World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i31.3865

World J Gastroenterol 2010 August 21; 16(31): 3865-3870
ISSN 1007-9327 (print)

EDITORIAL

First-line eradication of *Helicobacter pylori*: Are the standard triple therapies obsolete? A different perspective

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Received: February 23, 2010 Revised: May 29, 2010
Accepted: June 5, 2010
Published online: August 21, 2010

Abstract

Studies concerning the eradication of *Helicobacter pylori* have resulted in a proliferation of meta-analyses. To date, there are 303 meta-analyses cited in PubMed, 113 dealing with the therapy of the infection. A chronological analysis of the results of meta-analyses performed between 1998 and 2010 shows that first-line standard triple therapies achieved eradication rates on an intention-to-treat basis of around 80%; prolonging treatment to 14, but not 10 d should improve the results. The proton pump inhibitors have a similar efficiency, and giving a double dose is more efficient than the standard doses of these drugs. Triple and quadruple therapies proved to be equivalent. Based on meta-analytical data, the decrease in efficiency over time cannot be substantiated: eradication rates < 80% followed from the introduction of triple therapies. As alternatives, ranitidine bismuth citrate-, levofloxacin- or furazolidone-based therapies were shown to obtain the same eradication rates as standard triple regimens. Sequential therapies and quadruple non-bismuth-based therapies were superior to standard triple therapies but their use is limited to certain countries. In the author's opinion, and from a meta-analytical viewpoint, standard triple therapies cannot yet be considered obsolete. Furthermore, non-inferiority trials are proposed for the future, including assessment of local contemporary antimicrobial resistance profiles and the CagA and CYP2C19 status of the enrolled patients.

Key words: Antibiotics; Eradication; *Helicobacter pylori*; Meta-analysis

Peer reviewers: Annemarie de Vries, MD, PhD, Department of Gastroenterology and Hepatology, Erasmus MC, Room Ba 393, PO Box 2040, 3000 CA, Rotterdam, The Netherlands; Hidekazu Suzuki, Assistant Professor, Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan; Andrew Seng Boon Chua, MD, Department of Gastroenterology, Gastro Centre Ipoh, 1, lorong Rani, 31, lebuhraya Tmn Ipoh, Ipoh Garden South, IPOH 30350, Malaysia

Buzás GM. First-line eradication of *Helicobacter pylori*: Are the standard triple therapies obsolete? A different perspective. *World J Gastroenterol* 2010; 16(31): 3865-3870 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i31/3865.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i31.3865

BACKGROUND: META-ANALYSES IN THE EVALUATION OF *HELICOBACTER PYLORI* ERADICATION

The discovery of *Helicobacter pylori* (*H. pylori*) led to a tremendous scientific output with 28 441 papers published between 1983 and May 2010 (http://www.pubmed.com, accessed on 27 May, 2010). Randomised controlled trials (RCT) have emerged as the main method for assessing the efficiency of *H. pylori* eradication. The guidelines are based on the most recent results of RCTs[1-6]. It became clear that RCTs could not cover all aspects of anti-*H. pylori* treatments and thus, studies on eradicating the bacterium prompted many meta-analyses, developing

into a fashionable genre in scientific literature. In contrast with human studies, meta-analyses do not require ethical/institutional approval, they are much cheaper, while they only need a detailed literature survey - which is much easier in the age of the internet than before - and a professional statistical background. Meta-analysis itself is an evolving field of medical statistics: starting from simple summary statistics it applies increasingly sophisticated procedures. Its methodology is described in textbooks[7] and is available in software packages. Gastroenterology journals were keen to publish meta-analyses, which created an abundance of analyses, superfluous information, and even errors and confusion.

In spite of the high worldwide prevalence of *H. pylori*-related conditions, the eradication of the infection has not been the subject of megatrials with tens of thousands of cases, as has been the case with hypertension, hyperlipidemias or diabetes[8-10]. To date, there are 303 meta-analyses which have been published worldwide on the topic of *H. pylori*, 113 dealing with its eradication: these can be classified by subject as shown in Table 1. In this editorial, the current position of the standard triple therapies will be discussed from a meta-analytical perspective[11-34].

