ORIGINAL ARTICLE

Helicobacter pylori eradication with either seven-day or 10-day triple therapies, and with a 10-day sequential regimen

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BACKGROUND: *Helicobacter pylori* eradication rates achieved by standard seven-day triple therapies are decreasing in several countries, while a novel 10-day sequential regimen has achieved a very high success rate. A longer 10-day triple therapy, similar to the sequential regimen, was tested to see whether it could achieve a better infection cure rate.

METHODS: Patients with nonulcer dyspepsia and *H pylori* infection were randomly assigned to one of the following three therapies: esomeprazole 20 mg, clarithromycin 500 mg and amoxycillin 1 g for seven days or 10 days, or a 10-day sequential regimen including esomeprazole 20 mg plus amoxycillin 1 g for five days and esomeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg for the remaining five days. All drugs were given twice daily. *H pylori* eradication was checked four to six weeks after treatment by using a ^{13}C-urea breath test.

RESULTS: Overall, 213 patients were enrolled. *H pylori* eradication was achieved in 75.7% and 77.9%, in 81.7% and 84.1%, and in 94.4% and 97.1% of patients following seven-day or 10-day triple therapy and the 10-day sequential regimen, at intention-to-treat and per protocol analyses, respectively. The eradication rate following the sequential regimen was higher than either seven-day (P=0.002) or 10-day triple therapy (P=0.02), while no significant difference emerged between the latter two regimens (P=0.6).

CONCLUSIONS: The 10-day sequential regimen was significantly more effective than both triple regimens, while 10-day triple therapy failed to significantly increase the *H pylori* eradication rate achieved by the standard seven-day regimen.

Key Words: *Bacterial load*; Helicobacter pylori; *Sequential therapy*; *Triple therapy*

La suppression d'*Helicobacter pylori* : la trithérapie de 7 jours ou de 10 jours par rapport à la thérapie séquentielle de 10 jours

CONTEXTE : Le taux de suppression d'*Helicobacter pylori* obtenu par la trithérapie courante de 7 jours est en voie de diminution dans plusieurs pays, mais une nouvelle thérapie séquentielle de 10 jours atteint un très bon taux de réussite. Nous avons donc vérifié si la trithérapie prolongée à 10 jours, selon le modèle de la thérapie séquentielle, pouvait améliorer le taux de guérison de l'infection.

MÉTHODE : Des patients souffrant de dyspepsie non ulcéreuse et d'une infection à *H. pylori* ont été soumis au hasard à l'un des trois traitements suivants : ésoméprazole, 20 mg; clarithromycine, 500 mg et amoxycilline, 1 g, durant 7 jours ou durant 10 jours, en trithérapie; ou encore ésoméprazole, 20 mg et amoxycilline, 1 g durant 5 jours, puis ésoméprazole, 20 mg; clarithromycine, 500 mg et tinidazole, 500 mg durant les 5 derniers jours, en thérapie séquentielle de 10 jours. Les médicaments étaient tous à prise biquotidienne. La suppression d'*H. pylori* a été vérifiée de quatre à six semaines après le traitement à l'aide de l'épreuve respiratoire à l'urée marquée au carbone-13.

RÉSULTATS : Au total, 213 patients ont participé à l'étude. Il y a eu suppression d'*H. pylori* chez 75,7 % et 77,9 %; 81,7 % et 84,1 %; 94,4 % et 97,1 % des patients après la trithérapie de 7 jours ou de 10 jours ou encore après la thérapie séquentielle de 10 jours, selon l'analyse fondée sur le principe de vouloir traiter ou l'analyse fondée sur le protocole, respectivement. Le taux de suppression suivant la thérapie séquentielle a été plus élevé que celui atteint par la trithérapie de 7 jours (P=0,002) ou de 10 jours (P=0,02), et aucun écart significatif ne séparait les deux dernières modalités (P=0,6).

CONCLUSIONS : La thérapie séquentielle de 10 jours s'est montrée significativement supérieure à la trithérapie de 7 jours ou de 10 jours; de plus, la trithérapie de 10 jours n'a pas permis d'augmentation sensible du taux de suppression d'*H. pylori* par rapport à celui atteint par la thérapie courante de 7 jours.

