JOURNAL OF CLINICAL MICROBIOLOGY, Apr. 2001, p. 1319–1322 Vol. 39, No. 4
0095-1137/01/$04.00+0 DOI: 10.1128/JCM.39.4.1319–1322.2001

cagA Status and Eradication Treatment Outcome of Anti-*Helicobacter pylori* Triple Therapies in Patients with Nonulcer Dyspepsia

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Received 9 November 2000/Returned for modification 4 January 2001/Accepted 22 January 2001

The differences in eradication rates reported in clinical trials aiming to cure *Helicobacter pylori* infection cannot be entirely explained by the type of regimen, bacterial resistance, or lack of compliance. Using data from a clinical trial, a logistic regression model was constructed to determine whether *cagA* status, assessed by PCR, affects the outcome of eradication. Resistance to clarithromycin (10% of the strains) predicted failure perfectly. In the model ($n = 156$), a *cagA*-lacking strain (odds ratio [OR] = 2.2; 95% confidence interval [CI], (1.1 to 4.7), tobacco smoking OR = 3.1; 95% CI, 1.3 to 7.0), and a double dose of proton pump inhibitor in the treatment regimen (OR = 0.3; 95% CI, 0.2 to 0.7) were associated with the treatment outcome. The exact role of *cagA* in the outcome of *H. pylori* eradication therapy has not been explored. However, the type of histological lesions which it causes in the gastric mucosa may be implicated. Regardless of the mechanism involved, *cagA* status is a good predictive marker of eradication outcome.

Triple therapies used for the eradication of *Helicobacter pylori* generally include two antibiotics, i.e., clarithromycin and metronidazole or clarithromycin and amoxicillin, and a proton pump inhibitor. In several European multicenter studies, cure rates from 80 to 95% have been obtained using omeprazole (19), lansoprazole (25), or pantoprazole (11), except in France, where the cure rate varied from 70 to 80% (6).

These large multicenter studies have been performed in northern Europe where compliance is better and where resistance of *H. pylori* to antibiotics is lower than in Mediterranean countries (23). However, these European studies included exclusively (11, 19) or essentially (25) peptic ulcer disease (PUD) patients, while a large number of patients with nonulcer dyspepsia (NUD) were included in the French studies. Better eradication rates have been reported in PUD patients than in NUD patients, 73 versus 55%, respectively ($P = 0.016$) (29). A recent meta-analysis also indicated a better efficacy of these triple therapies in PUD patients than in NUD patients (eradication rates of 90.4 and 77.7% respectively [$P = 0.001$]) (15).

The *cagA* gene has been found more frequently in strains from PUD patients than in strains from NUD patients (12, 17, 30). The *cagA* gene is a marker for the *cag* pathogenicity island, which is associated with an increased inflammatory response at the gastric mucosal level (1, 10) and severe gastric disease (3, 4). Furthermore, the function of the protein produced by this gene has recently been determined by Stein et al. and Covacci et al. (8, 26).

The question of whether to eradicate *H. pylori* in NUD patients is still debated; therefore, it is interesting to consider the genotype of *H. pylori* strains when evaluating treatment outcome (5, 22, 27, 28). Although limited by a small sample size, one study has provided promising results on the subject (30). For answering the question, the most practical alternative is to consider clinical trials performed on NUD patients. The main advantages of clinical trials, despite their lack of representativity, are the quality of follow-up, data collection, and methodology.

Therefore, the following analysis was conducted to determine the factors involved in the outcome of eradication treatment, particular the *cagA* status of the *H. pylori* strain harbored. The data used came from a large multicenter clinical trial on *H. pylori* eradication, carried out on NUD patients (18), evaluating a 7-day triple therapy currently recommended in France and Europe (21, 32).

MATERIALS AND METHODS

Study data. The data were issued from a clinical trial carried out by the Aquitaine Gastro Association in southwest France, whose primary aim was to compare two different doses of proton pump inhibitor in a triple therapy for *H. pylori* eradication.

This multicenter, randomized, double-blind trial was conducted on patients with NUD, confirmed by endoscopy, with or without a history of past ulcers. The two arms of treatment were: amoxicillin (1 g twice a day b.i.d.), clarithromycin (500 mg b.i.d.), and pantoprazole (40 mg once a day (o.d.)) versus amoxicillin (1 g b.i.d.), clarithromycin (500 mg b.i.d.), and pantoprazole (40 mg b.i.d.). *H. pylori* status was assessed at inclusion by Campylobacter-like organism test and histology or culture and at 4 weeks after the end of treatment by histology and culture or urea breath test if the patient refused the posttreatment endoscopy.