Table 1 Topics of meta-analyses of *Helicobacter pylori* eradication between 1992-2010

Topics of meta-analysis	No. of studies
First-line triple therapies	25
PPI-based therapies	22
Ranitidine bismuth citrate-based therapies	3
Bismuth-based quadruple therapies	2
Non-bismuth-based quadruple therapies	1
Histamine H_2 receptor blockers + two different antibiotics	5
Rescue (second- and third-line) therapies	3
Sequential therapies	4
Alternative therapies	4
Eradication in functional dyspepsia	20
Eradication in peptic ulcer	10
Effect of CagA status on eradication	1
Gastric cancer prevention	5
Eradication in children	2
Eradication in prevention of NSAID-ulcers	1
Eradication in extradigestive diseases	5
Effect of probiotics on eradication results	5
Eradication and antimicrobial resistance	4
Effect of CYP polymorphism on eradication	2
Adverse effects of eradication	4
Multiple topics	11
Total	113

PPI: Proton pump inhibitors; NSAID: Nonsteroidal anti-inflammatory drugs; CYP: Cytochrome P450 isoenzyme.

ARE FIRST-LINE STANDARD TRIPLE THERAPIES OBSOLETE?

According to the Maastricht I consensus[1], in naive *H. pylori*-infected patients, a 7-d triple therapy consisting of any of the available proton pump inhibitors (PPI) b.i.d. + amoxicillin 1000 mg b.i.d. and clarithromycin 500 b.i.d. or metronidazole 400 or 500 mg q.i.d. is recommended. In the United States, the same regimens are given for 10-14 d[2]. The recommendations date from 1996 and 1998, and remained unchanged in subsequent guidelines[3,4]. The Second Asia-Pacific[5] and the revised Japanese consensus[6] both recommended 7-d regimens including PPI + amoxicillin 1000 mg + clarithromycin 500 mg or metronidazole 400 mg b.i.d., or PPI + clarithromycin 500 mg + metronidazole 400 mg b.i.d.

Meta-analyses of the first-line standard triple therapies demonstrated eradication rates of around 80% on an intention-to-treat (ITT) and over 85% on a per protocol (PP) basis[11-17], with the different PPIs achieving similar results[18,21-23,27]. The duration of treatment did[16] or did not[29] influence the rates of eradication. High-dose PPIs were more efficient than standard doses[18,30] (Table 2).

Before the consensus era, successful eradication was considered to be the curing of the infection in more than 80% of cases on an ITT basis. This level was proposed by Graham et al in 1989 and later even higher rates (85%-90%) were considered realistic[35,36]. This rate was later accepted by the guidelines and consensus conferences. Some experts observed that the efficiency of standard triple therapies over the range of 7-10-14 d has decreased in recent years (i.e. < 80%)[34-37] and proposed that they should possibly be abandoned as being no longer effective. In a recent overview of the topic, the results of large trials document this decrease[35]. These studies, however, seem to be grouped rather arbitrarily, not as systematic reviews and no meta-analytic workup was performed. In fact, as shown in Table 2, many meta-analyses are based on studies performed between 1993 and 2000 and show that the eradication rates of first-line standard therapies are around 80%. Looking at the 95% CI, it is obvious that in a variable proportion of the studies, the rate is well under 80%, thus the decrease in efficiency of PPI-based triple therapies is not a new phenomenon: it existed from the introduction of these regimens[11-18]. An analysis of European congress abstracts published between 1997 and 2004 revealed no decrease in the efficiency over time of first-line therapies[28]. Most of the data came from a Spanish centre, using standardized data extraction, with study quality assessment and upgraded statistical methodology, resulting in high-quality meta-analyses[14-16,18-24].

