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CME

Levofloxacin-Based Triple Therapy *versus* Bismuth-Based Quadruple Therapy for Persistent *Helicobacter pylori* Infection: A Meta-Analysis

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BACKGROUND: Levofloxacin-based triple therapy has been suggested as an alternative salvage therapy to bismuth-based quadruple therapy for persistent *Helicobacter pylori* (*H. pylori*) infection.

METHODS: A search of PUBMED, EMBASE, EBM Review databases and abstracts from recent Digestive Disease Week, United European Gastroenterology Week, and European Helicobacter Study Group conferences was performed. Randomized controlled trials (RCTs) comparing levofloxacin-based triple salvage therapy (levofloxacin + amoxicillin + PPI) to bismuth-based quadruple salvage therapy (bismuth + tetracycline + metronidazole + PPI) were selected for meta-analysis. Additionally, all prospective trials evaluating this levofloxacin-based triple therapy as salvage therapy were pooled to analyze optimal levofloxacin treatment duration and dosing. All selected trials confirmed prior treatment failure and post-salvage treatment eradication.

RESULTS: Four RCTs compared a 10-day regimen of levofloxacin-based triple therapy to 7-day bismuth-based quadruple therapy (n = 391 patients). Levofloxacin-based triple therapy was superior to quadruple therapy (RR = 1.41 [95% CI: 1.25–1.59]). Levofloxacin-based triple therapy was better tolerated than quadruple therapy with a lower incidence of side effects (RR = 0.51 [95% CI: 0.34–0.75]) and side effects prompting discontinuation of therapy (RR = 0.30 [95% CI: 0.10–0.89]). Eleven trials (n = 547 patients) evaluating levofloxacin-based triple therapy demonstrated higher eradication rates with 10-day *versus* 7-day regimen (87% [95% CI: 82%-92%] *vs* 68% [95% CI: 62%-74%]) yet eight trials (n = 477 patients) demonstrated no difference with 500 mg daily *versus* 250 mg b.i.d. dosing of levofloxacin (81% [95% CI: 78%-89%] *vs* 84% [95% CI: 66%-97%]).

CONCLUSIONS: A 10-day course levofloxacin triple therapy is more effective and better tolerated than 7-day bismuth-based quadruple therapy in the treatment of persistent *H. pylori* infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a highly prevalent chronic infection with a worldwide prevalence of nearly 50% and U.S. prevalence of 30–40% (1, 2). *H. pylori* is well recognized as a major factor in the pathogenesis of chronic gastritis, peptic ulcer disease, and gastric malignancies (3–5). Consequently, there has been great emphasis placed on the successful eradication of this infection. Multiple first-line treatments have been employed, and the most successful regimens achieve eradication rates ranging from 75% to 90% (3). Unfortunately, patients with persistent *H. pylori* infection despite a course of antibiotic therapy are more challenging to successfully cure of their infection (6).

A number of salvage regimens have been evaluated in patients with persistent *H. pylori* infection. Currently, the internationally recommended salvage therapy for persistent *H. pylori* infection is a bismuth-based quadruple drug regimen consisting of a proton pump inhibitor, bismuth salt, metronidazole, and tetracycline for a minimum of 7 days (7). The advantages of this regimen include wide availability, low cost, and reasonably good efficacy in the salvage setting relative to other regimens. However, a recent pooled analysis of trials which evaluated this regimen as salvage therapy for persistent *H. pylori* infection demonstrated a treatment failure rate of nearly 25% (6). In addition to the marginal eradication

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rate, other concerns which have been raised regarding bismuth-based quadruple therapy include the complexity of the regimen and the frequency of associated side effects (8–11).

Levofloxacin, a levorotatory isomer of ofloxacin, is a fluoroquinolone with antibacterial activity against a wide range of gram-positive and gram-negative organisms (12) including *in vitro* activity against *H. pylori* (13). This antibacterial activity coupled with its excellent bioavailability and ease of dosing (single daily dosing and co-ingestion with food) make levofloxacin an attractive therapy for *H. pylori* infection (14, 15). Recently, levofloxacin-based regimens have been studied as salvage therapy for persistent *H. pylori* infection. In general, the available clinical trials have involved small numbers of patients and demonstrated variable eradication rates, ranging from 63% to 94% (16, 17).

We systematically reviewed all randomized controlled trials (RCTs) which compared the eradication rates and tolerability of levofloxacin-based triple therapy to bismuth-based quadruple salvage therapy in the treatment of persistent *H. pylori* infection. By summarizing the data from RCTs, meta-analysis will provide greater statistical power and a more precise estimate of eradication rates with these salvage regimens in patients with persistent *H. pylori* infection. This analysis will also provide a more precise comparison of the frequency and severity of side effects associated with each salvage regimen. We also systematically reviewed all prospective trials (randomized or nonrandomized) evaluating levofloxacin-based triple therapy as a salvage therapy to more precisely estimate the impact of treatment duration and levofloxacin dosing schedule on eradication rates.

