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Review

Review of meta-analyses of vancomycin compared with new treatments for Gram-positive skin and soft-tissue infections: Are we any clearer?

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ABSTRACT

Vancomycin has been considered the standard of care for treatment of Gram-positive skin and soft-tissue infections (SSTIs). Its value has been questioned over the last decade owing to well acknowledged limitations in efficacy and tolerability and the emergence of newer meticillin-resistant *Staphylococcus aureus* (MRSA)-active antibacterial agents. However, no single agent has shown better results versus vancomycin in SSTI trials. The aim of this review was to identify and summarise data from meta-analyses (MAs) for the treatment of Gram-positive and MRSA SSTIs. A systematic search identified 21 published MAs examining the use of newer antibiotics and vancomycin in SSTIs. In terms of clinical and microbiological efficacy, linezolid (in Gram-positive and MRSA SSTIs) and telavancin (in MRSA SSTIs) were shown to be more effective than vancomycin. The safety of newer antimicrobials in general was comparable with vancomycin, except for telavancin, which was associated with more severe adverse events (AEs), and tigecycline owing to an all-cause mortality imbalance observed in all infections but not confirmed in SSTIs. Specific AEs were related to the use of newer agents, such as nephrotoxicity for telavancin, creatine phosphokinase elevations for daptomycin, and thrombocytopenia with linezolid. Some evidence suggests that daptomycin could be associated with reduced treatment duration, and linezolid with reduced length of intravenous treatment and hospital length of stay compared with vancomycin. Considering the limitations of this type of research and the comparative efficacy results demonstrated in head-to-head randomised controlled trials, data are still not sufficient to support the widespread use of new agents over vancomycin.

1. Introduction

The increasing body of research data in clinical medicine has led to the need for evidence synthesis studies [1]. Meta-analysis (MA) is defined as the use of statistical methods to summarise and combine the results of independent studies, usually randomised controlled trials (RCTs) [2,3]. Well conducted MAs can provide more precise estimates of treatment effects than results originating from individual studies [4]. Furthermore, they allow investigation of the consistency or differences in evidence across studies [5]. The number of MAs published in peer-reviewed journals is growing exponentially, demonstrating the increasing value that is attributed to this type of research by investigators, clinicians and policy-makers for evidence-based healthcare decision-making.

The treatment of Gram-positive skin and soft-tissue infections (SSTIs) represents a valid field for MA for a number of reasons. Over the last two decades, several antimicrobial agents have been added to the physicians' armamentarium for Gram-positive infections. SSTIs represent the most common indication for the regulatory approval of newer antimicrobials; consequently, there are many studies available for synthesis. These studies have been designed mainly as non-inferiority trials and were usually not powered to show statistical significance. Thus far, no single study has shown a statistically significant difference in efficacy of a newer agent versus vancomycin, which is reflected in the equal ratings among antimicrobials in published complicated SSTI (cSSTI) treatment guidelines [6–8]. Recent concerns over vancomycin efficacy and dosing strategies and the evolving epidemiology with the emergence of community-acquired meticillin-resistant *Staphylococcus aureus* (MRSA) and strains heteroresistant to glycopeptides have further complicated physicians' choices for appropriate treatment [7,9,10]. Finally, potential economic benefits, such as length of

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hospital stay for hospitalised patients, appear to differ based on the choice of antibiotic therapy and can influence treatment decisions owing to increasing economic pressure [11–13].

A significant number of MAs of newer MRSA-active agents in SSTIs have been published. The objective of this review was to identify and summarise data from published MAs for the treatment of Gram-positive SSTIs and MRSA SSTIs regarding the clinical efficacy and safety of MRSA-active antibiotics. Data from available MAs are reviewed as published and no evidence synthesis methods have been applied.

2. Methods

A search in PubMed and the Cochrane Database of Systematic Reviews was undertaken to identify MAs of original articles of MRSA-active agents published in the English language up to August 2014. The search terms included: 'metaanalysis' or 'meta-analysis' and the new MRSA-active agents: 'ceftaroline', 'ceftobiprole', 'dalbavancin', 'daptomycin', 'linezolid', 'glycopeptides', 'quinupristin/dalfopristin', 'tedizolid', 'teicoplanin', 'telavancin', 'oritavancin' and 'vancomycin'. Older agents with MRSA activity such as trimethoprim/sulfamethoxazole, doxycycline or clindamycin were not included in the review.

The search focused on retrieving MAs comparing antimicrobial agents for the treatment of cSSTIs or SSTIs. Use of the new classification of acute bacterial skin and skin-structure infection (ABSSI) in MAs was also allowed. The definitions of outcome measures of efficacy and safety were used as defined in the original MAs. Real-world studies such as observational studies or patient registries or pooled analyses of individual studies, where meta-analytic methods were not applied, were not included in this review. There was no restriction on publication date. Articles examining only paediatric studies or Gram-negative infections were excluded from the analysis.