REASONS FOR ERADICATION FAILURES

The main, but not the only, culprit for the lower eradication rates is antimicrobial resistance. Meta-analyses showed that macrolide resistance reduced the success rate of standard triple therapies by 20%-55%, and nitroimidazole resistance by 25%-50%[38-41]. Antimicrobial resistance, however, is always a local, and yet a uniform county/country/continental or even global phenomenon; therefore, determining of the local resistance rates must occur at the same time as the eradication trials - however, this rarely happens. Geographically, regions with low rates of eradication are not always the same as those with high antimicrobial resistance rates. Unfortunately, antimicrobial resistance

Table 2 First-line standard triple therapies for *Helicobacter pylori* eradication: chronological order and results of meta-analyses

Author	Databases, abstracts[1]	Study period	No. of studies	No. of patients	Eradication rate [ITT, (%) mean + 95% CI]	Duration of treatment (d)	Comments
Bazzoli *et al*[11]	Medline	1993-1996	14	507	LAC: 80.6 OAC: 69.6	7	L and O are equally efficient
Laheij *et al*[12]	Medline, abstracts	1983-1998	644	53228	PPI + A + C: 80.09 (NS)	7-14	
Huang *et al*[13]	Medline, PubMed, abstracts	1986-1998	82	6123	PPI + A + C: 89.5.6 (86.9-92.0) PPI + A + M: 90.8% (87.0-94.5)	7	C 500 mg b.i.d. achieved the best result
Gisbert *et al*[14]	PubMed	1986-1999	22	2862	PPI + A + C: 81 (76-85) PPI + A + N: 84 (79-89)	7	PAC and PAN have similar efficiency
Gisbert *et al*[15]	PubMed + abstracts	1995-1999	12	1170	RBC + A + C: 76.6 (72-81) RBC + CN: 87.2 (83-91) PPIAC: 73.7 (69-78) PPIAN: 74.9 (71-84)	7	RBC + AC and PPI + AC have similar efficiency, RBC + CN has higher efficiency than PPI + CN
Calvet *et al*[16]	Medline + abstracts	1990-1999	21	1349	PPI + 2AB 76 (68-86) 82 (77-86) 84 (79-8)	 7 10 14	Triple therapies of 14 d are superior to 7, but not 10 d regimens
Janssen *et al*[17]	Medline + abstracts	1994-2000	47	3541	RBC + A + C: 81 (71-96) RBC + N + C: 88 (78-94) PPI + A + C: 79 (24-95) PPI + N + C: 79 (42-100)	5-10	PPI + AC and NC are equally effective, RBCNC is superior to RBCAC
Vallve *et al*[18]	Medline + abstract	1996-2000	13	2391	Single dose PPI: 77.7 (72-77) Double dose PPI: 83.9 (81-85)	7	Single dose PPI triple regimens are less efficient
Vergara *et al*[19]	Medline + abstracts	1995-2002	134	3293	O: 74.7 (NS) L: 74.7 (NS) R: 77.9 (NS) E: 87.9 (NS)	7	PPIs are similar in standard triple therapy
Gené *et al*[20]	PubMed, abstracts	1995-2002	5	1118	Triple therapy: 79 (74-81) Quadruple therapy: 80 (77-84)	7-10	The effectiveness of triple and quadruple therapies is similar
Gisbert *et al*[21]	Medline, Embase, CINAHL, CCTR	1996-2002	7	2226	RAC: 79 (76-82) OAC: 77 (74-80) LAC: 77 (75-79)	7-14	R, O and L achieved similar results
Gisbert *et al*[22]	Medline, congress abstracts	1997-2003	12	1137	P + 2AB: 83 (78-88) O, L + 2AB: 81 (77-86)	7	P, O and L achieved similar results
Gisbert *et al*[23]	Medline, congress abstracts	1999-2003	4	816	E + 2AB: 85 (81-89) O + 2AB: 82 (78-86)	7	E + 2AB has comparable efficacy with O + 2AB
Gisbert *et al*[24]	Medline, Embase, CINAHLISIWS + congress abstracts	1997-2004	14	4435	RBC + C + A: 79.5 (72.2-83.7) PPI + C + A: 78.1 (73.6-84.1) RBC + C + N: 87.4 (82.8-93.6) PPI + C + N: 79.9 (73.6-84.8)	7-10-14 7-10-14 7-10-14 7-10-14	RBC or PPI + A + C are comparable, RBC + C + N is superior to PPI + C + N
Padol *et al*[25]	Medline, Embase, CCTR	1996-2005	17	1569	PPI + 2AB PM: 88.9 (81.2-97.6) HomEM: 70.9 (64.3-77.4) HetEM: 82.7 (75.3-89.2)	7-14	O, but not L and R effect is influenced by CYP2C19 status
Suzuki *et al*[26]	PubMed	1998-2005	14	1529	CagA +: 84% (79-89%) CagA-: 73% (65-82)	7-14	Presence of CagA is predictive for a successful eradication
Wang *et al*[27]	Medline, Embase, CCTR	2000-2005	11	2159	E + 2AB: 86% PPI + 2AB: 81%	7	E, O and P are of comparable efficiency
Buzás *et al*[28]	Abstracts	1997-2004	75	15634	PPI + 2AB: 81.4% (78.5-84.5) RBC + 2AB: 78.5% (70.5-84.3) PPI + 2AB + bismuth: 82.6% (76.0-89.2)	7	PPIs, RBC + 2AB and quadruple regimens are equally efficient as first-line therapies
Fuccio *et al*[29]	Medline, Embase, CCTR, abstracts	1996-2007	21	4831	PPI + 2AB: 75% (72-77) 80.7% (75.2-85.7) 78.2% (74.3-82.6)	 7 10 14	Extending triple therapy to 10-14 d is not useful
Villoria *et al*[30]	PubMed, ISIWS, Embase, CCTR CINAH, abstracts	1990-2007	6	1703	High-dose PPI: 82% (78-84) Standard dose PPI: 74% (NS)	7	High-dose PPIs are 8% more effective than standard doses in 7 d therapies
Zhao *et al*[31]	Medline, PubMed, Embase, ISIWB, CCTR, Chinese Databases	1999-2007	20	3330	PMs: 91.6 (83-99) HetEMs: 85.5 (79.6-92.3) HomEMs: 74.6 (70.1-79.8)	7-10-14	O and L effects are dependent on CYP2C19 genotype, R effect is not dependent

