Aliment Pharmacol Ther 1996; 10: 1021–1027.

Cure of Helicobacter pylori *infection in the elderly: effects of eradication on gastritis and serological markers*

A. PILOTTO, F. DI MARIO*, M. FRANCESCHI, G. LEANDRO†, G. SOFFIATI‡, M. SCAGNELLI§, L. BOZZOLA¶ & G. VALERIO

*Department of Geriatrics, 'S. Bortolo' Hospital, Vicenza, Italy; *Department of Gastroenterology, University of Padova, Padova, Italy; †Department of Gastroenterology, Castellana Grotte (BA), Italy;. ‡Clinical Biochemistry Laboratories, Vicenza, Italy; §Microbiology Unit, Vicenza, Italy; and ¶Clinical Pathology Unit, Vicenza, Italy*

Accepted for publication 28 July 1996

SUMMARY

Background: Specific data on anti-*H. pylori* treatments in elderly people are very scarce. The aim of the study was to evaluate in the elderly the efficacy of different anti-*H. pylori* therapies and the behaviour of serum anti-*H. pylori* antibodies, pepsinogen A and C, and PGA/PGC ratio induced by the anti-*H. pylori* treatment.

Methods: One hundred and twenty-one dyspeptic patients aged > 60 years (mean age, 73 years; range, 61–89 years) with *H. pylori*-positive gastric ulcers (17 patients), duodenal ulcers (33 patients) or chronic gastritis (71 patients) were treated with one of the following anti-*H. pylori* treatments: (A) omeprazole 20 mg/day plus azithromycin 500 mg/day for 3 days; (B) omeprazole 20 mg/day plus azithromycin 500 mg/day for 3 days plus metronidazole 250 mg q.d.s. for 7 days; (C) omeprazole 40 mg/day plus azithromycin 500 mg/day for 3 days plus metronidazole 250 q.d.s. for 7 days; (D) omeprazole 20 mg/day plus clarithromycin 250 b.d. for 7 days; (E) omeprazole 20 mg/day plus clarithromycin 250 b.d. for 7 days plus metronidazole 250 q.d.s. for 7 days; and (F) omeprazole 40 mg/day plus clarithromycin 250 mg b.d. for 7 days plus metronidazole 250 mg q.d.s. for 7 days. At the baseline and 2 months after therapy, endoscopy and serum anti-*H. pylori* antibodies, pepsinogen A and C, and PGA/PGC ratio were measured.

Results: Ten patients (8.2%) dropped out of the study. Six patients (4.9%) reported side-effects. The eradication rates of the six regimens, expressed using intention-to-treat and per protocol analysis, were, respectively: (A) 39% and 44%; (B) 50% and 56%; (C) 65% and 77%; (D) 47% and 50%; (E) 85% and 90%; and (F) 83% and 87%. The triple therapy for regimens E and F was significantly more effective than dual therapies (regimens A and D; intention-to-treat = $P < 0.007$, per protocol = $P < 0.001$) or the triple therapy for regimens B and C (intention-to-treat = $P < 0.009$, per protocol = $P < 0.03$). Patients cured of *H. pylori* infection showed a significant decrease in the activity of gastritis ($P < 0.0001$), a significant drop in IgG anti-*H. pylori* ($P = 0.0004$) and pepsinogen C ($P < 0.0001$), and an increase in PGA/PGC ratio ($P < 0.001$), while patients remaining *H. pylori*-positive showed no changes in the serum parameters.

Conclusions: In the elderly, triple therapy with omeprazole + metronidazole + clarithromycin for 1 week is well tolerated and highly effective; anti-*H. pylori* antibody and PGC serum levels decrease soon after anti-*H. pylori* therapy only in patients cured of *H. pylori* infection.

INTRODUCTION

The prevalence of *Helicobacter pylori* infection is known to increase with age, in countries with low and high socio-economic conditions;[1–3] furthermore, it has been reported that upper gastrointestinal tract lesions, and particularly gastric ulcer and chronic gastritis, increase with age in dyspeptic patients.[4] However, specific data on

Correspondence to: Dr A. Pilotto, Ospedale Civile 'S. Bortolo', Via Rodolfi 37, 36100 Vicenza, Italy.

anti-*H. pylori* treatments in elderly people are somewhat rare. This fact is even more enhanced if we consider that elderly patients may present more problems than younger people regarding the dosage of drugs, side-effects and compliance.[5]

Elimination of *H. pylori* from the gastric mucosa induces an improvement in histological gastritis activity[6] and modifications in some serum parameters, such as specific anti-*H. pylori* antibodies[7,8] and pepsinogens A and C,[9,10] were reported to occur some months after the cure. However, until now few data have been published about elderly people[11] and there are conflicting opinions at present regarding the clinical usefulness of such serum parameters in the elderly.

