

J Antimicrob Chemother 2015; 70: 2376–2381
doi:10.1093/jac/dkv089 Advance Access publication 7 April 2015

First-line eradication rates comparing two shortened non-bismuth quadruple regimens against *Helicobacter pylori*: an open-label, randomized, multicentre clinical trial

Antonio Cuadrado-Lavín¹, J. Ramón Salcines-Caviedes², Ainhoa Diaz-Perez², Miguel F. Carrascosa^{3*}, María Ochagavía⁴, José Luis Fernandez-Forcelledo⁵, Marta Cobo², Pedro Fernández-Gil¹, Blanca Ayestarán⁶, Blanca Sánchez⁷, Cristina Campo⁸, Javier Llorca^{9,10}, Silvia Lorenzo¹¹ and Aitziber Illaro⁴

¹Department of Gastroenterology, Hospital Universitario Marqués de Valdecilla–Instituto de Investigación Marqués de Valdecilla (IDIVAL), Avda de Valdecilla s/n, 39008, Santander, Cantabria, Spain; ²Department of Gastroenterology, Hospital Comarcal de Laredo–IDIVAL, Avda Derechos Humanos s/n, 39770 Laredo, Cantabria, Spain; ³Department of Internal Medicine, Hospital of Laredo–IDIVAL, Avda Derechos Humanos s/n, 39770 Laredo, Cantabria, Spain; ⁴Department of Pharmacy, Hospital Universitario Marqués de Valdecilla–IDIVAL, Avda de Valdecilla s/n, 39008, Santander, Cantabria, Spain; ⁵Department of Gastroenterology, Hospital Comarcal Sierrallana, Barrio Ganzo, 39300 Torrelavega, Cantabria, Spain; ⁶Department of Pharmacy, Hospital Comarcal de Laredo–IDIVAL, Avda Derechos Humanos s/n, 39770 Laredo, Cantabria, Spain; ⁷Clinical Pharmacology Service–Clinical Trial Phase I Unit, Hospital Universitario Marqués de Valdecilla–IDIVAL, Avda de Valdecilla s/n, 39008 Santander, Cantabria, Spain; ⁸Clinical Trial Agency, IDIVAL, Edificio IDIVAL, Avda Cardenal Herrera Oria s/n, 39011 Santander, Cantabria, Spain; ⁹Group of Epidemiology and Computational Biology, University of Cantabria–IDIVAL, Santander, Cantabria, Spain; ¹⁰Consortio de Investigación Biomédica en Red de Epidemiología y Salud Pública, Spain; ¹¹Department of Pharmacy, Hospital Comarcal Sierrallana, Barrio Ganzo, 39300 Torrelavega, Cantabria, Spain

*Corresponding author. Tel: +34942638500; Fax: +34942607876; E-mail: miguel.carrascosa@scsalud.es

Received 12 January 2015; returned 12 February 2015; revised 3 March 2015; accepted 17 March 2015

Objectives: *Helicobacter pylori* eradication remains a challenge. Non-bismuth-based quadruple regimens (NBQR) have shown high eradication rates (ER) elsewhere that need to be locally confirmed. The objective of this study was to compare the first-line ER of a hybrid therapy (20 mg of omeprazole twice daily and 1 g of amoxicillin twice daily for 10 days, adding 500 mg of clarithromycin twice daily and 500 mg of metronidazole every 8 h for the last 5 days; OA-OACM) with that of a 10 day concomitant regimen consisting of taking all four drugs twice daily every day (including 500 mg of metronidazole every 12 h; OACM). A 10 day arm with standard triple therapy (OAC; 20 mg of omeprazole/12 h, 1 g of amoxicillin/12 h and 500 mg of clarithromycin/12 h) was included.

Patients and methods: Three hundred consecutive patients were randomized (1:2:2) into one of the three following regimens: (i) OAC (60); (ii) OA-OACM (120); and (iii) OACM (120). Eradication was generally confirmed by a [¹³C]urea breath test at least 4 weeks after the end of treatment. Adverse events and compliance were assessed. EudraCT: 2011-006258-99.

