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Optimised empiric triple and concomitant therapy for *Helicobacter pylori* eradication in clinical practice: the OPTRICON study

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SUMMARY

Background
Empiric triple therapy for *Helicobacter pylori* should be abandoned when clarithromycin resistance rate is >15–20%. Optimisation of triple therapy (high-dose acid suppression and 14-day duration) can increase eradication rates by 10%.

Aim
To compare the efficacy and safety of optimised triple (OPT-TRI) and nonbismuth quadruple concomitant (OPT-CON) therapies.

Methods
Prospective multicentre study in 16 Spanish centres using triple therapy in clinical practice. In a 3-month two-phase fashion, the first 402 patients received an OPT-TRI therapy [esomeprazole (40 mg b.d.), amoxicillin (1 g b.d) and clarithromycin (500 mg b.d) for 14 days] and the last 375 patients an OPT-CON treatment [OPT-TRI therapy plus metronidazole (500 mg b.d)].

Results
Seven-hundred seventy-seven consecutive patients were included (402 OPT-TRI, 375 OPT-CON). The OPT-CON therapy achieved significantly higher eradication rates in the per-protocol [82.3% (95% CI = 78–86%) vs. 93.8% (91–96%), $P < 0.001$] and intention-to-treat analysis [81.3% (78–86%) vs. 90.4% (87–93%), $P < 0.001$]. Adverse events (97% mild/moderate) were significantly more common with OPT-CON therapy (39% vs. 47%, $P = 0.016$), but full compliance with therapy was similar between groups (94% vs. 92%, $P = 0.4$). OPT-CON therapy was the only significant predictor of successful eradication (odds ratio, 2.24; 95% CI: 1.48–3.51, $P < 0.001$). The rate of participating centres achieving cure rates ≥90% favoured OPT-CON therapy (OPT-TRI 25% vs. OPT-CON 62%).

Conclusions
Empiric OPT-CON therapy achieved significantly higher cure rates (>90%) compared to OPT-TRI therapy. Addition of metronidazole to OPT-TRI therapy increased eradication rates by 10%, resulting in more mild adverse effects, but without impairing compliance with therapy.

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INTRODUCTION

Helicobacter pylori is a bacterial infection affecting 50% of world population and it is currently considered the main cause of gastritis, gastroduodenal ulcer disease and gastric cancer. The most recommended therapy in guidelines has been standard triple therapy, consisting of a proton pump inhibitor (PPI) and two antibiotics (most commonly clarithromycin, and either amoxicillin, and/or a nitroimidazole), prescribed for 7 to 10 days.[1–3] Due to increasing rates of clarithromycin resistance, triple therapy is no longer effective in many parts of the world, especially in central and southern Europe,[4] and novel therapies are definitely required.[5, 6]

Bismuth quadruple therapy has been lately recommended as the treatment of choice to overcome antimicrobial resistance, but availability concerns hamper its implementation in clinical practice, besides side effects and compliance with therapy.[6, 7] As such, nonbismuth quadruple regimens (adding a third antibiotic to triple therapy), either administered sequentially or concomitantly, have been postulated as valid alternatives if bismuth is not available.[7] These regimens include a PPI and three antibiotics (amoxicillin, clarithromycin and a nitroimidazole) taken in two phases (sequential treatment) or administered concurrently (concomitant treatment). Both nonbismuth quadruple therapies (sequential and concomitant) have extensively demonstrated their superiority over triple therapy in several meta-analyses.[8–12]

After promising initial results on sequential therapy,[8–10] evolving meta-analyses and reviews have shown much lower eradication rates for sequential therapy in Latin America, Southern Europe and Asia for both adults and children.[13–18] Therefore, sequential therapy exhibited higher susceptibility to failure in regions with high rates of antibiotic resistance. In this regard, sequential therapy recently failed to demonstrate an advantage over 14-day triple therapy[19, 20] and similar preliminary results have been recently reported in the USA.[21] As for concomitant therapy, eradication rates >90% have been recently reported in Spain, Italy and Greece, settings with increasing rates of antibiotic resistance.[22–24] In head-to-head comparative studies, concomitant therapy has shown a borderline advantage over sequential therapy[25]; however, concomitant therapy has not been compared to 14-day triple therapy yet. A longer duration, up to 14 days, and high-dose proton pump inhibitor (PPI) therapy (usually omeprazole 40 mg b.d or its equivalent) can increase eradication rates for triple therapy by 6–10% and 5% respectively.[7]

The aim of the present study was to compare the efficacy and safety of two empiric optimised triple (OPT-TRI) and nonbismuth quadruple concomitant (OPT-CON) therapies in clinical practice in Spain, a geographical area with increasing clarithromycin resistance rates.