METHODS

Literature Search

The following strategy was employed to identify relevant trials. Separate computer-assisted searches were performed utilizing the PUBMED, EMBASE, and EBM Review of Cochrane Central Register of controlled trials. Each search was performed on all English language articles through April 2005 using the exploded medical subject heading terms "levofloxacin" and "*H. pylori*." Additionally, all abstracts presented at the Digestive Disease Week from 2002 to 2005, United European Gastroenterology Week meetings from 2002 to 2004, and European Helicobacter Study Group's yearly workshop from 2000 to 2004 were manually searched. Finally, manual searches of reference lists from identified relevant papers were performed to identify any additional studies that may have been missed using the above-mentioned searches.

Study Selection Criteria

The titles and abstracts of all citations identified by the literature search were reviewed. Selection criteria were then applied to all potentially relevant studies. The selection criteria for inclusion in the meta-analysis were (a) RCT with parallel group design comparing levofloxacin-based triple therapy to bismuth-based quadruple therapy; (b) a levofloxacin-based triple therapy that included amoxicillin and a PPI; (c) confirmation of treatment failure to at least one prior course of standard triple therapy (based on urea breath testing or gastric mucosal biopsy for histology and/or culture and/or rapid urea testing); (d) intention-to-treat analysis; and (e) confirmation of infection eradication at least 4 wk after completion of treatment (based on urea breath testing or gastric mucosal biopsy for histology or culture).

A broader set of selection criteria was then applied to the same collection of potentially relevant studies for inclusion in the pooled analysis which would assess the effect of duration of therapy and levofloxacin dosing schedule on eradication rates. The criteria for inclusion were (a) a prospective trial assessing the efficacy of a levofloxacin-based triple therapy as a salvage treatment for persistent *H. pylori* infection; (b) a levofloxacin-based triple therapy that included amoxicillin and a PPI; (c) confirmation of treatment failure to at least one prior course of standard triple therapy (based on urea breath testing or gastric mucosal biopsy for histology and/or culture and/or rapid urease testing); (d) intention-to-treat analysis; and (e) confirmation of infection eradication at least 4 wk after completion of treatment (based on urea breath testing or gastric mucosal biopsy for histology or culture).

Data Extraction

Two investigators (R.S and W.C.) extracted the data from the studies meeting the selection criteria. Data were extracted concerning (a) study design; (b) number of patients enrolled in the study; (c) number of patients in each treatment arm; (d) testing used to confirm persistent infection prior to study enrollment; (e) drug regimen, including specific doses and treatment duration; (f) testing used to confirm eradication, including timing of such testing after completion of treatment; (g) number of patients in which *H. pylori* infection was successfully eradicated (either directly provided or calculated given the intention-to-treat and per protocol analyses); and (h) number of patients with side effects and number of patients discontinuing therapy due to side effects. There was greater than 95% agreement in data extraction between the two investigators.

Statistical Analysis

The primary study outcomes for the meta-analysis were (a) the eradication rate of levofloxacin-based triple therapy compared to bismuth-based quadruple therapy; (b) incidence of adverse events in the levofloxacin-based therapy *versus* bismuth-based quadruple therapy; and (c) incidence of therapy discontinuation due to adverse events in the levofloxacin-based therapy *versus* bismuth-based quadruple therapy. A pooled analysis was also planned to assess several secondary outcomes for levofloxacin-based triple therapy, including (a) eradication rates with 7 days of therapy *versus* 10 days of therapy; (b) eradication rates with levofloxacin 250 mg b.i.d. *versus* 500 mg q.d.

Following data extraction, eradication rates from intention-to-treat analyses were entered into Stata 8.2 (Stata, College Station, TX) and StatXact 5.0 software programs for the performance of meta-analysis. In summarizing the data from these comparative trials, risk ratio (RR) was used as the measure of association, and summary relative RRs along with its 95% CI were calculated based on a fixed-effects model using the methods of DerSimonian and Laird (18). A test of heterogeneity was also performed to establish if any clinical, methodological, or statistical variability existed among the studies used in meta-analysis. If significant heterogeneity exists, it would be inappropriate to combine the data for further analysis. Statistical significance for the test of heterogeneity was set at 0.10. The same method of meta-analysis was applied to the incidence of adverse events and discontinuation of therapy due to adverse events for the RCTs.