Results: ITT cure rates were: OAC, 70.0% (42/60) (95% CI: 58.3–81.7); OA-OACM, 90.8% (109/120) (95% CI: 85.6–96.0); and OACM, 90.0% (107/119) (95% CI: 84.6–95.4). PP rates were: OAC, 72.4% (42/58) (95% CI: 60.8–84.1); OA-OACM, 93.9% (108/115) (95% CI: 89.5–98.3); and OACM, 90.3% (102/113) (95% CI: 84.8–95.8). Both NBQR significantly improved ER compared with OAC ($P < 0.01$), but no differences were seen between them. Mean compliance was elevated [98.0% (SD=9.8)] with no differences between groups. There were more adverse events in the quadruple arms (OACM, 65.8%; OA-OACM, 68.6%; OAC, 46.6%; $P < 0.05$), but no significant differences between groups in terms of severity were seen.

Conclusions: Hybrid and concomitant regimens show good ER against *H. pylori* infection with an acceptable safety profile. They clearly displace OAC as first-line regimen in our area.

Keywords: concomitant, *H. pylori*, hybrid, non-bismuth-based quadruple regimens, randomized clinical trials

Introduction

Helicobacter pylori eradication remains a challenge, mainly due to a loss of efficacy of classic clarithromycin-based triple therapy regimens, which in turn is related to an increase in clarithromycin resistance.^{1,2} In order to overcome this shortcoming, new regimens have been proposed. In particular, much attention has been focused on two non-bismuth-based quadruple regimens (NBQR): sequential and concomitant. Sequential treatment consists of a 10 day treatment in which proton pump inhibitor (PPI) plus amoxicillin is given for 5 days followed by a PPI plus clarithromycin and a nitroimidazole for 5 days. The concomitant treatment is a quadruple regimen containing a PPI, amoxicillin, clarithromycin and a nitroimidazole for a variable period between 5 and 14 days. Both NBQR have shown a significant advantage over the standard triple therapy (omeprazole/amoxicillin/clarithromycin).^{3–5} A recent meta-analysis comparing these NBQR has revealed a significant advantage of concomitant therapy.⁶ The high eradication rates (ER) ($\geq 90\%$) that have been reported for NBQR support the most recent recommendations in European countries to incorporate them as first-line empirical treatments.^{2,7}

A hybrid NBQR that consists of continuing amoxicillin into the second part of the sequential treatment has recently displayed good results.^{1,8–10} Such results, however, have to be confirmed locally in an area like ours with low–intermediate resistance to clarithromycin ($\leq 15\%$), as previously reported.^{11,12} Furthermore, there is a need to explore whether shortening hybrid regimens maintains efficacy in addition to ameliorating safety and compliance.

Our objective was to compare the efficacy and safety of two 10 day NBQR (i.e. hybrid and concomitant) and assess both against omeprazole/amoxicillin/clarithromycin.

Patients and methods

Patients, treatments and follow-up

This was a multicentre, open-label, controlled, three arm, parallel-group, Phase IV non-commercial trial with imbalanced randomization (1:2:2) designed to examine the superiority of two NBQR against *H. pylori* over omeprazole/amoxicillin/clarithromycin. It was conducted at three centres in northern Spain from July 2012 to December 2013. Eligible participants were all *H. pylori*-positive adult consecutive patients aged 18–75 years who were referred to each centre, and met the eligibility criteria for eradication therapy according to the current recommendations.⁷ *H. pylori* infection was confirmed by at least one of the following methods: [¹³C]urea breath test, histology or rapid urease test. Written informed consent was obtained from all patients before enrolment. Previous *H. pylori* eradication therapy was an exclusion criterion for the study. Other exclusion criteria were: age < 18 years or > 75 years, serious concomitant illnesses, gastric surgery, allergy to any of the study drugs, intake of antibiotics or bismuth salts within the last month or PPIs within the last 2 weeks, and pregnancy or breastfeeding. The study was approved by the regional Ethics Committee and was registered in the European Union Clinical Trials Register Database (Clinicaltrialsregister.eu; EudraCT: 2011-006258-99).