The aims of this study were, therefore: (1) to evaluate the tolerance and efficacy, including both the eradication of *H. pylori* and the improvement in histological evidence of gastritis, of different anti-*H. pylori* treatments in elderly patients; and (2) to study the modifications induced by the cure of *H. pylori* infection in serum anti-*H. pylori* antibodies, pepsinogens A (PGA) and C (PGC).

MATERIALS AND METHODS

Patients and treatments

The study involved 121 elderly dyspeptic patients (60 males and 61 females, mean age 73 years, range 61–89 years) affected by endoscopically and histologically diagnosed active duodenal ulcers (33 patients), gastric ulcers (17 patients) or chronic gastritis (71 patients). At the beginning of the study all subjects were *H. pylori*-positive, as documented by means of gastric mucosa histology (two biopsies from the antrum and two from the body of the stomach) and the rapid urease test (CP test, Yamanouchi) performed on one or two biopsies from the gastric antrum. According to the Sydney system chronic gastritis was defined histologically as the presence of chronic inflammatory cells in the lamina propria, and chronic gastritis activity was graded into four grades: none, mild, moderate and severe, according to the density of neutrophil granulocytes in the lamina propria, in intra-epithelial sites or both.[12]

After diagnosis all patients received a clear explanation of the purpose of the study and those who gave their informed consent were consecutively assigned to one of the following six different regimens, according to a randomization list: (A) omeprazole 20 mg/day for 2–4 weeks plus azithromycin 500 mg/day for 3 days; (B) omeprazole 20 mg/day for 2–4 weeks plus azithromycin 500 mg/day for 3 days plus metronidazole 250 mg q.d.s. for 7 days; (C) omeprazole 40 mg/day for 2–4 weeks plus azithromycin 500 mg/day for 3 days plus metronidazole 250 mg q.d.s. for 7 days; (D) omeprazole 20 mg/day for 2–4 weeks plus clarithromycin 250 mg b.d. for 7 days; (E) omeprazole 20 mg/day for 2–4 weeks plus clarithromycin 250 mg b.d. for 7 days plus metronidazole 250 mg q.d.s. for 7 days; and (F) omeprazole 40 mg/day for 2–4 weeks plus clarithromycin 250 b.d. for 7 days plus metronidazole 250 mg q.d.s. for 7 days.

Omeprazole, both at 20 and at 40 mg/day, was administered for a period of 4 weeks (in gastric ulcer and duodenal ulcer patients) or 2 weeks (in chronic gastritis patients), and the antibiotics (both in double and triple schedules) were administered during the second week of omeprazole treatment, after histological confirmation of the presence of *H. pylori* in the gastric mucosa.

Follow-up and serum parameters

In all patients the following procedures were performed at baseline and 2 months after stopping the treatment: upper gastrointestinal endoscopy; gastric biopsies for histological examination (two from the antrum and two from the gastric body; H&E plus Giemsa modified stains) and the rapid urease test (CP test, one or two biopsies from the gastric antrum); and serum concentrations of IgG anti-*H. pylori* antibodies using an established enzyme-linked immunosorbent assay (ELISA method; Biolife, Milan, Italy).[13] The levels of specific anti-*H. pylori* antibodies were derived from a standard curve of IgG mass against optical density at 450 nm and the results were expressed in monoclonal units/mL (MU/mL): values beyond a cut-off point of 20 MU/mL were considered as positive; and serum PGA (RIA method, μg/mL) and PGC (RIA method, μg/mL) levels, and the PGA/PGC ratio.

All patients were clinically evaluated after 2 and 4 weeks to record side-effects and count the tablets: compliance was defined as 'good' when more than 90% of the tablets had been taken by the patients.

In gastric ulcer and duodenal ulcer patients an intermediate endoscopy (with gastric biopsies) was performed after 4 weeks to evaluate the healing rate of the ulcers.

