Sequential, concomitant and hybrid first-line therapies for *Helicobacter pylori* eradication: a prospective randomized study

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*Helicobacter pylori* eradication remains a challenge for physicians. Sequential, concomitant and the hybrid regimens have been proposed as novel, more effective therapies. We compare the efficacy of these therapies. Dyspeptic patients referred for upper endoscopy with *H. pylori* infection were enrolled. Patients were randomized to receive: (a) sequential therapy – 20 mg omeprazole and 1 g amoxicillin for 5 days, followed by 20 mg omeprazole, 500 mg clarithromycin and 500 mg tinidazole for the successive 5 days; (b) concomitant therapy – 20 mg omeprazole, 1 g amoxicillin, 500 mg clarithromycin and 500 mg tinidazole for either 5 days (5 day concomitant) or 14 days (14 day concomitant); or (c) hybrid therapy – 20 mg omeprazole and 1 g amoxicillin for 7 days, followed by 20 mg omeprazole, 1 g amoxicillin, 500 mg clarithromycin and 500 mg tinidazole for the successive 7 days. All drugs were given twice daily. Bacterial eradication was checked by using a [13C]urea breath test. In ‘intention-to-treat’ analysis, sequential therapy achieved the highest eradication rate, which was higher than that of 5 day concomitant therapy (90 vs 78.1%; *P* < 0.02). The success rate did not statistically differ among the sequential and either 14 day concomitant (90 vs 86.3%; *P* = not significant) or hybrid therapies (90 vs 82.7%; *P* = not significant). The 10 day sequential, 14 day concomitant and 14 day hybrid therapies, but not the 5 day concomitant regimen, achieved similarly high eradication rates. The lower therapeutic cost coupled with the lower number of tablets needed would favour the sequential therapy as the first-line *H. pylori* treatment in clinical practice.

INTRODUCTION

The *Helicobacter pylori* eradication rate following standard 7 day triple therapies has decreased in different countries (Graham & Fischbach, 2010; Gisbert & Calvet, 2011; McNicholl & Gisbert, 2012), and attempts to improve the efficacy by prolonging treatment duration to 10–14 days showed a small benefit (Fuccio *et al.*, 2007). Therefore, novel first-line therapies have been proposed, including the sequential, concomitant and, more recently, hybrid therapy regimens. The standard 10 day sequential therapy, consisting of a proton pump inhibitor (PPI) and amoxicillin dual therapy for the first 5 days, followed by a PPI, clarithromycin and tinidazole triple therapy for the successive 5 days, was pioneered in Italy in 2000 (Zullo *et al.*, 2000). Several trials showed a high efficacy of this therapy, with a success rate constantly higher than that of standard 7–10 day triple therapies (Zullo *et al.*, 2007). In the last few years, the concomitant regimen first introduced in 1998 (Okada *et al.*, 1998; Treiber *et al.*, 1998) has been revisited for *H. pylori* eradication. This regimen includes PPI, clarithromycin, amoxicillin and metronidazole, i.e. it is a bismuth-free quadruple therapy. However, different durations, widely ranging from only 3 to 14 days, have been proposed for this therapy, so a well-standardized regimen is lacking (Gisbert & Calvet, 2012). Different studies demonstrated a high (>90%) efficacy of concomitant therapy, even when administered for only 5 days (Treiber *et al.*, 1998, 2002; Nagahara *et al.*, 2000, 2001; Kongchayanun *et al.*, 2012), and in a recent pilot study an 85.5–91.6% eradication rate was achieved (Zullo *et al.*, 2013a). However, other studies suggested a longer regimen so that a standard therapy duration is unclear (Essa *et al.*, 2009; Graham & Fischbach, 2010). The 14 day hybrid therapy combines the sequential...
and concomitant therapies, with 7 day dual therapy followed by a 7 day quadruple therapy. To date, only a few studies have assessed the efficacy of this regimen (Hsu et al., 2011; Lim et al., 2013). To our knowledge, no study has involved a ‘head to head’ comparison among all these therapies. In addition, data on the eradication rate in those patients who had failure with these therapies are scant. Therefore, we designed a study aiming to compare sequential, concomitant and hybrid therapies as first-line treatment for H. pylori eradication, and to assess the efficacy of second- and third-line therapies in the eradication-failure patients.