*H*elicobacter pylori plays a crucial role in the pathogenesis of chronic active gastritis, peptic ulcer and mucosa-associated lymphoid tissue lymphoma, and its involvement in gastric carcinogenesis is also of mounting concern (1-4). Although the association between *H pylori* and nonulcer dyspepsia is still debatable, two comprehensive systematic reviews showed a small but significant benefit to curing this infection (5,6). *H pylori* causes significant morbidity and mortality with a relevant economic impact, thus requiring an appropriate therapeutic approach. A triple therapy, comprising proton pump inhibitor, clarithromycin and amoxicillin or metronidazole, is among the most used first-line treatments in primary medical care in several countries including Canada, the United States and Europe (7-10). However, during the past few years, different studies have found that the success rate following such regimens is decreasing in several countries. Indeed, two large

meta-analyses (11,12) showed that these therapies failed to eradicate *H pylori* in up to 20% of patients. Moreover, even lower cure rates have been observed in primary medical care settings, with bacterial eradication being achieved in only 61% to 76% of patients (8). Some studies have evaluated the efficacy of triple therapies administered for 10 days or even 14 days, with controversial results. However, a recent meta-analysis (13) has clearly shown that the 10-day regimen offers a disappointing therapeutic gain of only 3% compared with that of seven-day triple therapy. A different combination of the antibiotics available, consisting of a novel 10-day sequential regimen, has been recently studied (14). This schedule is a simple dual therapy (proton pump inhibitor plus amoxycillin) given for the first five days followed by a triple therapy (proton pump inhibitor, clarithromycin and tinidazole) for the remaining five days. This sequential regimen was proven to be highly successful in a very large, multicentre study compared with the standard seven-day triple therapy (92% versus 74%, respectively; intention-to-treat [ITT] analysis) (15).

It has been found that *H pylori* bacterial density in gastric mucosa is a factor involved in the antibiotic therapy outcome. Indeed, some studies have found that a high bacterial load is associated with a low eradication rate following both standard seven-day triple therapy and 14-day course of bismuth salts, tetracycline and metronidazole (16,17). To our knowledge, no data are available about the role of bacterial density on the efficacy of both 10-day triple therapy and a 10-day sequential regimen. The present study aimed to compare the efficacy of the 10-day sequential regimen with that of 10-day triple therapy; to further test whether the longer 10-day triple therapy was able to increase the eradication rate compared with the standard seven-day regimen; and to evaluate the role of bacterial load on therapeutic outcome.

PATIENTS AND METHODS

Patients

This was a prospective, parallel, open-label, two-centre, randomized study. The study population consisted of patients with dyspepsia – defined as pain or discomfort centred in the upper abdomen – who were referred by primary care physicians for upper endoscopy.

Consenting patients were enrolled if they were infected with *H pylori*. Patients enrolled in the present study had not been enrolled in other studies and had not been previously treated for *H pylori* infection. Patients were excluded if they were taking proton pump inhibitors, H_2-receptor antagonists or antibiotics in the four weeks preceding the study. Pregnant women, patients with known antibiotic allergy, and those with hepatic impairment or kidney failure were not enrolled. All participants gave written informed consent.

H pylori assessment

At entry, all patients underwent endoscopy with biopsies for histology (two samples from the antrum and two samples from the corpus) and a rapid urease test (one sample from the antrum) (CP-test, Italy). Patients were considered *H pylori*-positive if both tests were positive. Biopsy specimens were histologically assessed for the presence of *H pylori* (hematoxylin and eosin stain) and to assess bacterial density (Giemsa staining), as previously reported (18,19). Briefly, the following semiquantitative grading was used: mild (focal presence of a small amount of bacteria); moderate (intermediate amount between mild and marked); and marked

(diffuse presence of a large amount of bacteria). For the purposes of the present study, patients with peptic ulcer at endoscopy, defined as a mucosal ulceration 5 mm or greater in diameter in the stomach or duodenum, as well as those with a documented history of peptic ulcer were not enrolled. Bacterial eradication was checked four to six weeks after treatment completion by using a ^{13}C-urea breath test (Infai, Sofar, Italy). Citric acid (1.5 g) as a test meal and ^{13}C-urea (75 mg) as a water solution was given to the patients after collection of a baseline sample, obtained by blowing through a disposable plastic straw into a 20 mL container; an additional breath sample was collected 30 min later. The breath samples were considered positive if there was a greater than five per 1000 of $^{13}CO_2$ difference over baseline, according to the manufacturer's recommendations.

