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High dose amoxicillin-based first line regimen is equivalent to sequential therapy in the eradication of *H. pylori* infection

F. FRANCESCHI[1], V. OJETTI[1], M. GABRIELLI[1], C. PETRUZZIELLO[1], A. TORTORA[2], G. GASBARRINI[2], L.R. LOPETUSO[2], F. SCALDAFERRI[2], A. GASBARRINI[2]

[1]Internal Medicine Institute and [2]Internal Medicine and Gastroenterology; Catholic University of the Sacred heart, Rome, Italy

Abstract. – OBJECTIVE: ***Helicobater (H.) pylori*** **eradication rates with standard first-line triple therapy have declined to unacceptable levels. To date, amoxicillin-resistant *H. pylori* strains have rarely been detected. Whether increasing the dosage of amoxicillin in a standard 7 days eradicating regimen may enhance its efficacy is not known. The aim of this paper is to compare the efficacy of a 7 days high-dose amoxicillin based first-line regimen with sequential therapy.**

PATIENTS AND METHODS: We have retrospectively analyzed data from 300 sex and age matched patients, who underwent 3 different therapeutic schemes: (1) standard LCA, lansoprazole 30 mg bid, clarithromycin 500 mg bid and amoxicillin 1000 mg bid for 7 days; (2) high dose LCA (HD-LCA), lansoprazole 30 mg bid, clarithromycin 500 mg bid and amoxicillin 1000 mg tid for 7 days; (3) sequential LACT, lansoprazole 30 mg bid plus amoxicillin 1000 mg bid for 5 days, followed by lansoprazole 30 mg bid, clarithromycin 500 mg bid and tinidazole 500 mg bid for 5 days. Eradication was confirmed by 13C-urea breath test. Compliance and occurrence of adverse effects were also assessed.

RESULTS: Eradication rates were: 55% for LCA, 75% for HD-LCA and 73% for LACT. Eradication rates were higher in HD-LCA group compared to LCA ($p<0.01$), while no significant differences were observed in HD-LCA group compared to LACT (p=ns). Compliance and occurrence of adverse effects were similar among groups.

CONCLUSIONS: High-dose amoxicillin based eradicating treatment is superior to standard triple therapy and equivalent to sequential therapy; compared to the latter, the shorter duration may represent an advantage.

Key Words:
H. pylori, Eradication, Amoxicillin.

Introduction

Helicobacter (H.) pylori eradication still represents a big challenge for the modern medicine; just few years ago everybody thought that *H. pylori* was close to be successfully and easily cured in all infected patients but after a period of illusion[1]. *H. pylori* eradication rates are remarkably decreasing. In 2011, in fact, we are not able to provide the same high level of treatment success obtained for other common infections. The main problem is the decreasing effectiveness of most first-line regimens proposed by international guidelines[2]. Those disappointing results are essentially explained by the development of resistance to antibiotics, such as clarithromycin and metronidazole[3]. Current guidelines focus on regimens containing either clarithromycin (500 mg twice daily), a proton pump inhibitor (PPI) and amoxicillin (1000 mg twice daily), or the same regimen replacing amoxicillin with metronidazole (400 or 500 mg twice daily)[2]. The fact is that those guidelines strongly support clarithromycin and metronidazole-based regimens despite their decreased effectiveness. But even other guidelines share the same problem. In Italy, in fact, clarithromycin and metronidazole-based regimens are recommended as first-line schemes, despite an admission of "largely decreased" efficacy of standard triple therapy[4]. Thus, at present, clinicians are encouraged to use therapies consisting of a PPI, amoxicillin and clarithromycin, even in Countries where clarithromycin resistance is reported to be very high[3]. Poor results[5,6] have been obtained by studies carried out in southern and central European Country populations using this regimen while similar results have been reported in the United States[7].

