Localizador web
Artículo 105.116

CagA status and *Helicobacter pylori* eradication among dyspeptic patients

A.F. Novaes de Magalhães[a,b], A. Carvalhaes[b], J. Natan-Eisig[c], J.G. Paraíso-Ferraz[a], M. Trevisan[b] and S. Zaterka[a,d]

[a]Discipline of Gastroenterology. Department of Internal Medicine. Faculty of Medical Sciences. University of Campinas. Campinas. [b]Department of Gastroenterology. Hospital Vera Cruz. Campinas. Brazil. [c]Discipline of Gastroenterology. Department of Gastroenterology. University of São Paulo. School of Medicine. São Paulo. Brazil. [d]President. Núcleo Brasileiro de Estudos sobre *H. pylori.*

ABSTRACT

AIM: Triple therapy seems more effective in curing *Helicobacter pylori* infection in patients with peptic ulcer than in those with non-ulcer dyspepsia. It has been suggested that this difference depends on the expression of CagA protein that is more frequent in the former. The objective of this study was to investigate a potential association between serum CagA positivity, severity of gastric mucosal inflammation and eradication success among peptic ulcer and non-ulcer dyspepsia patients.

MATERIAL AND METHOD: Patients undergoing upper gastrointestinal endoscopy for investigation of dyspepsia at the Department of Gastroenterology, Hospital Vera Cruz, between March, 2000 and March 2001 were screened. *H. pylori* positive patients, as diagnosed by rapid urease test and histology were included. Severity of gastric mucosal inflammation was determined and serum CagA positivity was assessed using a commercially available ELISA assay prior to *H. pylori* 7-day eradication therapy with lansoprazole, clarithromycin and amoxicillin (30 mg, 500 mg and 1 g b.i.d., respectively). Eradication success was determined 8-24 weeks following completion of therapy.

RESULTS: Seventy-four patients were included in the study (mean age 40.8, range 18-67, female = 28). CagA positivity was observed in 48% of patients. Gastroduodenal peptic ulceration was found in 54% of patients. Serum CagA positivity was significantly higher among peptic ulcer patients (62.5%), while CagA negativity was significantly higher among non-ulcer dyspepsia patients (67.7%). Lymphocyte and eosinophil infiltration was significantly higher among CagA + patients, despite being comparable when distributed among peptic ulcer and non-ulcer dyspepsia patients. Eradication was successful in 93.2% of patients, regardless of CagA status on a per protocol analysis. Based on a per protocol analysis, eradication success was comparable among peptic ulcer and non-ulcer dyspepsia patients, regardless of CagA status.

CONCLUSION: Our results support the concept that CagA positivity is associated to peptic ulcer disease and to a higher severity of lymphocyte and eosinophil infiltration. Efficacy of treatment eradication of *H. pylori* may not be affected by serum CagA status.

CagA Y ERRADICACIÓN DE *HELICOBACTER PYLORI* EN PACIENTES CON DISPEPSIA

OBJETIVO: El tratamiento triple parece tener una eficacia mayor en la curación de la infección por *Helicobacter pylori* en los pacientes con úlcera péptica, en comparación con los pacientes que presentan dispepsia de origen no ulceroso. Se ha señalado que esta diferencia depende de la expresión de la proteína CagA, que es más frecuente en los primeros. El objetivo de este estudio ha sido la investigación de una posible asociación entre la positividad sérica para CagA, la intensidad de la inflamación de la mucosa gástrica y el buen resultado de la erradicación de la infección por *H. pylori* en pacientes con úlcera péptica y en pacientes con dispepsia de origen no ulceroso.

MATERIAL Y MÉTODO: El estudio se realizó en pacientes atendidos entre marzo de 2000 y marzo de 2001 en el Department of Gastroenterology, Hospital Vera Cruz; en todos los pacientes se había indicado la realización de endoscopia gastrointestinal alta como parte del estudio de un cuadro de dispepsia. Los participantes presentaron positividad para *H. pylori,* tanto en la prueba rápida de la ureasa como en el estudio histológico. Se determinó la intensidad de la inflamación de la mucosa gástrica y se evaluó la positividad sérica para CagA mediante el uso de una técnica de ELISA comercializada, todo ello antes de la administración de un ciclo de tratamiento de 7 días para la erradicación de *H. pylori* con lansoprazol, claritromicina y amoxicilina (30 mg, 500 mg y 1 g cada 12 h, respectivamente). El resultado de la erradicación se estableció a las 8-24 de semanas de la finalización del tratamiento.