Statistics

Results were evaluated using both 'per protocol' and

Table 1. Epidemiological and clinical characteristics of the patients divided according to the six different anti-*H. pylori* regimens

Regimen	No. of patients	No. of males	Mean age (years)	Age range (years)	No. of patients with: gastric ulcers	duodenal ulcers	chronic gastritis	No. of patients taking NSAIDS
A	18	12	77	60–87	2	3	13	2
B	20	8	73	60–83	3	7	10	4
C	20	8	68	60–74	1	2	17	0
D	19	9	79	60–92	3	9	7	3
E	20	10	74	60–84	2	3	15	0
F	24	13	77	60–92	6	9	9	3

'intention-to-treat' analysis; the 95% confidence intervals (95% CI) were also calculated. Statistical analysis was performed by means of the χ^2 test (comparison of the different eradication rates in patients treated with different anti-*H. pylori* therapies), Student's *t*-test for paired and unpaired data, and the Wilcoxon test (comparison of baseline clinical and epidemiological characteristics and serum concentrations of IgG anti-*H. pylori* antibodies, PGA and PGC before and after treatment), and the McNemar χ^2 test (comparison of the grades of chronic gastritis activity before and after treatment).

RESULTS

Healing and eradication rate

Table 1 shows the epidemiological and clinical characteristics of the patients divided according to the different treatments: no differences were found between the six groups of patients as regards sex, mean age, endoscopic diagnosis and nonsteroidal anti-inflammatory drug (NSAID) use.

After 4 weeks of treatment the endoscopy performed in 17 gastric ulcers and 33 duodenal ulcers documented healing of the ulcers in all patients, regardless of the treatment used to cure *H. pylori* infection.

Table 2 shows the *H. pylori* eradication rates expressed on the basis of per protocol and intention-to-treat analyses. These were less than 50% with dual therapies (regimens A and D); the eradication rates obtained with triple therapies based on omeprazole (at both 20 mg and 40 mg/day) plus metronidazole and azithromycin (regimens B and C) were also not sufficiently effective (less than 65%). On the other hand, the triple therapies with omeprazole, at 20 or 40 mg/day, plus metronidazole and clarithromycin (regimens E and F) documented eradication rates of over 85%. Regimens E and F were significantly ($P < 0.05$) more effective than regimens A, B and D. Because no differences as regards the eradication rates were observed between groups B and C (intention-to-treat = 50.0 vs. 65.0%, $P = 0.52$; per protocol = 55.6% vs. 76.5%, $P = 0.30$) and between groups E and F (intention-to-treat = 85.0 vs. 83.3%, $P = 1.00$; per protocol = 89.5 vs. 87.0%, $P = 1.00$), the patients in groups B and C and in groups E and F were evaluated together: the intention-to-treat and per protocol eradication rates were, respectively, 57.5 and 65.7% in regimens B and C (omeprazole + metronidazole + azithromycin), and 84.1 and 88.1% in regimens E and F (omeprazole + metronidazole + clarithromycin). The triple therapy for regimens E and F proved more effective than the dual therapies (intention-to-treat, $P < 0.007$; per protocol, $P < 0.001$) or the triple therapy for regimens B and C (intention-to-treat, $P < 0.009$; per protocol, $P < 0.03$) (see Table 2). Considering all groups we observed six patients (4.9%) with side-effects (two patients with regimen A, one with regimen B, one with regimen D and two with regimen E); however, only three subjects reported major side-effects (one patient with nausea, one with skin rash, and one with metallic taste and oral aphthae) which required suspension of the treatment. Ten patients (8.2%) dropped out of the study: three owing to side-effects (see above); one failed to take the drugs correctly, consuming less than 90% of the prescribed tablets; and six patients refused the endoscopic examination 2 months after stopping the treatment.