METHODS

Settings and participants

The OPTRICON study (OPtimised TRIple and CONcomitant therapy for *H. pylori* infection) is a prospective multicentre study, conducted from July 2013 to December 2013, within the frame of the European Registry on *H. pylori* Management (Hp-EuReg). The Hp-EuReg is an ongoing international multicentre project promoted by the European Helicobacter Study Group, which started in May 2013. The Hp-EuReg recruiters prospectively register the decisions taken during routine clinical practice, and their outcomes, regarding the management of *H. pylori* infection. As a routine clinical practice study, the disease management registered in the database must be done based on routine practice medical decision, excluding all decisions and outcomes based on, or controlled by, clinical study protocols. As part of the IRB approved Hp-EuReg protocol, study researchers may request access to the database for local and/or partial data analysis after approval by the Hp-EuReg scientific committee.

The OPTRICON promoters (JM-I and JPG) identified a shift of prescriptions to concomitant regimen after the publication of the III Spanish Consensus on *H. pylori* management.[26] The promoters proposed to compare shifting first-line eradication strategy from optimised triple to optimised concomitant regimens in Hp-EuReg participating centres actively recruiting patients who had not switched to concomitant therapy yet. Attending to its clinical and scientific relevance and methodology, as well as its ethics, the OPTRICON study received approval and technical support by the HP-EuReg project.

The OPTRICON study restricted its analysis to patients from Spanish centres actively recruiting in the Hp-EuReg empirically prescribing triple therapy (this is, without antibiotic susceptibility data) in routine clinical practice. All consecutive adult patients with *H. pylori* infection and not having received prior eradication therapy were eligible for enrolment. The diagnosis of *H. pylori* was based on positivity to ^{13}C-urea breath test or positivity of at least two different methods including

rapid urease test, culture or histology in those patients who underwent endoscopy. Exclusion criteria were as follows: (i) age under 18 years old, (ii) presence of severe comorbidities, including cardiovascular, respiratory, endocrine, renal, haematological and hepatic disorders, precluding participation, (iii) prior *H. pylori* eradication, (iv) previous surgery of the stomach such as partial gastrectomy, (v) allergy of any of the antibiotics used in the study, (vi) intake of antibiotics, PPIs, corticosteroids or nonsteroidal anti-inflammatory drugs within the last month, (vii) pregnancy or lactation, (viii) alcohol abuse or drug addiction and (ix) severe neurological or psychiatric disorder.

Study design

This was a two-phase study, aiming to compare optimised triple (OPT-TRI) and concomitant (OPT-CON) therapies in clinical practice. Optimisation was defined by both a duration of 14 days and using high-dose PPI therapy. We selected regimens containing esomeprazole 40 mg b.d as PPI therapy as this drug at this dose has recently shown the best clinical benefit in *H. pylori* eradication regimens, including powerful acid suppression and best overcoming CYP2C19 extensive metaboliser genotype.[27, 28]

Over a first 3-month phase, centres prescribed an OPT-TRI therapy, consisting of esomeprazole 40 mg b.d, amoxicillin 1 g b.d and clarithromycin 500 mg b.d, after breakfast and dinner, for 14 days. In a second 3-month phase, the centres started prescribing an OPT-CON therapy, which consisted of an OPT-TRI therapy adding metronidazole 500 mg b.d along the whole treatment. All medications in both regimens were taken concomitantly after breakfast and dinner.

Follow-up

Patients were informed about potential side effects (mainly metallic taste, diarrhoea, abdominal pain, nausea and vomiting) during the treatment period. Compliance with therapy was defined as intake of 100% of the medication prescribed and was determined from a questionnaire. The incidence of adverse effects was evaluated by means of a specific questionnaire fulfilled during the performance of post-treatment urea breath testing. Adverse effects were classified as mild, moderate or intense, depending on the intensity of symptoms evaluated by the corresponding physician.

Eradication of *H. pylori* infection was defined as a negative ^{13}C-urea breath test with citric acid at least 4 weeks after completion of treatment, except for patients requiring a follow-up endoscopy due to gastric ulcer, in which histological examination of four samples taken from the body and the antrum stained with Giemsa was the diagnostic test. ^{13}C-urea breath test was performed after an overnight fast and PPIs discontinuation at least 2 weeks before.

End points of the study

The primary end point of the study was the intention-to-treat (ITT) *H. pylori* eradication rates for both treatments. Secondary end points were the per-protocol (PP) eradication rates and predictors of successful eradication of *H. pylori* and geographical variability in eradication rates among participating centres.

Statistical analysis

Analysis of *H. pylori* eradication was considered on an ITT basis (including all eligible patients enrolled in the study regardless of compliance with the study protocol; patients with unavailable data were assumed to have been unsuccessfully treated) and on a PP basis (including only patients fully adherent to the protocol and excluding patients with poor compliance with therapy and patients with unavailable data). The 95% confidence interval (95% CI) was calculated for categorical variables and the mean ± s.d. and/or range for quantitative variables. All analyses were performed stratifying by the regimen prescribed (OPT-TRI and OPT-CON).

