Antofloxacin, a novel fluoroquinolone, as a component of bismuth quadruple therapy for *Helicobacter pylori* eradication: a prospective, open-label, randomized trial

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Research

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Abstract

Background

Currently, the eradication rate of Helicobacter pylori (*H. pylori*) is markedly decreasing due to some antibiotics resistance, including clarithromycin, metronidazole, and levofloxacin. So, there is a considerable interest in evaluating new antibiotic combinations and regimens. Antofloxacin is a novel fluoroquinolone with broad-spectrum antibacterial activity against Gram-negative bacilli including *H. pylori* . This study is designed to evaluate the efficacy, safety and tolerability of 14-day antofloxacin-based bismuth quadruple therapy as a treatment regimen in Chinese patients with *H. pylori* infection.

Methods

We recruited 290 adult patients with *H. pylori* infection through upper endoscopy and histologic examination. Patients were randomly assigned to receive either antofloxacin-based bismuth quadruple therapy (ACLA therapy, antofloxacin 200 mg once daily, colloidal bismuth pectin 200 mg three times a day, lansoprazole 30 mg twice daily, and amoxicillin 1 g twice daily) for 14 days; or levofloxacin-based bismuth quadruple therapy (LCLA therapy, levofloxacin 500 mg once daily, colloidal bismuth pectin 200 mg three times a day, lansoprazole 30 mg twice daily, and amoxicillin 1 g twice daily) for 14 days. Eradication was assessed by 13 C-urea breath test after six-week treatment, the primary endpoint was the eradication rate by intention-to-treat (ITT) and per-protocol (PP) analyses.

Results

Allocated to ACLA were 145 (66F/70M, 42.1±12.8 years, 19.3% smokers, 13.1% alcohol drinker) and 145 (64F/81M, 41.1±12.2 years, 17.9% smokers, 12.4% alcohol drinker) patients to LCLA. 13 patients were lost to follow-up and 3 patients took < 80% of treatment drugs. The resistant rates for amoxicillin, levofloxacin and antofloxaci were 4.1% (12/290), 30.3% (44/145) and 0% (0/145), respectively. The ITT analysis showed eradication rates were 93.8% (136/145) in the ACLA group versus 86.2% (125/145) in the LCLA group (p =0.031). The PP analysis showed eradication rates were 97.8% (136/139) in the ACLA group versus 92.6% (125/135) in the LCLA group (p =0.000). The ACLA therapy exhibited lower rates of overall adverse events than LCLA therapy (33.8% vs. 42.0%), but the difference was not statistically significant (p =0. 159).

Conclusion

Antofloxacin-based bismuth quadruple therapy might be considered as an alternative for the eradication of *H. pylori* treatment, since it attained a successful eradication rate of 90% which was superior than levofloxacin-based bismuth quadruple therapy. Both regimens were well tolerated and safe.

Introduction

Helicobacter pylori (*H. pylori*) is one of the most common bacteria which infects more than half of all humans.[1] Eradication of *H. pylori* dramatically reduces the risk for chronic gastritis, peptic ulcer, gastric mucosa associated lymphoid tissue lymphoma, gastric cancer and metachronous gastric neoplasia after endoscopic treatment.[2] The most widely used first-line eradication regimen was standard triple therapy with a proton pump inhibitor (PPI) and amoxicillin, clarithromycin, or metronidazole for over a decade.[3] However, the eradication rate of *H. pylori* with standard triple therapy has fallen from initial heights of >90% to 65-70% in most countries due to antibiotic resistance.[4] Primary resistance rate to clarithromycin was reported 32 % in China, 20.6-40.7 % in Japan and higher than 20% in Western, Central, and Southern European countries and 48.2% in Turkey. [5-7] In China, metronidazole-containing triple therapy is not currently recommended as a first-line regimen as the resistance rates of *H. pylori* to metronidazole were 60-70 %.[8] Recent studies have reported levofloxacin resistance rates ranging from 20% to 50% in China[8] and 14 % in Europe.[6] Although the combination of levofloxacin-based triple therapy with bismuth can overcome the drug resistance to some extent, the high rate of drug resistance will inevitably reduce the eradication rate. [9, 10]