Correspondence: Prof. A.F. Novaes de Magalhães.
Rua F.A Coutinho, 9 Campinas. Brasil.
E-mail: fredericomagalhaes@terra.com.br

Received 2-2-2005; accepted for publication 5-5-2005.

RESULTADOS: En el estudio participaron 74 pacientes (edad media, 40,8 años; rango, 18-67 años; número de mujeres, 28). Se detectó positividad para CagA en el 48% de los pacientes. El 54% de ellos presentaba úlcera péptica gastroduodenal. La positividad sérica para CagA fue significativamente mayor en los pacientes con úlcera péptica (62,5%), mientras que la negatividad sérica para CagA fue significativamente mayor en los pacientes con dispepsia de origen no ulceroso (67,7%). La intensidad de la infiltración por linfocitos y eosinófilos fue significativamente mayor en los pacientes con positividad para CagA, a pesar de que dicha intensidad fue similar entre los pacientes con úlcera péptica y en los pacientes con dispepsia de origen no ulceroso. En un análisis de protocolo individualizado, la erradicación de la infección tuvo éxito en el 93,2% de los pacientes, con independencia de la positividad o negatividad para CagA. En este tipo de análisis, el buen resultado respecto de la erradicación de la infección fue comparable en los pacientes con úlcera péptica y en los pacientes con dispepsia de origen no ulceroso, con independencia de la positividad o negatividad para CagA.

CONCLUSIÓN: Nuestros resultados apoyan la posibilidad de que la positividad para CagA esté asociada a la enfermedad ulcerosa péptica y a una intensidad mayor de la infiltración por linfocitos y eosinófilos. La eficacia del tratamiento de erradicación de la infección por *H. pylori* puede no estar influida por la positividad o negatividad sérica para CagA.

OVERVIEW

Helicobacter pylori eradication is crucial in the treatment of peptic ulcer disease, and plays a key role in modifying the natural course of the disease[1,2]. However, the benefits of *H. pylori* on symptom control is controversial, specially in patients with non-ulcer dyspepsia[3]. The reduction in ulcer recurrence observed following eradication of the bacteria improves symptoms and quality of life of peptic ulcer patients, potentially reducing the risk of further ulcer complications. On the other hand, this may not be the case in functional dyspepsia patients[4].

It has been proposed that successful *H. pylori* eradication is more frequently observed in patients diagnosed with peptic ulcer compared to non-ulcer dyspepsia[5-14].

It has been observed that a bacterial virulence factor such as CagA gene positivity is mostly found in peptic ulcer patients, while most non-ulcer dyspeptic patients are CagA negative[12]. Therefore, an association between CagA positivity, peptic ulcer and effective *H. pylori* eradication may take place. The present study was designed to investigate whether there would be an association between CagA seropositivity, severity of gastric inflammation, peptic ulcer disease and the *H. pylori* response to triple therapy.

MATERIAL AND METHOD

Subjects

Patients (both sexes) undergoing upper gastrointestinal endoscopy for evaluation of dyspepsia at the Department of Gastroenterology, Hospital Vera Cruz, between March 2000 and March 2001 were considered for study participation. The inclusion criteria was the presence of *H. pylori* detected by histology (H&E and Giemsa staining) as well as by the rapid urease test. Patients with previous gastric surgery, gastric cancer, chronic liver disease, known biliary disease, pancreatic diseases, past history of upper gastrointestinal bleeding, previous *H. pylori* eradication treatment or antibiotic use 4 weeks prior to study entry were excluded. Written informed consent was obtained from all patients prior to entering the study, and the protocol was approved by the Hospital Vera Cruz Ethics Committee, in accordance with the Declaration of Helsinki.