Therapy regimens

In each centre, patients were randomly assigned using a computer-generated list to one of the following treatments:

1. A seven-day triple therapy comprising esomeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1 g, all given twice daily;

2. A 10-day triple therapy comprising esomeprazole 20 mg, clarithromycin 500 mg and amoxicillin 1 g, all given twice daily; or

3. A 10-day sequential regimen comprising esomeprazole 20 mg daily plus amoxicillin 1 g for the first five days, both given twice daily, followed by esomeprazole 20 mg, clarithromycin 500 mg and tinidazole 500 mg for the remaining five days, all given twice daily.

For each therapy regimen, the proton pump inhibitor was prescribed before breakfast and supper, whereas all antibiotics were given after these meals. Patients were asked to return at the end of the treatment to assess the compliance with therapy and to estimate the incidence of side effects. Compliance was defined as consumption of greater than 90% of the prescribed drugs and was determined by pill counts at the follow-up visit. Side effects were evaluated using a structured questionnaire by personal interview.

Statistical analysis

The sample size was a priori calculated based on available data in the literature. By hypothesizing a 95% eradication rate for the sequential regimen (18) and 80% for either 10-day or seven-day triple therapy (12), it was calculated that at least 68 patients per treatment arm were needed to find a statistically significant difference with a level of P<0.05 and a power of 0.85. The eradication rates and their 95% CIs at both ITT and per protocol (PP) analyses were calculated for each treatment regimen. For all other variables, χ^2, Fisher's exact test and Student's *t* test were used as appropriate, and P<0.05 was considered significant. The difference between the proportions eradicated using the three treatments was estimated for each centre. Before pooling those estimates, a Fisher's exact test was applied to investigate heterogeneity between the differences.

RESULTS

Eradication rates

Two hundred thirteen consecutive dyspeptic patients were enrolled in the study. As shown in Table 1, the three patient groups did not differ in age, sex, gastritis distribution and bacterial density in gastric mucosa. Overall, six patients (two patients

TABLE 1
Demographic and clinical characteristics of patients at entry into each treatment group

Patient characteristics (n)	Seven-day triple therapy	10-day triple therapy	10-day sequential therapy
Number of patients	70	71	72
Sex (male/female)	34/36	33/38	32/40
Age, mean ± SD (years)	54±12	53±16	55±14
Antral gastritis	59	59	61
Pangastritis	11	12	11
Intestinal metaplasia	13	13	15
Bacterial density			
Low	20	23	25
Moderate	44	40	39
Marked	6	8	8

TABLE 2
Eradication rates both at intention-to-treat (ITT) and per protocol (PP) analyses

Analysis	Seven-day triple therapy	10-day triple therapy	10-day sequential therapy
ITT (%)*	53/70 (75.7)	58/71 (81.7)	68/72 (94.4)
95% CI	66 to 86	73 to 91	89 to 100
PP (%)†	53/68 (77.9)	58/69 (84.1)	68/70 (97.1)
95% CI	68 to 88	75 to 93	93 to 100