METHODS

Patients. Consecutive patients complaining of dyspeptic symptoms referred for upper endoscopy to the Endoscopy Unit (Foggia) between January 2012 and July 2013 were considered for recruitment into the study. Exclusion criteria were: age <18 years, previous eradication-therapy failure, treatment with PPI and/or antibiotics in the previous month, previous gastric surgery, presence of either liver cirrhosis or kidney failure, alcohol abuse (>80 g per day), pregnancy, and known allergy to antibiotics. All patients underwent upper endoscopy with gastric biopsies. Two specimens (one from the gastric antrum and one from the gastric body) were used for a rapid urease test, and four specimens (two each from the gastric antrum and body) were used for histological examination and H. pylori detection. H. pylori infection was considered present when both tests were positive.

The presence of a peptic ulcer was defined as a mucosal ulceration ≥5 mm in diameter. For the purpose of the study, patients with duodenal or gastric ulcers were considered as having peptic ulcer disease, while those without an ulcer at endoscopy, a documented history of peptic disease and macroscopic mucosal abnormalities were considered as non-ulcer dyspepsia patients. Bacterial eradication was checked 6–8 weeks after treatment by using a [13C]urea breath test.

Therapy regimens. This was a prospective, open-label, randomized study performed in a single centre. Patients were randomized to receive one of the following four treatments: (a) sequential therapy – 20 mg omeprazole and 1 g amoxicillin for 5 days, followed by 20 mg omeprazole, 500 mg clarithromycin and 500 mg tinidazole for the successive 5 days; (b) concomitant therapy – 20 mg omeprazole, 1 g amoxicillin, 500 mg clarithromycin and 500 mg tinidazole for either 5 days (5 day concomitant) or 14 days (14 day concomitant); or (c) hybrid therapy – 20 mg omeprazole and 1 g amoxicillin for 7 days, followed by 20 mg omeprazole, 1 g amoxicillin, 500 mg clarithromycin and 500 mg tinidazole for the successive 7 days. For each therapy regimen, all drugs were given twice daily. When a patient showed H. pylori-eradication-therapy failure, a second-line therapy regimen with 20 mg omeprazole, 1 g amoxicillin and 250 mg levofloxacin (all twice daily) for 10 days was prescribed. Finally, a third-line therapy with high-dose 40 mg esomeprazole and 1 g amoxicillin (all three times daily) for 14 days was implemented. Patients were thoroughly instructed and motivated about the therapy. The pharmaceutical cost of each therapy regimen was calculated taking into account only branded drugs currently available in Italy, and by summing the cost of each single tablet needed to complete the entire treatment.

Therapy compliance and side-effects. Following a short informative discussion with the patient, including the benefits and risks of the antibiotic therapy, the time needed for explanation of the therapy schedule – provided in a pre-printed sheet – was calculated for each patient. The educational level of each patient was categorized into two classes: low (no school or elementary school) and high (high school, college or university). Compliance to the therapy was assessed at the end of the treatment by a personal interview. A pill intake >90% was considered as a good compliance. Side-effects were assessed by a structured questionnaire.

Statistical analysis. The eradication rates with 95% confidence intervals (95% CIs) were calculated for both ‘intention-to-treat’ (ITT) and ‘per-protocol’ (PP) analyses, considering all the enrolled patients or only those compliant to therapy, respectively, who performed a urea breath test. Data were compared by using the t-test for unpaired data and the chi-squared test, as appropriate. Differences were considered significant at a 5% probability level.

