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Sequential and Concomitant Therapy with 4 drugs are Equally Effective for Eradication of *H. pylori* Infection

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Abstract

Background & Aims—Sequential therapy with a proton pump inhibitor (PPI) and amoxicillin followed by a PPI, clarithromycin, and an imidazole agent reportedly have a better rate of curing *Helicobacter pylori* infection than PPI, amoxicillin, clarithromycin triple therapy. The concomitant administration of these 4 drugs (concomitant therapy) is also an effective treatment strategy. We compared the efficacies of sequential and concomitant therapy and analyzed the effects of antibiotic resistance in patients with *H. pylori infection*.

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Methods—In a randomized trial of 232 *H. pylori* -infected patients from 3 hospitals in Kaohsiung, Taiwan, patients were given 10 days of sequential (n=115) or concomitant (n=117) therapy. *H. pylori* status was confirmed by endoscopy or urea breath test.

Results—Intention-to-treat analysis demonstrated similar eradication rates for sequential (92.3%; 95% confidence interval [CI] 87.5%–97.1%) and concomitant therapy (93.0%; 95% CI: 88.3%–97.7%)(p=0.83). Per-protocol eradication results were similar between for sequential (93.1%; 95% CI: 90.7%–95.5%) and concomitant therapy (93.0%; 95% CI: 88.3%–97.7%) (p= 0.99). Univariate analysis showed that compliance and resistance to clarithromycin were independent determinants of eradication. Dual resistance did not influence the level of eradication in concomitant group, but significantly affected that of the sequential therapy. Clarithromycin resistance was less frequent than expected.

Conclusion—Sequential or concomitant therapy with a PPI, amoxicillin, clarithromycin, and an imidazole agent are equally effective and safe for eradication of *H. pylori* infection. Resistance to clarithromycin, compliance, and adverse events reduced the level of eradication. Concomitant therapy is more suitable for areas with dual resistance to antibiotics.

Introduction

Helicobacter pylori (*H. pylori*) infection is known to play a cardinal role in gastritis, peptic ulcer and gastric cancer {1994 3729/id}. The ability to reliably eradicate *H. pylori* infection is important for managing these diseases. In Taiwan, the overall prevalence of *H. pylori* infection is 54% and increases with age {Teh, 1994 3580/id}. Seven-day triple therapy (proton pump inhibitor (PPI), amoxicillin and clarithromycin) has been the recommended first-line therapy for *H. pylori* infection in Taiwan, Europe and many other countries {Malfertheiner, 2007 20078/id}{Bytzer, 2005 18003/id}{Vakil, 2007 19956/id}. However, increased antibiotic resistance had made this triple therapy less efficacious to where in most countries cure rates of <80 are now expected {Yamaoka, 2008 20515/id}{Huang, 2000 18947/id}{Zanten, 1999 18993/id}{Sheu, 2002 18889/id}{Bazzoli, 2002 16277/id}{Georgopoulos, 2002 15825/id}{Peitz, 2002 18906/id}{Vakil, 2004 18729/id;Fuccio, 2007 19812/id;Zagari, 2007 19605/id}{Graham, 2007 19814/id}{Fischbach, 2007 19815/id}{Fuccio, 2007 19812/id}.

Sequential therapy, as originally defined, is the sequential administration of a dual therapy (a PPI plus amoxicillin) followed by a Bazzoli-type triple therapy (a PPI plus clarithromycin and tinidazole) {Zullo, 2000 18733/id}. Each component is used for 5 days resulting in a 10 day regimen. Recent studies have shown that sequential therapy for *H. pylori* infection yielded acceptably high cure rates and when tested against standard triple therapy it has proven to be superior {Jafri, 2008 20343/id}. Similar results have been reported in both children and in adults. Importantly, sequential therapy failed in the presence of dual clarithromycin and metronidazole resistance {Vaira, 2007 19475/id}.

Sequential therapy is actually a quadruple therapy containing 3 antibiotics (amoxicillin, clarithromycin, and metronidazole) and an acid suppressive medication. Clinically, the sequential administration of the two different combinations is complex. It remains unanswered whether the sequential administration of the drugs actually plays a significant role in the improved outcome or whether it is unnecessarily complicates the regimen. Most of the studies of sequential therapy were done in Italy. A recent study in Spain showed lower than expected (based on the results from Italy) intention to treat analysis (ie, 84.2%: 95%CI = 77%–90%) {Sanchez-Delgado, 2008 20455/id}. Antimicrobial susceptibility was not evaluated and thus it remains unclear whether the lower than expected outcome was related to a high rate of dual resistance or to some other factors {Sanchez-Delgado, 2008 20455/id}.

