Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial

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Summary

Background Helicobacter pylori is associated with benign and malignant diseases of the upper gastrointestinal tract, and increasing antibiotic resistance has made alternative treatments necessary. Our aim was to assess the efficacy and safety of a new, single-capsule treatment versus the gold standard for H pylori eradication.

Methods We did a randomised, open-label, non-inferiority, phase 3 trial in 39 sites in Europe, comparing the efficacy and safety of 10 days of quadruple therapy with omeprazole plus a single three-in-one capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline (quadruple therapy) versus 7 days of omeprazole, amoxicillin, and clarithromycin (standard therapy) in adults with recorded H pylori infection. Patients were randomly assigned treatment according to a predetermined list independently generated by Quintiles Canada (Ville St-Laurent, QC, Canada). Our study was designed as a non-inferiority trial but was powered to detect superiority. Our primary outcome was H pylori eradication, established by two negative 13C urea breath tests at a minimum of 28 and 56 days after the end of treatment. Our assessment for non-inferiority was in the per-protocol population, with subsequent assessment for superiority in the intention-to-treat population (ie, all participants randomly assigned treatment). This study is registered with ClinicalTrials.gov, number NCT00669955.

Findings 12 participants were lost to follow-up and 101 were excluded from the per-protocol analysis. In the per-protocol population (n=339), the lower bound of the CI for treatment with quadruple therapy was greater than the pre-established non-inferiority margin of –10% (95% CI 15·1–32·3; p<0·0001). In the intention-to-treat population (n=440), eradication rates were 80% (174 of 218 participants) in the quadruple therapy group versus 55% (123 of 222) in the standard therapy group (p<0·0001). Safety profiles for both treatments were similar; main adverse events were gastrointestinal and CNS disorders.

Interpretation Quadruple therapy should be considered for first-line treatment in view of the rising prevalence of clarithromycin-resistant H pylori, especially since quadruple therapy provides superior eradication with similar safety and tolerability to standard therapy.

Funding Axcan Pharma Inc.

Introduction Infection with Helicobacter pylori is a substantial public health problem that affects 20–50% of people in industrialised nations and up to 80% in less-developed countries. H pylori is associated with many gastrointestinal disorders, including peptic ulcer disease, gastric carcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. In regions with high incidence of gastric carcinoma, eradication of H pylori is advocated to prevent the development of this disease. Further, patients benefit from eradication after endoscopic resection of early gastric carcinoma because it reduces the risk for metachronous gastric neoplasia.

In all international guidelines, including European guidelines from the Third Maastricht Consensus Conference, treatment with omeprazole—a proton pump inhibitor (PPI)—and a combination of amoxicillin and clarithromycin (standard therapy) is recommended as first-line therapy if clarithromycin resistance is 20% or less. Bismuth-containing therapy is proposed in regions with high in-vitro resistance to clarithromycin or metronidazole, because the addition of bismuth to other antibiotic regimens has been shown to improve H pylori eradication.

A previous international study, which assessed the efficacy and safety of 10 days of omeprazole with a single (three-in-one) capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline (quadruple therapy) for H pylori eradication in patients with peptic ulcer disease or non-ulcer dyspepsia, reported overall
eradication rates greater than 90%. This finding was corroborated by a North American study, which compared 10 days of this quadruple formulation with 10 days of standard therapy in patients with peptic ulcer disease; H pylori eradication rates were 88% for quadruple therapy and 83% for standard therapy. Quadruple therapy eradicated 92% of in-vitro metronidazole-sensitive and 80% of metronidazole-resistant strains, whereas standard therapy eradicated 92% of clarithromycin-sensitive H pylori but did not eradicate the organism in 78% of patients infected with strains resistant to clarithromycin in vitro. Antimicrobial resistance rates have increased since these trials, and treatments for H pylori need assessment. Accordingly, European health authorities have requested that quadruple therapy be compared with standard therapy (the gold standard) for 7 days in a clinical trial for registration purposes. We aimed to assess efficacy and safety of quadruple therapy for 10 days versus standard therapy given for 7 days for the eradication of H pylori. Special attention has been directed to pretherapeutic H pylori resistance to clarithromycin and metronidazole and the effect of resistance on the efficacy of treatment.