A randomization sequence was created using Stata 12/SE (StataCorp, College Station, TX, USA) statistical software using random block sizes of 10 and imbalanced according to the schedule 1:2:2 to allocate patients respectively to groups: (i) OAC—20 mg of omeprazole/12 h, 1 g of amoxicillin/12 h and 500 mg of clarithromycin/12 h; (ii) OA-OACM (hybrid therapy)—20 mg of omeprazole/12 h and 1 g of amoxicillin/12 h for 10 days adding 500 mg of clarithromycin/12 h and 500 mg of metronidazole/8 h

only for the last 5 days; and (iii) OACM (concomitant therapy)—20 mg of omeprazole/12 h, 1 g of amoxicillin/12 h, 500 mg of clarithromycin/12 h and 500 mg of metronidazole/12 h. All drugs were taken orally on a 10 day-based regimen. Allocation concealment was guaranteed. All drugs used were of generic branding and purchased from Normon Pharmaceutical Laboratories (Madrid, Spain). An investigator who did not have clinical involvement in the trial was in charge of allocating patients according to a computer-generated numerical sequence on a phone request for all centres. The coordinators and the investigators in the centres did not know the details of the allocation sequence. This study was regarded as an open trial keeping in mind the number of drugs to be taken, the different dosage schedules and the fact that the principal outcome (*H. pylori* ER) was not influenced by the unblinded design of the protocol. Personnel carrying out urea breath tests were blind to the treatment given. The study drugs were handed to the patient in a registered box prepared by a pharmacist that included all required pills and a day-by-day intake scheme. Compliance was assessed by personal interview and standard pill count after ending treatment. Patients who used $< 80\%$ of the study medication were considered non-compliant.

The primary endpoint (*H. pylori* ER by ITT) was defined as a negative [¹³C]urea breath test performed at least 4 weeks after completion of treatment, as recommended by the manufacturer (Otsuka Pharmaceutical Europe Ltd). If a patient required a follow-up endoscopy, eradication was considered achieved when two direct methods (i.e. histology and urease test) were negative 4 weeks after the end of treatment; this exception was only applied to four patients (one in the OAC arm and three in the OACM arm). Neither antibiotics nor PPI were allowed during the 4 or 2 week period, respectively, prior to *H. pylori* reassessment. As a secondary endpoint, safety was evaluated by means of recording adverse events through open-answer questions. All adverse events were evaluated by their doctors and classified according to their intensity and causality. Relevant method changes after trial commencement were not performed.

Statistical analysis

H. pylori ER were calculated by ITT and PP analyses. For ITT analysis, all randomized patients enrolled into the study were included; patients without an observed outcome were considered as treatment failures. For PP analysis, all protocol violators (i.e. non-compliant patients and patients lost to follow-up) were excluded. Categorical variables are described with percentages, and continuous variables are described with mean and standard deviation or median and range as appropriate. For univariate statistical analysis, a 95% CI, Student's *t*-test and Fisher's exact test were applied. Multivariate logistic regression analyses were also performed to evaluate independent predictive variables for eradication of *H. pylori*. The magnitude of the effect was described with OR and 95% CI. The variables chosen to be introduced in predictive models depended on the statistical significance in univariate analysis or at least those known to have potential events based on the literature. *P* values < 0.05 were considered statistically significant after Bonferroni adjustment when necessary. No interim analyses for efficacy or futility were conducted.

In order to estimate the sample size, we assumed the following parameters based on several previous studies:^{9,13–15} 80% ER in the control arm, 15% improvement in the intervention arms, α error before Bonferroni correction = 5%, and β error = 20%. With a 1:2 ratio (control:intervention arms), the estimated sample size was 60 patients in the control arm and 120 patients in the intervention arms. The statistical software package Stata 12/SE was used for the analyses.

