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Comparative Efficacy and Safety of Linezolid and Quinupristin-Dalfopristin in the Treatment of Vancomycin-Resistant Enterococcus Infections: A Meta-Analysis

Tomoki Watanabe[1,2]*, Rika Uchida[1], Satoko Handa[2], Manabu Shindo[1], Ichiro Kato[1] and Yasuhisa Kato[2]

[1]*Department of Pharmacy, National Hospital Organization Chiba Medical Center, Chiba, Japan*
[2]*Department of Drug Information, Division of Drug Information Analytics, School of Pharmacy, Showa University, Tokyo, Japan*

Abstract

Introduction: Vancomycin-resistant ***Enterococcus*** (VRE) is one of the most important causative organisms of nosocomial infections. Once VRE outbreaks occur in hospitals, enormous efforts must be made to control them, especially in wards housing neutropenic or transplant patients. The purpose of this meta-analysis was to investigate the efficacy and adverse event profile of linezolid versus that of Quinupristin-Dalfopristin for the treatment of VRE infections.

Methodology: Literature searches of PubMed, MEDLINE, and EMBASE databases were performed on April 5, 2017 using combined text words with the following MeSH/EMTREE terms: "linezolid" and "Quinupristin-Dalfopristin" and "***Enterococcus***" and "human." The odds ratios (ORs) with 95% confidence intervals (CIs) for individual studies were calculated and pooled separately. The pooled estimates were combined using the inverse variance weighting scheme and random effect method.

Results: A systematic search identified 674 articles, and five involving 333 patients were included in the final analysis. One study was a prospective randomized controlled trial, and four were retrospective studies. The mortality rate in the groups of patients treated with linezolid was significantly lower than that in patients treated with Quinupristin-Dalfopristin (OR: 0.47; 95% CI: 0.23 to 0.97; heterogeneity P=0.13, Z=2.05, P=0.04; I^2=44%; Begg's test: P=0.33; Egger's test: P=0.78). The clinical and microbiological responses indicated no significant differences between the linezolid and Quinupristin-Dalfopristin groups (58% and 43%, respectively, P=0.6; OR: 1.51; 95% CI: 0.75 to 3.04; heterogeneity P=0.32; Z=1.15, P=0.25; I^2=0%). The adverse event proiles differed between the Linezolid and quinupristin-dalfopristin groups.

Conclusion: Our results suggest a significantly lower mortality rate in patients treated with linezolid than in those treated with Quinupristin-Dalfopristin for VRE infections; however, this was limited by a variety of factors (mostly retrospective).

Keywords: Vancomycin-resistant *Enterococcus*; Linezolid; Quinupristin-Dalfopristin; Meta-analysis

Abbreviations: VRE: Vancomycin-Resistant *Enterococcus*

Introduction

Vancomycin-resistant *Enterococcus* (VRE) is one of the most important causative organisms of nosocomial infections. VRE was first reported in the UK and France in 1988 [1,2]. Since then, VRE has spread in medical settings worldwide including the US and European countries [3-5]. Linezolid, Quinupristin-Dalfopristin, and daptomycin are anti-infective agents used to treat vancomycin-resistant *Enterococcus faecium* (VREF) infections. Linezolid was the first oxazolidinone anti-infective agent approved in the US in 2000. It can be administered either intravenously or orally; however, its use poses the potential risk of bone marrow toxicity and neuropathy. Serotonergic drug interactions are another drawback of linezolid therapy. Birmingham et al. [6] showed that the evaluable clinical and microbiological response rates of linezolid in the treatment of VRE infections were 73% and 84%, respectively.

Quinupristin-Dalfopristin is a streptogramin antibiotic used for the treatment of VREF that was approved in the US and the UK in 1999. It should be used with caution owing to the risk of side effects (arthralgias, myalgias, and infusion-related side effects), potential drug-drug interactions, and low efficacy against *E. faecalis* [7]. Linden et al. [8] showed that the clinical response rate of Quinupristin-Dalfopristin in the treatment of VREF infections was 68.8% in an evaluable subset. Both linezolid and Quinupristin-Dalfopristin are bacteriostatic against VRE [9]. There are currently few studies comparing the outcomes of patients treated with linezolid versus those of Quinupristin-Dalfopristin for VRE infections. Thus, more studies are needed to evaluate the efficacy outcomes of linezolid and Quinupristin-Dalfopristin in the treatment of VRE infections.