Gastritis activity

Table 3 illustrates the histological modifications in chronic gastritis activity due to anti-*H. pylori* therapies: we found a significant improvement in the histological picture, both in patients who became *H. pylori*-negative

Table 2. Eradication rates, expressed as intention-to-treat and per protocol analysis, drop-outs and side-effects in patients divided according to the six different anti-*H. pylori* regimens

		Intention-to-treat		Per protocol			
Regimen	No. of patients	Eradication rate (95% CI)	Cumulative rates	Eradication rate (95% CI)	Cumulative rates	Drop-outs (No. of patients)	Side-effects (No. of patients)
A	18	38.9%* (16.4–61.4)	38.9 (16.4–61.4)	43.8%* (19.4–68.1)	43.8% (19.4–68.1)	2	2
B	20	50.0%* (28.1–71.9)	57.5% (42.2–72.8)	55.6%* (32.6–78.5)	65.7% (50.0–81.4)	2	1
C	20	65.0% (44.1–85.9)		76.5% (56.3–96.6)		3	0
D	19	47.4%* (24.9–69.8)	47.4% (24.9–69.8)	50.0%* (26.9–73.1)	50.0% (26.6–73.1)	1	1
E	20	85.5% (69.4–100)	84.1% (73.3–94.9)	89.5% (75.7–103.3)	88.1% (78.3–97.9)	1	2
F	24	83.3% (68.4–98.2)		87.0% (73.2–100.7)		1	0

Regimens: (A) omeprazole 20 mg/day + azithromycin; (B) omeprazole 20 mg/day + azithromycin + metronidazole; (C) omeprazole 40 mg/day + azithromycin + metronidazole; (D) omeprazole 20 mg/day + clarithromycin; (E) omeprazole 20 mg/day + clarithromycin + metronidazole; and (F) omeprazole 40 mg/day + clarithromycin + metronidazole.
Global χ^2 for intention-to-treat eradication rates: $P < 0.006$
Global χ^2 for per protocol eradication rates: $P < 0.005$
* $P < 0.05$ comparison of A, B and D vs. E or F.
Cumulative rates:
Comparison of A vs. B and C: intention-to-treat, $P = 0.30$; per protocol, $P = 0.24$.
Comparison of A vs. D: intention-to-treat, $P = 0.85$; per protocol, $P = 1.00$.
Comparison of D vs. E and F: intention-to-treat, $P < 0.007$; per protocol, $P < 0.001$.
Comparison of B and C vs. E and F: intention-to-treat, $P < 0.009$; per protocol, $P < 0.03$.

Table 3. Activity of chronic gastritis in elderly patients before (baseline) and after therapy for cure of *H. pylori* infection (*H. pylori*-negative = *H. pylori*-negative patients after treatment; *H. pylori*-positive = still *H. pylori*-positive after treatment)

Activity of gastritis	*H. pylori*-negative		*H. pylori*-positive	
		Baseline		
None	11 (14.1%)		2 (6.0%)	
Mild	24 (30.7%)	P = n.s.	7 (21.2%)	
Moderate–severe	43 (55.1%)		24 (72.7%)	
	$P < 0.001$	After therapy		$P = 0.002$
None	64 (82.0%)		6 (18.1%)	
Mild	13 (16.6%)	$P < 0.0001$	17 (51.5%)	
Moderate–severe	1 (1.2%)		9 (27.2%)	

after therapy ($P < 0.001$) and in those who remained *H. pylori*-positive after treatment ($P = 0.002$); however, the histological improvement was much more consistent in the *H. pylori*-negative group than in the *H. pylori*-positive group. In fact, while at the beginning of the study there were no differences in gastritis activity between patients who became *H. pylori*-negative after therapy and patients who were still *H. pylori*-positive (P = N.S.) 2 months after stopping the therapy, the *H. pylori*-negative patients presented a significantly better histological situation than the subjects who remained *H. pylori*-positive ($P < 0.0001$) (see Table 3).

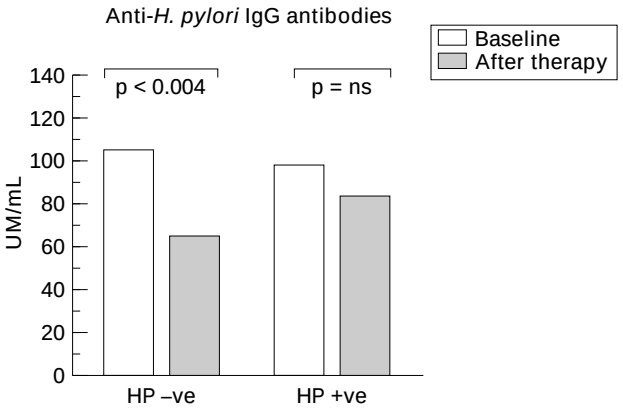

Figure 1. Anti-*H. pylori* IgG antibodies in elderly patients before (baseline) and after therapy for cure of *H. pylori* infection (*H. pylori* −ve = *H. pylori*-negative patients after treatment; *H. pylori* +ve = still *H. pylori*-positive after treatment).