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In 1998, Treiber et al. {Treiber, 1998 9965/id} and Okada et al. {Okada, 1998 10528/id} both reported studies using the same four drugs (ie, an antisecretory drug, a macrolide, an imidazole and amoxicillin) given concomitantly instead of sequentially. In both studies 5 day concomitant therapy produced intention-to-treat (ITT) eradication rates of >90%. In addition, meta-analyses of 5 randomized controlled comparisons of concomitant and triple therapy (576 subjects) confirmed that concomitant therapy was superior to legacy triple therapy with ITT pooled OR of 2.86 (95% CI: 1.73–4.73) and per protocol (PP) pooled OR of 3.52 (95% CI: 1.95–6.38) {Essa, 2009 20548/id}.

The aim of this study was to compare sequential and concomitant administration of a non-bismuth containing, 4 drug 10 day treatment regimen for the treatment of *H. pylori* infection. In Taiwan the resistance rate of metronidazole is generally high and that of clarithromycin is increasing allowing the opportunity to compare sequential and comcomitant administration of the same drugs if patients with single and dual antibiotic resistance {Hu, 2007 20554/id;Poon, 2009 20630/id;Chang, 2009 20631/id}{Kuo, 2009 20550/id;Wu, 2006 20551/id}.

Methods

Setting and Participants

We surveyed patients who visited the gastroenterological clinic of Kaohsiung Medical University Hospital (KMUH), Kaohsiung Veteran General Hospital (KVGH) and Kaohsiung Municipal Hsiao-Kang Hospital (KMHH) between June 2007 and May 2008.

Patients with *H. pylori* infection were enrolled in this study. Pre-enrollment procedures included biopsy of the gastric mucosa where the presence of *H. pylori* was assessed by histological examination of the tissue, culture, and rapid urease testing. The presence of *H. pylori* was defined as (i) a positive result of culture (ii) positive results of both rapid urease test and histology. Blood samples were taken for routine laboratory tests including renal and liver function tests and complete blood count to ascertain that there were no abnormal tests that would preclude entry into the trial, treatment with antibiotics, and for study-related procedures.

Criteria for exclusion included: 1) previous surgery of the stomach such as partial gastrectomy. 2) use of antibiotics within the preceding 30 days. 3) Regular use of a PPI or bismuth compounds (>3 times per week) in the 30 days before enrollment. 4) Presence of serious medical condition(s) precluding participation or endoscopy with biopsy. 5) Patients previously treated for *H. pylori* infection. 6) Use of concomitant medication(s) known to interact with study medication. Simvastatin was permitted. 7) Presence of Zollinger-Ellison Syndrome. 8) Pregnancy or lactation. 9) Allergy to any medication in this study. 10) Contraindication(s) to the use of any of the study drugs. 11) Participating in any clinical trial within the last 30 days. 12) Unwillingness to abstain from alcoholic beverages. 13) Patients taking other medications including antipsychotics, or chronic NSAIDs were also excluded. Aspirin at a dose not more than 325 mg/day was permitted.

Interventions

A trained interviewer used a standardized questionnaire to obtain demographic data and medical history. The participants were randomly assigned to 10-day concomitant therapy consisting of esomeprazole (40 mg), amoxicillin (1 gram), clarithromycin (500 mg) and metronidazole (500 mg) given twice a day for 10 days or 10-day sequential therapy beginning with the PPI and amoxicillin given twice daily for 5 days [esomeprazole (40 mg), amoxicillin (1 gram)] following which the amoxicillin was discontinued and clarithromycin (500 mg) and metronidazole (500 mg) were given twice a day to complete the 10 day therapy. Patients were given written handout with instructions on how to take medications correctly.

Outcomes and Follow-up

Patients were asked to return 2 week after the start of drug administration to assess drug compliance and adverse effects. Drug compliance was assessed via pill counts. Compliance was defined as good (took more than 70% of the total medication) or poor by counting unused medication after the treatment was completed. Endoscopy with biopsy for rapid urease test, histology and culture was repeated 8 weeks (approximately 6 weeks after the end of therapy) later to evaluate *H. pylori* infection status.