Eradication rates by intention-to-treat analyses from all prospective studies, randomized and nonrandomized, were also pooled. A summary eradication rate and a 95% CI were calculated for four subgroups: 10-day course of levofloxacin therapy; 7-day course of levofloxacin therapy; levofloxacin 250 mg b.i.d. regimen; and levofloxacin 500 mg q.d. regimen. Summary estimates were obtained even if significant heterogeneity between individual trial results was present because the goal of this analysis was to make between-group comparisons based on the summary estimates. We then assessed if the summary rate in one subgroup was included in the 95% CI of the other subgroup. If the summary rate of one group was not included in the 95% CI of the other subgroup, the difference in the rates between the two subgroups was considered statistically significant. Two additional methods including a meta-regression and calculation of an odds ratio were performed to confirm the results of the between-group comparisons based on the summary estimates.

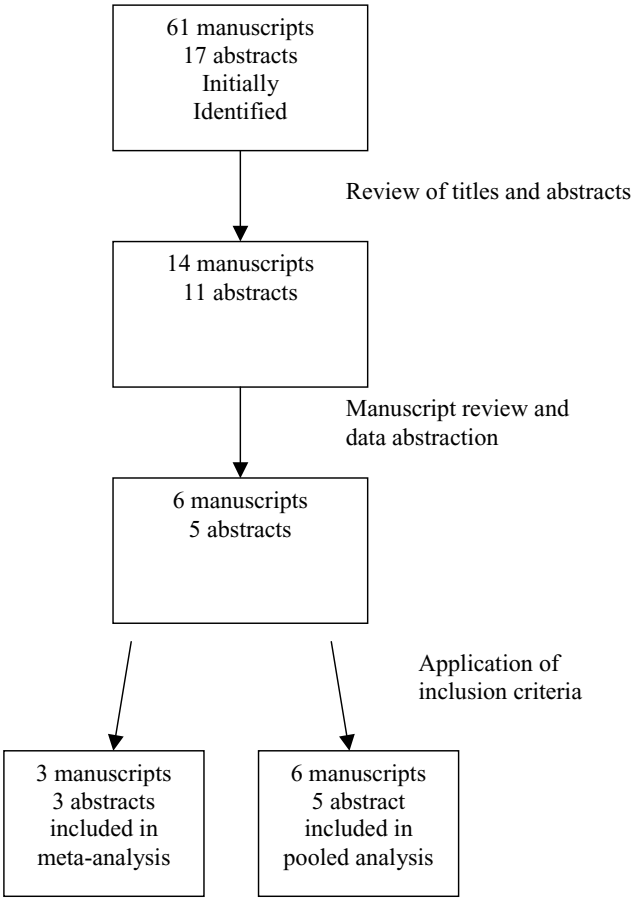

Figure 1. Results of search strategy.

RESULTS

Search Results

The results of the search strategy are summarized in Figure 1. Following a thorough review of the titles, abstracts, and manuscripts of the potentially relevant studies, three published manuscripts (16, 17, 19) and three abstracts (7, 20–22) met inclusion criteria for the meta-analysis comparing eradication rates and tolerability of levofloxacin-based triple therapy *versus* bismuth-based quadruple salvage therapy for persistent *H. pylori* infection. Characteristics of the six studies used in the meta-analysis are summarized in Table 1.

Five additional prospective studies met inclusion criteria for the pooled analysis assessing effects of duration of therapy on eradication rates. There were three studies published in full manuscript form (10, 23, 24) and two abstracts (25, 26). Eight of the 11studies in the pooled analysis assessed levofloxacin dosages of 250 mg b.i.d. or 500 mg q.d. The study by Wong *et al*. (21) and Cammarota *et al*. (10) administered levofloxacin in a dose of 500 mg b.i.d. and the study by Watanabe *et al*. (23) administered a dose of 200 mg b.i.d. Characteristics of the additional five studies used in the pooled analyses are summarized in Table 2.

Levofloxacin-Based Triple Therapy versus Bismuth-Based Quadruple Therapy for Persistent H. Pylori

Six trials directly compared a levofloxacin-based triple therapy *versus* bismuth-based quadruple salvage therapy (16, 17, 19–22). The results of these studies are summarized in Table 3. A meta-analysis of the eradication rates with intention-to-treat analyses demonstrated superiority of the levofloxacin-based triple therapy to bismuth-based quadruple therapy with a relative RR of 1.18 (95% CI: 1.08–1.29) (Fig. 2). However, there was significant heterogeneity present in this analysis ($p = 0.000$). This heterogeneity suggested that significant methodological differences existed among the studies making it inappropriate to combine them.

