

Azithromycin based triple therapy versus standard clarithromycin based triple therapy in eradication of *Helicobacter pylori* infection in Iran: a randomized controlled clinical trial

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Background/aims: In regarding to azithromycin's high tissue concentration, long biologic half life, low cost, and excellent anti bacterial profile for *Helicobacter pylori* in Iran, we sought to compare an azithromycin-based regimen with an already established clarithromycin-based regimen in regards to the eradication of *Helicobacter pylori* infection. **Material and Methods:** A prospective, open label, randomized controlled trial was conducted on 165 patients who presented to gastrointestinal clinics of QOM Medical University Clinics, with complaint of dyspepsia. All patients received upper gastrointestinal endoscopy, and underwent rapid urease test to confirm *Helicobacter pylori* infection. Patients were randomized to a treatment arm, which consisted of, clarithromycin, amoxicillin, and omeprazole, or another treatment arm consisting of azithromycin, amoxicillin, and omeprazole. Informed consent was obtained from all patients participating in the trial. Urease breath test was performed in patients 6 weeks after end of treatment to assess eradication. All side effects were recorded. Comparison between the two groups was made using a chi-square test. **Result:** Seventy six and 89 patients received regimen clarithromycin, amoxicillin, and omeprazole and azithromycin, amoxicillin, and omeprazole, respectively, and completed the study course. Per protocol, eradication rate was 83% with clarithromycin, amoxicillin, and omeprazole and 75% with azithromycin, amoxicillin, and omeprazole ($p=0.158$). Eradication rate for a subgroup of patients with peptic ulcer disease in two groups were 83% and 74%, respectively ($p=0.134$). Only one patient in each group was compelled to stop the treatment due to a severe skin hypersensitivity reaction. Other lesser side effects were comparable within the two groups. **Conclusion:** The results of this study suggest that azithromycin, amoxicillin, and omeprazole at best is as effective as clarithromycin, amoxicillin, and omeprazole; and this new therapy could be considered as an alternative choice for *Helicobacter pylori* eradication, especially in geographic areas with lower economic status.

Key words: Azithromycin, *Helicobacter pylori*, dyspepsia, rapid urease test, urease breath test

İran'da *Helikobakter pilori* enfeksiyonunun eradikasyonunda azitromisin bazlı üçlü tedavi ile standart klaritromisin tabanlı üçlü tedavinin karşılaştırılması: randomize kontrollü klinik çalışma

Amaç: Yüksek doku konsantrasyonu, uzun biyolojik yarı ömrü, mükemmel antibakteriyel profili ve İran'daki düşük maliyeti nedeniyle, *Helikobakter pilori* enfeksiyonu eradikasyonunda azitromisin bazlı rejim ile halen kullanılan klaritromisin bazlı rejimin karşılaştırılmasını amaçladık. **Gereç ve Yöntem:** QOM Tıp Fakültesi Gastroenteroloji Kliniği'ne dispepsi nedeniyle başvuran 165 hastada prospektif açık etiketli randomize kontrollü bir çalışma yapıldı. Bütün hastalara üst gastrointestinal sistem endoskopisi ve *Helikobakter pilori* enfeksiyonunun konfirmasyonu için hızlı üreaz testi yapıldı. Hastalar klaritromisin, amoksisilin ve omeprazol'den oluşan bir tedavi kolu ve azitromisin, amoksisilin ve omeprazol'den oluşan bir diğer kola randomize edildi. Çalışmaya katılan bütün hastalardan aydınlatılmış onam alındı. Hastalara tedaviden 6 hafta sonra eradikasyonu test etmek için üreaz nefes testi yapıldı. Bütün yan etkiler kaydedildi. İki grup arasındaki karşılaştırmalar ki-kare testiyle yapıldı. **Bulgular:** Çalışmayı klaritromisin, amoksisilin ve omeprazol ve azitromisin, amoksisilin ve omeprazol gruplarında sırasıyla 26 ve 89 hasta tamamladı. Per protokol eradikasyon oranı klaritromisin, amoksisilin ve omeprazol ile %83 ve azitromisin, amoksisilin ve omeprazol ile %75 idi. İki grupta peptik ülseri olan hastalardaki eradikasyon oranı sırasıyla %83 ve %74 idi ($p=0.134$). Her iki gruptan birer hastada ciltte ciddi hipersensitivite reaksiyonu nedeniyle ilaç kesilmesi gerekti. İki grupta daha az ciddi yan etkiler arasında fark yoktu. **Sonuç:** Bu çalışmanın sonuçlarına göre azitromisin, amoksisilin ve omeprazol, klaritromisin, amoksisilin ve omeprazol kadar etkindir ve özellikle düşük ekonomik düzeyli coğrafi bölgelerde *Helikobakter pilori* eradikasyon tedavisi için alternatif bir seçim olarak düşünülmelidir.