Results

All eligible patients who accepted participation were recruited. Figure 1 shows the patient flow chart, according to the CONSORT statement advice. The baseline demographic and

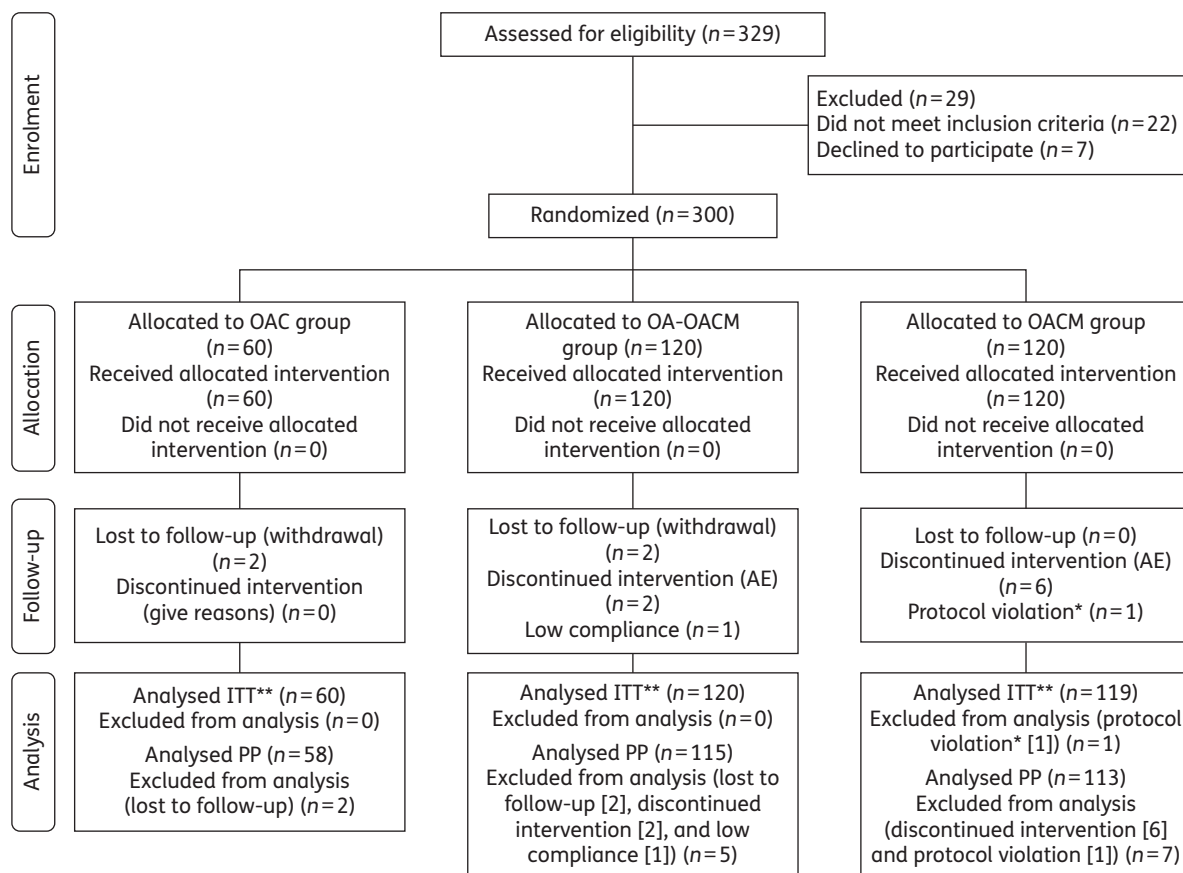


Figure 1. Flow diagram of the subjects enrolled in the study. AE, adverse events. *Diagnosis of *H. pylori* infection was based on serology in patient no. 48. **Patients without an observed outcome were considered as treatment failures.