Serum parameters

As illustrated in Fig. 1, 2 months after suspending therapy we found a significant decrease in the anti-*H. pylori* IgG antibody levels in patients who became *H. pylori*-negative (104 ± 11.4 vs. 64.4 ± 7.3 MU/mL, $P = 0.004$), but not in patients who remained *H. pylori*-positive after treatment (97.1 ± 22.5 vs. 82.0 ± 17.2 MU/mL, $P =$ N. S.). After treatment, seroconversion occurred in 12 of 78 cured patients (15.3%) and in one of 32 eradicated patients not cured (3.12%): the difference was not statistically significant.

Figure 2 illustrates the modifications in PGA, PGC and PGA/PGC ratio after treatment: 2 months after therapy a significant decrease in PGC (21.2 ± 1.6 vs. 12.2 ± 1.5 g/mL, $P < 0.0001$) but no change in PGA (148.4 ± 13.7 vs. 137.2 ± 11.9 g/mL, $P =$ N.S.), resulting in a significant increase in the PGA/PGC ratio (7.9 ± 0.5 vs. 10.3 ± 0.4, $P < 0.001$), was found in eradicated patients but not in subjects who remained *H. pylori*-positive after treatment (PGC, 19.8 ± 2.5 vs. 18.5 ± 2.4 g/mL, $P =$ N. S.; PGA, 159.6 ± 26.5 vs.