RESULTS

First-line therapies

A total of 440 patients were enrolled, and the clinical characteristics of the patients were comparable among the four therapeutic arms (Table 1). A similar time (mean ± SD) was needed for explicating the therapeutic schedules, being 4.3 ± 0.7, 3.4 ± 1, 3.5 ± 0.8 and 4.7 ± 1 min for sequential, 5 day concomitant, 14 day concomitant and hybrid therapies, respectively. In addition, no significant difference emerged between high- and low-educational-level patients in each therapeutic regimen (data not shown). Overall 3, 6, 8 and 7 patients in sequential, 5 day concomitant, 14 day concomitant and hybrid therapies, respectively, discontinued treatment due to side-effects. In addition, 2, 3, 2 and 8 patients, respectively, were lost to follow-up and were considered as drop-outs. Therefore, the final PP analysis
population consisted of 401 patients. In ITT analysis, sequential therapy achieved the highest eradication rate, which was higher than that of 5 day concomitant therapy (90 vs 78.1 %; \(P<0.02\)). The success rate did not statistically differ among the sequential and either 14 day concomitant (90 vs 86.3 %; \(P=\text{NS}\)) or hybrid therapies (90 vs 82.7 %; \(P=\text{NS}\)) (Table 2). In PP analysis, the eradication rate following the 5 day concomitant therapy was significantly lower than that of sequential therapy (85.1 vs 94.2 %; \(P<0.03\)), 14 day concomitant therapy (85.1 vs 95 %; \(P<0.03\)) and hybrid therapy (85.1 vs 95.7 %; \(P<0.02\)) (Table 2). The eradication rates achieved in ITT analysis were lower than those of PP analysis for either 14 day concomitant (86.3 vs 95 %, \(P<0.05\)) or hybrid therapies (82.7 vs 95.7 %, \(P<0.01\)), whilst the difference was not statistically significant for the other two regimens. The therapy cost was £22 (28 euros) for sequential therapy, £19 (23.7 euros) for 5 day concomitant therapy, £53 (66.4 euros) for 14 day concomitant therapy and £36 (44.8 euros) for the hybrid therapy regimen.

Side-effects

Overall, side-effects occurred in 19, 24.5, 26.3 and 22.7 % of patients following sequential, 5 day concomitant, 14 day concomitant and hybrid therapies, respectively. The complained side-effects are listed in Table 3. The difference was not statistically significant. Overall three patients (two vomiting, one urticaria) in sequential, six patients (two diarrhoea, two vomiting, one oral candidiasis, one pruritus) in the 5 day concomitant, eight patients (four diarrhoea, two abdominal pain, one vomiting, one vaginal candidiasis) in the 14 day concomitant, and seven patients (three diarrhoea, two abdominal pain, one vomiting, one pruritus) in the hybrid therapy discontinued treatment due to side-effects.

Rescue therapies

Overall, 27 out of 30 patients for whom first-line therapy failed, including 6, 15, 5 and 4 from sequential, 5 day concomitant, 14 day concomitant and hybrid therapies, respectively, accepted the second-line therapy with amoxicillin and levofloxacin. Three of these patients interrupted the treatment due to side-effects, and the infection was successfully cured in 19 cases, accounting for 70.3 % (95 % CI 53.1–87.5) and for 79.1 % (95 % CI 62.9–95.4) eradication in ITT and PP analysis, respectively. Three out of five patients for whom second-line treatment failed

### Table 2. Results of the first-line therapies

<table>
<thead>
<tr>
<th></th>
<th>Sequential</th>
<th>Concomitant</th>
<th>Hybrid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 day</td>
<td>5 day</td>
<td>14 day</td>
</tr>
<tr>
<td>Eradication rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage (95 % CI)</td>
<td>90 % (84.3–95.6)*</td>
<td>78.1 % (70.4–85.9)</td>
<td>86.3 % (79.9–92.7)</td>
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<tr>
<td>No. of patients</td>
<td>99/110</td>
<td>86/110</td>
<td>95/110</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Eradication rate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Percentage (95 % CI)</td>
<td>94.2 % (89.8–98.7)</td>
<td>85.1 % (78.2–92)†</td>
<td>95 % (90.7–99.2)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>99/105</td>
<td>86/101</td>
<td>95/100</td>
</tr>
</tbody>
</table>

*\(P<0.05\) as compared to 5 day concomitant therapy; the difference among 14 day concomitant, 5 day concomitant and hybrid therapies was not statistically significant.

†\(P<0.05\) as compared to sequential, 14 day concomitant and hybrid therapies; the difference among sequential, 14 day concomitant and hybrid therapies was not statistically significant.

### Table 3. Side-effects

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Sequential</th>
<th>Concomitant</th>
<th>Hybrid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 day</td>
<td>5 day</td>
<td>14 day</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>11</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>4</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Pruritus/urticaria</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Vaginal candidiasis</td>
<td>–</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>21 (19 %)</td>
<td>27 (24.5 %)</td>
<td>29 (26.3 %)</td>
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</tbody>
</table>
performed a third-line therapy, and two achieved bacterial eradication. The cumulative ITT and PP cure rates following all treatments (from first- to the third-line) were 103/110 (93.6%) and 103/104 (99.0%), 97/110 (88.2%) and 97/100 (97%), 98/110 (89.1%) and 98/99 (99.0%), and 94/110 (85.5%) and 94/95 (98.9%), for sequential, 5 day concomitant, 14 day concomitant and hybrid therapies, respectively. The differences were not statistically significant.

