Clarithromycin *versus* metronidazole in first-line *Helicobacter pylori* eradication. Prospective randomized study of 85 Tunisian adults

Hichem Loghmari*, Fethia Bdioui*, Wided Bouhlel*, Wissem Melki*, Olfa Hellara*, Nabil Ben Chaabane*, Leila Safer*, Abdelfettah Zakhama **, Hamouda Saffar*.

** Department of Gastroenterology and Hepathology*
*** Departement of Anatomopathology, Fattouma Bourguiba Universitary Hospital*
Monastir University, Monastir, Tunisia

H. Loghmari, F. Bdioui, W. Bouhlel, W. Melki, O. Hellara, N. Ben Chaabane, L. Safer, A. Zakhama, H. Saffar.

Clarithromycin versus metronidazole in first-line *Helicobacter pylori* eradication. Prospective randomized study of 85 Tunisian adults

LA TUNISIE MEDICALE - 2012 ; Vol 90 (n°01) : 31 - 35

H. Loghmari, F. Bdioui, W. Bouhlel, W. Melki, O. Hellara, N. Ben Chaabane, L. Safer, A. Zakhama, H. Saffar.

Comparaison de 2 protocoles de trithérapie anti-hélicobacter pylori incluant clarithromycine versus métronidazole.
Étude prospective randomisée de 85 cas

LA TUNISIE MEDICALE - 2012 ; Vol 90 (n°01) : 31 - 35

RÉSUMÉ

Prérequis : Malgré une forte résistance primaire au métronidazole (56,8%), son utilisation demeure plus répandue que celle de la clarithromycine dans le traitement de première ligne des infections à *Helicobacter pylori* (*H. pylori*) dans la pratique courante en Tunisie.
But : Comparer le taux d'éradication de l' *Hélicobacter* par la clarithromycine versus metronidazole chez des patients adultes.
Méthodes : De Juillet 2005 à Décembre 2007, 85 patients âgés de 18 à 75 ans présentant des lésions gastro-duodenales associées à une infection par *H. pylori* nécessitant son éradication ont été inclus dans l'étude. Ils ont été randomisés de manière à recevoir une trithérapie pendant 7 jours comprenant: Omeprazole + Amoxicillin + Clarithromycin (groupe OAC) ou Métronidazole (groupe OAM) deux fois par jour. Une seconde fibroscopie avec de nouvelles biopsies ont été pratiquées 6 semaines après la cure afin de contrôler l'éradication.
Résultats : Quatre-vingt-cinq patients ont mené le protocole à terme. Les groupes OAC et OAM incluaient respectivement 46 et 39 patients comparables en ce qui concerne l'âge, le sexe, la présentation clinique et les lésions initiales. Le taux global d'éradication était de 60%. Il était significativement plus élevé dans le groupe clarithromycine (69.6%) que dans le groupe métronidazole (48.7%): $p < 0,05$.
Conclusion : La Clarithromycine est plus efficace que le métronidazole dans le traitement d'éradication de *H. pylori*.

Mots-clés

Helicobacter pylori, éradication, résistance antibiotique, essai randomisé

SUMMARY

Background: Although primary resistance to metronidazole remains high (56,8%), it is more widely used than clarithromycin as a first-line *Helicobacter pylori* (*H. pylori*) treatment in the common Tunisian practice.
Aim: To compare the eradication rate in two protocols including clarithromycin versus metronidazole in Tunisian adults.
Methods: From July 2005 to December 2007, 85 patients aged 18 to75 years presenting with gastro-duodenal lesions with *H. pylori* infection and requiring its eradication were included in the study. They were randomized to receive alternatively a seven-day triple therapy including: Omeprazole + Amoxicillin + Clarithromycin (OAC group) or Metronidazole (OAM group) twice a day. A second endoscopy with new biopsies was carried out 6 weeks after treatment to control eradication.
Results: Eighty five patients finished the protocol. The OAC and OAM groups included 46 and 39 patients respectively. They were comparable with respect to age, gender, clinical presentation and initial lesions. The total eradication rate was 60%. It was significantly higher in the clarithromycin group (69.6%) than in the metronidazole group (48.7%): $p < 0.05$.
Conclusion: Clarithromycin is more effective than metronidazole in *H. pylori* eradication. It should be made available in our hospital's nomenclature. This would prevent iterative eradication courses and probably reduce treatment cost.