A multiple logistic regression analysis was performed using variables with both statistical significance on univariate analysis ($P \leq 0.1$) and clinical significance. We used a backward modelling strategy, and the log-likelihood ratio was the statistic for model comparison. The dependent variable was eradication of *H. pylori*, and the independent variables were age, sex, smoking (smokers and nonsmokers), diagnosis (peptic ulcer or functional/uninvestigated dyspepsia), treatment regimen, compliance and adverse events. The magnitude of the effect is described with the odds ratios and 95% CIs. *P*-values lower than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of patients

Seven-hundred and seventy-seven patients from 16 different Spanish centres were enrolled in the study (402 OPT-TRI, 375 OPT-CON). As for participating centres, four were located in Southern Spain (Seville and Malaga), five in Central Spain (Madrid, Tomelloso, Plasencia) and seven in Northern Spain (Asturias,

Barcelona, Zaragoza and Valladolid). The flow of patients through the study is displayed in Figure 1. Mean age was 49 years old, with a female preponderance (57%), and 21% had smoking habit. No differences were observed regarding baseline demographic and clinical characteristics of patients between both therapeutic groups (Table 1). The main indications for eradication of *H. pylori* infection were functional dyspepsia (36%), peptic ulcer disease (26%), non-investigated dyspepsia (20%) and family history of gastric cancer (7%). Seventy-six patients (10%) received eradication therapy due to miscellaneous indications (unexplained iron-deficiency anaemia or vitamin B12 deficiency, long-term PPI intake, atrophic gastritis and intestinal metaplasia, MALT lymphoma or before starting NSAIDs).

Eradication rates of *H. pylori* infection

Eradication rates by PP and ITT analysis are shown in Table 2. Cure rates were statistically significant higher for the OPT-CON therapy in both the PP [93.8% (95% CI = 91–96%) vs. 82.3% (78–86%), $P < 0.001$] and the ITT [90.4% (87–93%) vs. 81.3% (78–86%), $P < 0.001$] analysis.

Side effects and compliance with therapy

Overall, side effects were significantly more common with the OPT-CON therapy [157/402 (39.1%) vs. 176/375 (46.9%), $P = 0.016$], on account of more diarrhoea, abdominal pain, nausea, vomiting and fatigue, but not metallic taste (see Table 3). Nonetheless, this higher rate of side effects did not result in differences regarding full compliance with therapy between both therapies [OPT-TRI 376/402 (93.5%) vs. OPT-CON 344/375 (91.7%), $P = 0.2$].

Predictors of successful *H. pylori* eradication

In the univariate analysis, gender (88.6% male vs. 82.6% female, $P = 0.1$), full compliance with therapy (86.8% full compliance vs. 71.9% partial compliance, $P = 0.004$) and the specific therapy prescribed (90.4% OPT-CON vs. 81.3%, $P < 0.001$) were associated with *H. pylori* eradication. The remaining variables were not associated with