Table 1. Demographic and clinical characteristics of patients for the total cohort and therapeutic subgroups after randomization

	Total cohort	OAC	OA-OACM	OACM	P
Number of patients	300	60	120	120	
Male/female, n/n	115/185	25/35	49/71	41/79	0.45
Age (years), median (range)	44 (18–69)	45 (20–65)	41 (18–66)	47 (24–69)	0.07
Smoking habit (number of cigarettes/day), mean (SD)	3.8 (7.4)	3.0 (6.5)	4.0 (7.1)	4.0 (8.1)	0.68
Alcohol intake (g/day), mean (SD)	3.8 (15.0)	2.9 (9.5)	2.0 (9.4)	6.0 (20.5)	0.11
Co-medication, n (%)	139 (46.3)	24 (40.0)	53 (44.2)	62 (51.6)	0.42
Indication, n (%)					0.67
functional dyspepsia	221 (73.7)	46 (76.7)	93 (77.5)	82 (68.3)	
gastric/duodenal ulcer	50 (16.7)	10 (16.7)	16 (13.3)	24 (20.0)	
familial gastric cancer ^a	25 (8.3)	4 (6.7)	9 (7.5)	12 (10.0)	
intestinal metaplasia/gastric atrophy	4 (1.3)	0 (0.0)	2 (1.7)	2 (1.7)	
Diagnostic method, n (%)					0.57
rapid urease test	172 (57.3)	38 (63.3)	72 (60.0)	62 (51.7)	
histology	104 (34.7)	19 (31.7)	40 (33.3)	45 (37.5)	
urea breath test	15 (5.0)	2 (3.3)	5 (4.2)	8 (6.7)	
combined ^b	7 (2.3)	0 (0.0)	3 (2.5)	4 (3.3)	

^aGastric cancer in first-degree relatives.

^bCombined refers to a positive test obtained by two methods: a rapid urease test and histology.

Table 2. Outcomes of the three arms of the study in terms of efficacy (ER); univariate analysis

Group	n	% (95% CI)	OR (95% CI)	P
ITT analysis				
OAC	42/60	70.0 (58.3–81.7)	1	—
OA-OACM	109/120	90.8 (85.6–96.0)	4.3 (1.8–10.1)	0.002
OACM	107/119	90.0 (84.6–95.4)	3.82 (1.7–8.9)	0.004
PP analysis				
OAC	42/58	72.4 (60.8–84.1)	1	—
OA-OACM	108/115	93.9 (89.5–98.3)	5.9 (2.1–16.1)	0.001
OACM	102/113	90.3 (84.8–95.8)	3.5 (1.5–8.5)	0.01

Table 3. Outcomes of the three arms of the study in terms of efficacy (ER); multivariate analysis^a

Group	ITT		PP	
	OR (95% CI)	P	OR (95% CI)	P
OAC	1	—	1	—
OA-OACM	4.8 (1.9–11.6)	0.002	6.2 (2.3–16.6)	<0.001
OACM	4.9 (2.0–12.0)	0.002	4.8 (1.9–12.0)	0.002

^aMultivariate analysis after adjusting for age, sex, associated drugs, number of cigarettes, clinical indication and alcohol intake in grams (P values after Bonferroni adjustment).

Table 4. Treatment compliance (%) throughout the study

Group	Mean (SD)
OAC	99.6 (2.1)
OA-OACM	98.5 (7.0)
OACM	96.7 (13.7)
Total cohort	98.0 (9.8)