Antofloxacin (ATFX) is an 8-amino derivative of levofloxacin which has been approved by the China Food and Drug Administration (CFDA) in 2009 for the treatment of acute bacterial exacerbations of chronic bronchitis due to Klebsiella pneumoniae, acute pyelonephritis and cystitis due to Escherichia coli, and wound infection and multiple epifolliculitis due to Staphylococcus aureus or coagulase-negative staphylococci.[11, 12] Considering that other fluoroquinolones, such as sitafloxacin and gemifloxacin, are used for treatment of *H. pylori*[13-15] and antofloxacin exhibits high antibacterial activity against quinolone-resistant, methicillin-resistant in vitro and in vivo,[11] we wanted to investigate whether antofloxacin might be an option for the treatment of infections caused by *H. pylori*. We did a randomized controlled trial to compare the efficacy of antofloxacin-based with levofloxacin-based bismuth quadruple therapy in treatment of *H. pylori*.

Methods

Subjects and study design

This is a single-center, prospective, open-label study that was performed at the Gastroenterology Department of 900th Hospital of PLA in China from January 2019 to October 2019. Patients were considered eligible for enrollment if they were aged 18 years or older and had documented *H. pylori* infection through upper endoscopy and histologic examination. Exclusion criteria included age < 18 years; previous attempt of *H. pylori* eradication therapy; gastric malignancy; pregnancy or lactation; use of antimicrobial agents in the past month; presence of severe general condition, such as heart failure, renal failure or liver dysfunction; history of gastrectomy; allergic reaction to agents used in this study. Participants provided written informed consent before enrolment. They were investigated with a standardized questionnaire that demographic data and medical history were recorded. This trial was approved by the local ethical committee.

Randomization and interventions

Participants were assigned by a computer-generated code with random, permuted blocks into two groups to receive antofloxacin-based or levofloxacin-based bismuth quadruple therapy. The former group (ACLA group) received antofloxacin 200 mg once daily, colloidal bismuth pectin 200 mg three times a day, lansoprazole 30 mg twice daily, and amoxicillin 1 g twice daily for 14 days; and the latter group (LCLA group) received levofloxacin 500 mg once daily, colloidal bismuth pectin 200 mg three times a day, lansoprazole 30 mg twice daily, and amoxicillin 1 g twice daily, all given twice daily for 14 days. Lansoprazole and colloidal bismuth pectin were given 30 minutes before meals and antibiotics were given 30 minutes after meals.

Antibiotic Susceptibility Test

Gastric biopsy specimens were cultured on Brucella agar plates with 10% sheep blood and IsoVitalex enrichment medium which incubated under microaerobic conditions (37°C, 5% O_2, 10% CO_2, and 85% N_2) for one week. The minimum inhibitory concentration (MIC) was measured by the PDM Epsilometer test (E-test) [16] to assess susceptibility of *H. pylori* strains to amoxicillin, levofloxacin, antofloxaci. The antibiotic resistance breakpoints were ≥0.5 mg/L for amoxicillin, ≥1.0 mg/L for levofloxacin in accordance with previous reports.[17] Moreover, we defined resistance breakpoints for antofloxaci ≥1.0 mg/L.

CYP2C19 polymorphism

CYP2C19 polymorphism was analyzed to characterize PPIs metabolism. Blood sampling for genotyping of *CYP2C19* was performed using real-time PCR to identify genotypes of *CYP2C19*,including the *CYP2C19* wild-type (*CYP2C19*1*) gene and the two mutated alleles (*CYP2C19*2* and *CYP2C19*3*).[18] Patients were classified into three groups: homogeneous extensive metabolizer (homEM; *CYP2C19*1/CYP2C19*1*); heterogeneous extensive metabolizer (hetEM; *CYP2C19*1/ CYP2C19*2* and *CYP2C19*1/CYP2C19*3*); and poor metabolizer (PM; *CYP2C19*2/CYP2C19*2*, *CYP2C19*2/CYP2C19*3*, and *CYP2C19*3/CYP2C19*3*).