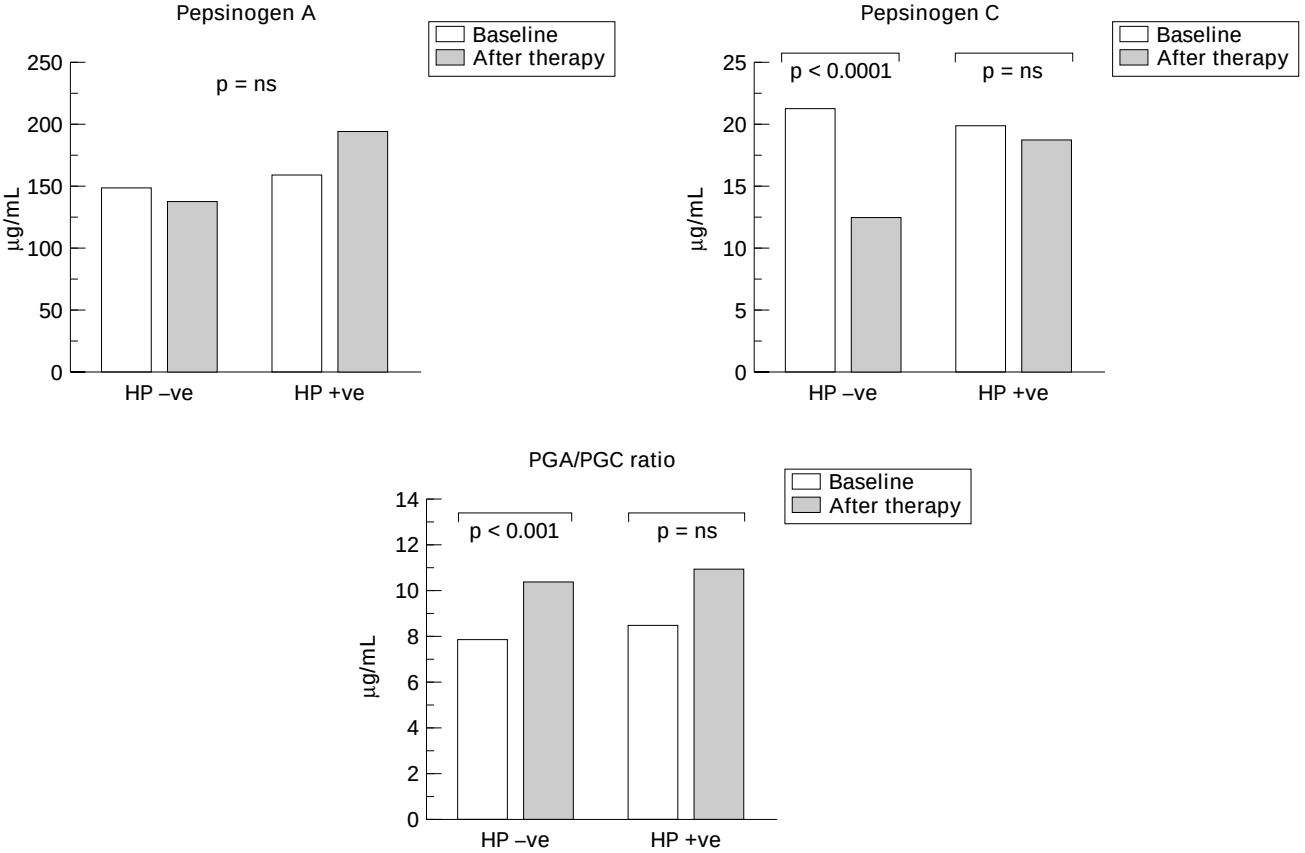

Figure 2. Serum pepsinogen A (PGA), pepsinogen C (PGC) and PGA/PGC ratio in elderly patients before (baseline) and after therapy for cure of *H. pylori* infection (*H. pylori* −ve = *H. pylori*-negative patients after treatment; *H. pylori* +ve = still *H. pylori*-positive after treatment).

191.6 ± 34.6 g/mL, P = N.S.; PGA/PGC ratio, 8.37 ± 0.6 vs. 10.85 ± 1.21, P = N.S.).

DISCUSSION

The 'ideal' therapy for curing *H. pylori* infection has yet to be established: numerous regimens of treatment have been proposed using two, three and even four drugs concomitantly for different periods.[14–19] All of these treatments, however, had never been studied specifically in elderly patients.

In this study we report that azithromycin, plus either omeprazole alone or omeprazole and metronidazole, is not sufficiently effective for the cure of *H. pylori* in the elderly. Azithromycin is a macrolide with a documented anti-*H. pylori* activity *in vitro* and with pharmacokinetic characteristics enabling its clinical use for a brief period (3–7 days for bronchopneumonia infections) and also at low dosages (500–1000 mg/day) with only one administration a day.[20,21] At present, the only paper published on the use of azithromycin (1000 mg/day for 7 days) in association with omeprazole (40 mg/day for 4 weeks) for the cure of *H. pylori* infection reported an eradication rate of 90%;[22] other studies have reported varying results.[23,24] Our low eradication rates, therefore, may be due to the brief period (3 days) of azithromycin treatment or to the pharmacokinetic characteristics of azithromycin, which is acid-unstable *in vitro*, presenting a decrease in the anti-*H. pylori* activity when the pH drops from 7.5 to 5.5;[25] this may also explain why in our study azithromycin is more effective when associated with metronidazole and omeprazole at the dosage of 40 mg/day than 20 mg/day.

In agreement with other studies performed in non-elderly patients we report that clarithromycin is very effective in the cure of *H. pylori* in the elderly when associated with nitroimidazole and omeprazole both at 20 and 40 mg/day.[26,27] The excellent eradication rate obtained with clarithromycin associated with the lower dosage of omeprazole may reflect the high susceptibility of elderly people to the gastric acid inhibitory effect of omeprazole.[28] In fact, it has been reported that the optimal dose of omeprazole to inhibit gastric acid secretion in elderly people is 20 mg/day,[29] and that in elderly patients with peptic ulcers omeprazole 20 mg/day for 4 weeks is as effective in healing ulcer lesions as omeprazole 40 mg/day.[30]

In this study side-effects were very rare: only six patients reported side-effects and only three (2.4%) dropped out as a result of side-effects. It may be that the short duration of the antibiotic therapy (1 week for the clarithromycin regimes) is mainly responsible for this fact. As regards compliance, our data confirm that these medication regimes can be correctly used by elderly patients too: once again, the short duration of the therapy and the adequate explanations may help to ensure valid compliance.

In this study, the eradication of *H. pylori* from the gastric mucosa induced a dramatic decrease in the activity of chronic gastritis: this is known to occur in the adult population after eradicating *H. pylori* infection,[6,31] but it remains to be proven in the elderly who, more often than younger patients, present gastric atrophy and/or intestinal metaplasia which are histologically irreversible processes.[32] Atrophic gastritis was rare in our population, while a histologically reversible chronic active gastritis was noticed much more frequently.