Daptomycin is a cyclic lipopeptide antibiotic with activity against VRE [9]. Two recent meta-analyses showed lower mortality for VRE bacteremia treatment with linezolid than with daptomycin, but these studies were limited by a variety of factors [10-12].

The purpose of this meta-analysis was to compare the efficacy and adverse event profiles of linezolid versus those of Quinupristin-Dalfopristin in the treatment of VRE infections.

Materials and Methods

Literature search

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

***Corresponding author:** Tomoki Watanabe, Department of Pharmacy, National Hospital Organization Chiba Medical Center, 4-1-2 Tsubakimori, Chuo-ku, Chiba-Shi, Chiba 260-0042, Japan, Tel: +81-043-251-5311; Fax: +81-043-251-8922; E-mail: www.tomoki@gmail.com

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statement [13]. Literature searches of the PubMed MEDLINE database (from January 1, 1966) and EMBASE (from January 1, 1974) were performed on April 5, 2017, using combined text words with the following MeSH/EMTREE terms: "linezolid" and "Quinupristin-Dalfopristin" and "*Enterococcus*" and "human." The references of the identified studies and reviews were also scanned to identify additional relevant studies, and no language restriction was imposed.

Study selection and data extraction

Study selection and data extraction were conducted independently by two investigators (TW and RU), and disagreements or uncertainties were resolved by discussion among all the authors to reach a consensus. Studies were included in this meta-analysis if they were published clinical trials or observational studies that simultaneously reported the outcome (mortality) of the treatment of VRE infections with linezolid and Quinupristin-Dalfopristin. Articles were excluded from the analysis if they were reviews or letters, and all prospective and retrospective studies were included. Only the most recent study was included when duplicated studies on the same population were identified. The following information was extracted from each study: author, publication year, country, study duration, study design, study size, mean age, type of infection, acute physiology and chronic health evaluation (APACHE) II score, duration of treatment, mortality, clinical response, and microbiological response. The primary outcome assessed in this meta-analysis was overall mortality. The clinical and microbiological responses were also evaluated. Attempts were made to contact the corresponding authors of studies with insufficient data when necessary.

Statistical analysis

The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and pooled separately for individual studies. The pooled estimates were combined using the inverse variance weighting scheme and random effect method [14]. The heterogeneity among the studies was estimated using the I2 and Cochran's Q statistics [14]. The publication bias was investigated using funnel plots and further assessed using Begg's rank correlation and Egger's linear regression tests [15,16]. All statistical analyses were performed using the Review Manager Version 5.3 (Revman, The Cochrane Collaboration, Oxford, UK).

Results

Search results

The systematic search identified 674 articles, which included 20 duplicates. After title and abstract screening, 175 full-text articles were reviewed, and 170 were subsequently excluded. During the process of abstracting data from the identified articles and reviews, no additional references were identified, and five articles were subsequently included in the final analysis (Figure 1).

Study characteristics

The characteristics of the eligible studies are shown in Table 1. One study was a prospective randomized controlled trial, and four were retrospective studies [17-21]. All the studies were single-center experiences published between 2004 and 2010 in the US and Korea, and 333 patients were identified. Sample sizes of 208 and 125 patients were selected for the linezolid and Quinupristin-Dalfopristin groups, respectively. The attempts to contact the corresponding authors of the four studies with insufficient data yielded no additional data [18-21].

Meta-analyses

The five included studies reported the mortality of 333 patients treated with linezolid (n=208) and Quinupristin-Dalfopristin (n=125) [17-21]. The mortality rate was significantly lower in patients treated with linezolid than it was in those treated with Quinupristin-Dalfopristin (OR: 0.47; 95% CI, 0.23 to 0.97; heterogeneity P=0.13; Z=2.05, P=0.04; I^2=44%; Begg's test: P=0.33; Egger's test: P=0.78 (Figure 2a). Clinical responses were reported in only one study and, therefore, we could not perform a meta-analysis. The clinical response was comparable

