First-line therapies for *H. pylori* infection in Italy: a pooled-data analysis

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Abstract

Background: **Curing H. pylori infection remains challenging, and the use of most effective first-line therapy represents a therapeutic cornerstone. To monitor the efficacy of first-line therapies in Italy, we designed a systematic review with pooled-data analysis of data published in the last 15 years.**

Methods: **The search was focused on standard regimens and adult patients. Studies that included modified therapy regimens, pediatric patients, case series with less than 5 patients, and those in language other than English were excluded.**

Results: **A total of 40 studies, with 74 therapeutic arms and 13,539 patients were evaluated. Among the 14-day triple therapies, the combination with proton pump inhibitor (PPI), clarithromycin and amoxicillin achieved the highest (77.9%) success rate, whilst the lowest success rate (62.7%) was observed following the 14-day PPI, clarithromycin and tinidazole regimen. The overall efficacy of triple therapies significantly decreased from 75.7% to 72.1% in the last decade. Sequential (88.3% on 3431 patients), concomitant (88.8% on 376 patients), and the bismuth-based quadruple therapy with three-in-one capsule, containing bismuth subcitrate potassium (140 mg), metronidazole (125 mg), tetracycline (125 mg) (90.4% on 999 patients) achieved similarly high eradication rates, but data on concomitant are still limited. The bismuth-based was associated with the higher (38.7%) incidence of side-effects.**

Conclusions: **Data found that all triple therapies, irrespective of drug combination and therapy duration, should be abandoned in Italy due to their unacceptable low success rates. Monitoring the efficacy of standard first-line therapies in other countries could be clinically useful for both patients and clinicians.** (Acta gastroenterol. belg., **2022,** 85, **295-299**).

Keywords: Helicobacter pylor, first-line therapy, treatment, antibiotic, therapy regimens.

Introduction

H. pylori infection plays a pivotal role in the pathogenesis of different benign (peptic ulcer disease, non-ulcer-dyspepsia) and malignant (gastric MALT-lymphoma and carcinoma) gastroduodenal diseases through a multistep process in which chronic active gastritis is the first step (1-3). Some extra-digestive disorders (idiopathic thrombocytopenic purpura, idiopathic iron deficiency anaemia) have been also associated with this infection (4,5). Following forty years, the ideal treatment for *H. pylori* is still lacking, and increasingly more complex treatments were introduced, from the initial dual therapies to the actual quadruple regimens (6-8). Despite the use of these drug combinations, *H. pylori* eradication still fails in a definite quote of cases, so that 10%-20% of patients need of two or more treatments. Indeed, curing the infection following first-line therapy failure is challenging, largely due to secondary bacterial resistance towards the available antibiotics (9,10). Therefore, the use of more effective first-line therapies represents a cornerstone in the therapeutic management of *H. pylori* infection. Based on these observations, it is clinically useful to monitor the efficacy of the available therapy regimens in different areas. We therefore designed a systematic review with pooled-data analysis of data on standard regimens used as first-line therapy in the last 15 years in Italy.

Materials and Methods

Literature review

Computer-assisted search was performed on PubMed for studies published from January 01, 2005 through April 30, 2021, by using the exploded medical subject heading terms '*Helicobacter pylori* therapy AND Italy'. The search was limited on first-line treatments, including triple therapies, bismuth-free (sequential, concomitant) and bismuth-based (classic regimen and three-in-one capsule, containing bismuth subcitrate potassium (140 mg), metronidazole (125 mg), and tetracycline (125 mg), that is Pylera® or Tryplera in Belgium) quadruple therapies (Table 1). Only studies in which these therapies were administered to adult patients for the standard (or longer) duration were considered, and the eradication rates were accordingly calculated. Standard therapy length was ≥7 days for triple regimens and ≥10 days for bismuth-free and bismuth-based quadruple therapies. Those studies including modified drug combinations (i.e., doxycycline, ciprofloxacin, moxifloxacin, azithromycin, etc.) were excluded. Following abstract evaluation, the full text of all relevant studies was retrieved, and manual searches of reference lists from identified relevant articles were performed to identify any additional studies that might have been missed. When more than one publication from the same investigator or group was available, only the most updated version including the entire sample size was considered. Studies that included

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Table 1. — **First line therapy regimens for H. pylori eradication**

Therapy	Schedule	Duration
Triple	PPI standard dose, clarithromycin 500 mg, and tinidazole 500 mg or amoxicillin 1 g, all b.i.d	7-10-14 days
Concomitant	PPI standard dose, amoxicillin 1 g, clarithromycin 500 mg, and tinidazole 500 mg, all b.i.d	10-14 days
Sequential	PPI standard dose and amoxycillin 1 g, all b.i.d for 5 days followed by PPI standard dose, clarithromycin 500 mg, and tinidazole 500 mg, all b.i.d for 5 days	10 days
Quadruple with Pylera®* Classic quadruple	PPI standard dose bid and Pylera 3 tablets q.i.d. PPI standard dose, tetracycline 500 mg b.i.d, metronidazole 250 qid, bismuth subcitrate salts 240 b.i.d.	10-14 days 14 days

