**Name of journal:** ***World Journal of*** ***Gastroenterology***

**ESPS Manuscript NO: 28706**

**Manuscript Type: LETTER TO THE EDITOR**

**Role of concomitant therapy for *Helicobacter pylori* eradication: A technical note**

Losurdo G *et al.* Concomitant treatment for *H. pylori*

Giuseppe Losurdo, Floriana Giorgio, Andrea Iannone, Mariabeatrice Principi, Michele Barone, Alfredo Di Leo, Enzo Ierardi

**Giuseppe Losurdo, Andrea Iannone, Floriana Giorgio, Mariabeatrice Principi, Michele Barone, Alfredo Di Leo, Enzo Ierardi.** Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari, 70124 Bari, Italy

**Author contribution**: Losurdo G, Ierardi E and Di Leo A conceived the article; Iannone A, Giorgio F, Principi M and Barone M collected the data; Losurdo G and Ierardi E wrote the article; all Authors read and approved the final version of the manuscript.

**Conflict-of-interest** **statement:** No potential conflicts of interest relevant to this article were reported.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Correspondence to: Enzo Ierardi, Professor,** Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy. [ierardi.enzo@gmail.com](mailto:ierardi.enzo@gmail.com)

**Telephone:** +39-80-5594034

**Fax:** +39-80-5593088

**Received:** July 11, 2016

**Peer-review started:** July 13, 2016

**First decision:** August 19, 2016

**Revised:** August 27, 2016

**Accepted:** September 12, 2016

**Article in press:**

**Published online:**

**Abstract**

We read with interest the recent meta-analysis by Lin *et al* who evaluated the effectiveness of concomitant regimen for *Helicobacter pylori* (*H. pylori*) in Chinese regions. They found that 7-day concomitant regimen is undoubtedly superior to 7-day triple therapy (91.2% *vs* 77.9%, *P* < 0.0001). However, it is a common belief that a triple therapy lasting 7 days should be definitively removed from the clinical practice for its ineffectiveness. Only its prolongation to 14 d may give satisfactory success rate. Thus, the assessment of an old and outdated treatment versus a more recent and successful one does not seem to bring novel and useful information. Moreover, a 7-day duration has not been ascertained for concomitant regimen, as main guidelines recommend a 10-day schedule for this scheme. Therefore, only studies comparing 10-day concomitant versus 14-day triple seem to be appropriate according to current Guidelines and would clarify which regimen is the most suitable worldwide. Additionally, in this meta-analysis concomitant and sequential therapy showed similar performances, despite it is common opinion that sequential is more prone than concomitant therapy to fail when metronidazole resistance occurs, and China is characterized by high rate of resistance to this antibiotic. None of the included studies evaluated *a priori* antibiotic resistances, and the lack of this detail hampers the unveiling of this apparent contradiction. In conclusion, the lack of the evaluation of the quality of included trials as well as their high heterogeneity constitute a burdensome limit to draw solid conclusions in this meta-analysis. On the bases of these considerations and the low number of examined trials, we believe that further studies and the knowledge of antibiotic resistances will support with high quality evidence which is the best regimen and its optimal duration.

**Key words**: *Helicobacter pylori*; Eradication; Sequential; Concomitant; Triple therapy; Antibiotic resistances

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip**: Concomitant therapy is one of the most effective first line regimen for *Helicobacter pylori* eradication. The comparison with other regimens (sequential or triple) in a selected geographical region (China in this case) implies several issues. The low number of included studies, the lack of quality evaluation and the high heterogeneity may undermine the strength of a meta-analysis. Therefore, further studies are needed to prove which is the best first line eradication treatment in China, according to the geographical differences in antibiotic resistances.

Losurdo G, Giorgio F, Iannone A, Principi M, Barone M, Di Leo A, Ierardi E. *World J Gastroenterol* 2016; In press

**TO THE EDITOR**

We read with interest the recent meta-analysis by Lin *et al*[1], who evaluated the effectiveness of concomitant regimen for *Helicobacter pylori* (*H. pylori*) in Chinese regions in a first line context. The choice of deal with this eradication treatment in a selected geographical area is absolutely appropriate, since, as we have already demonstrated[2], a single therapeutic approach is not fitting worldwide. Indeed, geographical variations in antibiotic resistance rates strongly influence the outcome, therefore the most proper regimen should be considered on the basis of the antibiotic resistance pattern in each area.