Ten-day sequential versus seven-day triple therapy: P=0.002; 10-day sequential versus 10-day triple therapy: P=0.02; Seven-day triple versus 10-day triple therapy: P=0.6; †10-day sequential versus seven-day triple therapy: P=0.004; 10-day sequential versus 10-day triple therapy: P=0.034; Seven-day triple versus 10-day triple therapy: P=0.6

in each treatment group) stopped the treatment within three days, and they did not undergo ^{13}C-urea breath testing. Therefore, the final PP population consisted of 207 patients. *H pylori* infection was cured in 53 patients treated with seven-day triple therapy, in 58 of those receiving 10-day triple therapy and in 68 treated with the 10-day sequential regimen. By ITT analysis, no significant difference emerged in eradication rates between the two participating centres for each treatment schedule. In detail, *H pylori* infection was successfully cured in 77.9% and 75.7%, in 84.1% and 81.7%, and in 97.1% and 94.4% following seven-day triple therapy, 10-day triple therapy and 10-day sequential regimen, at both ITT and PP analyses, respectively. As shown in Table 2, the eradication rates achieved by the sequential regimen were significantly higher than both seven-day and 10-day triple therapies, both at ITT and PP analyses. Although the 10-day regimen tended to give better results when compared with seven-day therapy, no statistically significant difference in the eradication rate was found. In the patient group treated with seven-day triple therapy, the *H pylori* eradication rate was significantly lower in patients with a high (moderate or marked) bacterial density compared with those with a low (mild) bacterial load in the stomach (70.8% versus 95%; P=0.02). Of interest, such a phenomenon was not similarly evident for 10-day triple therapy; the trend was not statistically significant (80.9% versus 90.9%; P=0.2). With the sequential regimen, the trend was also not significant (95.6% versus 100%; P=0.4).

Compliance and side effects
Compliance with the therapy was good (greater than 95% of prescribed drugs) in all but six patients, who had stopped the treatment early because of side effects. Seven patients (10%) treated with seven-day triple therapy complained of side effects (two with diarrhea, two with abdominal pain, one with urticaria and one with glossitis), and two of them interrupted treatment. Nine patients (12.7%) receiving 10-day triple therapy reported side effects (two with abdominal pain, three with diarrhea, two with glossitis, nausea/vomiting in one and pruritus in one), and two of them stopped treatment. Eight patients (11.1%) receiving the 10-day sequential regimen complained of side effects (three with diarrhea, three with abdominal pain, one with glossitis and one with

nausea/vomiting); two of the eight patients interrupted treatment. No statistically significant difference in the incidence of side effects emerged among the three treatment regimens. All side effects were self-limiting after therapy ended.

DISCUSSION

Triple therapies endorsed by either Canadian or European guidelines are currently the most preferred first-line therapy regimens in clinical practice worldwide (2,20). For instance, these therapeutic approaches are used by 85%, 84% and 67% of primary-care physicians in Italy, Israel and the United States, respectively (8-10). However, the *H pylori* eradication rates following triple therapy are decreasing substantially in several countries. Indeed, an unacceptable (less than 80%) success rate has been consistently found in several European and Asian countries as well as in the United States and Canada (21-29), with an eradication rate as low as 25% reported in a recent study (30). Moreover, bacterial eradication following a failed initial standard triple therapy is notoriously difficult to achieve; this further questions the suitability of such a therapy regimen (31). An overall disappointing cure rate after seven-day triple therapy has been further confirmed in the present study, especially in those patients harbouring a high bacterial density. Therefore, continued searching for novel therapeutic approaches to cure *H pylori* is needed, the best first-line treatment being also regarded as the best 'rescue' therapy for such a frequent, worldwide infection (31). Unfortunately, the rational, simple attempt to increase the duration of triple therapy to beyond seven days has been disappointing, and the results of the present investigation are in agreement with those of other studies (13,32). However, our data found that the efficacy of the prolonged triple therapy regimen did not seem to be affected by the bacterial load as much as seven-day therapy was, although neither the relatively small sample size nor the semi-quantitative method used allows us to draw definitive conclusions.