For patients who refused follow-up endoscopy, UBT was used to evaluate *H. pylori* status. The technicians who performed the *H. pylori* tests (culture, rapid urease test and UBT) or filled in the questionnaires as well as the pathologists were blinded to the eradication regimens the patients received.

All participants gave written informed consent. The Medical Committee of the Kaohsiung Medical University Hospital approved the study. Questionnaire of life style and adverse events were also completed.

Questionnaire—The questionnaire contained questions regarding personal history of smoking and alcohol drinking. The questionnaire was locally derived and not a validated or previously published quality of life questionnaire. Quality of life was not assessed. Smokers were defined as those who consumed more than 1 pack of cigarettes a week and drinkers were those who drank more than 1 cup of alcoholic beverage per day. The adverse events evaluated included abdominal pain, diarrhea, constipation, dizziness, taste perversion, headache, anorexia, nausea, vomiting and skin rash. Those who considered those symptoms disturbed their daily life were defined to have major adverse effects. Those who experienced these symptoms but did not consider them a disturbance to their daily life were defined to have minor adverse effects.

Culture and pathological examination—Biopsy specimens were rubbed on the surface of a Columbia blood agar plate and then incubated at 35°C under microaerobic conditions for 4–5 days. The result for the Gram stain was considered positive when a curvy, Gram-negative bacterium was found. Culture of *H. pylori* was considered positive if one or more colonies showed Gram-negativity, oxidase (+), catalase (+), urease (+) and spiral or curved rods in morphology. The biopsy specimens were fixed with formalin, embedded in paraffin and stained with hematoxylin and eosin. They were interpreted and reported by the same pathologist.

The results of CLO test (Delta West Bentley, WA Australia) were interpreted as positive if the color of the gel turned pink or red 6 hours after examination at room temperature. The ^{13}C-urea was manufactured by the Institute of Nuclear Energy Research, Taiwan. One hundred ml of fresh whole milk was used as the test meal. This detailed procedure was reported previously {Wu, 2003 20458/id}.

Antimicrobial resistance

One antral gastric biopsy specimen was obtained for isolation of *H. pylori*, using previously described culture methods {Hsu, 2002 15117/id}. *H. pylori* sub-culturing was done by rubbing the specimens on the surface of a Campy-BAP agar plate [Brucella agar (Difco, Sparks, MD, USA) + IsoVitalex (Gibco, Grand Island, NY, USA) + 10% whole sheep blood] followed by incubation at 37°C under microaerobic conditions (5% O_2, 10% CO_2 and 85% N_2) for 4–5 days. *H. pylori* strains were tested for clarithromycin, tetracycline, metronidazole, amoxicillin and levofloxacin susceptibility using the *E*-test (AB Biodisck, Solna, Sweden). *H. pylori* strains with a minimal inhibitory concentration (MIC) value >0.05 mg/L, > 4 μg mL^{-1}, >8 μg mL^{-1},

>0.5 μg mL^{-1} and >1 μg mL^{-1} were considered to be resistant to tetracycline, metronidazole, amoxicillin and levofloxacin respectively {Alarcon, 1999 12649/id}.

Objectives—To compare sequential and concomitant administration of a non-bismuth containing, 4 drug 10 day treatment regimen for the treatment of *H. pylori* infection. The trial was designed as a noninferiority trial.

Outcomes—The primary outcome was the ITT *H. pylori* eradication rates for the two treatments. The secondary outcomes were the per protocol PP eradication rates, and the eradication rates in relation to pretreatment antimicrobial susceptibility. Finally, the side effects encountered were compared.