However, the results of this meta-analysis deserve special considerations. First, three studies compared 7-day concomitant versus 7-day conventional triple therapy, demonstrating that concomitant regimen is significantly superior to 7-day triple therapy (91.2% *vs* 77.9%, *P* < 0.0001). However, it is a common belief that a triple therapy lasting 7 days should be definitively abandoned, due to the disappointingly low success rate. Currently, only the prolongation of triple therapy to 14 d can be advised to overcome this limit[3,4]. Moreover, the outcome of a meta-analysis should be the comparison of two regimens that may have a similar effectiveness; the assessment of an old and outdated treatment versus a more recent and successful one could not bring novel and useful information. The search strategy of this systematic review did not retrieve trials evaluating concomitant versus 14-day triple therapy in China, but only this comparison could state whether concomitant is really more effective than triple therapy. Furthermore, the duration of 7 d for concomitant therapy is not considered optimal, since Guidelines recommend a 10-day regimen[3,5]. Additionally, the comparison between 10-day concomitant and 10-day triple therapy showed a similar success, even if this analysis was based only on one study and this aspect could cause to judge the result questionable.

Another issue involves the comparison of concomitant versus sequential regimen. Herein, it has been demonstrated a similar eradication rate (86.9% and 86% respectively, *P* = 0.69). This finding is in agreement with other meta-analyses[6,7] and previous experiences in Western countries[8,9]. However, it is common opinion that sequential therapy is more prone to fail when metronidazole resistance occurs[10]. Indeed, Georgopoulos *et al*[11] showed that the success rate of sequential regimen decreased from 89.8% to 70%, while a reduction of only 2% occurred for concomitant regimen in the presence of metronidazole resistance. This observation does not seem to agree with the results of this meta-analysis, since China and Far East are considered as high metronidazole resistance areas[2]. Therefore, concomitant therapy would be expected to achieve a higher success rate than sequential therapy. Furthermore, in order to support this consideration, a recent trial in Korea showed eradication rates of 77.8% for concomitant and 70.6% for sequential regimens at intention-to-treat analysis[12]. This controversial aspect could be explained only by the analysis of metronidazole resistance in treated patients. On the other hand, Authors themselves observed that this issue was not investigated in included trials.

Finally, we believe that the lack of quality assessment and the high heterogeneity of included studies constitute a relevant limit to draw solid conclusions in this meta-analysis. Therefore, further studies and the knowledge of antibiotic resistance pattern will support with high quality evidence the assessment of the best regimen and its optimal duration[13-17].

**REFERENCES**

1 **Lin LC**, Hsu TH, Huang KW, Tam KW. Nonbismuth concomitant quadruple therapy for Helicobacter pylori eradication in Chinese regions: A meta-analysis of randomized controlled trials. *World J Gastroenterol* 2016; **22**: 5445-5453 [PMID: 27340362 DOI: 10.3748/wjg.v22.i23.5445]

2 **Ierardi E**, Giorgio F, Losurdo G, Di Leo A, Principi M. How antibiotic resistances could change Helicobacter pylori treatment: A matter of geography? *World J Gastroenterol* 2013; **19**: 8168-8180 [PMID: 24363506 DOI: 10.3748/wjg.v19.i45.8168]

3 **Zagari RM**, Romano M, Ojetti V, Stockbrugger R, Gullini S, Annibale B, Farinati F, Ierardi E, Maconi G, Rugge M, Calabrese C, Di Mario F, Luzza F, Pretolani S, Savio A, Gasbarrini G, Caselli M. Guidelines for the management of Helicobacter pylori infection in Italy: The III Working Group Consensus Report 2015. *Dig Liver Dis* 2015; **47**: 903-912 [PMID: 26253555 DOI: 10.1016/j.dld.2015.06.010]

4 **Losurdo G**, Leandro G, Principi M, Giorgio F, Montenegro L, Sorrentino C, Ierardi E, Di Leo A. Sequential vs. prolonged 14-day triple therapy for Helicobacter pylori eradication: the meta-analysis may be influenced by 'geographical weighting'. *Int J Clin Pract* 2015; **69**: 1112-1120 [PMID: 26138290 DOI: 10.1111/ijcp.12687]

5 **Fallone CA**, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, Jones NL, Render C, Leontiadis GI, Moayyedi P, Marshall JK. The Toronto Consensus for the Treatment of Helicobacter pylori Infection in Adults. *Gastroenterology* 2016; **151**: 51-69.e14 [PMID: 27102658 DOI: 10.1053/j.gastro.2016.04.006]