Analysis of individual RCTs revealed a clear difference in eradication rates between 10-day courses of levofloxacin-based triple therapy and 7-day courses of levofloxacin-based triple therapy. Therefore, a *post hoc* meta-analysis was performed comparing the 10-day courses of levofloxacin-based treatment to bismuth-based quadruple salvage therapy demonstrating superiority of the levofloxacin-based therapy

Table 1. Characteristics of Studies Used in Meta-Analysis (as Well as Pooled-Analysis)

Study (Country)	Study Design	Patient Enrollment	Prior Treatment	Test Confirming Infection	Treatment Regimen	Testing Confirming Eradication
Nista *et al*. (17) (Italy)	RCT	280 (four treatment arms)	C 500 mg b.i.d. + A 1 gm b.i.d. + R 20 mg b.i.d.	UBT & Bx for histology	L 500 mg q.d. + A 1 gm b.i.d. + R 20 mg b.i.d. × 10 d L 500 mg q.d. + Tn 500 mg b.i.d. + R 20 mg b.i.d. × 10 d B 120 mg q.i.d. + T 500 mg q.i.d. +M 500 mg t.i.d. +R 20 mg b.i.d. × 7 d B 120 mg q.i.d. +T 500 mg q.i.d. + M 500 mg t.i.d. + R 20 mg b.i.d. × 10 d	UBT 6 wk after therapy
Perri *et al*. (16) (Italy)	RCT	180 (three treatment arms)	C 500 mg b.i.d. + A 1 gm b.i.d. + O 20 mg b.i.d. × 7 d	UBT	RBC 400 mg b.i.d. + A 1 gm b.i.d. + Tn 500 mg b.i.d. × 7 d L 500 mg q.d. + A 1 gm b.i.d. + P 40 mg b.i.d. × 7 d B 240 mg b.i.d. + T 500 mg q.i.d. + M 500 mg b.i.d. + P 40 mg b.i.d. × 7 d	UBT 4–6 wk after therapy
Bilardi *et al*. (19) (Italy)	RCT	90 (two treatment arms)	Regimen not stated Patients failed 1–6 prior treatments	UBT & Bx for histology	L 250 mg b.i.d. + A 1 gm b.i.d. + P 40 mg b.i.d. × 10 d B 240 mg b.i.d. + T 250 mg q.i.d. + M 500 mg b.i.d. + O 20 mg b.i.d. × 7 d	UBT 4 wk after therapy
Wong *et al*. (21) (Abstract) (Hong Kong)	RCT	63 (two treatment arms)	Not stated	RUT & Bx for culture and histology	L 500 mg b.i.d. + A 1 gm b.i.d. + La 30 mg b.i.d. × 7 d B 120 mg q.i.d. + T 500 mg q.i.d. + M 400 mg t.i.d. + La 30 mg b.i.d. × 7 d	UBT 6 wk after therapy
Nista *et al*. (20) (Abstract) (Italy)	RCT	95 (three treatment arms)	C 500 mg b.i.d. + A 1 gm b.i.d. + E 20 mg b.i.d.	UBT	L 500 mg q.d. + A 1 gm b.i.d. + E 40 mg q.d. × 10 d L 500 mg q.d. + Az 500 mg q.d. + E 40 mg q.d. × 10 d B 120 mg q.i.d. + T 500 mg q.i.d. + M 500 mg t.i.d. + R 20 mg b.i.d. × 7 d	UBT 6 wk after therapy
Nista *et al*. (22) (Abstract) (Italy)	RCT	146 (three treatment arms)	C 500 mg b.i.d. + A 1 gm b.i.d. + R 20 mg b.i.d.	UBT	L 500 mg q.d. + A 1 gm b.i.d. + R 20 mg b.i.d. × 10 d L 500 mg q.d. + A 1 gm b.i.d. + R 20 mg b.i.d. × 7 d B 120 mg q.i.d. + T 500 mg q.i.d. + M 500 mg t.i.d. + R 20 mg b.i.d. × 7 d	UBT 6 wk after therapy

RCT = randomized controlled trial; UBT = urea breath test; RUT = rapid urea test; Bx = mucosal biopsy; L = levofloxacin; A = amoxicillin; R = rabeprazole; Tn = tinidazole; B = bismuth; C = clarithromycin; T = tetracycline; M = metronidazole; RBC = ranitidine bismuth citrate; P = pantoprazole; O = omeprazole; E = esomeprazole; Az =azithromycin; d = days.

(RR = 1.41 [95% CI: 1.25–1.59]) (Fig. 3). This meta-analysis did not demonstrate statistically significant heterogeneity ($p = 0.269$). An overall eradication rate was also calculated by combining the results from these four RCTs revealing 87% (95% CI: 79–96%) eradication rate for the levofloxacin-based therapy compared to 60% (95% CI: 45–74%) eradication rate for bismuth-based quadruple therapy.