Table 5. Adverse events in the study population

	Total cohort (n=300)	OAC (n=60)	OA-OACM (n=120)	OACM (n=120)	P
Adverse events ^a	187 (62.3)	27 (45.0)	81 (67.5)	79 (65.8)	0.012
metallic taste	66 (22.0)	11 (18.3)	25 (20.8)	30 (25.0)	0.55
diarrhoea	95 (31.7)	7 (11.7)	40 (33.3)	48 (40.0)	0.001
nausea, dyspepsia	93 (31.0)	13 (21.7)	44 (36.7)	36 (30.0)	0.12
headache	56 (18.7)	4 (6.7)	26 (21.7)	26 (21.7)	0.03
mucosal complaints ^b	22 (7.3)	3 (5.0)	8 (6.7)	11 (9.2)	0.56
anxiety	8 (2.7)	2 (3.3)	4 (3.3)	2 (1.7)	0.68
dizziness	3 (1.0)	1 (1.7)	1 (0.8)	1 (0.8)	0.84
others	38 (12.7)	3 (5.0)	15 (12.5)	20 (16.7)	0.08

Data are shown as n (%).

^aNumber of adverse events relative to all patients included in each cohort (total, OAC, OA-OACM and OACM cohorts).

^bIncludes aphthous stomatitis, vulvar pruritus and probable local fungal infection.

clinical characteristics of the total cohort and each therapeutic group are listed in Table 1. The three groups were similar in terms of age, gender, smoking habit, use of co-medication and indication for *H. pylori* eradication. Functional dyspepsia was the most common indication for *H. pylori* eradication (73.7%). There was only one protocol deviation that referred to a patient included in the OACM group who did not fulfil the inclusion criteria—he was included on the basis of positive *H. pylori* serology. This case was also excluded from the ITT analysis. Overall, four patients (two in the OAC group and two in the OA-OACM group) were lost to follow-up. Finally, six patients in the OACM group and two patients in the OA-OACM group discontinued the assigned treatment due to adverse events. Another patient in the OA-OACM group had low compliance and was also excluded from the PP analysis. In summary, 299 patients were included in the ITT analysis and 286 in the PP analysis (see Figure 1).

Tables 2 and 3 summarize the outcomes of the three arms in terms of ER and Tables 4 and 5 show data on compliance and adverse events during the study. NBQR showed significantly better ER against *H. pylori* than the OAC in both ITT and PP analysis (Tables 2 and 3). No statistical differences were found between the two alternative regimens. After adjusting for age, sex, co-medication, number of cigarettes, alcohol consumption in grams and indication, in the multivariate analysis, the results were unaltered (Table 3).

Compliance with the assigned treatment was high with no significant statistical differences between the three arms (Table 4), although more patients in the quadruple arms discontinued the intervention because of adverse events or poor tolerance to the respective treatments (not significant) (Figure 1). Additionally, there was a higher rate of adverse events in the quadruple arms of the study that reached statistical significance in terms of frequency (Table 5). In particular, diarrhoea and headache were more frequent in quadruple regimens compared with the OAC (Table 5). However, there were no differences between the three arms in terms of the severity of the adverse events and no serious side effects were reported throughout the study.

Discussion

The present study demonstrates similar high ER (~90%) of two NBQR (hybrid and concomitant) against *H. pylori* in our area,

clearly exceeding that achieved by the OAC (70%). Although the NBQR were associated with a greater number of adverse events, we did not find differences in either severity of adverse events or compliance between the arms.

A 10 day concomitant NBQR is currently recommended as a first-line choice in Spain, a suggestion that is supported by solid evidence indicating ER ~90%.^{3,4,7} Our study, which shows similar ER with two NBQR, is also comparable to another recent Spanish clinical trial.¹⁶ Sequential NBQR, although initially promising,^{17,18} has recently revealed poor results and is no longer considered a good option for overcoming antibiotic resistance.^{19–23}

A hybrid NBQR consisting of dual therapy with a PPI and amoxicillin for 14 days with clarithromycin and metronidazole added for the last 7 days (all of them twice daily) has shown 97.4% ER on ITT.⁹ A 90% ER has recently been reported in Spain and Italy with a similar regimen in a study where high rates of antibiotic resistance were seen, while others reached just 80% ER in Italy.^{8,24} A shorter duration of this new regimen (10–12 days) has recently been achieved, showing high ER (93%–95%).¹³ We have obtained results comparable to a 10 day hybrid regimen in an area with higher rates of resistance to clarithromycin, which are also in accordance with the aforementioned Spanish study.^{8,11,13} This evidence shows that optimized hybrid and concomitant therapies can eradicate *H. pylori* in >90% of patients in areas of growing antibiotic resistance.²⁵