Amoxicillin is a key drug in all eradicating regimens, mostly due to the fact that *H. pylori* resistance rate to this antibiotic has been shown to be very low all over the world[3]. After its administration, amoxicillin achieves maximum plasma concentration in a period ranging from 1 to 3 hours and the drug half-life ranges from 1.5 to 2 h[8]. Its effect in an acid environment such as the gastric mucosa

Corresponding Author: Francesco Franceschi, MD; e-mail: francesco.franceschi@rm.unicatt.it

depends on the pH. *H. pylori* can survive over the pH range 4-8; active replication occurs in the presence of a pH oscillating between 6 and 7, and that is the phase during which amoxicillin is capable of eradicate the infection[9]. In standard *H. pylori*-eradicating regimens, amoxicillin is administered bid. However, if we fully consider the pharmacological characteristics of this drug, there is a rationale to increase either the frequency of administration or the dosage. Natably, in other infections, such as pneumonia or acute otitis media in children, a high-dosage amoxicillin based therapy is strongly recommended[10]. Concerning its application in the treatment *H. pylori* infection, a recent study conducted on an animal model clearly showed that we may increase the eradication rate by increasing the dosage of amoxicillin[11]. On the other hand, the effect of a high-dose amoxicillin based therapy in *H. pylori*-positive humans is not known.

In this study, we have hypothesized that increasing the dosage and the frequency of administration of amoxicillin in a standard 7 days anti-*H. pylori* regimen may lead to an improvement of its efficacy, by increasing the eradication rates. Therefore, we have designed a study aimed at verifying our hypothesis.

Patients and Methods

We have retrospectively analyzed the data of 300 *H. pylori* positive patients with dyspeptic symptoms (160 females, mean age 43±12 years), who did not receive a previous eradication therapy or antimicrobial agents within the previous 3 months, bismuth compounds, proton pump inhibitors and H2 receptor blockers, laxatives, antidiarrheals, probiotics. Individuals with alcohol and/or addictive drugs abuse, known previous gastrointestinal diseases, major concomitant diseases, including psychic disorders, and pregnant or lactating women were excluded from the study.

H. pylori status was initially determined by 13-C Urea Breath Test (UBT) or rapid urease test and histology performed on mucosal biopsies (two samples from the antrum and two from the corpus) in patients who agreed to undergo upper endoscopy and the effect of the therapy was evaluated six weeks after the end of the treatment by UBT. A delta value higher that 3.5 units defined infected subjects[12]. We have also analyzed data concerning the prevalence of GI symptoms before and after the end of the treatment.

Eradicating schemes performed by patients (100 sex and age matched patients each group) are listed below:

1. Standard triple therapy (LCA): lansoprazole 30 mg bid, clarithromycin 500 mg bid and amoxicillin 1000 mg bid for 7 days;
2. High-dose amoxicillin triple therapy LCA (HD-LCA): lansoprazole 30 mg bid, clarithromycin 500 mg bid and amoxicillin 1000 mg tid for 7 days;
3. Sequential therapy (LACT): lansoprazole 30 mg bid plus amoxicillin 1000 mg bid for 5 days, followed by lansoprazole 30 mg bid, clarithromycin 500 mg bid and tinidazole 500 mg bid for 5 days.

Endoscopic findings of all patients enrolled are listed in Table I.

The study was conducted in accordance with the Declaration of Helsinki. None of the patients or authors received any honorary or economic benefits for the participation in this study.

Endpoints

Primary endpoint of the study was to compare the eradication rate of a high amoxicillin-based regimen to that achieved with sequential therapy and standard triple therapy.

Secondary endpoints were to assess the occurrence of side effects among different treatment groups.

Table I. Endoscopic findings in patients undergoing different H. pylori eradicating regimens.

	LCA	HD-LCA	LACT	p
Erosive duodenitis	16	12	14	ns
Erosive gastritis	4	6	6	ns
Erosive gastroduodenitis	8	12	10	ns
Peptic ulcer	6	8	8	ns
Duodenal hyperemia	20	18	20	ns
Gastric hyperemia	10	10	14	ns
Unknown (no EGDS)	36	34	32	ns
No. of patients	100	100	100	

Table II. Occurrence of side effects among patients undergoing different eradicating regimens. Reported side-effects were mild diarrhoea, dysgeusia, headache and nausea.

	(%)	No. of pts	*p*
LCA	20	20/100	
LACT	24	24/100	
HD-LCA	22	22/100	
LCA vs. LACT			ns
LCA vs. HD-LCA			ns
LACT vs. HD-LCA			ns

Statistical Analysis

The eradication rates were calculated for each treatment regimen. Eradication rates were compared using Mann-Whitney *U*-testing. A *p* value of less than 0.05 was considered significant. The confidence interval of 95% was calculated.

Results

H. pylori infection was successfully cured in 55 patients of the LCA group (55%), 75 patients of the HD-LCA group (75%) and 73 patients of the LACT group (73%). Eradication rates were higher in HD-LCA group compared to LCA ($p<0.01$), while no significant differences were observed in HD-LCA group compared to LACT (p=ns, Figure 1).