Adverse events were less common with 10-day levofloxacin-based triple therapy *versus* bismuth-based quadruple salvage therapy. Three of the four RCTs reported the

Table 2. Characteristics of Studies Used Only in Pooled Analysis

Study (Country)	Study Design	Patient Enrollment	Prior Treatment	Test Confirming Infection	Treatment Regimen	Testing Confirming Eradication
Watanabe *et al*. (23) (Japan)	Prospective uncontrolled	33	C 200 or 400 mg b.i.d. + A 750 mg b.i.d. + La 30 mg b.i.d.	Bx for culture and histology	L 200 mg b.i.d. + A 1 gm b.i.d. +La 30 mg b.i.d. × 7 d	UBT at 4–8 wk
Zullo *et al*. (24)(Italy)	Prospective uncontrolled	36	PPI + C + A × 7 d or PPI + A + M × 7 d	RUT & Bx for histology	L 250 mg b.i.d. + A 1 gm b.i.d. + R 20 mg b.i.d. × 10 d	UBT at 6–8 wk or RUT and Bx
Cammarota *et al*. (10) (Italy)	Prospective, culture guided	94	PPI + C + A × 7 d or PPI + A + M × 7 d	Bx for culture	L 500 mg b.i.d. + A 1 gm b.i.d. + O 20 mg b.i.d. × 7 d	UBT at 8 wk
Gatta *et al*. (25) (Abstract) (Italy	Prospective uncontrolled	107	Standard triple therapy consisting of C + A + PPI	RUT, Bx for culture and histology (two of three)	L 250 mg b.i.d. + A 1 gm b.i.d. +E 40 mg b.i.d. × 10 d	Bx at 4–6 wk
Festa *et al*. (26) (Abstract) (Italy)	Prospective uncontrolled	30	Standard triple therapy consisting of C + A + O	UBT	L 500 mg q.d. + A 1 gm b.i.d. + O 20 mg b.i.d. × 7 d	UBT at 4–6 wk

Abbreviations: RCT = randomized controlled trial; UBT = urea breath test; RUT = rapid urea test; Bx = mucosal biopsy; L = levofloxacin; A = amoxicillin; C = clarithromycin; R = rabeprazole; Tn = tinidazole; B = bismuth; T = tetracycline; M = metronidazole; P + pantoprazole; O = omeprazole; La = lansoprazole; E = esomeprazole; PPI = proton pump inhibitor; d = days.

frequency of adverse events with levofloxacin-based triple therapy (18.1% or 26/144) and bismuth-based quadruple salvage therapy (32.5% or 49/151) (17, 19, 20). Meta-analysis revealed a significant difference in the frequency of adverse events, which favored levofloxacin-based triple therapy (RR = 0.51 [95% CI = 0.34–0.75]) (Fig. 4). This meta-analysis did not demonstrate statistically significant heterogeneity ($p = 0.12$).

The four RCTs demonstrated that adverse events were less likely to prompt discontinuation of therapy with 10 days of levofloxacin-based triple therapy (0.5% or 1/190) *versus* bismuth-based quadruple therapy (6.6% or 14/211) (17, 19,

Table 3. Results of RCTs

Study	Treatment Arm	Patient Enrolled	Patients with *H. pylori* Successfully Eradicated	Eradication Rate (95% CI)	Number of Patients with Side Effects	Number of Patients Discontinuing Therapy Due to Side Effects
Ten-day course of levofloxacin therapy						
Nista *et al*. (17)	Levofloxacin triple therapy	70	66	94%	7	0
	Quadruple therapy	70	44	63%	15	5
Nista *et al*. (20)	Levofloxacin triple therapy	30	26	87%	8	0
	Quadruple therapy	35	25	71%	21	4
Bilardi *et al*. (19)	Levofloxacin triple therapy	44	31	70% (53–87%)	11	1
	Quadruple therapy	46	17	37% (23–47%)	13	1
Nista *et al*. (22)	Levofloxacin triple therapy	46	42	91%	Not reported	0
	Quadruple therapy	50	34	68%	Not reported	4
Seven-day course of levofloxacin therapy						
Perri *et al*. (16)	Levofloxacin triple therapy	60	38	63% (51–76%)	3	1
	Quadruple therapy	60	50	83% (74–93%)	17	3
Wong *et al*. (21)	Levofloxacin triple therapy	33	21	64%	Not reported	Not reported
	Quadruple therapy	30	22	73%	Not reported	Not reported
Nista *et al*. (22)	Levofloxacin triple therapy	50	37	74%	Not reported	0
	Quadruple therapy	50	34	68%	Not reported	4