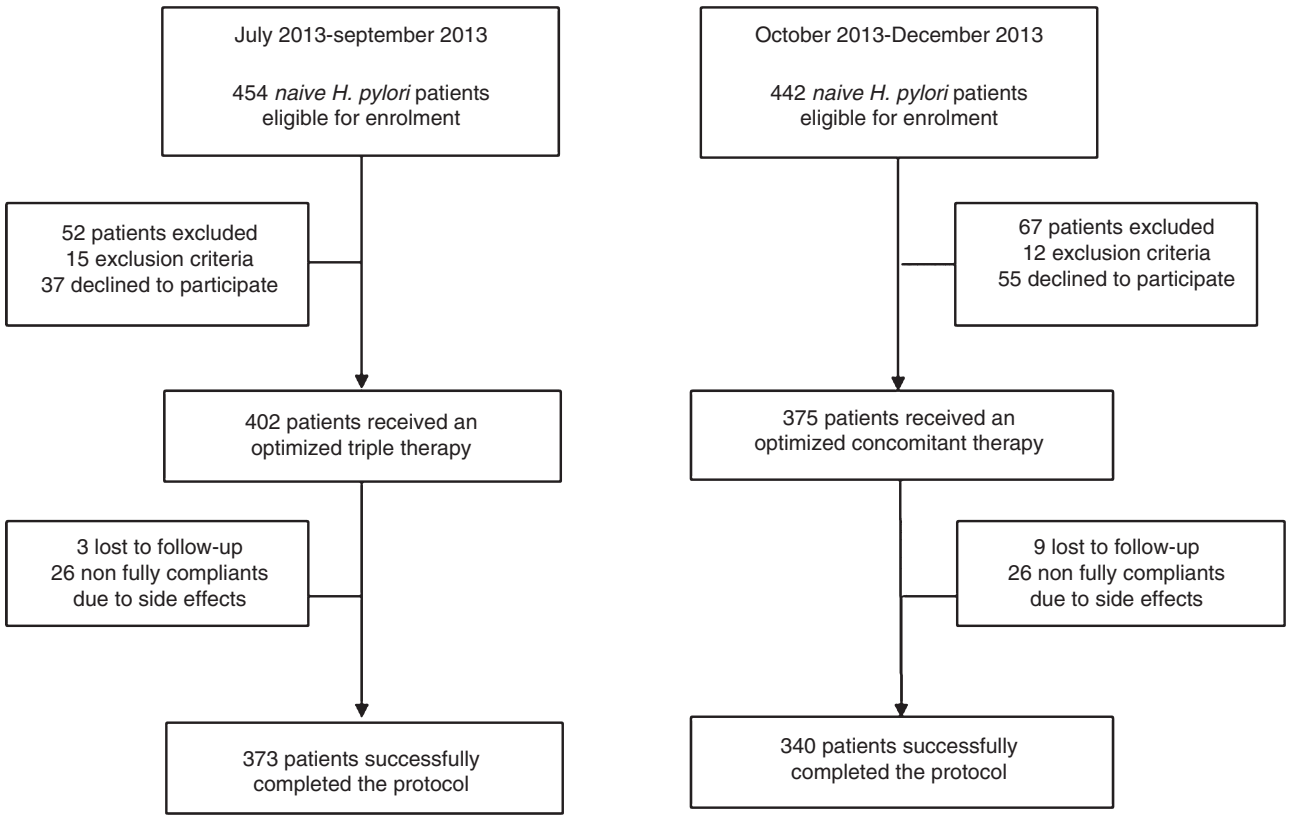

Figure 1 | Flow chart of patients during the study. OPT-TRI, optimised triple therapy; OPT-CON, optimised concomitant therapy.

Table 1 | Baseline characteristics of the total cohort of patients (n = 777) and for each therapy (optimised triple, n = 402; optimised concomitant, n = 375) prescribed in the study

	Optimised triple therapy	Optimised concomitant therapy	*P*
Age, mean (range),	50 (18–84)	48 (18–88)	0.8
Female gender, *n* (%)	225 (56%)	225 (60%)	0.3
Smoking habit, *n* (%)	84 (20%)	86 (23%)	0.7
Indication for eradication			
Functional dyspepsia	153 (38%)	129 (34%)	0.4
Peptic ulcer disease	109 (27%)	97 (25%)	0.5
Non-investigated dyspepsia	67 (16%)	88 (23%)	0.1
Family history of gastric cancer	32 (8%)	26 (7%)	0.6
Miscellaneous	41 (10%)	35 (9%)	0.7

Table 2 | Efficacy (by per-protocol and intention-to-treat analysis) for both optimised triple and optimised concomitant therapies in the study

	Optimised triple therapy	Optimised concomitant therapy	*P*
Per protocol	307/373 (82.3%)	319/340 (93.8%)	<0.001
Intention-to-treat	327/402 (81.3%)	339/375 (90.4%)	<0.001

H. pylori eradication: age (85.8% < 50 years vs. 85.6% > 50 years, P = 0.5), smoking habit (85.4 non-smokers vs. 87.6 smokers, P = 0.29), indication (85.6% dyspepsia vs. 88.1% ulcer, P = 0.22) and the presence of side effects (85.6% none vs. 85.9% yes, P = 0.49).

In the multivariate logistic regression analysis, treatment with the OPT-CON therapy (vs. OPT-TRI) remained the only significant factor of successful eradication (odds ratio, 2.24; 95% CI: 1.48–3.51, P < 0.001).

Geographical variation in eradication rates

The efficacy of both therapies was variable depending on the evaluated geographical area. Eradication rates for either treatment in each of the participating centres are displayed in Figure 2. Overall, the rate of centres obtaining optimal cure rates (≥90%) clearly favoured OPT-CON therapy [OPT-TRI 25% (4/16) vs. OPT-CON 62% (10/16)]. The top four recruiting centres, including 394 patients (50%), achieved all ITT eradication rates ≥90% with the OPT-CON therapy (Tomelloso 94.5%, Barcelona Teknon 90%, Madrid Sanchinarro 93.5% and Sevilla Macarena 90%). In these centres, excepting Sevilla Macarena (91.7%), cure rates for the OPT-TRI therapy were inferior (Tomelloso 85.2%, Barcelona Teknon 70% and Madrid Sanchinarro 84.6%).

Eradication rates for both therapies notably varied between provinces and even within the same province. Cure rates in Madrid were consistent with a better performance of an OPT-CON therapy (>90% in all three centres), whereas Seville showed, on the contrary, consistent good results for an OPT-TRI therapy (>90% in two centres). As for Malaga (two centres) and Barcelona (three centres), results were diverse and less predictable. Of note, neither OPT-TRI nor OPT-CON achieved 90% eradication rates in two different centres from Zaragoza.