**Methods**

**Participants**

Our trial was done at 39 sites in France, Germany, Ireland, Italy, Poland, Spain, and the UK, between June 11, 2008, and June 22, 2009; it was a randomised, open-label (technicians unaware of study drug allocation), non-inferiority, phase 3 trial. Eligible patients were aged 18 years or older with confirmed H pylori and upper gastrointestinal symptoms. Women were eligible if they were not pregnant or nursing, and if they were of child-bearing potential they were required to use medically acceptable contraception for the duration of the study and 30 days thereafter. Patients were excluded if they had previously used antibiotics to eradicate adequately recorded infection with H pylori, contraindications to study drugs, substantial organ impairment, severe or unstable cardiopulmonary or endocrine disease, undergone surgery of the upper gastrointestinal tract, evidence of bleeding or iron-deficiency anaemia, Barrett’s oesophagus or high-grade dysplasia, dysphagia, or history of malignancy. Patients were excluded if they had history of drug or alcohol misuse within 1 year of the trial, or continuously used antidiabetic drugs (including PPIs during the 2 weeks before the ¹³C urea breath test), antibiotics or bismuth compounds (more than three times per week, 1 month before screening), systemic glucocorticoids, non-steroidal anti-inflammatory drugs, or anticoagulation or platelet aggregation inhibitors (except acetylsalicylic acid ≤100 mg per day).

Written informed consent was obtained from all patients before enrolment. Our protocol and one amendment were approved by investigators’ research ethics, investigational review, or independent ethics boards or committees. Our study was done in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for Good Clinical Practice.

**Procedure**

We screened participants up to 1 month before they were randomly assigned treatment. Eligible patients who had not been treated with contraindicated drugs underwent a urea breath test during their first visit; patients who had been treated with contraindicated drugs were allowed a 2-week washout before the breath test. All patients with positive breath tests underwent endoscopy of the upper gastrointestinal tract and six biopsies (four from pyloric antrum; two from the gastric body). Antral biopsy specimens were submitted for rapid urease test, histology, and centralised microbiology (ie, done in one laboratory), including culture and testing for metronidazole and clarithromycin resistance. Patients had to be positive for H pylori by both urea breath test and rapid urease test, and with one confirmatory test (histology, culture, or PCR [amendment to protocol]) for participation. Sensitivity testing was by Etest (AB Biodisk, Solna, Sweden). Clarithromycin resistance was defined as a minimum inhibitory concentration (MIC) of 1·00 μg/mL or greater, intermediate resistance was defined as 0·25 μg/mL to less than 1·00 μg/mL, and sensitivity was defined as less than 0·25 μg/mL. Metronidazole resistance was defined as MIC greater than 8 μg/mL and sensitivity as 8 μg/mL or less.

Patients were randomly assigned (1:1) quadruple or standard therapy according to a predetermined list supplied to each site. The sponsor recruited sites and generated the randomisation schedule through a third party (Quintiles Canada, Ville St-Laurent, QC, Canada) without accessing or influencing the randomisation lists; this process also masked treatment allocation from the investigators.

Study drugs were proprietary three-in-one capsules containing 140 mg bismuth subcitrate potassium, 125 mg metronidazole, and 125 mg tetracycline hydrochloride (Axcan Pharma, Mont-Saint-Hilaire, QC, Canada); 500 mg clarithromycin capsules (Abbott, Abbott Park, IL, USA); 500 mg amoxicillin capsules (GlaxoSmithKline, Brentford, Middlesex, UK); and 20 mg omeprazole capsules (AstraZeneca, LP, Wilmington, DE, USA). In the 10-day quadruple regimen, three three-in-one capsules were taken four-times daily (after meals and at bedtime), and swallowed whole with 250 mL of water. An omeprazole capsule was taken with the three single three-in-one capsules after morning and evening meals. In the 7-day standard regimen, omeprazole, amoxicillin, and clarithromycin capsules were taken twice daily (before morning and evening meals). Patients were asked to refrain from consuming alcohol during the entire treatment period.
and for 48 h after the last dose, and not to take the study drugs with milk, other dairy products, or antacids. Two combination tablets (200 mg aluminium hydroxide, 200 mg magnesium hydroxide, and 25 mg simeticone; Sanofi-Aventis, Paris, France) could be taken as rescue medication up to four-times daily.

Our primary efficacy outcome was \( H \) \( pylori \) eradication, established by two negative urea breath tests at least 28 and 56 days after the end of treatment (week 6 and week 10 visits). Secondary objectives were to compare eradication as a function of antibiotic resistance and disease or disorder (non-ulcer dyspepsia, peptic ulcer disease); monitor safety through adverse events, laboratory abnormalities, and plasma bismuth concentrations at baseline, end of treatment, and end of study; and assess compliance through pill count.