Anahtar kelimeler: Azitromisin, *Helikobakter pilori*, dispepsi, hızlı üreaz testi, üre nefes testi

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a ubiquitous human gastric infection, with different worldwide prevalence noted (1-6), and it is a known cause of peptic ulcer disease (PUD) as well as gastric cancer (7-9). Eradication in patients with *H. pylori* related PUD leads to a significant decrease in ulcer recurrence (10,11). The role of *H. pylori* in patients with non ulcer dyspepsia (NUD) is uncertain (12). In geographic areas such as Iran that has a high incidence of gastric cancer, *H. pylori* eradication in first degree relatives of gastric cancer patients as well as mass eradication of other asymptomatic infected persons may be justifiable. Over the past decade, anti-*H. pylori* therapy has undergone a remarkable evolution. However, optimal treatment has not yet been established. Reported eradication rates in different trials are considerably variable, and depend on different drug combinations as well as the treatment duration. Furthermore, many drug combinations have suboptimal eradication rates. Antibiotic resistance due to wide spread injudicious drug use, racial differences, social and other factors related to drug compliance and also many other local variables may be causative factors. In contradiction with European and Brazilian (13) studies, it appears that treatment should be given for more than 7 days in other countries including Iran and USA (10,11,14). The issue of cost further complicates the choice of therapy, es-

pecially in underdeveloped countries. The standard therapeutic regimen currently available consists of an association of a proton-pump inhibitor (PPI) and clarithromycin, with either amoxicillin or metronidazole (15,16). Increasing resistance to clarithromycin and its decreasing efficacy against *H. pylori* has prompted the search for alternative therapies. The azilide antibiotic, azithromycin, is a potentially attractive therapeutic agent for *H. pylori* given its excellent mean inhibitory concentration for this organism as well as its high tissue and mucus penetration, and long biological half-life (17-19). However, results from the available published trials utilizing azithromycin are conflicting (20,21). The purpose of this study is to investigate the effect of azithromycin based triple therapy in *H. pylori* eradication in comparison to standard clarithromycin based triple therapy in Iran.

MATERIAL and METHODS

Between 2007 and 2009, adult patients with dyspepsia attended gastrointestinal clinics of QOM Medical University and underwent upper gastrointestinal endoscopy. Rapid urease test (RUT) was performed for all patients with peptic ulcer disease (PUD), gastric or duodenal erosion, and for those without any pathology noticed in upper GI endoscopy testing but had a positive family history of gastric cancer in their first degree rela-

Table 1. Characteristics of patients who completed the study course

	OAC	OAA	Significance
Number of patients	76	89	p=0.24
Age (medium)	37.9865	34.7500	p=0.39
Male/female ratio	54/22	46/43	p=0.02
Endoscopic diagnosis			
Duodenal ulcer (DU)	56	55	
Gastric ulcer (GU)	4	4	
Both DU and GU	1	2	p=0.45
Erosion	7	12	
No pathology	8	16	

Table 2. Reported Side effects in all patients participated in two groups

	OAC(n=76)	OAA(n=89)	Significance
Diarrhea	7	11	p=0.38
Bitter tongue	9	2	p=0.03
Headache	1	2	p=0.46
Skin rash	3	2	p=0.46

tives. Those with *H. pylori* infection were invited to participate in the study. Exclusion criteria were history of receiving anti-*H. pylori* therapy, gastric cancer, pregnancy, gastric outlet obstruction, and history of hypersensitivity to drugs used in the study. Two hundred thirty six patients that met the above described criteria were enrolled and randomized to receive ten days course of either omeprazole 20 mg/bid, amoxicillin 1000 mg/bid and clarithromycin 500 mg/bid (OAC), or to receive omeprazole 20 mg/bid, amoxicillin 1000 mg/bid and azithromycin 250 mg/bid for four days and 250 mg/daily thereafter (OAA). To randomize the participants, sequentially numbered identical containers were administered serially. Adverse side effects reported by the patients were registered at the end of treatment course. Six weeks after termination of therapy, urease breathe test (UBT) was performed to confirm *H. pylori* eradication. Seventy six and 89 patients receiving OAC and OAA regimens completed the study course, respectively. The demographic and clinical characteristics of the study groups were compared statistically utilizing the chi-squared test (Table 1). The results of treatment were compared by chi-squared test or Fisher's exact test for comparison of proportions with a 95% confidence interval (CI). Significance was accepted at a P-value of <0.05.

