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Linezolid versus vancomycin for meticillin-resistant *Staphylococcus aureus* infection: a meta-analysis of randomised controlled trials

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ABSTRACT

Linezolid is the first available oxazolidinone, possessing broad-spectrum activity against Gram-positive bacteria and a favourable pharmacokinetic profile. The aim of this study was to compare the efficacy and safety of linezolid with vancomycin, the gold-standard treatment, for meticillin-resistant *Staphylococcus aureus* (MRSA)-related infections. A meta-analysis of randomised controlled trials (RCTs) identified in PubMed, the Cochrane Library and Embase was performed. Nine RCTs, involving 5249 patients, were included in the meta-analysis. The results indicated that linezolid was associated with superior efficacy compared with vancomycin for MRSA-related infection in terms of clinical treatment success [8 RCTs, 2174 patients, odds ratio (OR) = 1.77, 95% confidence interval (CI) 1.22–2.56] and microbiological treatment success (9 RCTs, 1555 patients, OR = 1.78, 95% CI 1.22–2.58). Although no difference was found regarding the overall incidence of drug-related adverse events (AEs) and serious AEs (SAEs) between the linezolid and vancomycin therapy groups (drug-related AEs, 8 RCTs, 5034 patients, OR = 1.20, 95% CI 0.98–1.48; SAEs, 5 RCTs, 2072 patients, OR = 1.00, 95% CI 0.74–1.36), the linezolid therapy group was associated with significantly fewer patients experiencing abnormal renal function (reduced by ca. 60% compared with the vancomycin therapy group; 4 RCTs, 2531 patients, OR = 0.39, 95% CI 0.28–0.55), which is a well-recognised limitation of vancomycin. This meta-analysis provides evidence that linezolid possesses significant advantages compared with vancomycin and may be a superior alternative for MRSA-related infection.

1. Introduction

Since its first appearance in 1960, meticillin-resistant *Staphylococcus aureus* (MRSA) has become a major community-acquired and nosocomial pathogen worldwide, which is capable of causing serious healthcare- and community-associated infections, including skin and soft-tissue infections (SSTIs), pneumonia and deep-seated infections such as endocarditis and osteomyelitis [1]. During the past two decades, MRSA-associated infections have significantly increased and have become a challenge for clinicians because of its high mortality and limited therapeutic options as well as the heavy cost burden [1,2].

The outcome of MRSA-associated infection depends on timely diagnosis and treatment, which involves appropriate antimicrobial therapy directed against MRSA. Absent or inadequate antibiotic therapy results both in increased failure rates and mortality. Historically, vancomycin has been the drug of choice for the treatment of MRSA infections because of its broad-spectrum activity against Gram-positive bacteria, and it has for a long time been considered the gold standard [3]. However, it is now being challenged by the increasing emergence of vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) [4,5]. Poor tissue penetration, adverse effects such as nephrotoxicity, and the need for intravenous (i.v.) access are also well-recognised limitations of vancomycin [3].

The growing rate of MRSA infection and limited therapeutic options calls for new antibiotics. During the past decade, several antimicrobial agents, including linezolid, daptomycin, tigecycline and newer glycopeptides such as dalbavancin, have been introduced into the therapy of MRSA-related infection. Among these agents, linezolid (the first available oxazolidinone, which inhibits bacterial protein synthesis by preventing formation of the 70S initiation complex) has the main advantage [6]. Linezolid possesses excellent in vitro and in vivo activity against a broad range of Gram-positive bacteria, including MRSA and VRSA, and is approved for the treatment of Gram-positive pathogens including MRSA infections such as hospital-acquired and community-acquired pneumonia and complicated SSTIs. Excellent tissue penetration and

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nearly 100% oral bioavailability, which allows an earlier switch to oral administration and possible earlier discharge of patients from hospital, are also notable properties of linezolid [7].

Several randomised controlled trials (RCTs) have compared the efficacy and safety of linezolid with vancomycin for MRSA-related infections [8–16]. However, the results were not completely consistent and did not necessarily draw a solid conclusion. We propose that pooling the analysis of the current studies may provide better evidence. The aim of the study reported here was to compare more conclusively the efficacy and safety of linezolid versus vancomycin for MRSA-related infections by performing a meta-analysis of relevant RCTs. This meta-analysis follows the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [17].