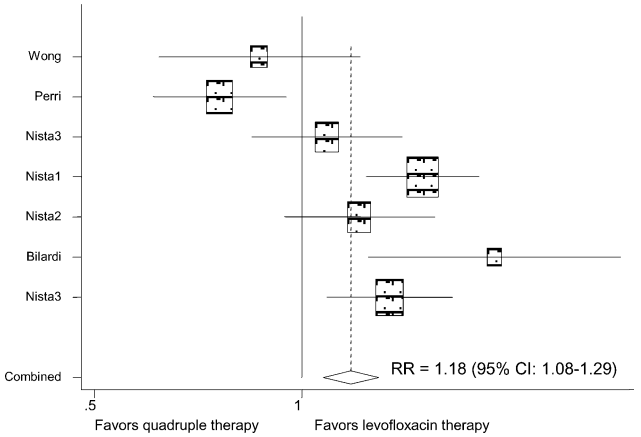

Figure 2. Relative risk of *H. pylori* eradication with levofloxacin-based triple therapy compared to bismuth-based quadruple therapy Relative RR of individual studies (95% CI): Wong = 0.87 (0.62, 1.21); Perri = 0.76 (0.61, 0.95); Nista3 = 1.09 (0.85, 1.40); Nista1 = 1.50 (1.24, 1.81); Nista2 = 1.21 (0.94, 1.56); Bilardi = 1.91 (1.25, 2.91); Nista3 = 1.34 (1.09, 1.66).

20, 22). A meta-analysis revealed a significant difference in the discontinuation of therapy due to adverse events, which favored levofloxacin-based triple therapy (RR = 0.30 [95% CI = 0.10–0.89]) (Fig. 5). This analysis did not demonstrate statistically significant heterogeneity ($p = 0.61$).

Effect of Levofloxacin Dosage and Treatment Duration on Efficacy of Therapy

Eleven prospective trials, randomized and nonrandomized, totaling 12 treatment arms and 547 patients had intention-to-treat eradication rates comparing the efficacy of 7 days of levofloxacin-based triple therapy with that of 10 days of therapy. Pooled analysis demonstrated clear superiority of the 10-day course over the 7-day course of therapy with an eradication rate of 87% (95% CI of 82–92%) *versus* 68% (95% CI of 62–74%), respectively. This conclusion was confirmed with a meta-regression analysis as well as a calculation of an odds ratio in favor of the 10-day course of therapy.

Eight prospective trials, randomized and nonrandomized, totaling 9 treatment arms and 477 patients had intention-to-treat eradication rates comparing the efficacy of 250 mg b.i.d. of levofloxacin with that of 500 mg q.d. of levofloxacin. The pooled analysis demonstrated no difference in 250 mg b.i.d. dosing with that of 500 mg q.d. dosing with eradication rates of 84% (95% CI of 78–89%) *versus* 81% (95% CI of 66–97%), respectively. The meta-regression analysis also confirmed that no difference in eradication rates existed between the different dosing regimens of levofloxacin.

DISCUSSION

In general, the most important predictors of *H. pylori* treatment failure include pretreatment antibiotic resistance (27) and patient noncompliance with the medical regimen (11). The current background resistance rates of *H. pylori* in the United States are 37% for metronidazole and 10% for clarithromycin (28). Conversely, resistance to tetracycline and amoxicillin remains a rare occurrence (29). In patients with persistent *H. pylori* infection, the corresponding rates are typically even higher and greatly influenced by the constituents of the failed initial treatment regimen (30). It is likely that metronidazole resistance plays a role in the significant failure rate of bismuth-based quadruple salvage therapy.

Compliance with any medical therapy is influenced by the complexity of the dosing regimen (number of pills and frequency) and the frequency and severity of associated side

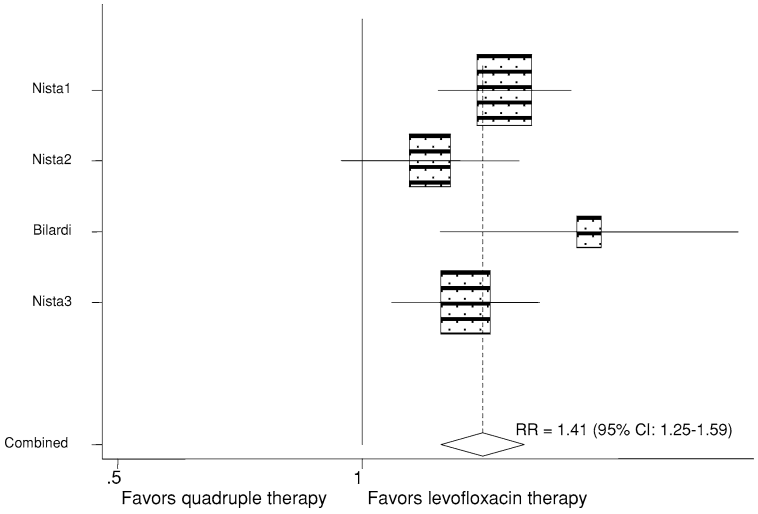

Figure 3. Relative risk of *H. pylori* eradication with 10 days of levofloxacin-based triple therapy compared to 7 days of bismuth-based quadruple therapy Relative RR of individual studies (95% CI): Nista1 = 1.50 (1.24, 1.81); Nista2 = 1.21 (0.94, 1.56); Bilardi = 1.91 (1.25, 2.91); Nista3 = 1.34 (1.09, 1.66).