DISCUSSION

This comparative study demonstrates a significantly higher effectiveness of an OPT-CON therapy over an OPT-TRI therapy. Two combined different optimisation measures (lengthening therapy and increasing PPI dose) were carried out for both therapies, so the 10% therapeutic gain with OPT-CON therapy was exclusively due to the addition of a nitroimidazole to an OPT-TRI therapy. Upon this strategy, only the OPT-CON therapy achieved successful eradication rates (>90%), significantly increasing mild side effects but without jeopardising full compliance with therapy. In an era of increasing antibiotic resistance, especially upon bismuth and/or tetracycline unavailability, our findings corroborate optimisation is the way forward to maximise the efficacy of newer and previously used regimens.[29, 30]

At the present time, clarithromycin resistance rates are steadily growing worldwide, with some exceptions

Table 3 | Side effects for both optimised triple and optimised concomitant therapies

	Optimised triple therapy	Optimised concomitant therapy	*P*
Overall	157 (39%)	176 (47%)	0.016
Severe	10 (2.5%)	12 (3%)	0.5
Metallic taste	124 (31%)	120 (32%)	0.38
Severe	4	6	
Diarrhoea	38 (9%)	69 (17%)	<0.001
Severe	0	1	
Abdominal pain	38 (9%)	55 (12%)	0.016
Severe	0	1	
Nausea	31 (7%)	56 (15%)	0.001
Severe	2	1	
Vomiting	8 (2%)	24 (6%)	0.002
Severe	2	1	
Aphthous stomatitis	14 (3%)	19 (5%)	0.2
Severe	2	2	
Fatigue	4 (1%)	22 (6%)	<0.001
Severe	0	0	
Oropharyngeal candidiasis	5 (1.2%)	8 (2.1%)	0.5
Severe	0	0	
Vulvovaginal candidiasis	4 (1%)	6 (1.5%)	0.8
Severe	0	0	
Rash	2 (0.5%)	2 (0.5%)	0.9
Severe	0	0	
Headache	1 (0.2%)	2 (0.4%)	0.8
Severe	0	0	

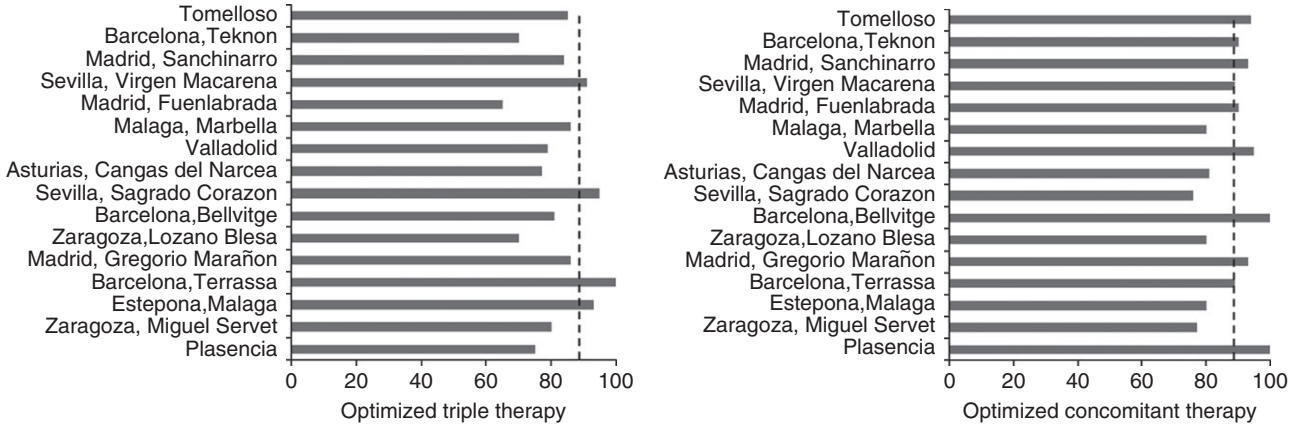

Figure 2 | Geographical variation in intention-to-treat eradication rates among the 16 Spanish participating centres (the vertical dotted line indicates a 90% eradication rate threshold). OPT-TRI, optimised triple therapy; OPT-CON, optimised concomitant therapy.

such as Taiwan and Northern Europe.[4, 6] Resistance rates in Spain have been reported to grow moderately from 14% before 2008[4] to 18% between 2007 and 2012,[31] coming definitely to a threshold where a change in clinical practice is recommended.[7, 26] Our results prove a significant advantage of an OPT-CON therapy over an OPT-TRI therapy in many Spanish centres, but not all, still prescribing triple therapy. When the pattern of antimicrobial resistance is unknown, only eradication regimens that are expected to provide cure rates at least over 90% should be prescribed as empiric therapy, besides they should always be optimised in terms of efficacy, dose, duration and dosing interval.[6] Therefore, a switch to an optimised nonbismuth quadruple

concomitant therapy might be warranted in clinical practice when empirically treating *H. pylori*. In this line of thought, the recent III Spanish Consensus Conference on *H. pylori* infection recommended a 10–14-day concomitant regimen as first-line therapy, saving triple therapy for settings where a high efficacy in clinical practice has been documented.[26]

