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Sequential Therapy for First-Line *Helicobacter pylori* Eradication: 10- or 14-Day Regimen?

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ABSTRACT

Background & Aim: Standard 10-day sequential therapy is advised as first-line therapy for *Helicobacter pylori* (*H. pylori*) eradication by current Italian guidelines. Some data suggested that a 14-day regimen may achieve higher eradication rates. This study compared the efficacy of sequential therapy administered for either 10- or 14-days.

Methods: This prospective, multicenter, open-label study enrolled patients with *H. pylori* infection without previous treatment. Patients were receiving a sequential therapy for either 10 or 14 days with esomeprazole 40 mg and amoxicillin 1 g (5 or 7 days) followed by esomeprazole 40 mg, clarithromycin 500 mg and tinidazole 500 mg (5 or 7 days), all given twice daily. Bacterial eradication was checked using ^{13}C-urea breath test. Eradication cure rates were calculated at both Intention-to-treat (ITT) and per-protocol (PP) analyses.

Results: A total of 291 patients were enrolled, including 146 patients in 10-day and 145 in the 14-day regimen. The eradication rates were 87% (95% CI = 81.5-92.4) and 90.3% (95% CI = 85.5-95.1) at ITT analysis with the 10- and 14-day regimen, respectively, and 92.7% (95% CI = 88.3-97) and 97% (95% CI = 94.2-99.9) at PP analysis (p =0.37). Among patients, who earlier had interrupted therapy, bacterial eradication was achieved in 8 out of 9 who completed the first therapy phase and performed at least ≥3 days of triple therapy in the second phase.

Conclusion: This study found that both 10- and 14-day sequential therapies achieved a high eradication rate for first-line *H. pylori* therapy in clinical practice.

Key words: *Helicobacter pylori* – sequential therapy – eradication.

Abbrevations: CI: confidence intervals; ITT: intention to treat; PP: per protocol; SD: standard deviation; UBT: urea breath test.

INTRODUCTION

Despite the fact that its prevalence is decreasing, *H. pylori* is still a widespread infection causing benign and malignant diseases [1]. Unfortunately, no therapy regimen achieves bacterial eradication in all patients, the treatment for the infection remaining challenging [2]. Current Italian guidelines suggested the use of either 14-day triple therapy or 10-day sequential therapy for first-line therapy [3]. However, data of different Italian studies showed that prolonged triple therapy achieved a success rate of only 77% in 619 patients, even when a high-dose proton pump inhibitor was used [4-6]. On the contrary, a high success rate was obtained following 10-day sequential therapy in Italy [7], as well as in several other countries [8]. However, a recent network meta-analysis showed that sequential therapy for 14 days achieves the highest effectiveness as compared to all the other regimens [9]. Although helpful, data of a network meta-analysis cannot overcome the need to test a specific therapy in a particular region before selecting the best available treatment [10]. Therefore, we designed a prospective study to compare the efficacy of sequential therapy administered for either 10- or 14-days regimen in clinical practice.

PATIENTS AND METHODS

Patients

This was a prospective, multicenter, open-label study enrolling adult patients referred for dyspeptic symptoms in the Endoscopy Units of the seven involved centres. All patients

with *H. pylori* diagnosed at the histological examination of antral and gastric body biopsies, never previously treated for the infection, were invited to participate. Patients with known allergy to penicillin or macrolides were excluded, as well as those with relevant diseases. Bacterial culture with antibiotic susceptibility testing on agar was performed in a single centre (Bologna), by using commercial selective medium Pylori Agar as routinely performed [7]. Patients received a sequential therapy for either 10 or 14 days with esomeprazole 40 mg and amoxicillin 1 g (5 or 7 days) followed by esomeprazole 40 mg, clarithromycin 500 mg and tinidazole 500 mg (5 or 7 days). All drugs were given twice daily. A pre-fixed, computer generated list was used for randomization in each centre. At the end of therapy, the self-reported compliance and side-effects were assessed by a personal questionnaire. Following 6-8 weeks, standard ^{13}C-urea breath test (UBT) was performed to evaluate bacterial eradication rates. The study was performed according to the guidelines for Good Clinical Practice and the Declaration of Helsinki (1996 version, amended October 2000). Since no experimental drugs were administered, no adjunctive costs or procedures for the patients were required, no identification of patients was allowed, and no funds were received, our Investigational Review Board waived formal review and approval, deeming the study to be an extension of existing clinical practice.