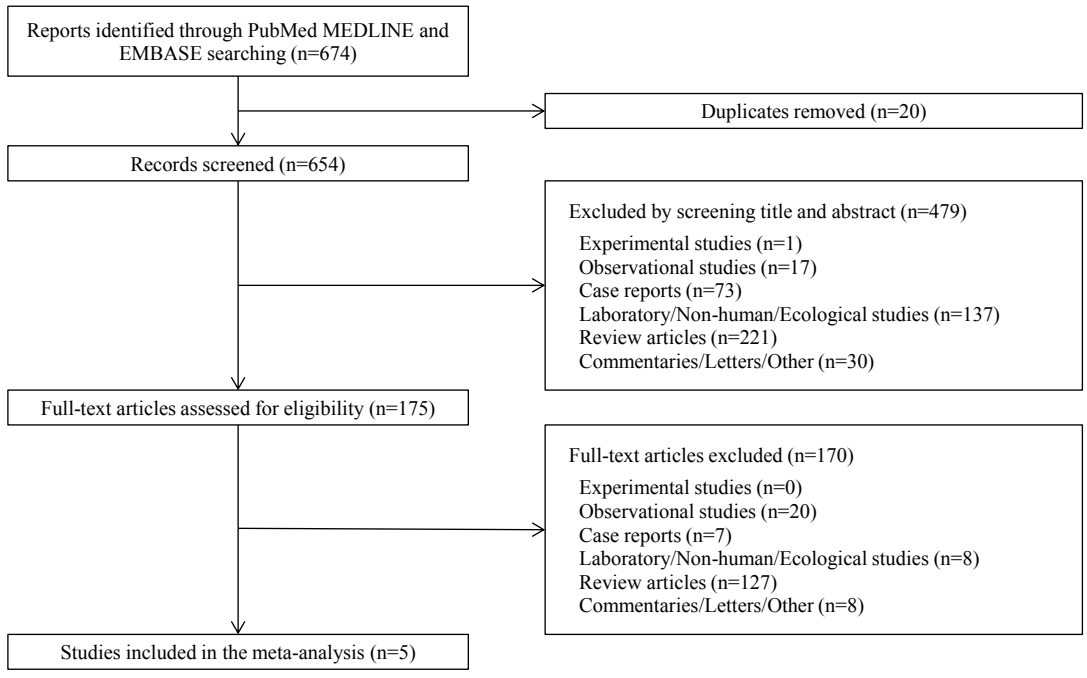


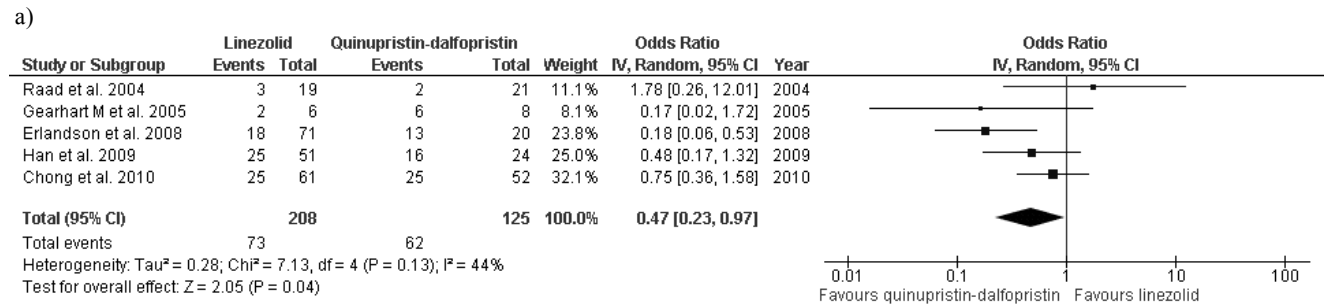
Figure 1: Flow diagram for selection of articles for inclusion in meta-analysis.