Patients returned for repeat examination and laboratory studies (including measurement of plasma bismuth in patients in the quadruple therapy group) within 1 week of the end of trial. Patients were instructed to return all drug containers at the end of trial visit to assess compliance. Patients returned for the first follow-up visit about 6 weeks after the start of treatment, but not before 28 days after the end of trial. Participants were re-examined and reassessed with a second urea breath test and routine laboratory studies. Breath tests were also done on all patients who did not complete their full course of therapy. Patients with a positive breath test at the first follow-up underwent repeat endoscopy with biopsies for reassessment of antibiotic resistance. If the results of the breath test were negative, the patient was scheduled for the end of study visit about 10 weeks after treatment onset, when a third set of breath test, routine examination, and clinical laboratory procedures (including serum pregnancy testing for women of childbearing potential) was done.

Figure: Trial profile

Quadruple therapy is omeprazole, bismuth, metronidazole, and tetracycline. Standard therapy is omeprazole, amoxicillin, and clarithromycin.

UBT=\(^{13}C\) urea breath test.
Statistical analysis

Our hypotheses for sample size calculations were based on previously documented \(H\) pylori antibiotic-resistance rates,\(^{11,14}\) 85% quadruple therapy eradication rates and 80% standard therapy eradication rates, \(\Delta\) (defining equivalence range or non-inferiority margin) of −10%, expected difference of 5%, power of 90%, and \(\alpha\) of 0.025 (one-sided). Our trial was designed as a non-inferiority trial but was powered to detect superiority. An estimated difference of 5%, power of 90%, and \(\alpha\) of 0.025 (one-sided). Our trial was designed as a non-inferiority trial but was powered to detect superiority. 135 patients per group (completers) were needed to show non-inferiority of the experimental drug versus active control on the basis of the primary efficacy variable. An estimated 30% of patients would not be included in the per-protocol analysis because of one or more major protocol deviations; therefore, 193 patients randomly assigned treatment per group were planned to protect the trial’s power. If non-inferiority was concluded with the per-protocol population, testing for superiority with the intention-to-treat population was permitted (we defined the intention-to-treat population as all participants randomly assigned treatment). SAS software (version 9.1.3 or higher) produced statistical outputs. Categorical variables were assessed with the Cochran-Mantel-Haenszel test adjusted for pooled sites (sites within each country) or countries with <12 intention-to-treat patients were incorporated into pooled sites). Eradication was confirmed with negative urea breath tests at both the week 6 and week 10 visits. A positive breath test at week 6 suggested that treatment had failed; these patients were classified as non-eradicated. Per-protocol patients did not need imputation of missing test results; both week 6 and week 10 assessments needed to be available for patients whose week 6 breath test was negative. In the event of missing intention-to-treat assessments, non-eradicated was imputed for missing (or done outside the allocated timeframe) breath test values. All other results were assessed on an observed-case basis.

The per-protocol population was used to assess primary efficacy. The primary analysis (comparing non-inferiority of the two drug combinations) was assessed through hypothesis testing and derivation of a two-sided 95% CI with an asymptotic normal approximation procedure with continuity correction. If the lower bound of this CI exceeded −10%, non-inferiority of quadruple versus standard therapy could be concluded. If the lower bound was −10% or lower non-inferiority was not supported. If the non-inferiority of quadruple over standard therapy was concluded with the per-protocol population, the same CI was derived with the intention-to-treat population. If the lower bound of this CI was greater than zero, superiority of quadruple over standard therapy could be concluded. If the urea breath tests were missing for week 6, week 10, or both, non-eradication was assumed for this component of the analysis. Sensitivity analyses were done with the intention-to-treat population without imputed data.

Two post-hoc analyses were done: the first used a different definition of eradication (one or more negative urea breath tests at the week 6 or week 10 visit, provided that it was done ≥28 days after the end of trial), and the second imputed patients with missing breath tests as treatment successes. No inferential analyses were done on safety data and no missing values were imputed. The number and percentage of patients with bismuth concentrations greater than 50 mg/L at all assessments were reported with descriptive statistics. Bismuth concentrations measured at screening, end of trial, and end of study were compared with paired t tests (quadruple therapy group). This study is registered with ClinicalTrials.gov, number NCT00669955.