Ideally, a first-line treatment for *H pylori* should be highly effective (greater than 90% eradication rate), safe, short and inexpensive. To find such a treatment, new therapeutic combinations have been pioneered in the past five years. A seven-day quadruple regimen, including a proton pump inhibitor plus bismuth salts, tetracycline and metronidazole, has been used as a first-line regimen in some studies. However, a meta-analysis failed to find a significant difference in the success rate between seven-day quadruple and standard triple therapy (33). Recently, high eradication rates (greater than 90%) were

achieved following a 14-day quadruple regimen in a pilot study (34), but side effects were experienced by as many as 49% of patients, so that its use in primary clinical practice has been questioned (35). New levofloxacin-based triple therapies achieving high *H pylori* eradication rates have been also proposed (36). However, levofloxacin is quite expensive, so this regimen is presumably suitable as a retreatment option in patients with eradication failure (37,38). High-dose lactoferrin supplementation to standard seven-day triple therapy has been found to significantly increase the infection cure rate in one pilot study (39) but not in another (40). Therefore, these data deserve to be confirmed in further studies.

The 10-day sequential regimen has been validated in a very large number of patients enrolled in several studies performed in Italy in the past few years (14,15,41-44). In detail, the sequential regimen has been shown to be highly effective (93.5% eradication rate in 1208 patients; 95% CI 92 to 95), safe, relatively short and cost-effective when compared with other strategies (43,45). In addition, we found previously that this sequential regimen was significantly more effective than seven-day triple therapy even in patients harbouring either clarithromycin- (79% versus 27%, respectively) or metronidazole-resistant strains (91% versus 67%, respectively) (14). The importance of such a sequential regimen has also been recently recognized by others (13,46).

The rationale of the sequential regimen is in the administration of an initial dual therapy with amoxycillin, which is able to eradicate *H pylori* in some patients and to reduce the bacterial load in all the remaining cases, without inducing bacterial resistance (15). Of interest, regimens containing amoxycillin may prevent the selection of secondary clarithromycin resistance (47). Furthermore, reducing the bacterial load significantly improves the response to the immediately subsequent short course of triple therapy, as clearly shown in another study (16). In addition, the sequential regimen exploits the efficacy of three different antibiotics, instead of the two in the triple standard therapy.

It has been argued that the higher effectiveness of the sequential regimen compared with seven-day triple therapy could be related to its duration, rather than to the sequential administration of drugs (48). In the present study, we found that the 10-day sequential regimen achieved very high eradication rates that were distinctly higher even when compared

with those of 10-day triple therapy. Therefore, it could be suggested that the higher successful cure rate achieved by the sequential regimen depends on the drug combination rather than on the length of the therapy (32).

We also found, for the first time, that the sequential regimen achieved similar eradication rates in patients with either high or low bacterial density. This was definitely different from what was observed with seven-day triple therapy. Such a finding adds further information to recent observations that the efficacy of the sequential regimen does not seem to be affected by factors that have been shown to drastically influence triple therapy success, such as presence of CagA-negative strains, antibiotic bacterial resistance, smoking habits and nonulcer dyspepsia (42). Of note, it was previously found that a 10-day levofloxacin-amoxicillin-based triple therapy achieved an acceptable eradication rate in patients who failed two or more therapeutic attempts (38). Recently, by using such a therapy regimen as retreatment, we were able to cure *H pylori* infection in 92% of patients harbouring both clarithromycin- and metronidazole-resistant strains (49). Therefore, such an approach could be also considered in the event of sequential regimen failure.

As far as compliance and side effects are concerned, we found that compliance was equally good for all three therapeutic regimens, given that therapy was stopped in only 2.8% of the enrolled patients. Moreover, in agreement with results from other studies (14,33), the overall incidence of side effects was acceptably low for each therapy regimen, without a significant difference among the three schedules, and all side effects were self-limiting after the therapy ended.

CONCLUSIONS

Standard seven-day triple therapy is continuing to give disappointing eradication rates, especially in patients harbouring a high bacterial load. Ten-day triple therapy failed to significantly increase the *H pylori* eradication rate achieved by the standard seven-day regimen. This clearly shows that triple therapy failure is due to an intrinsic weakness of such schedules rather than to duration of therapy. On the contrary, the 10-day sequential regimen was significantly more effective than both triple regimens, irrespective of bacterial density in the stomach. Therefore, the use of such an effective sequential regimen could be considered as first-line therapy in primary clinical practice.

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