradicate the infection in 100 percent of patients, and some regimens have a relatively high frequency of side effects. New treatments, consis-

ting of new drugs or new combinations of existing drugs, will undoubtedly be developed in the future. Various combinations of drugs are currently being tested in large-scale studies. Antimicrobial effectiveness in vivo is predicted poorly by sensitivity in vitro, and therefore the research process is complicated by the need to test new combinations of agents in infected humans (5, 7).

Until new treatments develop, we recommend that the regimen of first choice must be triple therapy with bismuth, metranidazole, and amoxicillin or tetracyclin because of its cost and similar efficacy to other therapeutic regimens.

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