Sample size—A formal efficacy (per protocol and intention to treat) analysis was planned with the primary analysis being done independent of the results of susceptibility testing. The primary comparator was the sequential therapy. The study was designed to demonstrate "equivalence" to the standard treatment using the lower bound 95% confidence limit around the difference in rates (delta) and to demonstrate that the lower bound 95% confidence limit of the point estimate lies above a threshold. Using the first method, the delta should remain less than 10%. Using the second method, the lower bound 95% confidence limit of the point estimate should be maintained above 80% to claim that the new therapy is efficacious. With a point estimate of 90%, we calculated that 80 patients would be needed to maintain the lower bound 95% confidence limit of the point estimate above this threshold. The 90% point estimate was based on the results of the prior sequential trials and on the premise that cure rates below 90% were undesirably low {Graham, 2009 20452/id}{Graham, 2007 19814/id}. We assumed the test regimen has a 90% cure rate for both arms, such that it would require 142 patients per arm to maintain the delta less than 10%. In contrast, two regimens with a 95% cure rate would require 75 patients per arm to maintain the delta less than 10%. The U.S. Food and Drug Administration suggests that the two therapies are considered equivalent if the "upper" limit of the confidence interval is less than 15%. Since the bounds of the intervals can be either positive or negative, we should check the absolute values of each bound. For example, if the confidence interval is, say, (−15.2%, 12.1%), because the absolute value of −15.2% is larger than 15%, the two treatments can differ each other by 15.2% and thus will be considered not equivalent; if, on the other hand, the confidence interval is (−11%, −2%), then we concluded equivalence with neither of the absolute values of the bounds is larger than 15%. A Monte Carlo simulation (500 × 500 runs) was conducted to estimate the sample size. Since the cure rates for all three therapies range from 90% to 95%, we found that sample sizes of 115 patients for each arm would be sufficient to achieve 80% power (ie, for a sample Size of 115 the power: 81.4%; LBb:78.4%; UBc:84.6% with a power: probability of being able to show the equivalence between two therapies; b LB: lower bound of the 95% confidence interval of power; c UB: upper bound of the 95% confidence interval of power. This would result in 230 patients with 115 per arm.

Randomization

H. pylori-infected patients were randomly assigned to sequential or concomitant therapies. Subjects and physicians were not blinded to which therapy the patients received. A study medication assignment table was prepared for each test site using a computer generated random number generator. A binary list of random assignments was provided for up to 150 subjects per site and subjects were assigned to one or the other therapy sequentially using concealed allocation until total study enrollment quota had been reached.

Statistical Analysis

Data Analyses—The distribution of gender and the initial endoscopic diagnosis between subjects in sequential and concomitant groups were compared by Chi-square statistics. The same method was applied to compare the efficacy and the frequency of side effects of the two regimens. The analyzed efficacy outcome was cure of *H. pylori* infection. The difference of patients' ages in the two groups was examined using Student *t*-test. A two-sided *p*-value of less than 0.05 was considered statistically significant. The data were analyzed using the SAS statistical package; all *p*-values were two-sided.

Eradication rates were evaluated by intention-to-treat (ITT) and per-protocol (PP) analyses. ITT analysis included all randomly assigned patients who had taken at least one dose of study medication. Patients with unknown infection status following treatment were considered treatment failures for the purposes of ITT analysis. The PP analysis excluded patients with unknown *H. pylori* status following therapy and those with major protocol violations. A *p*-value less than 0.05 was considered statistically significant. The plan was to determine the independent factors affecting the treatment response, clinical and bacterial parameters using univariate analysis. Then variables found to be significant by univariate analysis were to be subsequently assessed by a stepwise logistic regression method to identify independent factors for eradication outcome. However, as there were no differences in outcome of sequential and concomitant therapies we did not perform regression analysis. Examining for possible influencing factors (ex. dual resistance, compliance, etc) of the efficacy of each treatment, some possible factors were noted but case number of each subgroup was too small and precluded further regression analysis.

RESULTS

Characteristics of the study groups

A total of 232 *H. pylori*-infected patients were randomly assigned to sequential (n = 115) or concomitant (*n* = 117) therapies (see Flow sheet). The first patient was randomized on 26, Feb. 2007) and the last ended treatment on 25, January, 2008). The subjects were all included in the ITT analysis for *H. pylori* eradication. The baseline demographic and clinical characteristics of patients at entry are summarized in Table 1. Two groups had comparable age, gender, history of smoking and endoscopic findings.

Outcome of sequential and concomitant therapies

As shown in Table 2, ITT analysis demonstrated essentially identical eradication rates in two groups [sequential: 108/117 (92.3%), 95% CI: 87.5%–97.1% *vs.* concomitant: 107/115 (93%), 95% CI: 88.3%–97.7%; *p*-value = 0.83). The treatment score for both was Grade B [based on scoring cure rates as Grade A (<95%) through Grade F (>80%)] {Graham, 2007 19814/id}. For PP analysis, the success rates were not significantly different between the two groups (sequential: 108/116 (93.1%); 95% CI = 90.7%–95.5% *vs.* concomitant: 107/115 (93%); 95% CI = 88.3%–97.7%; *p*-value = 0.99). Eradication was confirmed by biopsy-based methods in 118 patients and 113 patients by UBT.

Both groups displayed good compliance rates (sequential: 95.7% *vs.* concomitant: 98.2%, *p*-value = 0.26). The results were the same when compliance was defined as taking >80 of the study medications.