*Three-in-one capsule containing bismuth subcitrate potassium (140 mg), metronidazole (125 mg), and tetracycline (125 mg).

pediatric patients, case series with less than 5 patients, and those in language other than English were excluded. When possible, the overall success rate achieved in studies published in the last 10 years was compared to that of those performed until to the 2010. Data on the reported side-effects following the different therapies were computed

Statistical analysis

Eradication rates and their 95% confidence intervals at both 'Intention-to-Treat' (ITT) analyses were computed for each subgroup. Comparison of cure rates was performed by using Chi-square test. Differences were considered significant at 5% probability level. Analyses were performed by using Statsoft 7.1 program for Windows 10.

Results

Descriptive analysis

A total of 683 citations were found on PubMed. Following title and abstracts review, 40 studies with a total of 74 therapeutic arms and 13,539 patients met inclusions criteria (11-50), whilst the others were ultimately excluded for different reasons (Figure 1). Overall, there were 23 studies (41 arms) on triple therapies (11-33), 10 (18 arms) on sequential therapy (34-43), 3 (4 arms) on concomitant therapy (37-38, 44), 2 (3 arms) on standard bismuth-based quadruple therapy (45,46), and 7 (8 arms) studies on the bismuth-based three-in-one capsule quadruple therapy (36,37, 44, 46-49). The distribution of contributing centers was provided in Figure 2.

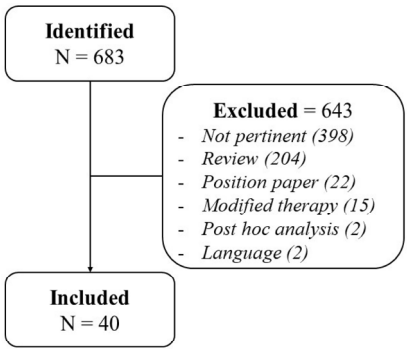

Figure 1. — The flow-chart of literature review.

Figure 2. — Number of studies and distribution of participating centres.

Eradication rates

Triple therapies

The combination with PPI, clarithromycin and amoxicillin cured the infection in 4193 out of 5750 treated patients (72.9%; 95% CI = 71.7-74), in 116 out of 149 (77.8%; 95% CI =71.1-84.5), and in 459 out of 589 (77.9%; 95% CI = 74.5-81.2) when administered for 7-, 10- and 14-day, respectively. The regimen with PPI, clarithromycin and tinidazole achieved an eradication rate of 76.1% (819/1076; 95% CI =72.3-78.6), 76.9% (40/52; 95% CI =65.4-88.3), and 62.7% (113/180; 95% CI =55.7-69.8) when administered for 7-, 10- and 14-day, respectively. Therapy with PPI, amoxicillin and tinidazole achieved an eradication rate of 67.2% (39/58; 95% CI =55.1-79.3), and 70.3% (19/27; 95% CI =53.1-87.5) when administered for 7- or 10-day, respectively. The cumulative success rate following triple therapies significantly (P <0.0001) decreased from 75.7% (2367/3126, 95% CI: 74.2-77.2) achieved until to 2010 to 72.1% (3431/4755, 95% CI: 70.8-73.4) in studies performed more recently.

Sequential therapy

The standard 10-day sequential therapy was used 10 studies (34-43), with an overall cure rate of 88.3% (3031/3431, 95% CI: 87.2-89.4). In a single study (38), a 14-day regimen were tested, achieving an eradication rate of 90.3% (131/145, 95% CI: 85.5-95.1). By taking into studies published before 2010 and those after, data found that the success rates were 87% (465/534, 95% CI: 84.2-89.9) and 88.6% (2697/3042, 95% CI: 87.5-89.7), respectively, without a statistically significant difference.

Concomitant therapy

Concomitant therapy was tested in only three studies, and the infection was overall achieved in 334 (88.8%; 95% CI =85.6-92) out of 376 patients (37-38, 44). In detail, the eradication rate was 85.9% (95% CI: 80.5-91.2) on 163 patients following a 10-day and 91% (95% CI:87.2-94.9) on 213 patients following the 14-day regimen, without significant difference.

Classic quadruple therapy

The classic bismuth-based regimen was administered for 10 days in two studies (45,46) and for 14 days in a single study (45), with an eradication rate of 92.1% (280/304, 95% CI: 89-95.1) and 91.5% (185/202, 95% CI: 87.7-95.4), respectively.