Key-words

Helicobacter pylori, eradication, antibiotic resistance, randomized clinical trial

A triple therapy consisting of a proton pump inhibitor (PPI) and two antimicrobial agents (amoxicillin and clarithromycin or metronidazole) is the first-line option for the eradication of *Helicobacter pylori* (*H. pylori*) according to worldwide guidelines including the Maastricht III consensus report [1] and the American College of Gastroenterology guidelines [2]. However, these triple therapies show a 20 to 30% eradication failure rate [3]. This failure is clearly attributed to primary resistance to antibiotics which is more frequently reported with metronidazole (25% on average in Europe) [3]. However, this antibiotic remains the first-line treatment in our hospital's common practice because of clarithromycin unavailability whereas *H. pylori* primary resistance to metronidazole in Tunisia seems high: 56.8% versus only 14.6% for clarithromycin, according to a recent study [4]. In addition, no comparative studies have been carried out in Tunisia to assess the real impact of this primary resistance on *H. pylori* eradication rate in clinical practice.

The primary objective of the present study was to compare *H. pylori* eradication rate in two protocols including clarithromycin versus metronidazole. The study was also aimed at finding out possible factors influencing eradication rate.

PATIENTS AND METHODS

Patients

This prospective randomized study was carried out over 30 months (July 2005-December 2007). It included successive patients aged 18 to 75 years presenting with one or more of the following lesions associated with *H. pylori* infection and requiring its eradication : duodenal ulcer, ulcerative bulbitis, gastric ulcer, erosive or ulcerative antritis or nodular gastritis. Pregnant women, patients with cirrhosis or renal failure and those on haemodialysis were excluded along with patients presenting gastric MALT (mucosa associated lymphoid tissue) lymphoma, peptic ulcer complication (stenosis, haemorrhage) or patients having received an eradication course, anti-secretories or antibiotics (< 15 days).

Methods

Each patient had a physical examination and a first oeso-gastro-duodenal endoscopy (OGDE 1) with gastric biopsies: one from the antrum and one from the corpus for the rapid urease test (Pronto Dry); two from the antrum and two from the corpus for the histological examination. The rapid urease test was read at 5 mn, 30 mn and 60 mn and was considered negative if the colour did not change at 60 mn. For the histological examination, biopsy specimens were fixed in 4% buffered formalin. The sections were stained with Giemsa and haematoxylin and eosin to search for *H. pylori* and determine its density. Gastritis activity was graduated according to the updated Sydney system [5] on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Patients who tested positive for *H. pylori* on the rapid urease test and/or the histological examination were randomized alternatively in two groups receiving a seven-day triple therapy. The OAC group received Omeprazole (20 mg), Amoxicillin (1g) and Clarithromycin (500 mg) b.i.d. The OAM group received Omeprazole (20 mg), Amoxicillin (1g) and Metronidazole (500 mg) b.i.d. Six weeks after the end of treatment, all patients were systematically re-examined and underwent a new physical examination in order to check for good compliance with treatment, possible side effects (tolerance to treatment) and progress of symptoms. A second upper endoscopy (OGDE 2) was carried out to describe the new endoscopic observations and perform a second series of biopsies: two from the antrum, two from the corpus and one from the angulus to confirm *H. pylori* eradication by histological examination (urea Breath test is unavailable in our hospital). Eradication was successful when *H. pylori* completely disappeared and gastritis activity improved.