As regards the modifications induced in serum parameters by the treatment, our study demonstrates that, even after just 2 months of suspending treatment, *H. pylori*-negative patients showed a significant reduction in IgG anti-*H. pylori* antibody levels and in PGC, with no changes in PGA, leading to a significant increase in the PGA/PGC ratio. Recently, we reported relatively low values of diagnostic accuracy for all these parameters in elderly people, i.e. 0.60 for anti-*H. pylori* antibodies, 0.53 for PGA, 0.60 for PGC and 0.68 for PGA/PGC ratio.[11] However, the fact that there was no change in the IgG anti-*H. pylori* antibodies or PGA and PGC values in patients whose *H. pylori* eradication treatment failed supports the conclusion that the study of these serum parameters could provide some clinical information in monitoring *H. pylori* treatment, especially in elderly patients in whom may it be impossible to perform other tests to verify *H. pylori* eradication, i.e. the ^{13}C-urea breath test or endoscopy with histological evaluation of gastric biopsies.

In conclusion: triple therapy for 1 week with omeprazole, at 20 or 40 mg/day, plus metronidazole 250 mg q.d.s. and clarithromycin 250 mg b.d., is well tolerated and highly effective as regards both eradication rate and an improvement in chronic gastritis activity; dual therapies with omeprazole and azithromycin (or clarithromycin) and triple therapy with omeprazole, metronidazole and azithromycin are well tolerated in the elderly but are not effective in the cure of *H. pylori* infection; anti-*H. pylori* antibodies and serum PGC levels decrease soon after anti-*H. pylori* therapy only in patients cured of *H. pylori* infection.

ACKNOWLEDGEMENTS

Statistical analysis was performed by G. Leandro, M. D., biostatistician.