In this trial, a total of 203 patients were randomized, 192 were included in the intention to treat analysis and finally 166 patients were included in the per protocol (PP) analysis (18). The description of the 37 patients excluded from the trial and the results of the clinical trial have been published (18).

Study population. The present analysis included the PP population of the above-mentioned trial, for whom the *cagA* gene status of the *H. pylori* strain was available. This population was chosen because the patients had indeed received a treatment which had or had not been successful.

***H. pylori* culture and resistance tests.** Culture of *H. pylori* was performed on selective and nonselective media (24) before treatment and 4 to 6 weeks after the end of treatment. The MICs of clarithromycin for *H. pylori* were determined by E-test.

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TABLE 1. Nucleotide sequences of primers used to detect the *cagA* gene[a]

Primer	Sequence (5′ to 3′)	Location
A1	GATAACAGGCAAGCTTTTGAGGGA	157–181
A2	CCATGAATTTTTGATCCGTTC	550–527
A3	ATGGGGAGTCATGATGGCATAGAACC	910–935
A4	ATTAGGCAAATTAAAGACAGCCACC	1626–1602

[a] The indicated primers were used in PCRs consisting of 40 cycles as follows: 1 min at 94°C, 1 min at 58°C, and 1 min at 72°C.

Bacterial suspensions equivalent to a McFarland opacity standard of 3 were prepared in brucella broth from 48-h-old agar plates and were used to flood Wilkins-Chalgren agar plates enriched with 10% human blood without antibiotics. After drying, E-test strips (AB Biodisk, Solna, Sweden) were placed on the plates which were incubated for 48 h in a microaerobic atmosphere (jars with GasPaks). Plates were read according to the manufacturer's recommendations.

The characteristics of the strains, cultured from biopsy specimens collected at inclusion, were studied. Strains were considered to be resistant to clarithromycin when the MIC was ≥1 mg/liter.

Determination of *cagA* status. The *cagA* status was determined by PCR after DNA extraction. The biospy samples were ground for 2 to 3 s with an electric tissue homogenizer and centrifuged for 5 min at 10,000 × *g*. The pellet was resuspended in 300 μl of extraction buffer (20 mM Tris-HCl, pH 8; 0.5% Tween 20), and proteinase K (0.5 mg/ml) was added. The mixture was incubated for 1 h at 56°C. Finally, the enzyme was inactivated by boiling for 10 min.

The *cagA* status was determined by amplification of internal fragments of the *cagA* gene, as described by Jenks et al. (16). Two sets of primers were used: the first one allowed the amplification of a 394-bp fragment (A1-A2), and the second allowed the amplification of a 717-bp fragment (A3-A4) (Table 1). The second amplification was performed only when the first was negative. A positive *cagA* status was defined as positive *cagA* PCR results with one of the two primer sets.

Statistical analysis. The present analysis of the clinical trial database was performed in order to identify variables which were predictive or linked to the success or failure of *H. pylori* eradication therapy, in particular, the *cagA* status of the strain.

A logistic regression model was constructed using information obtained at inclusion of the patients in the clinical trial as variables and the *H. pylori* status evaluated at the end of the trial as the outcome measure. The variables used concerned (i) the host: age, gender, body mass index (BMI) (considered to be normal for women between 20.2 and 26.6 kg/m^2 and for men between 21.6 and 28.2 kg/m^2 and abnormal otherwise), ethnic origin (Caucasian or others, including Mediterranean, black, and Asian), tobacco smoking (yes or no), alcohol consumption (yes or no), compliance based on the number of pills brought back (good compliance when <20% of the pills were brought back); (ii) *H. pylori* strain: the *cagA* status and susceptibility or resistance to clarithromycin as defined above; and (iii) the treatment received by the patient during the trial: pantoprazole o.d. versus pantoprazole b.i.d.

The EGRET statistical package (Statistic and Epidemiology Research Corporation, Seattle, Wash.) was used for univariate and multivariate analyses. All variables with a *P* value of 0.25 or less in the univariate analysis were included in the full model (13). A backward elimination procedure was then performed to reduce the number of covariables (13). Only significant covariables ($P \leq 0.05$) were retained in the models. The significance of the variables was tested using the likelihood ratio test. Confounding factors and interaction terms were taken into consideration as recommended (13). Estimated odds ratios (OR) and 95% confidence intervals (95% CI) were calculated from the coefficients.