The therapy regimens were generally well tolerated, and no serious adverse events were reported. Mild diarrhea, dysgeusia, headache and nausea were recorded in the validated questionnaire by 22% of patients (66 of 300 patients). No significant differences were observed among groups concerning the occurrence of the above-mentioned side effects (Table II).

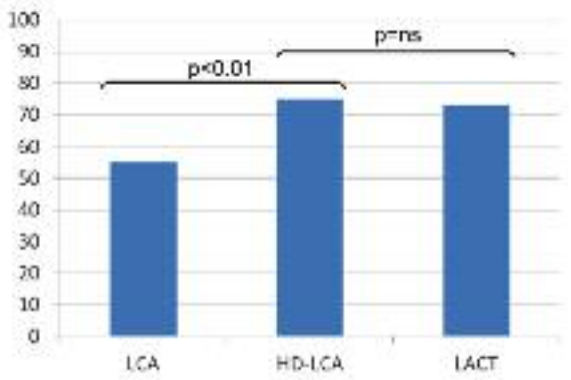

Figure 1.

Discussion

H. pylori eradication remains an amazing challenge for clinicians. There are many reasons that can explain these partial failures, such as the nature of the organism itself, the intragastric environment, the antibiotics used, the behavior and reactions of the host, and the compliance to the therapy[13]. In a society where antibiotics have been overused, seems to be clear that the most important predictor of *H. pylori* treatment effectiveness appears to be antimicrobial resistance[14]. In fact, the use of antibiotics to which the organism is not susceptible causes the selection and overgrowth of a pre-existing resistant subpopulation of *H. pylori* in the stomach[14]. There are several strategies that we can use to bypass these obstacles, such as to increase the number of antibiotics (thus improving the chance that one of them would kill the resistant organism), to pre-treat patients with agents able to reduce the bacterial load (e.g., bismuth or PPIs), and to increase the dose and durations of some drugs[15].

The present study provides evidence that increasing the dosage of amoxicillin of a standard clarithromycin-based triple therapy results in an improved efficacy, by increasing the number of successfully cured patients. Natably, the eradication rate provided by this new scheme is equivalent to that obtained by sequential therapy. Amoxicillin plays a crucial role in the anti-*H. pylori* strategy. It is the only antibiotic showing very low level of resistance all over the world, differently from the other antibiotics used in the first-line schemes, such as clarithromycin and metronidazole[14,15]. The best strategy would be, then, to work on dosage and frequency of administration of amoxicillin more than changing the combination of the other antibiotics for which resistance are markedly increasing. Definitely, in the last years, all researchers tested different combination of antibiotics, either in linear or sequential schemes, but none of them have tested the hypothesis that a better modulation of amoxicillin may be a key point for the eradication of *H. pylori*. There are some characteristics that make amoxicillin a drug with a very favorable profile. First, amoxicillin resistance is rare in most regions[16]. Secondly, *H. pylori* remains susceptible to amoxicillin, even in the presence of treatment failure, due to the occurrence of a phenomenon called "phenotypical antibiotic resistance", which consists on the existence of non-replicating or persisting bacterial populations[17,18]. These subgroups fluctuate between a non-replicat-

ing state, phenotypically resistant, and a replicating state, during which they respond to the antibiotic[19]. Therefore, increasing the duration of the eradicating treatment other than the dosage of the antibiotics may improve the efficacy of the therapy[19].

Conclusions

This study has been conducted on a reasonable number of patients even though is retrospective. Considering the importance of the topic, we believe that those results should be confirmed by further studies. Since *H. pylori* is a major risk factor for gastric cancer[20,21], increasing the eradication rate of current first-line anti-*H. pylori* regimens is too important to remain under-investigated.

Conflict of Interest

Francesco Franceschi is the author who accepts full responsibility for the conduct of the study. All authors have contributed to the conduction of this study and have fully approved the final draft submitted.