Seventy four patients (M = 46, F = 28, mean age 40.8 years old, range 18-67) agreed to participate in the study and were included in the study protocol. Twenty two patients were current smokers (29.7%). Upper gastrointestinal endoscopy following an overnight fast using a videoendoscope (Fujinon 200 HR, Tokyo, Japan) was employed for detection of gastroduodenal peptic lesions and collection of gastric biopsies (2 antrum and 2 corpus) for determination of *H. pylori* status[15]. Endoscopic and histologic gastritis were grade according to the Sydney System. A numeric score was employed to assess the degree of mucosal inflammation, lymphocyte, eosinophil, and neutrophil infiltration, as well as the presence of lymphoid follicules before receiving eradication treatment. Histological assessment was performed by a pathologist blinded to endoscopy and CagA positivity. Serum CagA status was assessed in all patients prior to eradication therapy using an Elisa assay (CagAssay, Biomérica, City, Country). Specificity and sensitivity of the assay used to detect CagA seropositivity was performed by testing eighty control sera from an adult population and 46 consecutive patients evaluated by the urease method. CagA positivity was found in five normal individuals. Among twenty nine patients with urease positivity on endoscopy, nineteen were also positive for CagA while in seventeen patients negative for the urease method, only one showed positivity for the presence of CagA.

The patients were subjected to eradication therapy consisting of a 7-day twice daily oral administration of lansoprazole 30 mg, amoxicillin 1 g and clarithromycin 500 mg (PyloriPac®, Medley Indústria Farmacêutica, Campinas, São Paulo, Brasil). *H. pylori* eradication was confirmed when both tests (histology and rapid urease) were negative, assessed 8-24 weeks following termination of eradication therapy. After completing the 7-day triple therapy, the patients did not take any antibiotics or proton-pump inhibitors.

Statistics

The relationship (per protocol and intention-to-treat analysis) between CagA status, presence of peptic ulcer, and the effect of the eradication treatment among the patients studied was assessed using Fisher's exact test. The severity of gastritis among CagA positive and negative patients was compared using unpaired «t» test. Differences were considered to be significant when $p < 0.05$.

RESULTS

Peptic ulceration (gastric ulcer [n = 5], duodenal ulcer [n = 35]) was detected in 40 patients (54%: 95% CI = 42.1-65.7%, M = 27, F = 13, mean age 40,1 years old, range 18-67), 27.5% being smokers. Thirty-four patients had a normal mucosa or non-erosive endoscopic gastritis (46%, M = 19, F = 15, mean age 41.7% years old, range 20-65), 32% smokers. Thirty six patients (48.6%, 95% CI = 36.8-60.5%, M = 25) were found to be CagA positive on the Elisa assay. A significantly ($p < 0.05$) higher proportion of peptic ulcer patients had serum CagA positivity: 25/40 (62.5%, 95% CI = 45.8-77.3%), while serum CagA positivity was significantly ($p < 0.05$) lower among non-ulcer dyspeptic patients: 11/34 (32.3%, 95% CI = 17.4-50.5%)

Fifteen patients (peptic ulcer = 10, non-ulcer dyspepsia = 5) refused to be subjected to a repeat endoscopy in order to assess *H. pylori* eradication. Therefore, eradication was determined in 59 patients (79.7%, 95% CI = 68.8-88.2%). Eradication was successful in 90-95%, on a per protocol analysis, regardless of CagA status (table I), and comparable among peptic ulcer and non-ulcer dyspepsia patients (table II). Histological assessment was performed on samples collected from patients that had *H. pylori* eradi-

TABLE I. **CagA + status among peptic ulcer and non-ulcer dyspepsia patients**

	CagA+, n (%)	CagA–, n (%)	Total, n
Peptic ulcer	25 (62.5)[a]	15 (37.5)	40
Non-ulcer dyspepsia	11 (32.3)	23 (67.7)[b]	34
Total	36 (48.6)	38 (51.4)	74

[a]p < 0.05 versus CagA–; [b]p < 0.05 versus CagA+.

TABLE II. ***Helicobacter pylori* eradication and CagA status**

	Per protocol, n (%)	Intention-to-treat, n (%)
CagA+	30/32 (92.7)	30/36 (83.3)
CagA–	25/27 (92.5)	25/38 (65.7)
Total	55/59 (93.2)	55/71 (74.3)

[a]p < 0.05 versus CagA–; [b]p < 0.05 versus CagA+.