Procedures

All patients were informed of the drug administration times, the common side effects of drugs and smoking cessation before eradication therapy. We provided all patients diary cards, educated them how to record these side effects during treatment. Post-treatment *H. pylori* status was evaluated by ^{13}C-urea breath test (^{13}C-UBT) at least 6 weeks after the end of treatment. All patients were required to stop PPI for at least 2 weeks and antibiotics for 4 weeks before ^{13}C-UBT. The adverse events and compliance were

assessed by a standardized outpatient clinic interview at the end of treatment. The adverse effects were recorded in a validated questionnaire included anorexia, diarrhea, nausea, vomiting, headache, skin rash, abdominal distension, abdominal pain, itching and photosensitivity. The severity of adverse events was classified as: none (no side effect), mild adverse events (no limitation in daily activities), moderate adverse events (partial limitation in daily activities), severe adverse events (profound limitation in daily activities). Compliance was acceptable when over 80% of the total drugs were taken.

Sample size estimation and Statistical Analysis

While no data on *H. pylori* eradication rates with first-line bismuth quadruple therapy with antofloxacin were available at the time that this study was started, we had a hypothesis that eradication rates were >90% in antofloxacin-containing bismuth quadruple therapy. According to an α-error of 0.05, a β-error of 0.10 and equivalence margin of -10%, at least 200 subjects (100 subjects in each group) would be required in the non-inferiority trial. Considering possible dropouts (approximately 10% of subjects) after randomization, sample size calculation rendered 290 patients to be the subjects of this study.

H. pylori eradication rates were performed on both per-protocol (PP) and intention-to-treat (ITT) analysis in the assessment of the primary endpoint of the study. The ITT analysis included all randomized patients. The PP analysis excluded the patients who have not taken at least 80% of treatment drugs, or did not return for a follow-up ^{13}C-UBT. The secondary endpoints were the frequency of side effects and treatment compliance. Student's t-test was used to test for quantitative variables in normal distribution, while Mann-Whitney U-test was used to analyze quantitative variables in abnormal distribution. Chi-square test ($\chi 2$) was used to test for qualitative variables. Whenever any of the expected cells were less than five, Fischer's exact test was used. Multiple logistic regression analyses with the following predictors of interest were used to assess factors affecting the eradication frequencies: gender, *CYP2C19* polymorphism, alcohol, and smoking. A p-value<0.05 was considered as statistically significant. We used IBM SPSS Statistics (version 26.0 for Mac) for all statistical analyses.

Results

Baseline characteristics

435 subjects were screened for eligibility, of these, 290 eligible subjects were randomly assigned to either ACLA group (n = 145) or LCLA group (n = 145) group. 6 patients in the ACLA group and 7 patients in LCLA group were lost to follow-up. No patient in the ACLA group and 3 patients in LCLA group took < 80% of treatment drugs (Fig. 1). Table 1 shows the demographic and clinical characteristics of the patients. There was no statistically significant difference between the two groups in terms of age, gender, smoking history, alcohol use, and cause of treatment. Different genotypes of CYP2C19 were observed in 290 patients: 136 were homEM, 109 were hetEM, and 45 was PM. There was no statistically significant difference in the distribution of CYP2C19 genotype groups among two groups.

Table 1
Demographic and clinical characteristics of the patients

	ACLA group (n = 145)	LCLA group (n = 145)	p value
Age (y, range)	42.1 ± 12.8 (19–66)	41.1 ± 12.2 (21–65)	0.500
Gender (male/female)	79/66	81/64	0.813
Smoking	28 (19.3%)	26 (17.9%)	0.763
Alcohol use	19 (13.1%)	18 (12.4%)	0.860
Cause of treatment			0.629
Functional dyspepsia	67	76	
Peptic ulcer	28	26	
Family history of gastric cancer	5	2	
Chronic atrophic gastritis	42	36	
Gastric polyp	3	5	
CYP2C19 polymorphism			0.795
homEM	69(47.6%)	67(46.2%)	
hetEM	52(35.9%)	57(39.3%)	
PM	24(16.5%)	21(14.5%)	