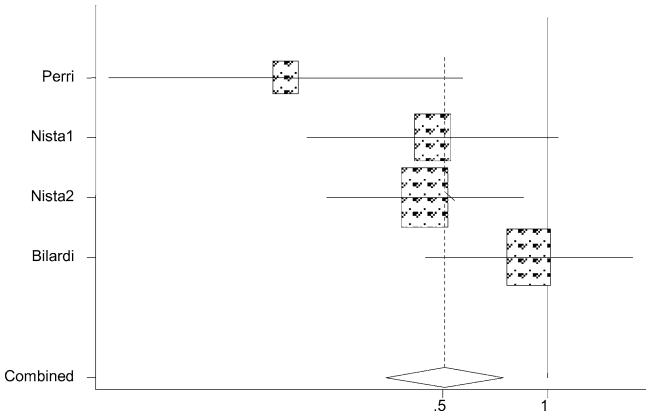

Figure 4. Relative risk for side effects of therapy with 10 days of levofloxacin-based triple therapy *versus* 7 days of bismuth-based quadruple therapy Relative RR of individual studies (95% CI): Perri = 0.18 (0.05, 0.57); Nista1 = 0.47 (0.20, 1.07); Nista2 = 0.44 (0.23, 0.85); Bilardi = 0.88 (0.44, 1.76).

effects. Disadvantages of bismuth-based quadruple therapy include the large daily pill count (potentially exceeding 18 pills), dosing frequency (typically four times daily), and frequent side effects (occurring in >50% of patients in some studies (8–10)). Related to these drawbacks, more effective, simpler, and better tolerated salvage regimens for persistent *H. pylori* infection are needed.

Levofloxacin-based triple therapy offers a number of advantages over bismuth-based quadruple therapy. First and foremost, a 10-day course of levofloxacin-based triple therapy appears to be more effective at eradicating persistent *H. pylori* infection than bismuth-based quadruple therapy. Our results have also shown better overall tolerance of the levofloxacin-based triple therapy compared to bismuth-based quadruple therapy. In combination with the very low rate of levofloxacin and amoxicillin resistance among *H. pylori* strains, we speculate that the improved tolerability of this regimen leads to improved compliance and ultimately, greater eradication rates compared to bismuth-based quadruple therapy.

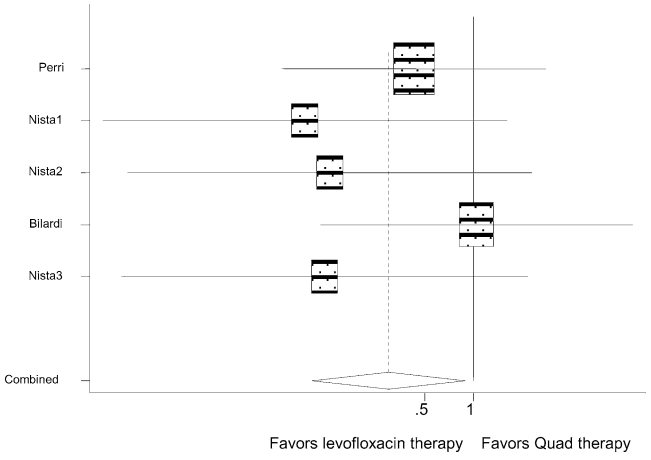

Figure 5. Relative risk of discontinuation of therapy due to side effects with 10 day levofloxacin-based therapy *versus* 7 days of bismuth-based quadruple therapy Relative RR of individual studies (95% CI): Perri = 0.43 (0.07, 2.81); Nista1 = 0.09 (0.01, 1.61); Nista2 = 0.13 (0.01, 2.31); Bilardi = 1.04 (0.11, 9.67); Nista3 = 0.12 (0.01, 2.18).

This study also provides valuable information regarding the optimal means of administering this regimen in the salvage setting. A 10-day course of levofloxacin-based triple therapy proved superior to a 7-day course of therapy. Although the increased duration of therapy could theoretically negatively impact compliance, this concern appears to be more than offset by the improved tolerability of this regimen (22). Additionally, our study did not demonstrate any benefit of twice daily dosing *versus* once daily dosing of levofloxacin. In the hopes of improving compliance, it would then seem reasonable to use a 500 mg q.d. over the 250 mg b.i.d. dosing schedule. There is some emerging evidence to suggest that levofloxacin dosing greater than 500 mg q.d. provides higher tissue concentrations which may lead to more effective treatment outcomes in respiratory infections (31). However, for *H. pylori* infection, there is little to no evidence that increasing the dose of levofloxacin results in greater eradication rates. One small study using levofloxacin at a dosage of 500 mg b.i.d. for 7 days actually demonstrated an eradication rate of only 64% (21). However, this study has not been published as a full manuscript and included a significant number of patients who had failed multiple previous courses of eradication therapy (eradication rates were 54% for those failing >1 course of therapy *versus* 79% in those failing only one course of therapy). Whether or not improved eradication rates can be achieved with the use of a higher dose of levofloxacin for longer periods of time remains to be determined.