According to our results, one can speculate an equally optimised 14-day sequential therapy might achieve higher eradication rates compared to an OPT-TRI therapy. In fact, a recent study from Taiwan exhibited an advantage of 14-day sequential therapy over 14-day triple therapy (90.7% vs. 82.3% on an ITT basis).[32] However, this study was conducted in a setting with a low rate of clarithromycin resistance (9%). In addition, the efficacy of 14-day sequential therapy is now know to be seriously challenged by metronidazole resistance and dual resistance to both clarithromycin and metronidazole,[6] as shown in studies conducted in Europe, Asia and Latin-america.[13–18]

Unlike sequential therapy, concomitant therapy is highly successful in the presence of isolated clarithromycin or metronidazole resistance and though impaired by dual clarithromycin–metronidazole resistance, its effectiveness is less undermined than that of sequential therapy.[6] In fact, concomitant therapy has shown better cure rates when facing either clarithromycin-, metronidazole- or, mainly, dual-resistant strains,[33] and recent studies have reported cure rates ≥90% with concomitant therapy in Southern Europe (Spain, Italy and Greece).[22–25] Besides, concomitant therapy has demonstrated a significant advantage over sequential therapy when compared head-to-head in a recent meta-analysis.[34] Finally, concomitant therapy is least complex for patients, just adding a nitroimidazole to a triple therapy. We should acknowledge the outcomes of the present study are population specific and generalisability to any other population can only be made upon the same pattern of resistance.[6] Therefore, an optimised concomitant therapy seems to be the best nonbismuth quadruple replacement for triple therapy, at least for most European countries, some Asian countries, and possibly the USA, where clarithromycin resistance rates are steadily increasing but metronidazole resistance still remains at moderate levels (<30–40%). It is important to point out that the choice of a 10-day or 14-day duration might depend on local efficacy data. Our results in Spain with standard 10-day concomitant therapy remained between 85% and 90% ITT efficacy,[25, 35] whereas all studies with a 14-day duration and high-dose PPI therapy have exceeded the 90% threshold,[23, 36] including the present study as well. However, a 10-day high-dose PPI concomitant therapy has been recently shown to suffice to reach cure rates over 90% in Greece,[24, 37] where clarithromycin resistance rate is as high as 40%.

Eradication rates for either OPT-TRI and OPT-CON therapy in the present study notably differed among different provinces and even within the same province. These results confirm general recommendations cannot be suggested for a whole country, but geographical variations need to be always considered when prescribing a *H. pylori* therapy.[38] As such, one should probably use what works best locally and eradication therapy should be individualised based on antibiotic resistance rates (if unknown, based on careful monitoring of eradication success in clinical practice), besides prior history of antibiotic intake to identify high-risk groups for resistance.[6] We observed a single geographical area in Spain (Seville) where an OPT-TRI consistently achieved cure rates >90%, unlike the remaining provinces. Our results also corroborate concomitant therapies in most settings, but not all, are superior to triple therapies, which preferably always optimised can still have a role in certain conditions (i.e. low clarithromycin resistance). One can speculate that differences between the different sites reflected the difference in metronidazole resistance, but this hypothesis cannot be tested without susceptibility data.

The present study has several limitations to acknowledge. The major limitations are not being a randomised trial and the lack of antimicrobial susceptibility data. A randomised controlled trial is the gold standard for comparing eradication regimens for *H. pylori* infection. Randomly exposing patients to a therapy known to be inferior in Spain (triple therapy), however, would have been an unethical approach.[38] Cure rates for 10-day triple therapy in Spain have been lately reported clearly insufficient, ranging between 71% and 80%.[28, 39] However, an optimised triple therapy had never been assessed before in our country. Notwithstanding solid local data[23, 25, 31, 39] and international consensus evidence[1–3, 7] on the inefficacy of triple therapy, individual centres and doctors in Spain have been slowly adapting their treatment of choice according to the new evidence. As such, we felt that a clinical comparison between the best triple therapy and a similarly optimised nonbismuth quadruple therapy, in settings where triple therapy remained the standard treatment in our county, was the best and ethical strategy to evaluate and boost this switch. Regarding the absence of microbiological data, it is out of question they are essential to understand the efficacy

of eradication regimens in clinical trials. However, this study was conducted on a clinical basis, where almost all therapies are prescribed empirically. *H. pylori* culture is currently an invasive, time-consuming method, not always available, offering quite low sensitivity and requiring significant cost.[40] Until reliable noninvasive methods to evaluate *H. pylori* antibiotic susceptibility data are not available yet, the cost-effectiveness of *H. pylori* culture might be questionable upon the presence of highly-effective empiric bismuth and nonbismuth concomitant quadruple therapies.[22–25, 41]