Essa *et al*[32]	PubMed, Embase, CCTR + abstracts	1990-2008	9	1054	Triple therapies: 76.8 (72.2-81.2) Concomitant quadruple therapy: 89.7% (86.8-92.1)	5-10 7	Concomitant quadruple therapy is superior to standard triple therapy
Luther *et al*[33]	Medline, Embase, Google Scholar, CCTR, ACP Journal Club	1996-2009	9	1679	PPI + AC: 77.0 (71-84) PPI + 2AB + Bi: 78.3 (71.7-84.6)	7	Triple and quadruple therapies yielded similar suboptimal results

[1]Abstracts of the Digestive Diseases Week, United European Digestive Week and European Helicobacter Study Group annual meetings. Abbreviations: A: Amoxicillin; AB: Antibiotic; Bi: Bismuth compound C: Clarithromycin; CCTR: Cochrane Controlled Trials Register; CI: 95% confidence interval; E: Esomeprazole; ISIWB: Institute of Scientific Information Web of Science; ITT: Intention-to-treat; HetEM: Heterozygous extensive metabolizers; HomEM: Homozygous extensive metabolizers; L: Lansoprazole; N: Nitroimidazole; P: Pantoprazole; PM: Poor metabolizers; PPI: Proton pump inhibitor; O: Omeprazole; R: Rabeprazole; RBC: Ranitidine bismuth citrate.

determinations are largely neglected even in developed countries. It seems that the 27 years from the discovery of *H. pylori* were not enough for the medical community to understand that chronic gastritis and peptic ulcers are infectious diseases and doctors must think as infectionists in their therapeutic judgements. A recent study from California stated that the "epidemic" of antimicrobial-resistant infections was related to insufficient funding, surveillance, control, prevention, research and development and misguided regulation of antibiotic use, including in agriculture and especially for food animals[42]. In fact, none of the guidelines cited[1-6] or experts/opinion leaders[43] contraindicate explicitly the use of clarithromycin or metronidazole; they only outline the levels of antimicrobial resistance in which these compounds should be avoided.