Several methodological weaknesses may limit the validity and generalizability of this meta-analysis. Initially, the findings of the meta-analysis demonstrated a superiority of levofloxacin-based triple therapy over bismuth-based quadruple salvage therapy. However, this analysis also demonstrated statistically significant heterogeneity calling into question the validity of combining these results into a meta-analysis. Analysis of individual RCTs indicated that 7-day *versus* 10-day treatment duration led to markedly different eradication rates, which likely contributed to the heterogeneity seen in the initial meta-analysis. This led to the performance of a *post hoc* meta-analysis comparing only studies utilizing a 10-day course of levofloxacin-based triple therapy to 7 days of bismuth-based quadruple salvage therapy. This corrected the heterogeneity and still demonstrated superiority of levofloxacin-based therapy. There is also the theoretical concern for publication bias. We considered the creation of a funnel plot to determine if we could identify evidence of publication bias. However, given the small number of studies included in this review, there were not enough data points to

perform a funnel plot with any interpretative value. We therefore created scatter plots evaluating eradication rates against year of publication and eradication rates against sample size from the studies used in this systematic review. Acknowledging the small number of studies included, we found no trend to suggest significant publication bias. Lastly, there are no studies involving patients from North America. The studies included were conducted in Italy, China, and Japan. It is well established that antibiotic resistance profiles of *H. pylori* vary among different geographical regions (32). Such resistance profiles are likely to significantly impact on the efficacy of both bismuth-based quadruple salvage therapy and levofloxacin-based triple therapy (29), and thus, may limit generalizability of these results to European or North American populations.

Although there is little data addressing the prevalence of levofloxacin resistance among *H. pylori* strains, the reports available suggest such resistance to be relatively uncommon (33). There is evidence to suggest that quinolone resistance is easily acquired, particularly in regions with high use (34). This may be a concern in countries such as the United States where quinolones are used to treat a variety of common infections affecting the urinary tract, respiratory tract, and skin. Though we were not able to identify data on levofloxacin resistance among *H. pylori* strains from the United States, a recent abstract from Canada reported a levofloxacin resistance rate of 6–8% (33). A particularly attractive feature of this regimen is its effectiveness in patients infected with strains of *H. pylori* resistant to clarithromycin and/or metronidazole. Gatta *et al*. demonstrated excellent eradication rates of 87% in 107 patients, 80% of which had *H. pylori* resistant to both clarithromycin and metronidazole (25). Some have suggested that levofloxacin-based salvage therapy be reserved for patients with documented or suspected resistance (29). Unfortunately, this recommendation is not practical in the United States where testing for antimicrobial resistance is neither recommended nor readily available. It makes sense to suggest that bismuth-based quadruple therapy be considered in patients who have not been previously exposed to regimens containing tetracycline or metronidazole. Levofloxacin-based triple therapy would be reserved for those that had been treated with a regimen containing tetracycline or metronidazole or could not tolerate bismuth-based quadruple therapy.

In conclusion, our analysis demonstrates that a 10-day course of levofloxacin-based triple therapy is more effective and better tolerated than 7 days of bismuth-based quadruple therapy for the treatment of persistent *H. pylori* infection. We recommend that a randomized, controlled trial comparing levofloxacin-based triple and bismuth-based quadruple therapy be perfomed in a U.S. population with persistent *H. pylori* infection to confirm the results of our meta-analysis. However, on the basis of these results, we propose that levofloxacin-based triple therapy provides an effective alternative salvage regimen to bismuth-based quadruple therapy.

STUDY HIGHLIGHTS

What is Current Knowledge

- Eradication failure in the treatment of *H. pylori* infection is primarily due to antimicrobial resistance and patient non-compliance
- Salvage therapies for persistent *H. pylori* infection are associated with higher failure rates than primary therapies
- The most commonly recommended salvage therapy for persistent *H. pylori* infection is at least 7 days of bismuth-based quadruple therapy
- Levofloxacin-based triple therapy is a recently described salvage regimen for persistent *H. pylori* infection

What is New Here

- A 10 day course of levofloxacin-based triple therapy provided a higher eradication rate than a 7 day course of bismuth-based quadruple therapy in patients with persistent *H. pylori* infection
- Levofloxacin-based triple therapy was better tolerated and associated with a lower likelihood of discontinuation than bismuth-based quadruple therapy
- Levofloxacin 500mg given once daily and levofloxacin 250mg given twice daily yield equivalent eradication rates for persistent *H. pylori* infection

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