Role of the funding source

The trial was conceived and designed by the sponsor and the principal investigator (PM). The principal investigator substantially contributed to designing the trial, wrote the first and final drafts of the report and decided, in consultation with the other authors, to submit for publication. All authors had full access to the data.
Results

The figure shows the trial profile. 204 patients assigned to receive quadruple therapy and 195 assigned to receive standard therapy completed the study, with lack of efficacy in 11 and 56 respectively. Two patients in the quadruple therapy group did not receive the study drugs; safety analyses were done on the remaining 438 patients. Table 1 shows the baseline characteristics of the two groups.

Treatment with quadruple therapy fulfilled criteria for non-inferiority to standard therapy in the per-protocol population. Accordingly, the intention-to-treat population was used for superiority testing, and quadruple therapy was significantly better than standard therapy in eradicating *H pylori* (all p<0·0001; table 2). In the per-protocol population, eradication rates were greater for quadruple than for standard therapy; in the intention-to-treat population with missing urea breath test data imputed as positive (ie, persistent infection), eradication rates were lower for both groups (table 2). Post-hoc analysis (eradication defined as one or more negative breath tests at first follow-up [week 6] or end of study [week 10] and no positive breath tests) confirmed the superiority of quadruple therapy. There was an imbalance in the number of patients excluded from the per-protocol analysis due to missing breath tests (figure); post-hoc analysis imputing patients with missing breath tests as treatment successes showed the same degree of difference between groups.

Baseline *H pylori* in-vitro metronidazole sensitivity was similar between the quadruple (71% [103 of 145 participants]) and standard therapy groups (69% [90 of 131]; p=0·695); metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per-protocol population (p=0·283; table 3). Baseline clarithromycin sensitivity was also similar between the quadruple (77% [112 of 145]) and standard therapy groups (81% [106 of 131]; p=0·464); however, this sensitivity seemed to significantly affect the efficacy of standard therapy (p<0·0001; table 3). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (no eradication in eight [80%] of ten patients with resistant bacteria vs 31 [26%] of 121 with non-resistant bacteria; p=0·001).

Although few patients with peptic ulcer disease were...
The proportion of patients with treatment-emergent adverse events (TEAEs) were similar between the treatment groups (table 4). Gastrointestinal symptoms, including dyspepsia and diarrhoea, were the most commonly reported TEAEs and were more common in the standard than the quadruple therapy group. Compliance exceeded 95% in both treatment groups.

The proportion of patients with treatment-emergent adverse events (TEAEs) were similar between the treatment groups (table 4). Gastrointestinal symptoms, including dyspepsia and diarrhoea, were the most commonly reported TEAEs and were more common in the standard than the quadruple therapy group. Severe TEAEs (dyspepsia, upper-abdominal pain, nausea, eructation, headache, dysgeusia, and generalised infection) were more common in the standard (7% [16 of 222 participants]) than the quadruple therapy group (5% [11 of 216]). Incidence of serious TEAEs and discontinuations due to a TEAE were similar between groups (<2.0%). Four patients in the quadruple therapy group reported a total of seven serious adverse events (eczema, psychotic episode, Escherichia coli or Proteus mirabilis urinary tract infection, renal artery stenosis, acute renal failure, and small bowel neuroendocrine carcinoma); two patients in the quadruple therapy group withdrew because of treatment-limiting adverse events (epigastric pain, dyspepsia, nausea, and abdominal pain). Three patients in the standard therapy group reported a total of nine serious adverse events (arrhythmia, emesis, pyrexia, dehydration, under-nourishment, vascular dementia, acute appendicitis, exacerbation of chronic pancreatitis, and aggravation of the general condition); three patients in the standard therapy group withdrew because of treatment-limiting adverse events (epigastric pain, tachycardia, hyperhidrosis, and cardiovascular complications). The sole death during the trial was suicide of a patient in the standard therapy group 2 months after study entry—we did not deem this related to the study drug. No clinically significant changes were reported in physical examination, vital signs, or laboratory indices. Bismuth plasma concentrations increased slightly with quadruple therapy (45 [22%] of 209 patients in this group developed plasma bismuth concentrations of 4–20 μg/L after having undetectable baseline values of <4 μg/L). All bismuth concentrations increased slightly with quadruple therapy (45 [22%] of 209 patients in this group developed plasma bismuth concentrations of 4–20 μg/L after having undetectable baseline values of <4 μg/L). All bismuth concentrations were below the toxic threshold (50 μg/L). Five (3%) of 200 patients treated with quadruple therapy had detectable plasma bismuth concentrations at the end of study visit versus three (1%) of 210 who had detectable plasma bismuth concentrations at baseline.