RESULTS

In the per protocol analysis, 63 out of 76 patients in OAC and 67 out of 89 patients in OAA group responded to treatment and were noted to have complete eradication of *H. pylori* infection (P=0.158). In the subgroup of patients with peptic ulcer disease, 51 out of 61 patients receiving OAC regimen and 45 out of 61 patients receiving OAA regimen responded to treatment, respectively (P=0.134). Although 17 (22.3%) in the OAC group and 31 (16.8%) in the OAA group had experienced at least some degree of side effect, only one patient in each group could not complete the courses because of noted severe skin eruptions (Table 2).

DISCUSSION

Although multiple drugs have been effective in vivo and in vitro against *H. pylori*, no drug combination to date has been totally effective. In a pooled analysis of anti-*H. pylori* treatment regimens, clarithromycin based triple regimens with 76%-85% eradication rate have been considered the most effective anti-*H. pylori* therapeutic strategies (7,18,

25). The MACH 1 study (22) demonstrated an intention to treat (ITT) eradication rate of 91% with omeprazole 20 mg bid, amoxicillin 1000 mg bid, and clarithromycin 500 mg bid, while Rinaldi et al (23) and the MACH 2 study (24) demonstrated ITT eradication rates of 83 and 78%, respectively, with the same 1-week triple therapy regimen. In more recent studies, bismuth based quadruple therapy has been best in regards to eradication rate, probably due to the emergence of macrolid resistant strains (25). Eradication rate in another study has been as low as 35.6% (26). The most acceptable duration has been determined to be between ten and fourteen days (25,27). Although shorter courses of treatment (i.e. one to five days) have demonstrated eradication rates of 89% to 95%, and has increased patient compliance potential (28,29). Nevertheless, in the USA and most of the developing countries short course therapy has seen suboptimal results (10,11,14). The azilide antibiotic, azithromycin, is acid stable and has a very good in vitro activity against *H. pylori*. Azithromycin has an excellent mean inhibitory (MIC) and bactericidal (MBC) concentrations for this organism of 0.25 mg/L and 0.5 mg/L, respectively (17,30). The drug bioavailability is greatly reduced when given with food. After oral administration, the drug preferentially concentrates in the tissue rather than plasma (30, 31). This accounts for the long biological half-life of azithromycin, which is measured in days rather than hours (27,30,31). When comparing to clarythromycin, it is less expensive and more affordable as well. The above mentioned characteristics make azithromycin an attractive choice to include in anti *H. pylori* regimens. So far multiple trials utilizing azithromycin based regimens with different methods, drug combinations, treatment durations, and with paradoxical results have been conducted (1,20,21,30-36). Several studies obtained good efficacy in *H. pylori* eradication with short-term triple therapy using azithromycin, amoxicillin, and a proton pump inhibitor (33,37). In respect to the high biologic half life of azithromycin, several trials have tested azithromycin 500 mg/d for 3 days administered in fasting patients, in combination with a proton pump inhibitor and amoxicillin. The cure rates on an ITT analysis, ranged from 22% to 93% (20,33,38,39). Higher milligram doses may be more effective (31). In a Russian study, a seven day course of triple therapy with only three days coverage of azithromycin 1000 mg once daily resulted in 72% ITT eradication (21). In a randomized control trial in which pan-

toprazole, amoxicillin, and either clarithromycin or azithromycin were administered for seven days, eradication rates were 81% and 78% respectively and both regimens were considered to be suboptimal (40). In a Korean study, seven days course of levofloxacin, azithromycin and omeprazole have not been demonstrated to be more effective than seven days standard triple therapy (41). The low eradication rates observed in aforementioned studies may be due in part to short duration of azithromycin use, low total azithromycin dose, or variation in antibiotic resistance profile of *H. pylori* in different geographic areas of the world. To take into account these probabilities, our study utilized azithromycin for an entire ten day course of treatment, and with a higher dosage comparing to previous studies. The study showed that there is no significant difference between azithromycin based triple therapy and standard clarithromycin based triple therapy in *H. pylori* eradication. This study

also shows that endoscopic findings have no impact on the eradication rate. Unsatisfactory result of azithromycin based regimen in *H. pylori* eradication may be due to emergence of azithromycin resistant strains of *H. pylori* in recent years in Iran. Although the drug is short lived in the Iranian market, its widespread use by general practitioners in more recent years for mono-therapy for respiratory tract infection may have caused emergence of drug resistant variants of *H. pylori*.

Azithromycin based triple therapy is no better than standard clarithromycin triple therapy, but because of its equal efficacy and low cost, it can be used in *H. pylori* eradication regimens, especially in areas with lower level of socioeconomic status. Its widespread use as mono-therapy for respiratory tract infection may cause emergence of resistant strains, and further decrease its efficacy against *H. pylori* infection in the future.

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