Statiscal analysis

The data were collected, recorded and analyzed by a data-processing software (SPSS, version 11.0). The p values were measured by the Chi 2 test. A variance analysis was carried out to compare the two groups. The difference was considered statistically significant only when $p < 0.05$.

RESULTS

Out of the 120 patients included in the study, only 85 finished the protocol: 46 in the OAC group and 39 in the OAM group. The OAC group was composed of 26 men (56.5%) and 20 women (43.5%) aged 19 to 71 (mean age = 39.9 years). The OAM group included 18 men (46.2%) and 21 women (53.8%) aged 18 to 72 (mean age = 40.3 years). The two groups were comparable with respect to age, gender and symptom types and duration (Table 1).

Tableau 1 : Patients'clinical characteristics in the two groups.

	OAC group (n = 46)	OAM group (n = 39)	p
Gender (M/F)	26/20	18/21	0.231
Mean age (years)	39.9	40.3	0.888
Duration (months)	31.7	29.9	0.827
Ulcerative pain (%)	39.1	38.5	0.564
Atypical symptoms (%)	60.9	61.5	0.564

n : number, OAC : omeprazole - amoxicillin - clarithromycin, OAM : omeprazole - amoxicillin - metronidazole, M : male, F : female.

The distribution of initial endoscopic lesions between the two groups is reported in Table 2 without any significant differences. In seven cases, *H. pylori* was positive on the urease test and not detected by the histological examination. Conversely, the urease test was negative in three cases whereas *H. pylori* was spotted histologically. Thus, the urease and the histological tests were 96.5% and 92% sensitive respectively. During the clinical control, treatment observance was considered to be good according to the medical interrogation as well as treatment tolerance in the two groups, except for one patient from the OAC group who, despite digestive discomfort,

did not stop the treatment. Symptom improvement was reported by 29 patients (63%) in the OAC group compared to 18 (46.2%) in the OAM group without any statistical differences (p = 0.09).

Tableau 2 : Distribution of initial endoscopic lesions between the two groups.

	OAC group (n = 46)	OAM group (n = 39)	p
Duodenal ulcer (n/%)	16/34.8	17/43.6	0.272
Ulcerative bulbitis (n/%)	11/23.9	9/23.1	0.567
Nodular gastritis (n/%)	14/30.4	7/17.9	0.140
Ulcerative antritis (n/%)	4/8.7	4/10.3	0.547
Gastric ulcer (n/%)	3/3.5	1/2.2	0.438

n : number, OAC : omeprazole - amoxicillin - clarithromycin, OAM : omeprazole - amoxicillin - metronidazole.

The second endoscopic examination was normal in 24 cases (52.1%) of the OAC group and 20 (51.2%) of the OAM group. The results of the first and the second endoscopies are reported in figure 1 (OAC group) and figure 2 (OAM group).

Figure 1 : . Distribution of endoscopic lesions before and after anti-Helicobacter pylori treatment in the OAC group.

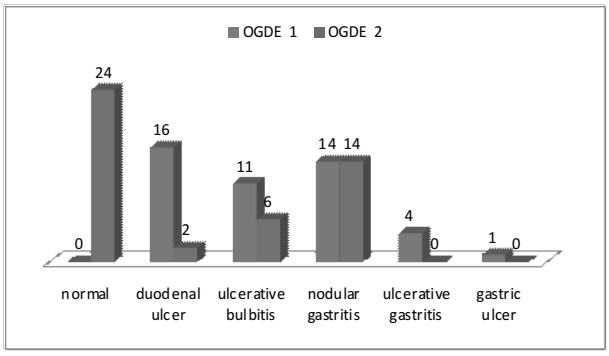
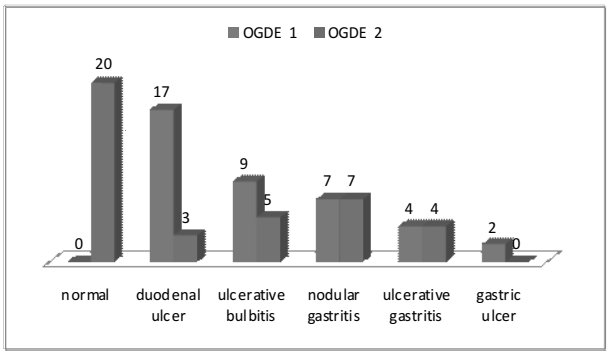