Author and year	Country	Study duration	Study design	Study size (no. of patients)		Mean age (SD)		Type of infection (no. of patients)	APACHE II, mean (SD)		Duration of treatment, mean days (SD)	
				LZD	Q-D	LZD	Q-D		LZD	Q-D	LZD	Q-D
Raad et al., 2004 [17]	US	1998–2001	Prospective, randomized study	19	21	54.2 (16.0)	53.4 (14.4)	Bacteremia (37), surgical wound infection (2), and upper urinary tract infection (1)	13.8 (4.1)	14.3 (3.8)	14.7 (9.6)	10.9 (4.6)
Gearhart M et al., 2005 [18]	US	1995–2002	Retrospective study	6	8	NA	NA	Sites of VRE cultures in the infected patients were blood, peritoneal fluid, bile, urine culture, feces, others (detailed data was not shown).	NA	NA	NA	NA
Erlandson et al., 2008 [19]	US	1993–2005	Retrospective study	71	20	34.0 (29.0)	44.7 (19.2)	Bacteremia (91)	17.0 (6.6)	21 (6.9)	14 (range, 3–70)	12 (range, 2–42)
Han et al., 2009 [20]	Korea	1998–2007	Retrospective study	51	24	58 (44–66) [a]		Bacteremia (75)	14 (12–20) [a]		14 (7–20) [a]	
Chong et al., 2010 [21]	Korea	2003–2007	Retrospective study	61	52	50 (17)	51 (16)	Bacteremia (113)	18 (7)	16 (6)	16 (9)	12 (8)

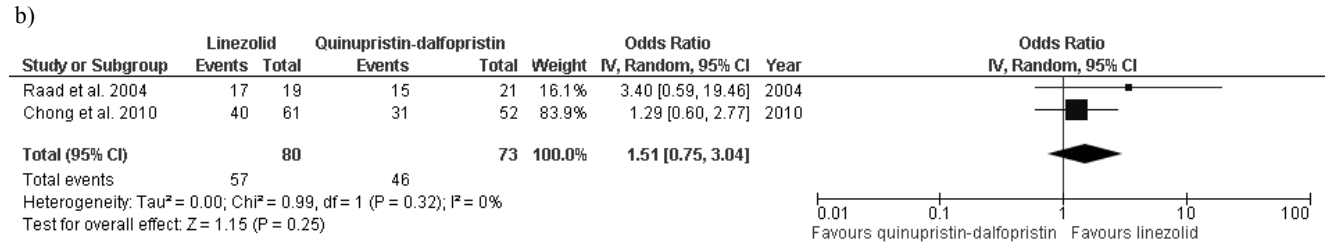
APACHE, Acute Physiology and Chronic Health Evaluation; LZD: Linezolid; NA: Not Applicable; Q-D: Quinupristin-Dalfopristin; SD: Standard Deviation; VRE: Vancomycin Resistant *Enterococcus*

[a] interquartile range.

Table 1: Characteristics of eligible studies.



Forest plot of comparison: Linezolid versus quinupristin-dalfopristin; Outcome: mortality. (Begg's test, $P = 0.33$; Egger's test, $P = 0.78$)



Forest plot of comparison: Linezolid versus quinupristin-dalfopristin; Outcome: microbiological response.

Figure 2: Forest plot showing effect of linezolid versus quinupristin-dalfopristin in the treatment of vancomycin-resistant Enterococcus infections; a: Forest plot of comparison: Linezolid versus quinupristin-dalfopristin; Outcome: mortality. (Begg's test: P=0.33; Egger's test: P=0.78); b: Forest plot of comparison: Linezolid versus quinupristin-dalfopristin; Outcome: microbiological response.

between the linezolid and Quinupristin-Dalfopristin groups (58% and 43%, respectively, P=0.6) [17]. Two studies reported microbiological responses, and the results indicated no significant difference between the linezolid and Quinupristin-Dalfopristin groups (OR: 1.51; 95% CI, 0.75 to 3.04; heterogeneity P=0.32; Z=1.15, P=0.25; I^2=0%, (Figure 2b) [17,21]. Begg's and Egger's tests were not carried out for microbiological response because only two studies were included.

Discussion

The results of this meta-analysis suggest that the mortality rate of the groups of patients treated with linezolid was significantly lower than that of the Quinupristin-Dalfopristin-treated groups. The Quinupristin-Dalfopristin group tended to show a lower rate of clinical and microbiological responses than the linezolid group did, but the differences were not significant. More studies would be needed to make reliable quantitative statements about the differences in the clinical and microbiological responses between the linezolid and Quinupristin-Dalfopristin groups.