Eradication rates of *H. pylori*

For the ITT analysis, the eradication rates of H. pylori were 93.8% (136/145; 95% CI: 89.8%-97.8%) in the ACLA group and 86.2% (125/145; 95% CI: 80.5%-91.9%) in the LCLA group. For the PP analysis, the eradication rates were 97.8% (136/139; 95% CI: 92.2%-100%) in the ACLA group and 92.6% (125/135; 95% CI: 88.1%-97.1%) in the LCLA group. ACLA therapy was superior to LCLA therapy in both the ITT (p = 0.031) and PP analysis (p = 0.000) (Table 2). Multiple regression analyses showed that the eradication rates of two therapies were not significantly affected by gender, smoking, alcohol, and CYP2C19 polymorphism (Table 3).

Table 2
Eradication rates in the two groups

	ACLA group	LCLA group	p value
ITT analysis	136/145(93.8%)	125/145 (86.2%)	0.031
95% CI	89.8%-97.8%	80.5%-91.9%	
PP analysis	136/139 (97.8%)	125/135 (92.6%)	0.000
95% CI	92.2%-100%	88.1%-97.1%	

Table 3
Multiple regression analyses in eradication rates

	Eradication rates (%)	χ2	p value
Gender		0.246	0.620
Female	105/124(84.68%)		
Male	122/148(82.43%)		
Smoking		1.714	0.190
No	190/224(84.82%)		
Yes	37/48 (77.08%)		
Alcohol		0.746	0.388
No	202/240(84.17%)		
Yes	25/32 (78.13%)		
CYP2C19 polymorphism		0.522	0.759
homEM	103/126(81.75%)		
hetEM	87/103 (84.47%)		
PM	37/48 (86.05%)		

Adverse events and compliances

After the exclusion of 13 patients for lost to follow-up, the rates of adverse events did not significantly differ between the two groups (33.8% (47/139) by ACLA and 42.0% (58/138) by LCLA, p = 0.159). 7.9% (11/139) of the ACLA patients and 10.1% (14/138) of the LCLA patients reported at least two adverse events during eradication therapy. The most common adverse events were diarrhea, abdominal distension and pain, headache, skin rash, and nausea in the two groups. Moreover, 1 patient developed

photosensitivity in the LCLA group but not in ACLA group (Table 4). The severity of total adverse events showed similar between the two groups (p = 0.524). 2 patients in the ACLA group had severe adverse events of headache (n = 1) and vomiting (n = 1), and 5 patients in the LCLA group had severe adverse events of diarrhea (n = 2), vomiting (n = 1), headache (n = 1) and skin rash (n = 1). No patients in the ACLA group and 3 patients in the LCLA group discontinued treatment due to severe adverse events. Two treatment groups displayed excellent compliance rates (100% by ACLA vs. 97.8% by LAC; p = 0.080) (Table 5).

Table 4
Adverse effects reported by the patients during treatment

	ACLA group (n = 139)	LCLA group (n = 138)	p value
Total adverse event	47	58	0.159
≥ two adverse events	11	14	0.492
Anorexia	5	4	0.743
Diarrhea	7	13	0.159
Nausea	9	7	0.617
Vomiting	5	6	0.749
Headache	7	8	0.780
Skin rash	6	7	0.766
Abdominal distension	6	10	0.296
Abdominal pain	7	9	0.596
Bitter taste	2	4	0.404
Itching	4	8	0.233
Photosensitivity	0	1	0.315

Table 5
Severity of adverse events and compliance

	ACLA group (n = 139)	LCLA group (n = 138)	p value
Severity of adverse events			0.524
None	92	79	
Mild	36	44	
Moderate	9	10	
Severe	2	5	
Took < 80% of drugs	0	3	0.080

Bacterial antibiotic resistances on eradication therapy

The resistant rates for amoxicillin were not statistically significant in the two groups (4.8% by ACLA vs. 3.4% by LCLA; p = 0.555), The resistant rates for levofloxacin and antofloxaci were 30.3% (44/145) and 0% (0/145) respectively. Among the antibiotics-resistant strains, the ACLA group had a higher eradication rate than the LCLA group (85.7% vs. 80.5%), but the difference was not statistically significant(p = 0.743). Among the antibiotics-susceptible strains, the ACLA group also had a higher eradication rate than the LCLA group (98.5% vs. 97.9%), but the difference was not statistically significant(p = 0.731) (Table 6).