2. Methods

2.1. Data sources

This study was performed using a pre-specified search strategy and study eligibility criteria. An extensive search of PubMed (up to September 2012), the Cochrane Central Register of Controlled Trials (up to Cochrane Library Issue 10, 2012) and Embase (1980 to Sep 2012) was performed with the aim of identifying relevant RCTs for the meta-analysis. The search was restricted to RCTs. Search term combinations were 'linezolid', 'methicillin-resistant *Staphylococcus aureus*', 'MRSA' and 'vancomycin'. The language of the research papers was not restricted. All reference lists from relevant articles and reviews were hand-searched for additional eligible studies. Experts in the field were also consulted, who subsequently confirmed the results of the search for RCTs and were unable to identify any additional eligible study. Articles that were not freely available to us were requested from the authors.

2.2. Study selection

Two reviewers (MMA and HS) independently carried out a literature search and examined relevant RCTs for further assessment. Only those RCTs that directly compared linezolid with vancomycin for patients with MRSA-related infection were selected for analysis. Specifically, clinical trials that met the following criteria were included in the meta-analysis: (i) prospective RCTs (blinded or non-blinded trials) that included patients of all ages with confirmed or suspected MRSA-related infections; (ii) random assignment of participants to linezolid or vancomycin treatment; (iii) available data including clinical treatment success, microbiological treatment success, mortality and adverse events (AEs); and (iv) adequate sample size for analysis. The following studies were excluded from the meta-analysis: (i) phase 1 and single-arm phase 2 trials because of lack of control groups; (ii) abstracts in the proceedings of scientific conferences; (iii) trials focusing on pharmacokinetic or pharmacodynamic variables; and (iv) experimental trials.

2.3. Qualitative assessment

Evaluation of the methodological quality of the RCTs included in the meta-analysis was performed independently by two reviewers (MMA and JDZ) using the Jadad scoring system, as follows [18]. One point was awarded for the presence of randomisation, blinding and data on study withdrawals, respectively. If the randomisation or blinding procedures were appropriate, one point was awarded for each procedure; no points were awarded if no data were provided on the methodology of the abovementioned procedures. Finally, if any of these procedures were not deemed appropriate, one point was deducted for each of the 'inappropriate' procedures. The maximum score that could be attributed to a RCT was 5. A RCT with a score >2 was considered to be of adequately good quality [19,20]. Standard criteria [allocation concealment, blinding, intention-to-treat (ITT) analysis and follow-up] were also used to appraise study quality in addition to the Jadad scoring system.

2.4. Data extraction

Two reviewers (MMA and HS) independently extracted data from the trials included in the meta-analysis using a pre-designed review form. In the case of any disagreement between the two reviewers, a third reviewer (JDZ) extracted the data and the results were attained by consensus. The authors of trials were contacted for missing data when necessary. Data on study characteristics (methodology, included population, study design, drug tested, publication details and funding source), endpoint data and AEs during the treatment and post-treatment period were extracted.

2.5. Analysed outcomes

The primary efficacy outcomes of this meta-analysis were clinical treatment success (defined as 'clinical cure', which was the disappearance of acute signs and symptoms related to infection with no requirement for further antibiotic therapy) assessed at the test-of-cure (TOC) visit and at end-of-treatment (EOT) based on clinically evaluable or ITT populations in each individual study, and all cause mortality in the ITT population during the study period. The secondary efficacy outcome was microbiological treatment success (defined as the eradication of baseline pathogens, or as presumed eradication based on the clinical outcomes when post-treatment cultures were not performed). The safety outcome included the proportion of patients reporting at least one drug-related AE, the proportion of patients reporting at least one serious AE (SAE) and the proportion of patients reporting the most frequent drug-related AEs by category (gastrointestinal-related AEs, thrombocytopenia, abnormal renal function and anaemia).

2.6. Data analysis and statistical methods

Statistical analyses were done with Review Manager v.5.1.7 (Cochrane Collaboration, Oxford, UK). The heterogeneity of the trial results was assessed by calculating a χ^2 test of heterogeneity and the I^2 measure of inconsistency. Publication bias was assessed by examining the funnel plot. A random-effects model was used by using the DerSimonian and Laird method for pooling odds ratios (ORs) and 95% confidence intervals (CIs) of all primary and secondary outcomes throughout the meta-analysis. A sensitivity analysis was performed by omitting one study in turn to investigate the influence of a single study on the overall meta-analysis estimate [21].

3. Results

3.1. Study selection process

The flow diagram in Fig. 1 shows the detailed screening and selection process applied before including trials in the meta-analysis. The search was performed in PubMed, the Cochrane Central Register of Controlled Trials and Embase. In total, 16 full papers from 63 studies were obtained for detailed evaluation and ultimately 9 RCTs that fulfilled all of the criteria for inclusion in the meta-analysis were identified.

3.2. Study characteristics

The main characteristics of the nine included RCTs (type of study design, characteristics of the included population, drugs