Statistical analysis

The sample size was calculated as for a 'non-inferiority' study. By expecting a 90% eradication rate following the 10-day regimen and a 95% with the 14-day therapy, with a power of 90% and significance level of 5%, a total of 236 patients (118 per arm) should have been enrolled. When considering a 10% drop-out rate, data of 260 patients (130 per arm) needed to be included. The eradication rates with 95% confidence intervals (CI) were calculated at both 'intention-to-treat' (ITT) (all patients who accepted to participate) and at 'per-protocol' (PP) (all patients who effectively performed therapy and UBT control) analyses. Patients who completed at least the first phase of therapy (i.e. 5 or 7 day with dual therapy) underwent UBT control, whilst those who performed a shorter therapy were considered as drop-outs. Before pooling data, a statistical comparison was performed among data from different centres to rule out heterogeneity. The Chi-squared test and the Fisher's exact test were used as appropriate, and a p level less than 0.05 was considered statistically significant.

RESULTS

The study enrolled 291 consecutive patients (M/F: 122/169; mean age: 49.3 ± 12.6 years). At endoscopy, 8 patients had duodenal ulcer, 3 gastric ulcer, 24 erosions (gastric or duodenal), whilst no endoscopic lesions were detected in the remaining 252 patients (Table I). Overall, 146 patients received the 10-day therapy and 145 the 14-day regimen, but 9 and 10 patients, respectively, were lost at follow-up. Following the 10-day regimen the infection was cured in 127 patients accounting for 87% (95% CI = 81.5-92.4) eradication rate at ITT and 92.7% (95% CI = 88.3-97) eradication rate at PP analyses. Following the 14-day regimen, the infection was cured in 131 patients accounting for 90.3% (95% CI = 85.5-95.1) eradication rate at ITT and 97% (95% CI = 94.2-99.9) eradication rate at PP analyses. Although the 14-day regimen achieved a +3.3% (at

Table I. Demographic and clinical characteristics of enrolled patients

	10-day therapy	14-day therapy	P value
Number of patients	146	145	-
Age (mean ±SD) (years)	48.2 ± 13.2	49.9 ± 11.6	0.48
Sex (male/female)	63/83	59/86	0.29
Upper endoscopy			0.10
- Duodenal ulcer	4	5	
- Gastric ulcer	2	1	
- Gastroduodenal erosions	11	13	
- No lesions	129	136	

Table II. Cure rate at intention-to-treat (ITT) and per-protocol (PP) analyses in different centres

Center	Therapy regimen	Enrolled	Drop-out	Not cured	ITT (%)	PP (%)
Bari	10	26	3	1	22/26 (84.6)	22/23 (95.6)
	14	28	1	0	27/28 (96.4)	27/27 (100)
Bologna	10	40	2	2	36/40 (90)	36/38 (94.7)
	14	40	2	2	36/40 (90)	36/38 (94.7)
Como	10	7	1	0	6/7 (85.7)	6/6 (100)
	14	6	1	0	5/6 (83.3)	5/5 (100)
Foggia	10	20	1	3	16/20 (80)	16/19 (84.2)
	14	20	1	0	19/20 (95)	19/19 (100)
Palermo	10	11	0	1	10/11 (90.9)	10/11 (90.9)
	14	10	0	1	9/10 (90)	9/10 (90)
Roma	10	32	1	2	29/32 (90.6)	29/31 (93.5)
	14	31	2	1	28/31 (90.3)	28/29 (96.6)
Trieste	10	10	1	1	8/10 (80)	8/9 (88.9)
	14	10	3	0	7/10 (70)	7/7 (100)
Total	10	142	9	10	127/146 (87)	127/137 (92.7)
	14	144	10	4	131/145 (90.3)	131/135 (97)

ITT analysis) and +4.3% (at PP) cure rate as compared to the 10-day regimen, no statistically significant difference emerged among groups (Table II). Data of eradication rates according to the pattern of antibiotic resistance are provided in Table III.

A total of 31 (21.2%) patients in the 10-day therapy complained of side-effects, causing early therapy interruption in 3 cases. In the 14-day regimen, 39 (26.9%) patients reported side-effects, and 8 failed to complete therapy. Data of patients who earlier interrupted therapy were provided in Table IV. As shown, bacterial eradication was achieved in 8 out of 9 patients who completed the first therapy phase and performed at least ≥3 days of triple therapy in the second phase. Overall, the most frequently complained side-effects without the need to withdraw therapy were: nausea (22 cases), bad taste (16 cases), abdominal pain (15 cases) and mild diarrhoea (6 cases).