Discussion

Our results show that 10 days of treatment with quadruple therapy yields \( H \) \( \text{pylori} \) eradication rates superior to 7 days of treatment with standard therapy. Standard therapy is at present the standard first-line treatment in Europe and elsewhere, but failure rates in about 40% of patients have been reported and continue to increase. Antibiotic resistance is the main factor that contributes to the failure of PPI-based triple therapy to adequately eradicate \( H \) \( \text{pylori} \). Resistance-inducing mutations happen spontaneously during bacterial replication, and previous antibiotic treatment for other infections favour the selection of drug-resistant \( H \) \( \text{pylori} \); resistance can rapidly emerge during the first course of treatment and parallels national antibiotic consumption. Clarithromycin is a key component of many first-line PPI-based triple therapies, and resistance to it is constantly rising (paralleled by increasing standard therapy failure). Conversely, the efficacy of metronidazole-containing combination therapy (with bismuth and tetracycline) is maintained in patients harbouring metronidazole-resistant \( H \) \( \text{pylori} \). The discrepancy is explained partly by metronidazole resistance

### Table 4: TEAEs in the treated population

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>Quadruple therapy (N=216)</th>
<th>Standard therapy (N=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a TEAE</td>
<td>101 (47%)</td>
<td>112 (51%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>65 (30%)</td>
<td>82 (37%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>22 (10%)</td>
<td>30 (14%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>14 (7%)</td>
<td>28 (13%)</td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>18 (8%)</td>
<td>16 (7%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (7%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (4%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Faeces discoloured</td>
<td>9 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Eructation</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>CNS disorders</td>
<td>33 (15%)</td>
<td>29 (13%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>12 (6%)</td>
<td>22 (10%)</td>
</tr>
<tr>
<td>Headache</td>
<td>18 (8%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>3 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>17 (8%)</td>
<td>18 (8%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (3%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>0</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>General disorders and administration-site conditions</td>
<td>14 (7%)</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>5 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>8 (4%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>7 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>3 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

Quadruple therapy is omeprazole, bismuth, metronidazole, and tetracycline. Standard therapy is omeprazole, amoxicillin, and clarithromycin. TEAE=treatment-emergent adverse event.
as assessed in vitro, but does not adequately relate to in-vivo states, partly because of metronidazole–bismuth synergism that overcomes resistance. Further, metronidazole resistance is complex and associated with the presence of redox-related bacterial-gene mutations (rdxA, frxA, ferric uptake regulator protein).

Bismuth has an established history in the treatment of Helicobacter pylori. Colloidal bismuth subcitrate has potent anti-H pylori activity (MIC 4–32 μg/mL), and in-vitro resistance has not been induced. Further, bismuth increases eradication when included in double, triple, and quadruple regimens. In our trial, eradication rates with quadruple therapy were similar (about 88–93%) to those of previous studies that used the same three-in-one capsule with 20 mg omeprazole twice daily. Such high eradication rates contrast with those reported from a meta-analysis by Luther and colleagues that compared the efficacy of bismuth-based quadruple therapy (about 78% eradication) with standard therapy (about 77%). Although standard therapy dosing regimens were consistent across trials, they were highly variable for bismuth-based quadruple therapy; further, choice of bismuth salt also varied.

Although we could postulate that inclusion in the three-in-one capsule is ideal, head-to-head trials are needed to establish the bismuth dosing regimen that provides maximum eradication.

Concerns have been raised about toxic effects related to bismuth. There have been rare reports of heavy-metal poisoning and encephalopathy at plasma bismuth concentrations greater than 50 μg/L in patients treated with bismuth subgallate and greater than 20 g per day bismuth subcitrate for 6 months to 20 years. In our trial, with little bismuth exposure and use of a colloidal bismuth subcitrate formulation, bismuth concentrations were below the toxic threshold. Data from a recent systematic review and meta-analysis of 35 randomised controlled trials showed that stool discolouration (clinically irrelevant) was the only adverse effect significantly associated with bismuth ingestion.

Inclusion of antisecretory therapy (PPIs) in H pylori-eradication regimens is crucial to optimise the local activity of antibiotics via synergism, and our trial clarifies the timing of PPI in relation to meals. By contrast with giving a PPI with amoxicillin and clarithromycin (whose stability and activity are highly dependent on high pH), there is no such need with tetracycline and metronidazole.