Table 6
Bacterial antibiotic resistances on eradication therapy

	ACLA group	LCLA group	p value
AMO-R	7/145(4.8%)	5/145(3.4%)	0.555
ANT-R	0/145(0.0%)	-	-
LEV-R	-	44/145(30.3%)	-
Eradication rates			
Antibiotics-R	6/7(85.7%)	33/41(80.5%)	0.743
Antibiotics-S	130/132(98.5%)	92/94(97.9%)	0.731
AMO-R, amoxicillin-resistant; ANT-R, antofloxaci-resistant; LEV-R, levofloxacin-resistant.			

Discussion

This is the first prospective randomized trial to show that antofloxacin is effective in eradication of H. pylori infection. The data clearly demonstrated that ACLA therapy had a markedly higher eradication rate

than of LCLA therapy, whether using ITT (93.8% vs. 86.2%) or PP analysis (97.8% vs. 92.6%). Among the antibiotics- resistant and antibiotics-susceptible strains, the ACLA group achieved a higher eradication rate. A treatment success rate ≥ 90% is generally desirable for bacterial infections, and ACLA therapy started with an excellent eradication rate.

Moreover, our study also gathered a full set of baseline information such as demographic data and clinical characteristics, antibiotic resistance rates and CYP2C19 polymorphisms to improve the reliability of our findings. We observed no resistance of H. pylori to antofloxacin, suggesting that this agent may be ideal for the first phase of bismuth quadruple therapy. As we known, quinolones have been widely used in clinical practice for decades, and many patients are likely to have used this kind of drug before H. pylori eradication therapy because of their efficient and broad-spectrum antibacterial activity. However, the high rate of resistance to quinolone manifests that quinolone-based regimens may not be a good choice. At present, the drug resistance rate of levofloxacin has reached 20%-50% in China.[19, 20] Although the levofloxacin-based bismuth quadruple therapy can surmount the drug resistance to a degree, [9] the high rate of drug resistance will inevitably reduce the eradication rate. Antofloxacin, new-generation quinolones, is an improved version of LEV with an extra-NH2 group in the C-5 position which was invented in China in the late 1990s and approved in 2009.[21] Antofloxacin have been continuously and intensively studied to remedy this situation and develop antibiotics exhibiting high potency, long half-lives of elimination, few adverse effects, and low risk of drug resistance.[22] Our findings verify the previously reported, satisfactory results without the serious problem of resistance as levofloxacin.

In our study, the PP and ITT eradication rates for LCLA therapy were 92.6% and 86.2%, respectively. Subgroup analysis showed that the cure rate for levofloxacin-resistant strains in LCLA therapy was only 80.5% (33/41), but the eradication rate for levofloxacin-susceptible strains in LCLA therapy was 97.9% (92/94) in a satisfactory level. We found that 30.3% of H. pylori isolates showed some degrees of resistance to levofloxacin, similar to the results of other studies indicating that the primary resistance rate to levofloxacin is 20%-50% in China.[10] Antibiotic resistance is the main factor that contributes to the failure of LCLA therapy to adequately eradicate H. pylori. To increase the eradication rate of initial treatment as much as possible, the international consensus also does not recommend using the levofloxacin-containing regimen as an initial treatment.[2, 10, 23]

We analyzed CYP2C19 polymorphism to characterize PPIs metabolism. PPIs not only result in more stable acid-sensitive antibiotics but also possess direct anti-H. pylori activity. [24] PPIs are commonly metabolized by hepatic cytochrome P450 enzymes, especially the CYP2C19 genotype which is polymorphic, and various mutations. [25] Several previous studies have showed that a significant difference in the H. pylori eradication rate has been reported between HetEM and HomEM (OR = 1.90; 95% CI, 1.38–2.60; P < 0.0001) but not between PM and HetEM. The CYP2C19 homEM genotype was an independent factor for eradication failure in first-line H. pylori eradication therapy. [26–28] In our study, multiple regression analyses showed that the eradication rates of two therapies were not significantly affected by CYP2C19 polymorphism. One reason is that patients were assigned to receive lansoprazole-

containing therapy, the eradication rates were not significantly different between PM and HomEM with rabeprazole and lansoprazole therapy reported in previous studies[24].