REFERENCES

1 Graham DY, Malaty HM, Evans DG, *et al*. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States. Effect of age, race and socioeconomic status. Gastroenterology 1991: 100: 1495–501.
2 Veldhuyzen Van Zanten SJ, Pollak PT, Best LM, Bezanson GS, Marrie T. Increasing prevalence of *Helicobacter pylori* infection with age: continuous risk of infection in adults rather than cohort effect. J Infect Dis 1994; 169: 434–7.
3 Pilotto A, Fabrello R, Franceschi M, *et al*. *Helicobacter pylori* infection in asymptomatic elderly subjects living at home or in a nursing-home: effects on gastric function and nutritional status. Age Ageing 1996; 25: 245–9.
4 Green LK, Graham DY. Gastritis in the elderly. Gastroenterol Clin North Am 1990; 19: 273–92.
5 Meyer BR, Reidenberg MM. Clinical pharmacology and ageing. In: Evans JG, Williams TF, eds. Oxford Textbook of Geriatric Medicine. Oxford University Press: Oxford, 1992: 105–16.
6 Kang JY, Tay HH, Wee A, *et al*. Effect of colloidal bismuth subcitrate on symptoms and gastric histology in non-ulcer dyspepsia. A double blind placebo controlled study. Gut 1990; 31: 476–80.
7 Kosunen TU, Seppala K, Sarna S, Sipponen P. Diagnostic value of decreasing IgG, IgA, and IgM antibody titres after eradication of *Helicobacter pylori*. Lancet 1992; 339: 893–5.
8 Plebani M, Di Mario F, Stanghellini V, Delle Fave G. Serological tests to monitor treatment of *Helicobacter pylori*. Lancet 1992; 340: 51–2.
9 Hunter FM, Correa P, Fontham E, *et al*. Serum pepsinogens as markers of response to therapy for *Helicobacter pylori* gastritis. Dig Dis Sci 1993; 38: 2081–6.
10 Wagner S, Haruma K, Gladziwa U, *et al*. *Helicobacter pylori* infection and serum pepsinogen A, pepsinogen C, and gastrin in gastritis and peptic ulcer: significance of inflammation and effect of bacterial eradication. Am J Gastroenterol 1994; 89: 1211–8.
11 Pilotto A, Franceschi M, Leandro G, *et al*. The clinical usefulness of serum pepsinogens, specific IgG anti-HP antibodies and gastrin for monitoring *Helicobacter pylori* treatment in older people. J Am Geriatr Soc 1996; 44: 665–70.
12 Misiewicz JJ, Tytgat GNJ, Goodwin CS, *et al*. The Sydney System: a new classification of gastritis. In: Working Party Reports of the 9th World Congress of Gastroenterology. Melbourne: Blackwell Scientific Publications, 1990: 1–10.
13 Talley NJ, Newell DG, Ormand JE, *et al*. Serodiagnosis of *Helicobacter pylori*: comparison of enzyme-linked immunosorbent assays. J Clin Microbiol 1991; 29: 1635–9.
14 Chiba N, Rao BV, Rademaker JW, Hunt RW. Meta-analysis of the efficacy of antibiotic therapy in eradicating *H. pylori*. Am J Gastroenterol 1992; 87: 1716–27.
15 Marshall BJ. *Helicobacter pylori*. Am J Gastroenterol 1994; 89: S116–28.
16 Noach LA, Bertola MA, Schwartz MP, Rauws EAJ, Tytgat G. Treatment of *H. pylori* infection: an evaluation of various therapeutic trials. Eur J Gastroenterol Hepatol 1994; 6: 585–92.
17 Walsh JH, Peterson WL. The treatment of *Helicobacter pylori* infection in the management of peptic ulcer disease. N Engl J Med 1995; 333: 984–91.
18 De Boer W, Driessen W, Jansz A, Tytgat G. Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. Lancet 1995; 345: 817–20.
19 Bell GD. Conference report: duodenal ulcer trials reported at the European *Helicobacter pylori* Study Group, Edinburgh 1995. Aliment Pharmacol Ther 1996; 10: 49–54.
20 Czinn S, Carr H, Aronoff S. Susceptibility of *Campylobacter pyloridis* to three macrolide antibiotics (Erythromycin, Roxythromycin and CP 62.993) and Rifampin. Antimicrob Agents Chemother 1986; 30: 328–9.
21 Retsema J, Girard A, Schelkly W, *et al*. Spectrum and mode of action of Azithromycin (CP-62.993), a new 15-membered-ring macrolide with improved potency against Gram-negative organisms. Antimicrob Agents Chemother 1987; 31: 1939–47.
22 Marchi M, Vacondio R, Bagnulo A, Mengoli M. Azithromycin–omeprazole. Treatment for eradication of *Helicobacter pylori*. Minerva Gastroenterol Dietol 1994; 40: 47–9.
23 Al-Assi MT, Genta RM, Karttunen TJ, Cole RA, Graham DY. Azithromycin triple therapy for *Helicobacter pylori* infection: azithromycin, tetracycline and bismuth. Am J Gastroenterol 1995; 90: 403–5.
24 Dal Bò N, Ferrana M, Salandin S, *et al*. Azithromycin: a new useful therapeutic strategy for the eradication of *Helicobacter pylori* infection. Am J Gastroenterol 1994; 89: 1368 (A332).
25 Darmaillac V, Bouchard S, Lamouliatte H, Megraud F. Macrolides and *Helicobacter pylori*. Determination of MICs and effect of pH. Gut 1995; 37 (Suppl. 1): A91(Abstract).
26 Bazzoli F, Zagari RM, Fossi S, *et al*. Short-term low-dose triple therapy for the eradication of *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1994; 6: 773–7.
27 Dalla Libera M, Pazzi P, Carli G, *et al*. High effectiveness and safety of one-week antibiotic regimen in *Helicobacter pylori* eradication. Aliment Pharmacol Ther 1996; 10: 203–6.
28 Pilotto A, Vianello F, Di Mario F, *et al*. Effect of age on gastric acid, pepsin, pepsinogen group A and gastrin secretion in peptic ulcer patients. Gerontology 1994; 40: 253–9.
29 Lind T, Cederberg C, Olansson M, Olbe L. Omeprazole in elderly duodenal ulcer patients: relationship between reduction in gastric acid secretion and fasting plasma gastrin. Eur J Clin Pharmacol 1991; 40: 557–60.
30 Pilotto A, Di Mario F, Battaglia G, *et al*. The efficacy of two doses of omeprazole for short- and long-term peptic ulcer treatment in the elderly. Clin Ther 1994; 16: 935–41.
31 Valle J, Seppala K, Sipponen P, Kosunen T. Disappearance of gastritis after eradication of *Helicobacter pylori*. Scand J Gastroenterol 1991; 26: 1057–65.
32 Rugge M, Di Mario F, Cassaro M, *et al*. Pathology of the gastric antrum and body associated with *Helicobacter pylori* infection in non-ulcerous patients: is the bacterium a promoter of intestinal metaplasia? Histopathology 1993; 22: 9–15.