In our trial, two negative urea breath tests in the allocated timeframe were needed for a patient to be deemed successfully treated. In view of the high accuracy of the breath test, treatment guidelines and most studies and meta-analyses judge eradication to be confirmed after one breath test 4–6 weeks after completion of treatment. In our study, seven patients had a negative breath test at week 6 and a positive test at week 10 (two on quadruple therapy, five on standard therapy); confirmation of a negative test was obtained in 437 of 438 patients. The extremely conservative approach of imputing all patients with one breath test outside the allocated timeframe as non-eradicated explains the underestimation of eradication in the intention-to-treat population.

Criticisms of our study might include the varying treatment duration in each group and choice of metronidazole-resistance test. The effect of varying standard therapy durations has been assessed in a recent meta-analysis of 21 studies, with data showing that the extension of standard therapy beyond 7 days provided a slight increase (about 5%) in eradication when the longest duration (14 days) was assessed. However, when the four highest-quality trials (as assessed by the Jadad scale) from this analysis were considered, prolonging treatment with standard therapy beyond 7 days (with extension up to 10 days) was not associated with additional benefit. A randomised trial of patients infected with H pylori showed that extending treatment with standard therapy for up to

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Panel: Research in context

Systematic review

We searched published work with PubMed, Ovid Medline, Abridged Index Medicus, and various gastrointestinal congresses (including the American Gastroenterological Association, Digestive Disease Week, and the United European Gastroenterology Week). Publications were limited to 1980 or later. Search terms included “Helicobacter pylori”, “peptic ulcer disease”, “eradication”, “guideline”, “therapy”, and “treatments”. Authors independently extracted and validated references. Data from systematic reviews of randomised controlled trials, individual randomised controlled trials, systematic reviews of cohort studies, cohort studies, systematic reviews of case-control studies, case-control studies, case series, and opinions without explicit critical appraisal were prioritised for inclusion in descending order. Our search was limited to studies in English.

Interpretation

Our trial compared the efficacy and safety of omeprazole, amoxicillin, and clarithromycin (standard therapy; first-line treatment in international guidelines) and omeprazole, bismuth subcitrate potassium, metronidazole, and tetracycline (quadruple therapy) and, as shown by the results of our systematic review, is the first large-scale comparative study of these treatments for the eradication of H pylori in nearly a decade. Data from our study corroborate the safety and tolerability of bismuth in Europe and highlight the effect of antibiotic resistance on eradication efficacy between combination treatments. Clarithromycin-resistant H pylori continues to increase in prevalence, and although rates of metronidazole resistance are also high, the results from our study showed that clarithromycin resistance reduces the efficacy of standard therapy, whereas resistance to metronidazole has a slight effect on the efficacy of quadruple therapy.
14 days did not provide any benefit over 7 days of treatment. Regarding quadruple therapy, 10 days of treatment is advocated by international guidelines\(^6\) and is the approved duration of treatment in some countries. 7 days of quadruple therapy has not been rigorously assessed.

There is no recommendation for metronidazole testing. Etest is convenient to use and its results relate well with agar dilution\(^7\), although Etest can overestimate resistance, our results are consistent with previous data.\(^8\)

Our trial is the first large-scale comparative study of the efficacy and safety of standard and quadruple therapy for the eradication of \(H\) pylori in nearly a decade (panel). In view of the variable availability of bismuth across Europe, the findings of our trial provide assurance to clinicians on the safety and tolerability of bismuth. Furthermore, we highlight the effect of antibiotic resistance on eradication efficacy between combination therapies. Although several other new eradication strategies have been proposed, their efficacy and use in practice need to be corroborated.\(^9\)\(^,\)\(^10\)\(^,\)\(^11\)\(^,\)\(^12\)

10 days of treatment with quadruple therapy was superior to 7 days of standard therapy for \(H\) pylori eradication in patients with or without the presence of history of peptic ulcer disease. Clarithromycin-resistant \(H\) pylori isolates continue to increase in prevalence throughout the world, and although rates of metronidazole resistance are also high, clarithromycin resistance reduces the efficacy of standard therapy whereas metronidazole resistance has little effect on the efficacy of quadruple therapy. In regions with high levels of clarithromycin resistance, treatment with quadruple therapy should be considered as first-line therapy for \(H\) pylori eradication.

**Contributors**

PM, MG, and MR contributed to the study concept and design.

PM, FB, J-CD, and KC enrolled and treated patients and collected data. FM provided central microbiological review. All authors contributed to analyses and interpretations of results and the writing or review of the paper.

**Pylera Study Group investigators**


**Conflicts of interest**

PM, FB, J-CD, and KC have received payment from Axcan Pharma for research and clinical trials. MG and MR are employees of Axcan Pharma.

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**References**