Adverse events—Major adverse events were reported in 67 (28.9%) of the 232 patients (Table 2). 30.7% (36/117) of sequential group and 26.9% (31/115) of concomitant group reported at least one adverse event during eradication therapy. The frequency was similar between the two groups (*p*-value = 0.40). Bad taste and dizziness were the two most common adverse events. In the sequential group, two patients discontinued the treatment because of skin rash. In the concomitant group, one patient stopped the treatment due to severe headache. Altogether, three patients discontinued the treatment due to major adverse events.

Antibiotic resistance

H. pylori strains were successfully isolated from 167 of all enrolled patients who underwent bacterial culture during the initial endoscopy. The rates of resistance were: amoxicillin - 0.6% (1/167), metronidazole = 33.5% (56/167, clarithromycin = 6.6% (11/167), levofloxacin = 10.2% (17/167) and tetracycline = 0.6% (1/167) of the patients, respectively.

Factors influence efficacy of anti-*H. pylori* therapy

Table 3 listed the clinical and bacterial factors influencing the efficacy of eradication therapy. Among all resistances of antibiotics, only clarithromycin resistance had significant influence on successful eradication in sequential group in crude analysis (present *vs.* absent: 57.1% *vs.* 96.1%; *p*-value <0.0001), however the total number with clarithromycin resistance was low such that this would be better evaluated in populations where clarithromycin resistance was more prevalent. Those with resistance of clarithromycin and metronidazole (dual resistance) had significantly lower eradication rate after sequential therapy (present vs. absent: 33.3% *vs.* 95.1%; *p*-value < 0.0001), but not after concomitant therapy (present vs. absent: 75.0% *vs.* 92.4%; *p*-value = 0.22). Again the low number of patients makes the possibility of a type II error likely. The presence of major adverse event was also a predictor of eradication in sequential group (present *vs.* absent: 80.8% *vs.* 95.6%; *p*-value = 0.01). For concomitant therapy, drug compliance significantly influenced the outcome of treatment efficacy (good *vs.* poor: 93.8% *vs.* 50.0%; *p*-value = 0.02). In sequential group, the adverse effects rate was 30.7% but the compliance rate was 95.7%. Smoking habit did not affect the result in either group.

Discussion

H. pylori eradication rate following triple therapies has substantially decreased requiring a search for novel therapeutic approaches to cure *H. pylori* infections {Graham, 2007 19814/id}. Sequential therapy was one approach to overcoming the resistance problem and our study showed that the administration of a PPI and three antibiotics whether given sequentially or concomitantly had good success. It also showed that there appears to be nothing special with the sequential approach which may be more complicated than is necessary. Previous studies suggested that sequential therapy was superior to legacy triple therapy because of its improved outcome in the presence of clarithromycin-resistant strains {Vaira, 2007 19475/id}. We found no significant effect of antibiotic resistance on the eradication rate with concomitant therapy possibly because of the longer duration of therapy with one or all of the components of the concomitant therapy {Sheu, 2002 18889/id}{Okada, 1999 11998/id;Treiber, 2002 13838/id}{Scott, 1998 10572/id}{Graham, 2008 20314/id}.

It has previously been suggested that sequential therapy was likely to fail in the presence of dual clarithromycin and metronidazole resistance {Vaira, 2007 19475/id}{Moayyedi, 2007 19974/id} and our data support the generalizability of that conclusion. Empiric therapies are given without pretreatment antimicrobial susceptibility testing and the choice of an empiric therapy should be based on knowledge that the combination is successful in the local population of *H. pylori* infected. Because pretreatment antimicrobial susceptibility testing is not currently practical as only a few laboratories are prepared to provide the services required, concomitant therapy appears more suitable for patients in high endemic areas of dual resistance. However, post eradiation confirmation of cure testing is recommended to both confirm cure and for early identification of increasing antimicrobial resistance {Graham, 2009 20452/id}{Graham, 2008 20314/id}.

As noted above, more than a decade ago, 5 day concomitant therapy produced intention-to-treat (ITT) eradication rates of >90% {Treiber, 1998 9965/id}{Okada, 1998 10528/id}. Neither sequential nor concomitant therapy achieved 95% or greater cure rates (iie, to Grade A results) {Graham, 2007 19814/id}. We recently described an approach to efficiently evaluate *H. pylori* therapies that takes into account drug, dose, and duration {Graham, 2009 20452/id}. The outcome of both sequential and concomitant therapies are both subject to improvement. For example, sequential therapy might be improved by continuing the amoxicillin throughout the entire treatment period instead of stopping it after 5 days and both might be improved by increasing the duration of therapy {Graham, 2008 20316/id}.