A meta-analysis has reported that smoking is a vital factor underlying the successful treatment of H. pylori infections. Smoking might decrease blood perfusion and mucus secession of stomach, which could reduce the delivery of antibiotics to the gastric mucosa. In addition, smoking causes excessive gastric acid secretion which could lead to failure of treatment.[29] Multiple regression analyses in our study showed that the eradication rates of two therapies were not significantly affected by smoking. The reason for this might be that patients were told in advance to quit smoking during treatment. The previous study showed that smoking cessation during H. pylori therapy increased 8.4% eradication rates among smokers, treatment achieved similar results between smokers who gave up smoking during eradication therapy and nonsmokers.[30]

Our findings suggest that ACLA and LCLA therapies were well tolerated and shared comparable drug compliance. In addition, the ACLA therapy exhibited lower rates of overall adverse events than LCLA therapy (33.8% vs. 42.0%), but the difference was not statistically significant (p = 0. 159). Bismuth is considered safe as the doses of bismuth used in the quadruple regimen are relatively low and are administered for a short time period. [31] The incidences of side effects were not statistically significant when comparing a triple therapy with or without the addition of bismuth. [9] The common adverse events in patients receiving antofloxacin included nausea, vomiting, headache, diarrhea, anorexia, abdominal distension and pain. Photosensitivity caused by levofloxacin has not occurred in ACLA therapy. Previous study found that antofloxacin relatively had more photostable and a weaker photosensitizer compared with levofloxacin.[21] The severities of adverse events in all the patients receiving ACLA and LCLA therapy were mild to moderate. There were rare severe adverse events in the ACLA group except that 2 patients had severe adverse events of headache and vomiting.

This study had several novel findings. First, this is the first randomized trial to show that ACLA therapy was more effective than LCLA therapy. Second, we assessed the antibiotic susceptibility in 290 patients within this randomized trial, estimation of eradication rates in these subgroups of resistant subjects may achieve a more reliable conclusion. Third, we used multivariate logistic regression analysis to assess some factors such as gender, smoking, alcohol, and CYP2C19 polymorphism which may influence the successful treatment of H. pylori infections. Finally, we found that the frequencies of adverse effects were lower in patients treated with ACLA therapy than in those treated with LCLA therapy, though there was no statistical difference.

This study has some limitations. First, this trial was not a double-blind placebo-controlled trial so that it was at risk for detection bias. Second, this trial was conducted in a single center. Third, the antofloxacin is not widely available in other countries and the regimens that we used were somewhat unconventional. Therefore, larger studies on larger groups of patients are needed to confirm the results.

In conclusion, the present results could state that antofloxacin is safe and effective in eradication of H. pylori. Antofloxacin-based bismuth quadruple therapy might be considered as an alternative for the eradication of H. pylori treatment, since it attained a successful eradication rate of 90% which was superior than LCLA therapy.

Abbreviations

ACLA: antofloxacin-based bismuth quadruple therapy; LCLA: levofloxacin-based bismuth quadruple therapy; ITT: intention-to-treat analyses; PP: per-protocol analyses; AMO-R: amoxicillin-resistant; ANT-R: antofloxaci-resistant; LEV-R: levofloxacin-resistant.

Declarations

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Availability of data and materials

All data analysed during this study are included in this published article.

Ethics approval and consent to participate

The study was approved by the Ethical committee of 900th Hospital of PLA. Participants provided written informed consent before enrolment.

Consent for publication

Not applicable.

Disclosures of interest

The authors have no disclosures or conflicts of interest to report.

Authors' contributions

He Xiaojian, Wang Wen designed the study, He Xiaojian developed the methodology, He Xiaojian wrote the manuscript. He Xiaojian, Wang Wen, Li Dazhou, Liu Gang, Jiang Chuanshen collected the data. He Xiaojian performed the analysis. All the authors participated sufficiently in the work and approved the final version of the manuscript.