TABLE III. ***Helicobacter pylori* eradication (per protocol and intention-to-treat) among CagA+ and CagA– patients**

	Per Protocol		Intention-to-treat	
	CagA+, n (%)	CagA–, n (%)	CagA+, n (%)	CagA–, n (%)
Peptic ulcer	21/22 (94.4)	11/11 (100)	21/25 (84)	1/15 (73)
Non-ulcer dyspepsia	9/10 (90)	14/16 (87)	9/11 (81.8)	14/23 (60.3)

cation tested. Therefore, analysis of gastric mucosal inflammation, leukocyte infiltration and development of lymphoid follicules was investigated in 79.7% of patients. The severity of mucosal inflammation was comparable (p = 0.08) among serum CagA positive and negative patients. However, a significantly (p < 0.05) higher eosinophil and lymphocyte mucosal infiltration was observed in CagA positive patients (fig. 1). Similar neutrophil infiltration and lymphoid follicule development was observed among both groups (fig. 1). No differences were observed on the histological severity score when peptic ulcer and non-ulcer dyspeptic CagA positive and negative were analyzed.

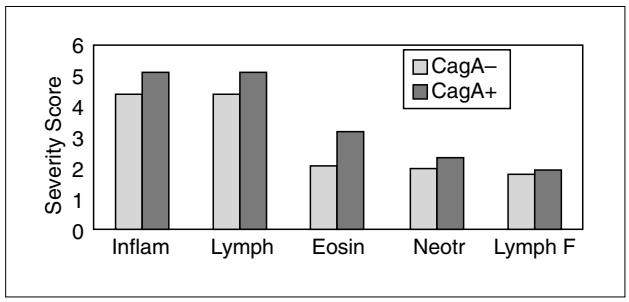

Fig. 1. Severity of mucosal inflammation among serum CagA positive and negative patients.

DISCUSSION

A lower eradication rate has been demonstrated among *H. pylori* positive, non-ulcer dyspeptic patients[5-13]. Several factors may contribute to this observation, including a reduced severity of gastric mucosal inflammation, likely related to a «less virulent» bacteria. It has been proposed that $VacA_{S2}$, CagA negative *H. pylori* infected patients are more resistant to eradication therapy[5,10,12,13]. Whether this is a result of an increased primary bacterial resistance to antibiotics or to differential drug availability to the gastric mucosa in this particular scenario remains to be elucidated. As consequence, a 10-14 day eradication schedule has been proposed over the commonly employed 7-day triple therapy for peptic ulcer disease, more frequently associated with virulent *H. pylori* ($VacA_{S1}$, CagA positive)[9]. However, several reports have been published suggesting that *H. pylori* eradication rates are not influenced by CagA status[16-19]. Our results showed an eradication efficacy comparable among peptic ulcer and non-ulcer dyspepsia patients, regardless of CagA status. Anycase total numbers are very limited in each group, specially in CagA positive dyspeptic patients, so caution should be taken when interpreting our results. The limited number of patients included can be the explanation for a negative result due to a type B error in the statistic analysis. A high drop-out rate was observed in the study, specially on the CagA negative group. It should be noted that this is a single-center study, and several patients refused to be subjected to a repeat endoscopy.

Gastric mucosal inflammation, characterized by lymphocyte and eosinophil infiltration, was more severe among CagA positive patients. Whether there is a relationship between the degree of mucosal inflammation and the ability of antibiotics to reach the gastric mucosa and the bacteria remains to be elucidated. Therefore, the results of the present study indicate that, despite the presence of *H. pylori* CagA seropositivity being associated with a more severe gastric mucosal inflammation, *H. pylori* eradication rates may not be affected by CagA seropositivity status.