Bismuth-based three-in-one capsule quadruple therapy

The bismuth-based three-in-one capsule quadruple therapy was used for 10 days in 7 studies (36,37, 44, 47-50) and for 14 days in a single study (44), with eradication rate of 90.1% (719/798, 95% CI:88-92.1) and 91.5% (184/201, 95% CI: 87.7-95.3), respectively, without significant difference. Therefore, an overall eradication rate of 90.4% (903/999, 95% CI: 88.5-92.2) was observed by using these bismuth-based therapies. Since this drug formulation was introduced only recently, studies testing its efficacy were published between 2017 and 2019.

Side-Effects

Data on side-effects following triple therapies were reported in 13 studies, and a total of 457 (14.2%, 95% CI: 13-15.4) out of 3213 patients complained of at least one of them. Seven studies computed the incidence of side-effects following sequential therapy, and the rate was 19.9% (95% CI: 17.8-22; 285 out of 1428). During concomitant therapy (3 studies), 92 (24.4%, 95% CI: 20.1-28.8) out of 376 patients experienced side-effects. With bismuth-based regimens, side-effects occurred in 83 (16.4%, 95% CI: 13.1-19.6) out of 506 patients and in 307 (38.7%, 95% CI: 35.3-42.1) out of 793 patients following the classic and bismuth-based three-in-one capsule quadruple therapies, respectively. The mostly reported side-effects included abdominal pain, mild diarrhoea, nausea, altered taste, vomiting, headache and dizziness.

Discussion

Curing H. pylori infection remains challenging for clinicians. When considering that bacterial eradication following a therapy failure is increasingly more difficult to achieve, using of the best first-line therapy could represent the optimal therapeutic strategy. Therefore, to monitor the efficacy of different standard first-line therapies during time is useful for H. pylori infection management. Data of present systematic review provided some clinically relevant information. Unfortunately, all triple therapies achieved disappointingly low success rates, without a substantial difference among standard and longer (14-day) schedules. Moreover, an even significant decrease of efficacy occurred in the more recent studies. Therefore, the use of these simple and tolerated therapies in our country is largely unjustified if not unethical. Likewise, this depends on the increased primary resistance towards clarithromycin (37.8%), metronidazole (33.6%), and double resistance clarithromycin-metronidazole (20.7%) observed on H. pylori isolates in Italy (51).

Data found that the 10-day sequential therapy is the second most studied first-line therapy in Italy, achieving an eradication rate approaching 90%, and prolonging the duration until 14 days failed to significantly increase its efficacy. Of note, the success rate remained stable during years, with a cumulative 89% eradication rate in the last 10 years. Indeed, an acceptable high success rate of sequential therapy even in H. pylori resistant strains was documented (35)..

Overall, the concomitant therapy appeared to be equally successful than sequential therapy. Unfortunately, the available data come from only 3 studies which show that the 14-day therapy achieved a not significant 5% higher cure rate as compared to the 10-day regimen. Therefore, more data are needed to understand the reliability of these results. Both bismuth-based quadruple therapies achieved high (90%-91%) eradication rates. Disappointingly, the incidence of side-effects during this therapy was the highest, almost 40%, that is a value distinctly higher than 25%, 20% and 13% registered with concomitant, sequential and triple therapies, respectively. Of note, the incidence rate of side-effect following the bismuth-based three-in-one capsule quadruple therapy we observed is keeping with the 42% rate calculated in a recent meta-analysis, so that data are consistent (52). This could be a matter for concern when such a therapy is implemented in clinical practice on a large number of patients. Moreover, pharmaceutic cost of this therapy (74.04 € in Italy) is higher than that of both 10-day concomitant (48.8 €) and that of sequential therapy (29.4 €) in Italy (53). Therefore, it could be wise to use the bismuth-based three-in-one capsule quadruple therapy as second or rescue therapy, as recently suggested (54).

The points of strength of this study are the extensive review of all available data on standard first-line therapies produced in Italy in the last 15 years, also providing the trend of success rate in last decade. Moreover, we observed that data were provided by 42 different centres, distributed in all country, so that data are consistent and generalizable. Data provided in our systematic review could be generalized in other countries with a similar pattern of primary resistance towards clarithromycin and metronidazole, such as Belgium (55). On the contrary, a limitation is the study design which prevents a direct comparison among different regimens.

In conclusion, data of this study suggest that sequential, concomitant and bismuth-based quadruple therapy achieve similarly high success rate as first-line therapy, but the latter regimen causes side-effects more frequently than other regimens. All triple therapies, irrespective of drug combination and therapy duration, should be abandoned in Italy due to their unacceptable low success rates. Monitoring the efficacy of standard first-line therapies in other countries could be clinically useful for both patients and clinicians.

Support

None.

Conflicts of interest

All authors have no conflict of interest and have nothing to disclose.

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