In conclusion, an empiric OPT-CON therapy achieved significantly higher cure rates (>90%) compared to an OPT-TRI in Spanish centres still prescribing triple therapy in clinical practice. Addition of metronidazole to an optimised triple therapy increased eradication rates by 10%, resulting in a higher rate of mild adverse events but without impairing compliance with therapy. Therefore, an OPT-CON therapy might be preferable as empiric first-line therapy for *H. pylori* in areas with increasing clarithromycin resistance rates. Important geographical variations of efficacy were observed among the participating centres, even achieving >90% cure rates with an OPT-TRI in few centres. Thus, there might be still a role for an optimised triple therapy, either upon know clarithromycin susceptibility or empirically limited to settings where successful cure rates (>90%) have been previously identified by careful monitoring of clinical practice.

AUTHORSHIP

Guarantor of the article: Javier Molina-Infante.

Authors contribution: JM-I: Study concept and design; analysis and interpretation of data; drafting of the manuscript; statistical analysis, study group coordinator and principal investigator. AJL, TA, MR-T, AP-A, MS, JB, EM-N, BJG-R, JMB, JG-C, AB, AH-M, IM, IA, MTH-B, FB: Acquisition of data; critical revision of the manuscript. AGM, COM and JPG: Study concept and design; analysis and interpretation of data; statistical analysis; critical revision of the manuscript; obtained funding; study supervision. All authors approved the final version of the manuscript.

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REFERENCES

1. Chey WD, Wong BC. American College of Gastroenterology Guideline on the management of *Helicobacter Pylori* infection. *Am J Gastroenterol* 2007; **102**: 1808–25.
2. Malfertheiner P, Megraud F, O'Morain C, *et al.* Current concepts in the management of *Helicobacter pylori* infection: the Maastricht III Consensus Report. *Gut* 2007; **56**: 772–81.
3. Fock KM, Katelaris P, Sugano K, *et al.* Second Asia-Pacific Consensus Guidelines for *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2009; **24**: 1587–600.
4. 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.
5. Graham DY, Fischbach L. *Helicobacter pylori* treatment in the era of increasing antibiotic resistance. *Gut* 2010; **59**: 1143–53.
6. 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.
7. 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.
8. Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. *Ann Intern Med* 2008; **148**: 923–31.
9. Tong JL, Ran ZH, Shen J, Xiao SD. Sequential therapy vs. standard triple therapies for *Helicobacter pylori* infection: a meta-analysis. *J Clin Pharm Ther* 2009; **34**: 41–53.
10. Gatta L, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple therapy for *Helicobacter pylori* infection: systematic review and meta-analysis of randomized controlled trials in adults and children. *Am J Gastroenterol* 2009; **104**: 3069–79.
11. Essa AS, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for *Helicobacter pylori* eradication. *Helicobacter* 2009; **14**: 109–18.
12. Gisbert JP, Calvet X. Update on non-bismuth quadruple (concomitant) therapy for eradication of *Helicobacter pylori*. *Clin Exp Gastroenterol* 2012; **5**: 23–34.
13. Horvath A, Dziechciarz P, Szajewska H. Meta-analysis: sequential therapy for *Helicobacter pylori* eradication in children. *Aliment Pharmacol Ther* 2012; **36**: 534–41.
14. Zullo A, Hassan C, Ridola L, De Francesco V, Vaira D. Standard triple and sequential therapies for *Helicobacter pylori* eradication: an update. *Eur J Intern Med* 2013; **24**: 16–9.
15. Kate V, Kalayarasan R, Ananthakrishnan N. Sequential therapy versus standard triple-drug therapy for *Helicobacter pylori* eradication: a