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Figures

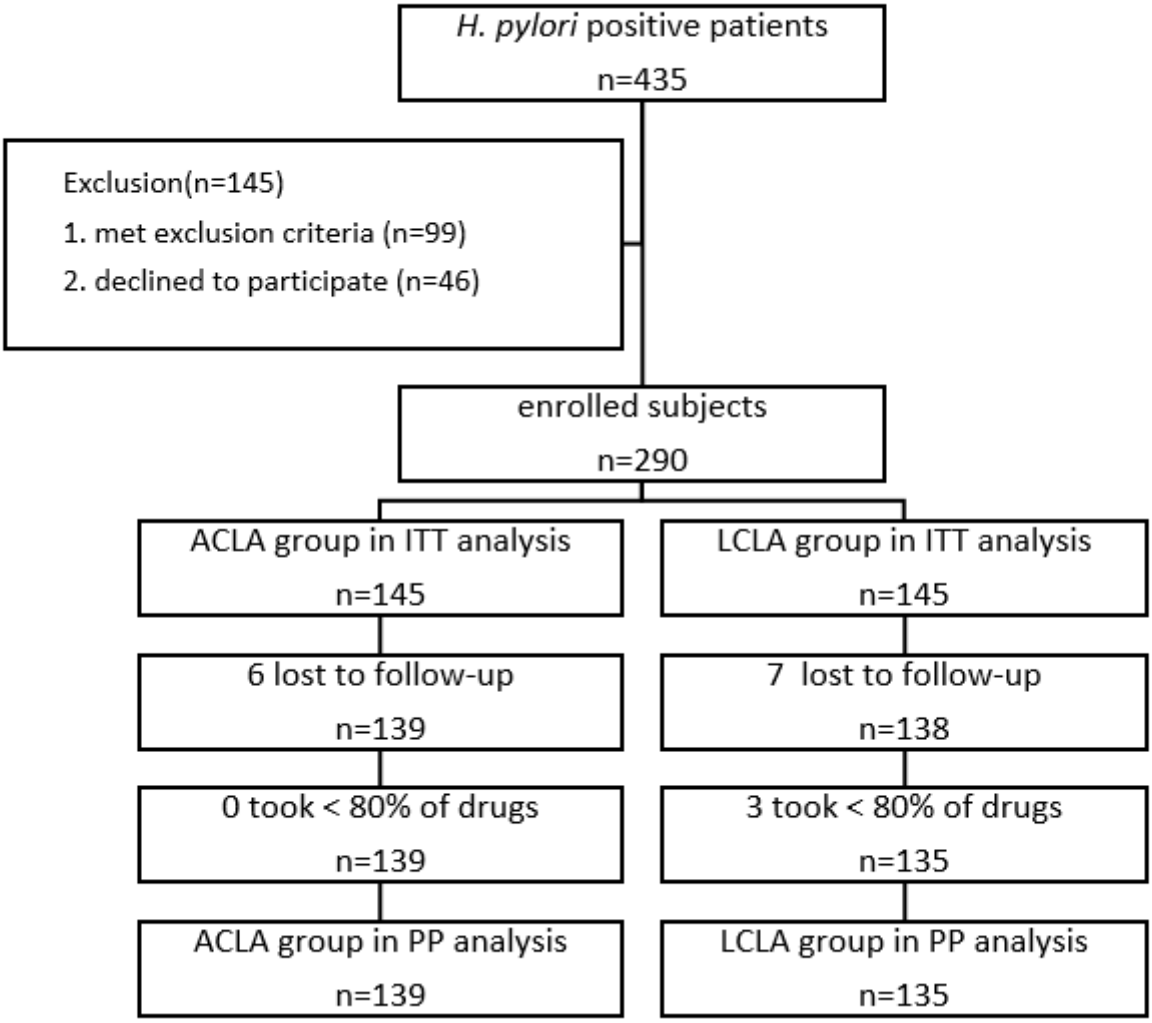

Figure 2

Flowchart of the study