The rate of adverse events obtained with our NBQR was slightly higher than, but similar to, results previously reported and was significantly higher than that achieved with OAC.⁸ Considering the mild degree of such adverse events, the benefits outweighed the risks. A recent meta-analysis has concluded that there were no significant differences between the three NBQR in terms of adverse events or compliance.²⁶

One limitation of our study is that it was carried out in a single region and the results will need to be confirmed in regions with different patterns of resistance. Moreover, we did not perform a concurrent *in vitro* susceptibility study to check for *H. pylori* resistance. Nevertheless, a recent report from our group and the last European survey on antibiotic resistance of *H. pylori* showed that our region was still a low-resistance area (~14%) at the time this study was designed and initiated.^{11,12} Finally, we changed the dosage schedule of metronidazole in our hybrid therapy (500 mg/8 h) compared with other hybrid and concomitant regimens (500 mg/12 h), which could affect one-to-one comparisons. A simpler dose schedule could have achieved similar ER and better patient acceptance and this deserves future study.

In summary, hybrid and concomitant NBQR show high ER (≥90%) using a short 10 day regimen. Consequently, they should be considered as first-line options in our area. In contrast, the OAC regimen must no longer be recommended in this region.

Acknowledgements

We gratefully acknowledge Mrs Marien Cacho and Enma Fernández (members of the nursing team) for their invaluable assistance with this study.

Funding

This study was funded by a grant from the Spanish Ministry of Health and Social Politics (grant number, EC11-528).

Transparency declarations

We purchased Developmental Editing from American Journal Experts. This service offers advice on how to improve the organization of the manuscript and edits the text for English language and grammar.

Author contributions

A. C.-L. (1–9), J. R. S.-C. (1–5, 7, 9), A. D.-P. (1–5, 7, 9), M. F. C. (3, 4, 5, 7–9), M. O. (1, 2, 4, 7, 9), J. L. F.-F. (1, 2, 4, 5, 7–9), M. C. (1, 2, 4, 5, 7–9), P. F.-G. (1, 2, 4, 5, 7, 9), B. A. (1, 2, 5, 7, 9), B. S. (2, 4, 5, 7–9), C. C. (1, 4, 7–9), J. L. (1, 3, 5–9), S. L. (2, 5, 7, 9) and A. I. (2, 5, 7, 9). Key: 1, study concept and design; 2, acquisition of data; 3, analysis and interpretation of data; 4, drafting of the manuscript; 5, critical revision of the manuscript for important intellectual content; 6, statistical analysis; 7, administrative, technical or material support; 8, study supervision; and 9, this author has approved the final version of the manuscript.