Figure 2 : Distribution of endoscopic lesions before and after anti-Helicobacter pylori treatment in the OAM group.



OAM : omeprazole - amoxicillin - metronidazole.
OGDE 1 : First oeso-gastro-duodenal endoscopy.
OGDE 2 : Second oeso-gastro-duodenal endoscopy.

The histological examination showed the absence of *H. pylori* in 51 out of the 85 cases. The total eradication rate was 60%. It was significantly more important in the OAC group (32/46 = 69.6%) that in the OAM group (19/39 = 48.7%), p = 0.041. In the same way, improvement and/or absence of gastritis activity was/were noted in 32 cases (69.5%) of the OAC group versus 18 (46.1%) of the OAM group with a significant difference, p = 0.025. Eradication rate was not influenced by age, gender or duration of the disorders. A better eradication rate was observed in duodenal ulcer compared to nodular gastritis but without any statistically significant differences, p = 0.141 (Table 3).

Tableau 3 : Eradication rate according to age, gender, duration of symptoms and endoscopic lesions

	Eradication (n / %)	p
Age		
< 30 years (n = 25)	15 / 60	
> 30 years (n = 60)	36 / 60	0.593
Gender		
Male (n = 44)	28 / 63.6	
Female (n = 41)	23 / 56	0.313
Duration of symptoms		
< 1 year (n = 46)	24 / 52.2	
> 1 year (n = 39)	23 / 59	0.341
Endoscopic lesions		
Duodenal ulcer (n =33)	22 / 66.6	
Nodular gastritis (n = 21)	10 / 47.6	0.141

DISCUSSION

In Tunisia, no therapeutic studies on the results of *H. pylori* eradication have been published and no comparative studies have been conducted so far. To our knowledge, this is the first study to give eradication rates obtained from Tunisian bacterial strains. It shows a low total eradication rate (60%). But, first-line triple therapy including clarithromycin was more effective than metronidazole: 69.6% *vs* 48.7%. *H. pylori* eradication failure can be explained by several factors, the first being non compliance or bad treatment observance. The assessment of this observance remains difficult in practice and primarily based on the interrogation of the patients. This factor is, a priori, ruled out in this study as we did our best to explain how the drug is administered and we insisted on good observance. Non compliance with one of these represented an exclusion criteria from the protocol. Eradication failure is mainly due to bacterial resistance to antibiotics. Amoxicillin resistance remains rare (< 1%) although it has long been used [3]. This is also the case for Tunisia (0%) [4]. On the other hand, resistance to clarithromycin and metronidazole is frequent and has an