Smoking has often been shown to reduce the effectiveness of anti-*H. pylori* therapy {Suzuki, 2006 20629/id}{Broutet, 2003 15809/id}{Moayyedi, 2007 19974/id;Treiber, 2002 13838/id} and appeared possibly important in the Spanish sequential trial {Sanchez-Delgado, 2008 20455/id}. In our study we did not find a significant effect of smoking. However, the prevalence of smoking was relatively low in our study population.

In conclusion, both sequential therapy and concomitant therapy showed good eradication rates. Resistance of clarithromycin, compliance and adverse events all are known to influence the outcome of eradication therapy. Concomitant therapy is less complex than sequential therapy such that compliance may be better in clinical use. In addition, it may be more suitable than sequential therapy for areas with an increased prevalence of dual resistances.

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Table 1

Demographic distribution of the subjects receiving different eradication regimens

Characteristics	Concomitant therapy (n = 115)	Sequential therapy (n = 117)
Age (year) (mean ± S.D)	51.8 ± 11	51.7 ± 12
Gender (male/female)	60/55	61/56
Smoking	23/75 (30.7%)	28/78 (35.9%)
Endoscopic findings		
Gastritis	36	32
Gastric ulcer (GU)	18	15
Duodenal ulcer (DU)	45	48
GU+DU	7	13
Others	9	9

Table 2

The outcomes of concomitant and sequential therapies

	Concomitant therapy	Sequential therapy	*p*-value
Eradication rate			
Intention-to-treat	107/115 (93%)	108/117 (92.3%)	0.83
Per-protocol	107/115(93%)	108/116 (93.1%)	0.99
Compliance	113/115 (98.2%)	112/117 (95.7%)	0.26
Side effect	31/115 (26.9%)	36/117 (30.7%)	0.40
Diarrhea	3/115 (2.6%)	2/117 (1.7%)	0.64
Constipation	0	0	-
Abdominal pain	3/115 (2.6%)	5/117 (4.3%)	0.49
Anorexia	4/115 (3.5%)	2/117 (1.7%)	0.40
Nausea	9/115 (7.8%)	3/117 (2.6%)	0.07
Vomiting	2/115 (1.7%)	2/117 (1.7%)	0.99
Skin rash	3/115 (2.6%)	1/117 (0.8%)	0.30
Headache	5/115 (4.3%)	5/117 (4.3%)	0.98
Dizziness	13/115 (11.3%)	10/117(8.5%)	0.48
Bad taste	18/115 (15.7%)	12/117 (10.3%)	0.22
Fatigue	5/115 (4.3%)	13/117 (11.1%)	0.05

Table 3

Univariate analysis of the clinical factors influencing the efficacy of the two regimens

Eradication rate	Concomitant therapy	*p*-value	Sequential therapy	*p*-value
Resistance (n = 167)	n = 83		n = 84	
metronidazole	92.3% (24/26)	0.81	90.0% (27/30)	0.25
clarithromycin	75.0% (3/4)	0.22	57.1% (4/7)	<0.0001
tetracycline	0	-	100% (1/1)	0.80
levofloxacin	100% (5/5)	0.44	83.3% (10/12)	0.09
amoxicillin	100% (1/1)	0.76	0	-
Dual resistance* (n = 167)	n = 83	0.22	n = 84	<0.0001
present	75.0% (3/4)		33.3% (1/3)	
absent	92.4% (73/79)		95.1% (77/81)	
Adverse event (n = 232)	n = 115	0.48	n = 117	0.01
present	90.3% (28/31)		80.8% (21/26)	
absent	94.1% (79/84)		95.6% (87/91)	
Compliance (n = 232)	n = 115	0.02	n = 117	0.29
Good**	93.8% (106/113)		92.9%(104/112)	
poor	50.0% (1/2)		80.0% (4/5)	
Smoking (n = 232)	n = 115	0.32	N = 117	0.72
present	96.9% (31/32)		93.8% (30/32)	
absent	91.6% (76/83)		91.8% (78/85)	

* dual resistances (both resistances of metronidazole and clarithromycin)

** good compliance was defined as >70% of prescribed medication