References

- Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143–53.
- Malfertheiner P, Megraud F, O'Morain CA et al. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence Consensus Report. *Gut* 2012; **61**: 646–64.
- Gisbert JP, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 2011; **34**: 604–17.
- Gisbert JP, Calvet X. Update on non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*. *Clin Exp Gastroenterol* 2012; **5**: 23–34.
- Sanchez-Delgado J, Calvet X, Bujanda L et al. Ten-day sequential treatment for *Helicobacter pylori* eradication in clinical practice. *Am J Gastroenterol* 2008; **103**: 2220–3.
- Adrian G, McNicholl OPN, Gisbert JP. Sequential and concomitant treatments in *H. pylori* eradication: a network meta-analysis. *Gastroenterology* 2014; **146**: S–395.
- Gisbert JP, Calvet X, Bermejo F et al. [III Spanish Consensus Conference on *Helicobacter pylori* infection]. *Gastroenterol Hepatol* 2013; **36**: 340–74.
- Molina-Infante J, Romano M, Fernandez-Bermejo M et al. Optimized nonbismuth quadruple therapies cure most patients with *Helicobacter pylori* infection in populations with high rates of antibiotic resistance. *Gastroenterology* 2013; **145**: 121–8.e1.
- Hsu PI, Wu DC, Wu JY et al. Modified sequential *Helicobacter pylori* therapy: proton pump inhibitor and amoxicillin for 14 days with clarithromycin and metronidazole added as a quadruple (hybrid) therapy for the final 7 days. *Helicobacter* 2011; **16**: 139–45.
- Graham DY, Lu H, Yamaoka Y. Therapy for *Helicobacter pylori* infection can be improved: sequential therapy and beyond. *Drugs* 2008; **68**: 725–36.
- Cuadrado-Lavin A, Salcines-Caviedes JR, Carrascosa MF et al. Antimicrobial susceptibility of *Helicobacter pylori* to six antibiotics currently used in Spain. *J Antimicrob Chemother* 2012; **67**: 170–3.
- Megraud F, Coenen S, Versporten A et al. *Helicobacter pylori* resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; **62**: 34–42.
- Wu JY, Hsu PI, Wu DC et al. Feasibility of shortening 14-day hybrid therapy while maintaining an excellent *Helicobacter pylori* eradication rate. *Helicobacter* 2014; **19**: 207–13.
- Cuadrado-Lavin A, Salcines-Caviedes JR, Carrascosa MF et al. Levofloxacin versus clarithromycin in a 10 day triple therapy regimen for

first-line *Helicobacter pylori* eradication: a single-blind randomized clinical trial. *J Antimicrob Chemother* 2012; **67**: 2254–9.

15 Gisbert JP, Calvet X. Review article: the effectiveness of standard triple therapy for *Helicobacter pylori* has not changed over the last decade, but it is not good enough. *Aliment Pharmacol Ther* 2011; **34**: 1255–68.

16 McNicholl AG, Marin AC, Molina-Infante J *et al.* Randomised clinical trial comparing sequential and concomitant therapies for *Helicobacter pylori* eradication in routine clinical practice. *Gut* 2014; **63**: 244–9.

17 Zullo A, Rinaldi V, Winn S *et al.* A new highly effective short-term therapy schedule for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2000; **14**: 715–8.

18 De Francesco V, Zullo A, Hassan C *et al.* Two new treatment regimens for *Helicobacter pylori* eradication: a randomised study. *Dig Liver Dis* 2001; **33**: 676–9.

19 Fakheri H, Taghvaei T, Hosseini V *et al.* A comparison between sequential therapy and a modified bismuth-based quadruple therapy for *Helicobacter pylori* eradication in Iran: a randomized clinical trial. *Helicobacter* 2012; **17**: 43–8.

20 Molina-Infante J, Perez-Gallardo B, Fernandez-Bermejo M *et al.* Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential

regimens for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2010; **31**: 1077–84.

21 Greenberg ER, Anderson GL, Morgan DR *et al.* 14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial. *Lancet* 2011; **378**: 507–14.

22 Molina-Infante J, Gisbert JP. Optimizing clarithromycin-containing therapy for *Helicobacter pylori* in the era of antibiotic resistance. *World J Gastroenterol* 2014; **20**: 10338–47.

23 Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014; **12**: 177–86.e3; Discussion e12–3.

24 Zullo A, Scaccianoce G, De Francesco V *et al.* Concomitant, sequential, and hybrid therapy for *H. pylori* eradication: a pilot study. *Clin Res Hepatol Gastroenterol* 2013; **37**: 647–50.

25 Federico A, Gravina AG, Miranda A *et al.* Eradication of *Helicobacter pylori* infection: which regimen first? *World J Gastroenterol* 2014; **20**: 665–72.

26 Wang B, Wang YH, Lv ZF *et al.* Efficacy and safety of hybrid therapy for *Helicobacter pylori* infection: a systematic review and meta-analysis. *Helicobacter* 2015; **20**: 79–88.