REFERENCES

1. Chiba N, Rao BV, Rademaker JW, Hunt RH. Meta-analysis of the efficacy of antibiotic therapy in eradicating *Helicobacter pylori*. Am J Gastroenterol. 1992;87:1716-27.
2. NIH Consensus Development Panel. *Helicobacter pylori* in peptic ulcer disease. J Am Med Assoc. 1994;272:65-9
3. Armstrong D, Hunt RH. *Helicobacter pylori* and dyspepsia: a conceptual approach in *Helicobacter pylori*. En: Hunt RH, Tytgat GNS, editors. Basic Hechanisms to Clinical Cure 1996. London: Kluwer Academic Publishers: 1996. p. 324-39.
4. Talley NJ, Stanghelini V, Heading RC, et al. Functional gastrointestinal disorders. Gut. 1999;45 Suppl 2:1137-42.
5. Broutet N, Marais A, Lamoulliatte H, et al. CagA status and eradication treatment outcome of anti-*H. pylori* triple therapies in patients with non-ulcer dyspepsia. J Clin Microbiol. 2001;39:1319-22.
6. De Francesco V, Sgarro C, Cela E, Stoppino V, Minenna F, Faleo D, et al. *Helicobacter pylori* eradication rates in non-ulcer dyspepsia (NUD) and duodenal ulcer (DU) patients. Gut. 2001;49 Suppl 11:A94.

7. Gisbert JP, Marcos S, Gisbert JL, Pajares JM. *Helicobacter pylori* eradication therapy is more effective in peptic ulcer than in non-ulcer dyspepsia. Eur J Gatroenterol Hepatol. 2001;13: 1303-7.
8. Houben MHMG, Schraffordt Koops HS, Rauws EAJ, at al. Efficacy of PPI-triple therapy in *H. pylori* positive patients with ulcer disease versus patients with non-ulcer-dyspepsia. Gut. 1999;43 Suppl 2:A85.
9. Huang JQ, Hunt RH. Eradication of *Helicobacter pylori* infection in the management of patients with dyspepsia and non-ulcer dyspepsia. Yale J Biol Med. 1998;71:125-33.
10. Saruc M, Goksel F, Ozkaya S, et al. The effect of cagA status on response to *H. pylori* eradication therapy in Western Turkey. Bras J Med Biol Res. 2001;34:1435-9.
11. Van der Hulst RWM, Weel JFL, Verheul SB, et al. Treatment of *Helicobacter pylori* infection with low or high dose omeprazole combined with amoxicillin and the effect of early retreatment. Aliment Pharmacol Ther. 1996;10:165-71.
12. Van Doorn LJ, Figueiredo C, Sanna R, et al. Clinical relevance of the cagA, vacA and iceA status of *Helicobacter pylori*. Gastroenterology. 1998;115:58-66.
13. Van Doorn LJ, Quint WGV, Schneeberger PM, et al. Association between vacA and cagA status of *Helicobacter pylori* and the efficacy of a 1 day quadruple therapy. Lancet. 1997; 350:71.
14. Zullo A, Rinaldi V, Hassan C, Festuccia F, Lauria V, Diana F, et al. Different *Helicobacter pylori* eradication rates between non-ulcer dyspepsia and peptic ulcer patients. Gut. 1999;43 Suppl 2:A92.
15. Misiewicz JJ, Price AB, Tytgat GNJ. Working party report to the World Congress of Gastroenterology, Sydney 1990. J Gastroenterol Hepatol. 1991;6:207-34.
16. Rudi J, Reuther S, Seig A, Hoerner M, Stremmel W. Relevance of underlying disease and bacterial vacA and cagA status of the efficacy of *Helicobacter pylori* eradication. Digestion. 2002; 65:11-5.
17. Mantzaris FJ, Archavlis E, Kourtessas D, et al. Activity and severity of gastritis and *Helicobacter pylori* load do not influence the outcome of OAC-10. Gut. 1999;43 Suppl 2:A89.
18. Spenard J, Colin P, Pharma A. Is there a difference in eradication rate of *Helicobacter pylori* between peptic ulcer patients and non-ulcer dyspepsia patients? A survey of 1666 patients. 9th United European Gastroenterology; 2001.
19. Vakil N, Kovacs T, Ignatowicz W, et al. Comparable *H. pylori* eradication rates in peptic ulcer disease and non-peptic ulcer disease patients treated with rabrepazole based triple therapy. Gastroenterology. 2002;122:1201.