6 **Kim JS**, Park SM, Kim BW. Sequential or concomitant therapy for eradication of Helicobacter pylori infection: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2015; **30**: 1338-1345 [PMID: 25867718 DOI: 10.1111/jgh.12984]

7 **He L**, Deng T, Luo H. Meta-analysis of sequential, concomitant and hybrid therapy for Helicobacter pylori eradication. *Intern Med* 2015; **54**: 703-710 [PMID: 25832929 DOI: 10.2169/internalmedicine.54.3442]

8 **De Francesco V**, Hassan C, Ridola L, Giorgio F, Ierardi E, Zullo A. Sequential, concomitant and hybrid first-line therapies for Helicobacter pylori eradication: a prospective randomized study. *J Med Microbiol* 2014; **63**: 748-752 [PMID: 24586031 DOI: 10.1099/jmm.0.072322-0]

9 **McNicholl AG**, Marin AC, Molina-Infante J, Castro M, Barrio J, Ducons J, Calvet X, de la Coba C, Montoro M, Bory F, Perez-Aisa A, Forné M, Gisbert JP. Randomised clinical trial comparing sequential and concomitant therapies for Helicobacter pylori eradication in routine clinical practice. *Gut* 2014; **63**: 244-249 [PMID: 23665990 DOI: 10.1136/gutjnl-2013-304820]

10 **Graham DY**, Lee YC, Wu MS. Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014; **12**: 177-86.e3; Discussion e12-3 [PMID: 23751282 DOI: 10.1016/j.cgh.2013.05.028]

11 **Georgopoulos SD**, Xirouchakis E, Martinez-Gonzales B, Zampeli E, Grivas E, Spiliadi C, Sotiropoulou M, Petraki K, Zografos K, Laoudi F, Sgouras D, Mentis A, Kasapidis P, Michopoulos S. Randomized clinical trial comparing ten day concomitant and sequential therapies for Helicobacter pylori eradication in a high clarithromycin resistance area. *Eur J Intern Med* 2016; **32**: 84-90 [PMID: 27134145 DOI: 10.1016/j.ejim.2016.04.011]

12 **Chung JW**, Han JP, Kim KO, Kim SY, Hong SJ, Kim TH, Kim CW, Kim JS, Kim BW, Bang BW, Kim HG, Yun SC. Ten-day empirical sequential or concomitant therapy is more effective than triple therapy for Helicobacter pylori eradication: A multicenter, prospective study. *Dig Liver Dis* 2016; **48**: 888-892 [PMID: 27257049 DOI: 10.1016/j.dld.2016.05.005]

13 **Papastergiou V**, Georgopoulos SD, Karatapanis S. Treatment of Helicobacter pylori infection: meeting the challenge of antimicrobial resistance. *World J Gastroenterol* 2014; **20**: 9898-9911 [PMID: 25110420 DOI: 10.3748/wjg.v20.i29.9898]

14 **Losurdo G**, Iannone A, Giorgio F, Principi M, Di Leo A, Ierardi E. Letter: could sequential therapy extended to 14 days replace prolonged triple regimens for Helicobacter pylori treatment? *Aliment Pharmacol Ther* 2016; **43**: 844-845 [PMID: 26932415 DOI: 10.1111/apt.13544]

15 **Losurdo G**, Iannone A, Giorgio F, Ierardi E, Di Leo A, Principi M. A prospective trial in Saudi Arabia comparing the 14-day standard triple therapy with the 10-day sequential therapy for treatment of Helicobacter pylori infection: A further confirmation of "Geographic Weight". *Saudi J Gastroenterol* 2016; **22**: 77-78 [PMID: 26831611 DOI: 10.4103/1319-3767.173763]

16 **Ierardi E**, Losurdo G, Giorgio F, Iannone A, Principi M, Di Leo A. Quinolone-based first, second and third-line therapies for Helicobacter pylori. *World J Pharmacol* 2015; **4**: 274-280 [PMID: 24656156 DOI: 10.5497/wjp.v4.i4.274]

17 **Talebi Bezmin Abadi A**. Therapy of Helicobacter pylori: present medley and future prospective. *Biomed Res Int* 2014; **2014**: 124607 [PMID: 24800203 DOI: 10.1155/2014/124607]

**P-Reviewer:** Abadi ATB, Hori K, Lakatos PL, Tepes B, Zamani M **S-Editor:** Qi Y

**L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Italy

**Peer-review report classification**

Grade A (Excellent): A, A

Grade B (Very good): B, B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0