3. Results

Fig. 1 shows the selection process applied to identify MA articles that reported SSTI-related outcomes. The initial search identified 245 articles. After excluding duplicates and records other than MAs, the full text of 105 articles was retrieved and assessed for eligibility. Twenty-one MAs fulfilled the predefined criteria and were included in the review [16–36].

The main characteristics of the studies are shown in Table 1. Publication dates ranged from 2008 to 2014 and mainly focused on the effects of newer agents versus glycopeptides or β-lactams for suspected or documented Gram-positive infections. The most studied newer antimicrobial was linezolid with seven MAs, followed by tigecycline with four, daptomycin with three and one for telavancin. No MA examining specifically the rest of the antimicrobial agents was retrieved. Five studies compared multiple treatments. With regard to the therapeutic area of interest, seven studies focused exclusively on SSTIs (three focused only on MRSA as the causative agent of SSTIs). For the remaining studies that included data for all infections (5), all Gram-positive infections (4), surgical and non-surgical MRSA wound infections (3), MRSA infections (2) and *S. aureus* infections (1), the results for SSTIs subgroups were extracted and included in this review.

3.1. Meta-analyses of specific antibiotics in skin and soft-tissue infections

3.1.1. Daptomycin

Two MAs comparing the efficacy and safety of daptomycin versus other antimicrobials for SSTIs have been published. The first was published in 2010 [19]. It included four studies (three RCTs and one prospective open-label study) with a total of 1557 patients. An updated MA published in 2014 included only RCTs (six RCTs with 1710 patients) [35]. In the included studies, the daptomycin dose ranged from 4 mg/kg/day for 7–14 days, which was used in most studies, up to a high dose of 10 mg/kg/day for 4 days used in one study [37]. The comparators included antistaphylococcal penicillins and glycopeptides. Vancomycin was dosed according to trough levels in only one non-RCT, which was excluded from the second MA [38], whilst the rest used vancomycin standard dosage [1 g intravenous (i.v.) every 12 h]. No statistically significant difference was found between daptomycin and comparators in either MA regarding overall clinical [odds ratio (OR) = 1.05, 95% confidence interval (CI) 0.84–1.31] and microbiological (OR = 1.05, 95% CI 0.61–1.79) success in SSTIs as well as in the subgroups of MRSA, *S. aureus* and cSSTIs.

Of note, in the MA conducted by Bliziotis et al. [19], an analysis of time-dependent outcomes reported some evidence for shorter i.v. treatment duration (63% of patients required <1 week of i.v. therapy with daptomycin versus 33% of comparators [39]) and shorter total treatment duration (4 days of high-dose daptomycin equivalent to 8 days of i.v. therapy with comparators [37]). This signal should be interpreted with caution due to the limited number of studies, the heterogeneity observed in the daptomycin dose and duration of treatment as well as the choice of comparators and the severity of SSTIs. Daptomycin did not show similar benefits versus comparators in a RCT of uncomplicated SSTIs, which probably respond well to short-duration therapy [19].

The safety of daptomycin was similar to comparators with regard to treatment-related adverse events (AEs) (OR = 1.06, 95% CI 0.71–1.59) and there was a non-significant trend for less treatment discontinuations or mortality (OR = 0.71, 95% CI 0.46–1.10). Elevation of creatine phosphokinase (CPK) levels, an AE linked with daptomycin use, was reported in the second MA (not examined in the first) to be more frequent with daptomycin versus comparators (OR = 1.95, 95% CI 1.04–3.65) but on most occasions it was reversible during or after treatment. An almost 2-fold higher incidence of reported treatment-related AEs was observed in the daptomycin group in the study by Katz et al. [37], which could be associated with the use of a 2.5-fold higher daptomycin dose. However, this result should be interpreted cautiously due to the small number of patients included in this study.

A third MA that examined the efficacy and safety of daptomycin versus comparators for all infections was published in 2014 [36]. It included 13 published and unpublished trials, 7 of which were in SSTIs or cSSTIs. In the only SSTI-specific reported outcome of treatment success in the modified intention-to-treat (mITT) population, daptomycin demonstrated comparable efficacy versus controls (risk ratio = 1.01, 95% CI 0.95–1.07). The safety of daptomycin in all infections was comparable with controls for all-cause mortality and total treatment-related AEs, whilst serious adverse events (SAEs) were less with daptomycin. In specific AEs, daptomycin was related to a lower incidence of renal AEs, nausea and headache but to an increased incidence of reversible CPK elevations. Finally, a signal for potential shorter treatment duration with daptomycin versus comparators is discussed by the authors, which is derived from individual trials in SSTIs and could not be statistically compared.

3.1.2. Telavancin

One MA reporting SSTI-related outcomes reviewed and synthesised the available evidence from telavancin RCTs [26]. Four of the six RCTs included in the MA were performed in cSSTIs with a total of 2229 patients. These were two phase 2 (FAST) trials comparing telavancin i.v. at 7.5 mg/kg/24 h or 10 mg/kg/24 h with standard therapy (vancomycin or antistaphylococcal penicillin, chosen prior