Linezolid treatment has been associated with reversible myelosuppression as well as thrombocytopenia and a slight increase

Author and year	Adverse event	Linezolid, n (%)	Quinupristin-dalfopristin, n (%)	*P*-value [a]
Raad et al., 2004 [17]	Increased bilirubin	7/19 (37)	4/21 (19)	0.293
	Myalgias/arthralgias	0/19 (0)	7/21 (33)	0.009
	Nausea/vomiting, diarrhea	5/19 (26)	3/21 (14)	0.442
	Thrombocytopenia/leukopenia	2/19 (11)	0/21 (0)	0.219
Erlandson et al., 2008 [19]	*Clostridium difficile* colitis	1/71 (1)	NA	
	Diarrhea (non–*Clostridium difficile*)	1/71 (1)	NA	
	Lactic acidosis	1/71 (1)	1/20 (5)	0.393
	Leukocytosis	NA	2/20 (10)	
	Myalgias	NA	4/20 (20)	
	Neuropathy	1/71 (1)	NA	
	Thrombocytopenia	1/71 (1)	NA	
Chong et al., 2010 [21]	Thrombocytopenia	3/61 (5)	0/52 (0)	0.248

NA: Not Applicable

[a] Fisher's exact test two-sided *P*-value

Table 2: Adverse event profile for eligible studies.

in the risk of developing anemia [22]. Conversely, the most common systemic adverse events related to treatment with Quinupristin-Dalfopristin are arthralgias and myalgias [23]. The adverse event profiles for the eligible studies in our report are shown in Table 2. Raad et al. [17] showed that the rate of myalgias/arthralgias was 33% (7/21) in the Quinupristin-Dalfopristin study group (P<0.01); however, in all seven cases, myalgias/arthralgias resolved when the drug was discontinued. Chong et al. [21] reported that antibiotic-induced thrombocytopenia was observed only in three patients in the linezolid group (5%), but their platelet counts recovered after linezolid therapy was discontinued. These findings suggest differences in adverse event profiles of linezolid and Quinupristin-Dalfopristin groups.

The increasing incidence of antibiotic-resistant nosocomial pathogens including linezolid- and Quinupristin-Dalfopristin-resistant *Enterococcus* is a global problem [7,24,25]. Univariable analysis of a retrospective study revealed the risk factors for reduced linezolid susceptibility. These factors included allogeneic hematopoietic stem cell or solid organ transplants or both, as well as the administration of immunosuppressive medications including corticosteroids, non-corticosteroids, and linezolid within 1 year prior to the infection [26]. The intensive use of linezolid was subsequently associated with the development of decreased VREF susceptibility to this antibiotic [27]. Therefore, caution should be exercised in empiric therapy or therapy in patients with reduced susceptibility. Two recent meta-analyses showed that linezolid treatment of VRE bacteremia was associated with a lower mortality than daptomycin treatment was [10,11]. However, Anastasiou et al. [28] reported that resistance to linezolid and Quinupristin-Dalfopristin appeared to be independent of daptomycin susceptibility, and no significant cross-resistance was noted. Therefore, daptomycin has the potential to be a useful therapeutic agent for treating VRE infections.

Our study had several limitations that are worth mentioning. The majority of the included studies had some methodological limitations (mostly retrospective), and many lacked detailed case information. Furthermore, the attempts to contact the corresponding authors of studies with insufficient data were unproductive, as no additional data were obtained. There was also evidence of heterogeneity and publication bias. The differences in baseline risks between the groups in the included studies likely played a role in the bias since the linezolid-treated groups appeared to include fewer transplant recipients, APACHE II scores, and renal dysfunction than the Quinupristin-Dalfopristin-treated groups did. However, each of these studies targeted linezolid versus Quinupristin-dalfopristin in the treatment of VRE bacteremia and, therefore, we believe that our study contributes valuable information to the current efforts and strategies to control VRE infections.

Conclusion

Enterococcus is one of the most important causative organisms of nosocomial infection, and VRE outbreaks in hospitals need to be controlled aggressively and promptly to prevent the associated mortalities. Our results suggest that the mortality rate was significantly lower in the groups of patients treated with linezolid than in those treated with Quinupristin-Dalfopristin; however, these findings are limited by a variety of factors. Additional larger, randomized, controlled trials are needed to evaluate the efficacy and safety of linezolid and Quinupristin-Dalfopristin in the treatment of VRE infections. In addition, the antibiotic choice in the treatment of VRE for individual patients should be considered based on local availability, antibiotic resistance patterns, the risk of adverse events, and cost, and our findings would be useful in making informed decisions.

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Ethical Statement

Not required.

Authors Contributions

TW and RU performed the literature search, as well as the data collection, analysis, and interpretation. All authors conceived and designed the study, and read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

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