RESULTS

Sample. Among 166 patients included in the PP analysis of the initial trial, 156 patients for whom the *H. pylori* strains were available were included in the analysis of the present study. Strains from three patients could not be subcultured after initial culture, and in seven cases strains could not be recovered after thawing.

Among the 156 patients, 80 were male (51.3%), and the mean age was 51.7 years (range, 20 to 75 years; standard deviation, 14 years). The mean age of men and women was 49 and 54 years, respectively ($P = 0.38$). The BMI ranged from 17.4 to 38.2 kg/m^2; the mean BMI among men was 25.4 and that among women was 24.8 ($P = 0.35$). There were significantly fewer smokers among women (12 of 76 [15.8%]) than among men (25 of 80 [31.3%]) ($P = 0.02$). Concerning the outcome, treatment was successful in 109 patients (69.9%).

Sixteen of 156 strains were clarithromycin resistant (10.2%). Seventy-four of 156 strains (47.4%) were *cagA* positive using the first set of primers. Among the remaining 82 strains negative for *cagA*, 10 (12.2%) were positive using the second set of primers; i.e., in total, 84 of 156 (53.8%) strains were *cagA* positive. There was no difference in the proportion of *cagA*-positive strains among the clarithromycin-resistant (8 of 16 [50%]) and -susceptible (76 of 140 [54.3%]) strains ($P = 0.73$).

Relationship between *cagA* status of strain and eradication outcome. The univariate analysis (Table 2) showed that among the variable linked to eradication outcome at a sufficient level to be included in the regression model ($P \leq 0.25$), two variables were associated with success—a double dose of pantoprazole versus a single dose and a BMI superior to the normal—and four variables were associated with failure: infection with a *cagA*-lacking strain, older age, tobacco smoking, and an ethnic origin other than Caucasian. *H. pylori* was not successfully eradicated in any of the patients with clarithromycin-resistant strains. Among the other variables tested, such as gender and alcohol consumption, no association with eradication outcome was found.

TABLE 2. Relationships between *H. pylori* eradication failure and variables related to the host and the strains, in NUD patients ($n = 156$)[a]

Variable	Total sample		Eradication failure		OR for failure	95% CI	P^b
	No.	%	No.	%			
Treatment							
o.d.	80	51.3	32	40.0	1.00		
b.i.d.	76	48.7	15	19.7	0.37	0.18–0.76	0.007
BMI							
Normal	109	69.9	36	33.0	1.00		
Inferior to normal	20	12.8	6	30.0	0.87	0.31–2.45	0.791
Superior to normal	27	17.3	5	18.5	0.46	0.16–1.32	0.148
Susceptibility to clarithromycin							
Susceptible	140	89.7	31	22.1	1.00		
Resistant	16	10.3	16	100.0	NA[d]	NA[d]	NA[d]
cagA status of strain							
cagA$^+$	84	53.8	20	23.8	1.00		
cagA-lacking	72	46.2	27	37.5	1.92	0.96–3.40	0.065
Ethnic origin of patient							
Caucasian	134	86.5	38	28.4	1.00		
Others	21	13.5	9	42.9	1.89	0.66–5.38	0.18
Smoking status							
Nonsmoker	119	76.3	30	25.2	1.00		
Smoker	37	23.9	17	45.9	2.52	1.16–5.45	0.018
Age (continuous variable)[c]					0.98	0.95–1.0	0.069

[a] Results of univariate analysis.
[b] *P* not significant if >0.25 in univariate analysis.
[c] Mean for total sample, 51.7 years; mean for eradication, failure, 48.5 years.
[d] NA, not applicable.

TABLE 3. Results of multivariate analysis on variables associated with failure of eradication treatment of *H. pylori* infection[a]

Variable	Global sample (n = 156)		Clarithromycin-susceptible strains[b] (n = 140)	
	OR	95% CI	OR	95% CI
cagA-lacking strain	2.2	1.1–4.7	2.6	1.1–4.7
Double dose of pantoprazole	0.3	0.2–0.7	0.3	0.1–0.7
Smoker	3.1	1.3–7.0	4.2	1.6–10.9

[a] Significance for each model, $P < 0.001$.
[b] Susceptibility defined as MIC of <1 mg/liter.