important negative impact on eradication rate [3]. Primary resistance to clarithromycin varies from one country to another and tends to increase with time especially in Europe. This could be explained by the preferential use of triple therapies containing clarithromycin or the use of this antibiotic on a large scale [6]. Primary resistance to clarithromycin significantly decreases success rate of triple therapies using this antibiotic (less than 25% of the cases) [7]. Primary resistance to metronidazole is more frequent (on average 3 times higher than for macrolides) and seems to be steady in time [8]. In the same way, a correlation between the yearly consumption of nitro-imidazoles and resistance rate to metronidazole was highlighted in a Japanese study [9]. Furthermore, several studies have detected a greater resistance to metronidazole among women probably because of its wide use in the gynaecology- related infections [10]. In Tunisia, primary resistance to metronidazole is high and seems to have an impact on eradication rate (48.7%) according to our results. Yet, it is more widely used as a first-line treatment in the common practice. In comparison with Africa or developing countries, primary resistance to metronidazole in Tunisia (56,8%) is very close to the high figures reported in Turkey for example (49%) [11] or Saudi Arabia (48.2%) [12]. This resistance is more frequent in other countries like Iran (72.6%) [13] or Senegal (90%) [14]. It could be due to the abusive and inadequate broad use of metronidazole in these regions, particularly in intestinal and gynaecological infections. However, this finding is not always true as it is the case in the present study: eradication rate was lower in woman (56%) than in man (63.6%) without statistically significant difference, $p = 0.313$. Larger population studies are required to confirm this assumption. Furthermore, very few studies have been conducted in developing countries to assess the impact of resistance to metronidazole on eradication rate. A prospective study carried out in Turkey compared a triple therapy associating PPI-amoxicillin-clarithromycin with a quadruple therapy associating PPI-Bismuth-tetracyclin-metronidazole, found a statistically more important resistance rate with the latter (61.5% vs 24.5%, $p < 0.005$), but this study could not be taken into account because it did not actually compare metronidazole and clarithromycin [15]. In China, where metronidazole primary resistance is approximately 50%, a study similar to ours found very close eradication rate between the two protocols (82.2% for metronidazole and 86.2% for clarithromycin) [16]. However, it should be noted that the metronidazole population study group was made up of a large male majority (37M/8F). In a randomized prospective Moroccan study conducted between 1998 and 2000 and including 101 patients treated by PPI-amoxicillin-tinidazole and 93 patients treated by PPI-amoxicillin-clarithromycin for seven days, the eradication rate was respectively 33% and 63% with a significant difference ($p < 0.025$). The authors recommended the latter despite its higher cost (1247 vs 1742 Moroccan Dirham) [17]. This Moroccan study concluded that eradication success rates were higher with ulcers than with gastritis (43.8% vs 13.5%, $p < 0.025$), which is in accordance with the current study. Another more recent Moroccan trial (2006) similar to the present one has also found an eradication rate significantly higher with clarithromycin than with metronidazole as a first-line treatment (65.5% vs 53.1%, $p < 0.05$) [18]. On the other hand, resistance to clarithromycin is lower in our country (14.6%) and this figure is close to European data. According to the present results, the Clarithromycin-containing therapy offers the best eradication rates. The prevalence of resistant strains in Turkey went from 9.8% in 2000 [11] to 48.2% in 2007 [19]. The eradication rate obtained with clarithromycin as a first-line treatment remains poor with 24.5%, which is probably due to a constant increase in primary resistance to this antibiotic in Turkey [15]. In Saudi Arabia, the figures are higher (27.7%) [12]. Thus, the current European recommendations, suggest a first-line treatment should be adapted to primary resistance to antibiotics in each country. Triple therapies using clarithromycin remain recommended in populations where clarithromycin resistance is lower than 15-20% [1], which seems to be still the case in our country [4].

CONCLUSION

According to the current results, clarithromycin is more effective than metronidazole in the *H. pylori* eradication treatment in Tunisian bacterial strains. It is highly recommended that clarithromycin should be made available in Tunisian hospitals and used as a first-line treatment. This would prevent therapeutic failure and iterative eradication courses, thereby reducing treatment cost. Nevertheless, further prospective multicentre studies are necessary to support our findings as well as those related to *H. pylori* resistance kinetics in our country.