systematic review of recent evidence. *Drugs* 2013; **73**: 815–24.
16. Yoon H, Lee DH, Kim N, *et al.* Meta-analysis: is sequential therapy superior to standard triple therapy for *Helicobacter pylori* infection in Asian adults? *J Gastroenterol Hepatol* 2013; **28**: 1801–9.
17. Kim JS, Kim BW, Ham JH, *et al.* Sequential therapy for *helicobacter pylori* infection in Korea: systematic review and meta-analysis. *Gut Liv* 2013; **7**: 546–51.
18. Nyssen OP, McNicholl AG, Megraud F, *et al.* Meta-analysis of sequential vs. standard triple therapy for *Helicobacter pylori* eradication: final results of a Cochrane systematic review. *Gastroenterology* 2014; **146**(Suppl 1): S–393.
19. Gatta L, Vakil N, Vaira D, Scarpignato C. Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. *BMJ* 2013; **347**: f4587.
20. Nyssen OP, McNicholl AG, Megraud F, *et al.* Meta-analysis of sequential vs. standard triple therapy for *Helicobacter pylori* eradication: final results of a Cochrane systematic review. *Helicobacter* 2014; **19**(Suppl 1): 129.
21. Cross E, Genta RM, Dumbar KB, *et al.* Sequential therapy is not better at eradication of primary *Helicobacter pylori* infection when compared to standard triple therapy in the United States-a prospective, randomized evaluation in a United States population. *Gastroenterology* 2014; **1**: S–399.
22. Georgopoulos S, Papastergiou V, Xirouchakis E, *et al.* Evaluation of a four-drug, three-antibiotic, nonbismuth-containing "concomitant" therapy as first-line *Helicobacter pylori* eradication regimen in Greece. *Helicobacter* 2012; **17**: 49–53.
23. 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.
24. Georgopoulos SD, Xirouchakis E, Martinez-Gonzalez B, *et al.* Clinical evaluation of a ten-day regimen with esomeprazole, metronidazole, amoxicillin, and clarithromycin for the eradication of *Helicobacter pylori* in a high clarithromycin resistance area. *Helicobacter* 2013; **18**: 459–67.
25. 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.
26. Gisbert JP, Calvet X, Bermejo F, *et al.* III Spanish consensus conference on *Helicobacter pylori* infection. *Gastroenterol Hepatol* 2013; **36**: 340–74.
27. McNicholl AG, Linares PM, Nyssen OP, Calvet X, Gisbert JP. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 2012; **36**: 414–25.
28. Sahara S, Sugimoto M, Uotani T, *et al.* Twice-daily dosing of esomeprazole effectively inhibits acid secretion in CYP2C19 rapid metabolisers compared with twice-daily omeprazole, rabeprazole or lansoprazole. *Aliment Pharmacol Ther* 2013; **38**: 1129–37.
29. Sánchez-Delgado J, García-Iglesias P, Castro-Fernández M, *et al.* High-dose, ten-day esomeprazole, amoxicillin and metronidazole triple therapy achieves high *Helicobacter pylori* eradication rates. *Aliment Pharmacol Ther* 2012; **36**: 190–6.
30. Sierra F, Forero JD, Rey M, Botero ML, Cárdenas A. Pilot study: miscellaneous therapy is highly successful for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 2013; **37**: 1165–71.
31. Molina-Infante J, Gisbert JP. Update on the efficacy of triple therapy for *Helicobacter pylori* infection and clarithromycin resistance rates in Spain (2007-2012). *Gastroenterol Hepatol* 2013; **36**: 375–81.
32. Liou JM, Chen CC, Chen MJ, *et al.* Sequential versus triple therapy for the first-line treatment of *Helicobacter pylori*: a multicentre, open-label, randomised trial. *Lancet* 2013; **381**: 205–13.
33. Georgopoulos SD, Xirouchakis E, Mentris A. Is there a nonbismuth quadruple therapy that can reliably overcome bacterial resistance? *Gastroenterology* 2013; **145**: 1496–7.
34. McNicholl AG, Nyssen OP, Gisbert JP. Sequential and Concomitant Treatments in *H. pylori* Eradication: a Network Meta-Analysis. *Gastroenterology* 2014; **146**(Suppl 1): S–393.
35. Molina-Infante J, Pazos-Pacheco C, Vinagre-Rodriguez G, *et al.* Non-bismuth quadruple (concomitant) therapy: empiric and tailored efficacy vs. standard triple therapy for clarithromycin-susceptible *Helicobacter pylori* and vs. sequential therapy for clarithromycin-resistant strains. *Helicobacter* 2012; **17**: 269–76.
36. Gisbert JP, Molina-Infante J, Harb Y, *et al.* Non-Bismuth Quadruple (Concomitant) Therapy for Eradication of *H. pylori*: standard vs. Optimized (14-Day, High-Dose PPI) Regimen. *Gastroenterology* 2014; Suppl. 1: S–394.
37. Georgopoulos SD, Xirouchakis E, Zampeli E, *et al.* A randomised study comparing 10 days concomitant and sequential treatments for the eradication of *Helicobacter pylori*, in a high clarithromycin resistance area. *Helicobacter* 2014; **19**(Suppl 1): 80.
38. Graham DY, Fischbach LA. Letter: the ethics of using inferior regimens in *H. pylori* randomised trials. *Aliment Pharmacol Ther* 2012; **35**: 852–4.
39. 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.
40. Gisbert JP. Is culture necessary before first-line treatment for *Helicobacter pylori* infection? *Intern Med* 2011; **50**: 2717.
41. Malfertheiner P, Bazzoli F, Delchier JC, *et al. Helicobacter pylori* eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, openlabel, non-inferiority, phase 3 trial. *Lancet* 2011; **377**: 905–13.