Because the resistance to clarithromycin predicted failure perfectly, the inclusion of this characteristic in the model was impossible. Therefore, in the regression model (n = 156), two variables remained strongly associated with eradication failure—infection with a *cagA*-lacking strain (OR = 2.2; 95% CI, 1.1 to 4.7) and tobacco smoking (OR = 3.1; 95% CI, 1.3 to 7.0)—and one variable was associated with eradication success—a double dose of pantoprazole (OR = 0.3; 95% CI, 0.2 to 0.7) (Table 3). However, as the resistance characteristic of the strain was the main predictive factor of eradication treatment outcome, the same uni- and multivariate analyses were performed on susceptible strains only (n = 140), showing the same results (Table 3).

DISCUSSION

Although the clinical trial was not initially designed for this type of analysis, the following results were forthcoming: in NUD patients, there is a clear relationship between eradication failure and the *cagA* status of the infecting strain (Table 3).

Patients with NUD constitute an interesting study population, because they have a highly heterogeneous distribution of *cagA*, and therefore the need for a large sample is alleviated. Indeed, in contrast to PUD patients, for whom the range of *cagA*-positive strains is from 80 to 90% in Western countries, the *cagA* gene is present in only 50 to 70% of the strains isolated from NUD patients (10, 17). In the present study, 53.8% of the strains were *cagA* positive. Furthermore, this study provides new information to help resolve the debate over whether to eradicate *H. pylori* in patients with NUD (5, 22, 27, 28).

The presence of the *cagA* gene was detected by PCR. The sensitivity of PCR is similar to that of colony hybridization when strains with negative results are tested with a second set of primers (17). Therefore, in this population comprised of NUD patients, the information on the *cagA* status of the strain is reliable and is a good predictive factor for eradication outcome.

From a biological point of view, the relationship between eradication outcome and *cagA* status can be explained by at least two different mechanisms. First, the presence of the *cag* pathogenicity island, as reliably detected by *cagA* (16, 20), induces the secretion of interleukin 8, a proinflammatory cytokine, by the epithelial cells, and an increased inflammation of the gastric mucosa in comparison to those harboring *cagA*-lacking strains is constantly found (7). The consequent increased blood flow may favor better diffusion of the antibiotics. There are other examples of infectious diseases, such as meningitis and prostatitis, for which this is the case. Another possible explanation may be related to the fact that *cagA*-positive strains grow faster than *cagA*-lacking strains. This point has not been extensively studied but is reported by two authors (7, 31). Mutants in the *cag* pathogenicity island obtained by Censini et al. exhibited a lower growth rate. Since antibiotics are active during cell division, they are more active on rapidly growing bacteria than on bacteria in stationary phase. Furthermore, the growth rate may influence the density, which is higher in the case of *cagA*-positive strains, and indirectly the inflammation (2, 12). The role of the *cagA* gene on eradication outcome may logically be explained by its effect on gastric mucosa. In any case, the *cagA* gene produces its effect on the outcome and the existing link is undisputable.

Infection with strains resistant to clarithromycin consistently led to treatment failure and therefore could not be included in the model. Indeed, a model cannot be adjusted on a variable for which there are no patients in one category (14), for example, in this case, the category of resistant strains with eradication success. In order to avoid this problem inherent to the methodology, the analysis of *cagA* status alone was performed using both the entire sample and the subsample of patients harboring strains susceptible to clarithromycin only. The results were similar in both cases. As only 10% of the strains cultured were resistant, the results were valid whether or not these strains were included. Clarithromycin resistance was the strongest predictor of failure, and its global impact will be increasingly important as the prevalence rate of resistance augments. Amoxicillin resistance was not tested because no amoxicillin-resistant strains have yet been detected in France by the National Surveillance Network.

Finally, from a pragmatic viewpoint, it is possible to conclude that the *cagA* status of *H. pylori* is a good predictive factor for eradication outcome in NUD patients, independent of resistance status, at the present rate of clarithromycin resistance. This observation leads to two important recommendations. (i) In clinical practice, given the satisfactory correlation between the presence of the *cagA* gene in the strain and the serological detection of anti-CagA antibodies (9), when *H. pylori* eradication treatment is considered in NUD patients, it may be helpful in decision making to test for anti-CagA antibodies; a longer treatment may be necessary in CagA-negative patients. (ii) It should be mandatory that results of clinical trials in NUD patients be adjusted on the basis of *cagA* status of *H. pylori* strains.

ACKNOWLEDGMENTS

We thank Byk France Laboratories for supporting this study.

We also thank the Aquitaine Gastro Association, whose members included the patients, allowing this study to be performed, and Kathryn Mayo (Laboratoire de Bactériologie, Université Victor Segalen Bordeaux 2) for English corrections.

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