References

1. Malfertheiner P, Megraud F, O'Morain C, et al. Current concepts in the management of Helicobacter pylori infection. The Maastricht III Consensus Report. Gut 2007;102:1-18.
2. William D, Benjamin CY. American College of Gastroenterology Guidelines on the Management of Helicobacter pylori Infection. Am J Gastroenterol 2007;102:1808-25.
3. De Korwin J-D. Helicobacter pylori infection and antimicrobial agents resistance. Rev Med Intern 2004;(25):54-64.
4. Ben Mansour K, Burucoa C, Zribi M, et al. Primary resistance to clarithromycin, metronidazole and amoxicillin of Helicobacter isolated from Tunisian patients with peptic ulcers and gastritis: a prospective multicentre study. Ann Clin Microbiol Antimicrob. 2010; 9:22-8.
5. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and

grading of gastritis. The updated Sydney System. International workshop on the Histopathology of gastritis Houston 1994. Am J Surg Pathol 1996; 20:1161-81.
6. Loivukene K, Maaroos HI, Kolk H, Kull I, Labotkin K, Mikelsaar M. Prevalence of antibiotic resistance of Helicobacter pylori isolates in Estonia during 1995-2000 in comparison to the consumption of antibiotics used in treatment regims. Clin Microbiol Infect 2002;8:598-603.
7. Poon SK, Chang CS, Su J, et al. Primary resistance to antibiotics and its clinical impact on the efficacy of Helicobacter pylori lanzoprazole-based triple therapy. Aliment Pharmacol Ther 2002;16: 291-6.
8. Megraud F. H pylori antibiotic resistance: prevalence, importance and advances in testing. Gut 2004;53:1374-84.
9. Perez Aldana L, Kato M, Nakagawa S, et al. The relationship between consumption of antimicrobial agents and the prevalence of primary Helicobacter pylori resistance. Helicobacter 2002; 7: 306-9.
10. Meyer JM, silliman NP, Wang W, et al. Risk factors of Helicobacter pylori resistance in the United States: the surveillance of H pylori anti-microbial resistance partnership (sharp) study 1993-1999. Ann Intern Med 2002;136: 1-39.
11. Kantarçeken B, Yildirim B, Karincaoglu M, Aladag M, Himioglu F. Helicobacter pylori and antibiotic resistance. Turk J Gastroenterol 2000;11: 141-5.
12. Momenah A, Asghar AH. Prevalence and antibiotic resistance among Helicobacter pylori clinical isolates from main hospitals in the western region of Saudi Arabia. Pak J Med Sci 2008;24: 100-3.
13. Kohanteb J, Bazargani A, Saberi-Firoozi M, Mobasser A. Antimicrobial susceptibility testing of Helicobacter pylori to selected agents by agar dilution method in Shiraz-Iran. Indian J Med Microbiol 2007;25: 374-7.
14. SecK A, Mbengue M, Gassama-Sow A, Diouf A, Mourtalla Ka, Saad-Bouh Boye Ch. Antibiotic susceptibility of Helicobacter pylori isolates in Dakar, Senegal. J Infect Developing Countries 2009;3:137-40.
15. Gumurdulu Y, Serin E, Ozer B, at al. Low eradication of Helicobacter pylori with triple 7-14 days and quadriple therapy in Turkey. World J Gastroenterol 2004;10: 668-71.
16. Wei-Hao Sun, Xi-Long Ou, Da-Zhong Cao, et al. Efficacy of omeprazole and amoxicillin with either clarithromycin or metronidazole on eradication of Helicobacter pylori in Chinese peptic ulcer patients. World J Gastroenterol 2005;11: 2477-81.
17. Amrani N, Kanouni N, Bennani M, Serraj I. Helicobacter pylori eradication: which first intention tri-therapy? Acta Endoscopica 2003;33: 371-4.
18. Lahbadi M, Lahmidani A, El Mekkaoui N, et al. Eradication de l'Helicobacter pylori au Maroc: quelle trithérapie en première intention? Gastroenterol Clin Biol 2008;32:A206.
19. Onder G, Aydin A, Akarca U, Tekin F, Ozutemiz O, Ilter T. High Helicobacter pylori resistance rate to clarithromycin in Turkey. J Clin Gastroenterol 2007; 41:747-50.