Table III. Eradication according to the antibiotic resistance pattern peformed in single centre (Bologna)

Resistance pattern	10-day therapy (N = 22)	14-day therapy (N = 32)	Total
Cla-S Met-S	12/12	13/13 (1 drop out)	25/25 (100%)
Cla-R Met-S	2 drop-out	4/4 (1 drop out)	4/4 (100%)
Cla-S Met-R	3/3	8/8	11/11 (100%)
Cla-R Met-R	5/5	3/5	8/10 (80%)

Cla: clarithromycin; Met: metronidazole; S: susceptible; R: resistant.

Table IV. Outcome in patients who earlier interrupted therapy due to side-effects

Therapy assigned	Days of herapy	Outcome	Side-effects
14-day	7+6	Cured	Nausea
14-day	7+6	Cured	Abdominal pain
14-day	7+5	Cured	Nausea
14-day	7+5	Cured	Abdominal pain
14-day	7+4	Cured	Vomiting
14-day	7+3	Cured	Abdominal pain
14-day	7+1	Cured	Vomiting
14-day	3+0	Drop-out	Urticaria
10-day	5+3	Cured	Diarrhoea
10-day	5+3	Not cured	Nausea
10-day	2+0	Drop-out	Vomiting

DISCUSSION

Curing *H. pylori* infection still remains a challenge in clinical practice. The 10-day sequential therapy, suggested as first-line therapy in the current Italian guidelines [3], has been proven to be effective in several countries, achieving eradication rates as high as 91.1%-93.7% in Italy [7, 11], 92.5-95% in Turkey [12,13], 94.2% in Slovenia [14], 90% in Portugal [15], 90% in Belgium [16], 95.9% in Israel [17], 94% in Thailand [18], 91.9% in Taiwan [19], 90.3% in Singapore [20], and 88.6% in the United Arab Emirates [21]. In detail, the 10-day sequential therapy was found to be equally effective – but cheaper – than quadruple therapy with Pylera (each pill containing 140 mg bismuth subcitrate potassium, 125 mg metronidazole, and 125 mg tetracycline) for first-line therapy [22, 23]. However, a recent network meta-analysis showed that the 14-day sequential therapy achieved a higher eradication rate as compared to all the other first-line regimens [8]. Therefore, we performed a 'head to head' comparison between sequential regimens administered for either 10 or 14 days in clinical practice. Overall, data found that both therapies achieved high *H. pylori* eradication rates (87%-90.3% at ITT and 92.7%-97% at PP), without a statistically significant difference between treatments. In detail, the longer regimen tended to increase (+3%, +4%) the cure rate as compared to the standard 10-day therapy, but the therapeutic gain was not statistically significant, and the cost was increased (42.84 vs. 30.6 Euros in Italy). Therefore, it would appear that prolonging the sequential therapy is not cost-effective, at least in Italy. However, testing the efficacy of the 14-day sequential therapy could be useful in those areas where the standard 10-day regimen was proven to be not highly effective [4]. The high efficacy of both sequential regimens is noteworthy when considering the elevated levels of primary resistance towards both clarithromycin and metronidazole in *H. pylori* isolates found in Italy [24]. We found that high eradication rates were achieved when bacterial strains harboured a single resistance towards either clarithromycin or metronidazole, with an 80% cure rate even in those strains with dual resistance. A recent study found that bacterial resistance becomes relevant *in vivo* only when clarithromycin-resistant and metronidazole-resistant strains have high MIC values for at least one of these antibiotics [25].

In the past, several attempts were performed to further improve the efficacy of standard 10-day sequential therapy, by increasing duration or substituting clarithromycin with either levofloxacin or tetracycline [26]. However, no modified therapy schedule was found to be consistently superior to the standard 10-day regimen. In detail, a levofloxacin-based sequential therapy achieved high eradication rate in an Italian study where primary levofloxacin resistance was very low [27], but distinctly lower cure rates were achieved in several studies in other countries [25].

Noteworthy, by considering patients who early interrupted therapy in the present study, we observed that the infection was cured in all cases that completed the first 7 days dual therapy and at least 3 days of successive triple therapy. Although preliminary, these data suggest that the efficacy of a modified 'seven plus three'-day sequential therapy could be tested in a pilot study.

CONCLUSION

Our study found that both the 10- and 14-day sequential therapies achieved a high eradication rate as first-line *H. pylori* therapy in clinical practice, with no statistical difference between the two treatments.

Conflicts of interest: No conflicts of interest.

Authors' contributions: A.Z. and D.V. conceived the study. A.Z. and G.F. analysed data and prepared the manuscript. A.Z., G.F., G.S.,

P.P. V.de F. R.V., F.U, F.M, G.M., A.A and D.V. enrolled patients and critically reviewed the manuscript.

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