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References

1) Malfertheiner P, Link A, Selgrad M. Helicobacter pylori: perspectives and time trends. Nat Rev Gastroenterol Hepatol 2014; 11: 628-638.
2) Malfertheiner P, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ; European Helicobacter Study Group. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. Gut 2012; 61: 646-664.
3) Mégraud F. Current recommendations for Helicobacter pylori therapies in a world of evolving resistance. Gut Microbes 2013; 4: 541-548.
4) Zagari RM, Romano M, Ojetti V, Stockbrugger R, Gullini S, Annibale B, Farinati F, Ierardi E, Maconi G, Rugge M, Calabrese C, Di Mario F, Luzza F, Pretolani S, Savio A, Gasbarrini G, Caselli M. Guidelines for the management of Helicobacter pylori infection in Italy: the III Working Group Consensus Report 2015. Dig Liver Dis 2015; 47: 903-912.
5) Filipec Kanizaj T, Katicic M, Skurla B, Ticak M, Plecko V, Kalenic S. Helicobacter pylori eradication therapy success regarding different treatment period based on clarithromycin or metronidazole triple-therapy regimens. Helicobacter 2009; 14: 29-35.
6) Fischbach LA, Bravo LE, Zarama GR, Bravo JC, Ojha RP, Priest EL, Collazos T, Casabon AL, Guerrero LZ, Singh KP, Correa P. A randomized clinical trial to determine the efficacy of regimens containing clarithromycin, metronidazole, and amoxicillin among histological subgroups for Helicobacter pylori eradication in a developing country. Helicobacter 2009; 14: 100-108.
7) Graham DY, Lu H, Yamaoka Y. A report card to grade Helicobacter pylori therapy. Helicobacter 2007; 12: 275-278.
8) Qasim A, O'Morain CA, O'Connor HJ. Helicobacter pylori eradication: role of individual therapy constituents and therapy duration Fundam Clin Pharmacol 2009; 23: 43-52.
9) Scott D, Weeks D, Melchers K, Sachs G. The life and death of Helicobacter pylori. Gut 1998; 43(Suppl 1): S56-60.
10) Kiffer CR, Pignatari AC. Pharmacodynamic evaluation of commonly prescribed oral antibiotics against respiratory bacterial pathogens. BMC Infect Dis 2011; 11: 286.
11) Tran CD, Kritas S, Campbell MA, Huynh HQ, Lee SS, Butler RN. Novel combination therapy for the eradication of Helicobacter pylori infection in a mouse model. Scand J Gastroenterol 2010; 45: 1424-1430.
12) Di Rienzo TA, D'Angelo G, Ojetti V, Campanale MC, Tortora A, Cesario V, Zuccalà G, Franceschi F. 13C-Urea breath test for the diagnosis of Helicobacter pylori infection. Eur Rev Med Pharmacol Sci 2013; 17(Suppl 2): 51-58.
13. Danese S, Armuzzi A, Romano A, Cremonini F, Candelli M, Franceschi F, Ojetti V, Venuti A, Pola P, Gasbarrini G, Gasbarrini A. Efficacy and tolerability of antibiotics in patients undergoing H. pylori eradication. Hepatogastroenterology 2001; 48: 465-467.
14. O'Connor A, Gisbert JP, O'Morain C, Ladas S. Treatment of Helicobacter pylori Infection 2015. Helicobacter 2015; 20(Suppl 1): 54-61.
15. Molina-Infante J, Gisbert JP. Optimizing clarithromycin-containing therapy for Helicobacter pylori in the era of antibiotic resistance. World J Gastroenterol 2014; 20: 10338-10347.
16) Megraud F, Lehours P. Helicobacter pylori detection and antimicrobial susceptibility testing. Clin Microbiol Rev 2007; 20: 280-322.
17) Keren I, Kaldalu N, Spoering A, Wang Y, Lewis K.. Persister cells and tolerance to antimicrobials. FEMS Microbiol Lett 2004; 230: 13-18.
18) Lewis K. Persister cells, dormancy and infectious disease. Nat Rev Microbiol 2007; 5: 48-56
19) Tanimura H, Kawano S, Kubo M, Abe T, Goto M, Tanabe J, Asai A, Ito T. Does Helicobacter pylori eradication depend on the period of amoxicillin treatment? A retrospective study. J Gastroenterol 1998; 33: 23-26.
20) Franceschi F, Genta RM, Sepulveda AR. Gastric mucosa: long-term outcome after cure of Helicobacter pylori infection. J Gastroenterol 2002; 37(Suppl 13): 17-23.
21) Compare D, Rocco A, Nardone G. Risk factors in gastric cancer. Eur Rev Med Pharmacol Sci 2010; 14: 302-308.