Polymorphism of the CYP2C19 isoenzyme has been shown to result in significant differences of eradication rates between homozygous and heterozygous extensive metabolizers and poor metabolizers of omeprazole and lansoprazole, but not of rabeprazole; however, almost all the data are from Japan and China[29,31].

CagA positive status seems to affect eradication rates favorably, at least in Europe and North America[26]. Tailoring treatment after the determination of both CYP2C19 and CagA status yielded a 96% eradication rate *vs* 70% with standard triple therapy in Japan, without an increase in the final cost of successful eradication[44].

Eradication rates show significant geographical variations: a Canadian systematic review and meta-analysis revealed that although PPI-based triple regimens are recommended worldwide as first-line treatment, there are regional differences in success rates between Asia, Africa, North and South America and Europe that are not completely explained by antimicrobial resistance rates and local prevalence of the infection[45,46]. In our meta-analysis of European congress abstracts, we also found continental variations, without an east-west or north-south gradient[28]. Genetic differences of *H. pylori* strains infecting these populations might influence eradication rates but this has not yet been investigated.

ALTERNATIVE THERAPIES

Several alternatives to standard triple therapies have been proposed. Ranitidine-bismuth citrate (RBC) emerged in 1991 as a highly efficient drug in association with amoxicillin and clarithromycin; 3 meta-analyses showed that RBC-based triple therapies achieve similar rates of eradication to PPI-based regimens, and when given with nitroimidazoles are superior to PPI-based combinations[15,17,24]. The lack of worldwide availability and a fall in the product's promotion have led, however, to a limited use of this valuable compound. Levofloxacin given to 1926 cases in 11 studies as part of first-line triple therapy was superior to standard regimens (odds ratio 1.56, CI: 1.25-1.94)[31] and it was also found to be efficient and safe according to a Chinese meta-analysis[47]. Moxifloxacin, given in 4 studies to 772 patients, achieved 84.1% eradication as compared to the 73.6% of the standard therapy (relative risk: 1.13, CI: 1.01-1.27)[48], but resistance values forecast that the quinolones will suffer the same fate as macrolides. Furazolidone is cheap and useful in first-line treatment: when given with PPI + one antibiotic, it achieved eradication in 81.4% of cases, better than standard regimens (71.7%, odds ratio: 2.34, CI: 0.76-3.92), but this nitrofuran derivative has limited availability[49]. Three meta-analyses showed that 10-d sequential therapy is superior to standard regimens, but almost all studies are Italian: these data must be confirmed in other countries/populations before considering it a first-line therapy[50-52]. The non-bismuth concomitant quadruple therapies are also better than the standard regimens, and less complex than sequential therapy[33,36]. All of the regimens have their pros and cons: we still lack an ideal first-line therapy.

PROPOSAL FOR THE FUTURE

From a meta-analytical point of view, the decrease in the efficiency of standard triple therapies over time cannot be substantiated: sets of studies obtaining an eradication rate of less than 80% have existed from the beginning. Further studies are needed before abandoning them as being no longer effective. While there is no new antibiotic on the horizon that works against *H. pylori*, instead of the multistep approach of small pilot studies to identify effective new therapies, I would like to propose adequately powered non-inferiority trials with a pre-defined margin (10%, 15% or perhaps 20%) in which standard triple therapies are compared with the available alternatives, taking the antimicrobial resistance profile, CagA and CYP2C19

status into consideration. The design and methodology of non-inferiority trials are available[53]. If the inferiority of standard triple therapies is confirmed in this way, they can be abandoned and deleted from the guidelines. Until then, in this author's opinion, standard triple therapies should be given in most countries/regions as first-line therapies, according to the local guidelines. Furthermore, as leading authorities have stated, there is still much to be learned about the association of *H. pylori* with human disease and optimal therapy of these conditions[43].

ACKNOWLEDGMENTS

The secretarial help of Mrs. Jolán Józan (Semmelweis University, Department of Physiology, Budapest) and correction of the English manuscript by Mr. Douglas Arnott (EDMF Translation Services, Etyek, Hungary) are gratefully acknowledged.

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