**DISCUSSION**

*H. pylori* eradication remains a challenge for physicians, no therapy regimen being able to cure the infection in all treated patients (De Francesco et al., 2012). Based on the decreased success rate of standard triple therapies (Graham & Fischbach, 2010; Gisbert & Calvet, 2011; McNicholl & Gisbert, 2012), new therapy regimens have been introduced in the last decade. Among these therapies the standard sequential, concomitant and hybrid regimens emerged as the most promising. In Italy, the standard sequential regimen was largely proven to be highly effective with an eradication rate constantly higher than that of triple therapy (Zullo et al., 2013b), so its use as first-line therapy was endorsed by national guidelines (Caselli et al., 2007). On the contrary, data on concomitant and hybrid therapies are scant in our country (McNicholl et al., 2014). In the present study, a ‘head to head’ comparison among these therapy regimens was performed. The data showed that the sequential regimen achieved significantly higher eradication rates as compared to 5 day concomitant therapy, in both ITT and PP analyses. On the contrary, the eradication rate did not significantly differ among 10 day sequential, 14 day concomitant and 14 day hybrid therapies, suggesting that these three regimens could be considered equally effective as first-line therapy. Present eradication rates for 10 day sequential therapy are comparable to those obtained in 2004, suggesting a constant efficacy of this regimen in our geographical area (De Francesco et al., 2004). Moreover, the time needed for explicating these therapy schedules was equally short (less than 5 min), and it was not significantly affected by the educational level of patients. However, some aspects deserve consideration. When different therapies for a widely spread disease – such as *H. pylori* infection – are equally effective, the therapeutic cost should be considered. In Italy, the cost of sequential therapy is as much as 58 and 38% cheaper than that of 14 day concomitant and 14 day hybrid therapy, respectively. This would be a matter for concern when considering the thousands of patients who are treated every day worldwide. In addition, the overall number of tablets administered for the sequential therapy (50 tablets) is distinctly lower than that of either 14 day concomitant (112 tablets) or hybrid (84 tablets) therapies. Therefore, it is at least questionable to require patients to take more drugs to achieve the same result. Moreover, differently from the sequential regimen, following either 14 day concomitant or 14 day hybrid therapies the cure rate calculated in ITT analysis was significantly lower than that in PP analysis. This would indirectly suggest that, in clinical practice, a higher number of patients could abandon these therapies as compared to the sequential therapy, with relevant consequences in terms of peptic ulcer or neoplasia risk (Alakkari et al., 2011).

As far as retreatment is concerned, the levofloxacin-based triple therapy achieved a 70.3–79.1% eradication rate. The decreasing success rate following such a therapy has been recently highlighted (Zullo et al., 2010, 2013a), and is probably due to a high (22.1%) prevalence of primary levofloxacin resistance confirmed in Italy (Saracino et al., 2012). Moreover, such an observation also questions the utility of using a levofloxacin-based regimen as a first-line therapy (Zullo et al., 2013c). As a third-line therapy we chose a high-dose, 14 day esomeprazole and amoxicillin dual therapy, with the aim of achieving a deeper inhibition of gastric secretion to favour the efficacy of amoxicillin, which is the only antibiotic for which antibiotic resistance is extremely low even following repeated treatment (De Francesco et al., 2011). Although interesting, the data refer to a very small sample, so that the observations require further studies.

A possible limitation of our study could be the lack of primary-resistance assessment to different antibiotics for *H. pylori* strains. However, this was a study comparing these novel regimens as first-line therapy in clinical practice, where antibiotic assessment is not performed. Moreover, a selection bias is ruled out by randomization of patients so that the prevalence of primary antibiotic resistance is expected to be equally distributed among the therapeutic groups.

In conclusion, the data in this study showed that the 10 day sequential, 14 day concomitant and 14 day hybrid therapies, but not the 5 day concomitant regimen, achieved similarly high eradication rates. The lower therapeutic cost coupled with the lower number of tablets needed would favour the sequential therapy as first-line *H. pylori* treatment in clinical practice.

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