ORIGINAL ARTICLE

Comparison of vancomycin and linezolid in patients with peripheral vascular disease and/or diabetes in an observational European study of complicated skin and soft-tissue infections due to methicillin-resistant *Staphylococcus aureus*

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Abstract

Suboptimal antibiotic penetration into soft tissues can occur in patients with poor circulation due to peripheral vascular disease (PVD) or diabetes. We conducted a real-world analysis of antibiotic treatment, hospital resource use and clinical outcomes in patients with PVD and/or diabetes receiving linezolid or vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* complicated skin and soft-tissue infections (MRSA cSSTIs) across Europe. This subgroup analysis evaluated data obtained from a retrospective, observational medical chart review study that captured patient data from 12 European countries. Data were obtained from the medical records of patients $\geq$ 18 years of age, hospitalized with an MRSA cSSTI between 1 July 2010 and 30 June 2011 and discharged alive by 31 July 2011. Hospital length of stay and length of treatment were compared between the treatment groups using inverse probability of treatment weights to adjust for clinical and demographic differences. A total of 485 patients had PVD or diabetes and received treatment with either vancomycin (n = 258) or linezolid (n = 227). After adjustment, patients treated with linezolid compared with vancomycin respectively had significantly shorter hospital stays (17.9 ± 13.6 vs. 22.6 ± 13.6 days; $p < 0.001$) and treatment durations (12.9 ± 7.9 vs. 16.4 ± 8.3 days; $p < 0.001$). The proportions of patients prescribed oral, MRSA-active antibiotics at discharge were 43.2% and 12.4% of patients in the linezolid and vancomycin groups, respectively ($p < 0.001$). The reduction in resource use may result in lower hospital costs for patients with PVD and/or diabetes and MRSA cSSTIs if treated with linezolid compared with vancomycin.

Keywords: Diabetes, length of stay, length of treatment, linezolid, peripheral vascular disease, vancomycin
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Introduction

Patients with peripheral vascular disease (PVD) or diabetes are at high risk of developing complicated skin and soft-tissue infections (cSSTIs), and when they occur, these infections may be more challenging to treat [1,2]. The ability of some antibiotics to penetrate into soft tissues, especially the lower extremities, can be compromised in these patients, resulting in lower

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antibiotic concentrations at the infection site than in the plasma [3]. Vancomycin, in particular, has been shown to distribute poorly into the soft tissues of diabetic patients, which has been hypothesized as a mechanism for treatment failures [2].

The clinical impact of suboptimal vancomycin penetration into infected tissue is not well documented. Patients with vascular disease given vancomycin for culture-proven methicillin-resistant *Staphylococcus aureus* (MRSA) cSSTIs had lower clinical success rates (p 0.02) than patients receiving linezolid in a subgroup analysis of pooled data from two clinical trials [1]. In contrast, patients with diabetes mellitus given linezolid or vancomycin for culture-proven MRSA cSSTIs had similar clinical success rates in a subgroup analysis of data from three clinical trials [2].

To our knowledge, the effects of an antibiotic regimen on outcomes in patients with MRSA cSSTIs and comorbid PVD or diabetes mellitus have not been evaluated in a real-world setting. Therefore, we conducted a real-world analysis of antibiotic treatment, hospital resource use, and clinical outcomes in patients with PVD and/or diabetes receiving linezolid or vancomycin for the treatment of MRSA cSSTIs across Europe.

Materials and methods

This subgroup analysis evaluated data obtained from a retrospective, observational medical chart review study that captured patient information via 342 physicians in 12 European countries (the UK, Ireland, France, Germany, Italy, Spain, Portugal, Austria, Greece, Poland, Slovakia and the Czech Republic) [4–6]. Data were obtained from hospital records of patients aged 18 years of age or older who were hospitalized with a documented MRSA cSSTI between 1 July 2010 and 30 June 2011 and discharged alive by 31 July 2011. Patients were excluded from the study if they had suspected or proven diabetic foot infection, osteomyelitis, infective endocarditis, meningitis, joint infection, necrotizing fasciitis, gangrene, prosthetic joint infection or prosthetic implant/device infection, or significant concomitant infection at other sites (e.g. bacteraemia, pneumonia). To be included in this subgroup analysis, patients had to have received MRSA-targeted therapy with vancomycin or linezolid for the full duration of antibiotic therapy, either as monotherapy or in combination with other antibiotics.

Study investigators randomly selected hospital records for review for patients meeting the enrolment criteria. Data collected included demographic and clinical characteristics, MRSA-targeted intravenous (IV) and oral antibiotic use, hospital resource use and clinical outcomes. Additionally, records of patients with MRSA cSSTIs and PVD treated with linezolid were oversampled so as to have a sufficient sample size for comparisons.

Study investigators identified patients with PVD and/or diabetes following review of the patient's medical chart. The full analysis set for this sub-study included patients with PVD, diabetes, or both. The PVD analysis set included only patients with PVD, regardless of whether or not they had diabetes. The lower extremity cSSTI analysis set included all of the patients in the PVD analysis set who had a lower extremity cSSTI (foot, toes, leg or groin).

The primary outcome was hospital length of stay (LOS; total and by type of hospital unit). Secondary outcomes included MRSA-targeted antibiotic length of treatment (LOT; total and IV) and number of cSSTI-associated surgical procedures required during hospitalization. Clinical response at discharge was evaluated and defined as cure (resolution of all signs and symptoms/improvement to such an extent that further antimicrobial therapy was not necessary), improvement (improvement in signs and symptoms), failure (persistence, incomplete clinical resolution, or worsening in signs and symptoms), or indeterminate (inability to determine an outcome).

The primary study comparison was between vancomycin- and linezolid-treated patients. Inverse probability of treatment weights based on propensity scores were used to adjust for demographic and clinical differences between patients receiving these antibiotics. Variables used to construct the inverse probability of treatment weights included patient demographics (age, gender, race, body mass index, smoking history, intravenous drug abuse, alcohol use), clinical characteristics (diagnoses (PVD, diabetes, or both), comorbid conditions, cSSTI type, cSSTI source, cSSTI location, co-infection, MRSA infection within the past 12 months, previous MRSA infection, time to MRSA-targeted therapy), and hospital characteristics (type of hospital, location, early discharge protocol, discharge physician type). Weighted groups were compared using Pearson's chi-square test for categorical or ordinal characteristics and a *t* test for continuous characteristics. All inferences were made assuming a two-sided test with an α 0.05.

Results

The parent study cohort included a total of 1542 patients with a documented MRSA cSSTI (Fig. 1). This subgroup analysis included data from 485 patients with a documented MRSA cSSTI and PVD and/or diabetes treated with linezolid or vancomycin for the full duration of therapy.

Patients with PVD and/or diabetes

A total of 258 patients received vancomycin and 227 patients received linezolid. Although differences in demographic and