Infectious Diseases Now 51 (2021) 362–367

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

Daptomycin versus teicoplanin in the treatment of osteomyelitis: Results of the Göztepe retrospective cohort study

O.R. Sipahi[a,*], H.A. Erdem[a], H. Kahraman[a], E. Kurşun[b,f], B.M. Suntur[c], T. Demirdal[d], S.A. Nemli[d], M. Dizbay[e], M. Ulug[f], N. Öztoprak-Cuvalci[g], B. Arda[a], G. Quliyeva[a], M. Tasbakan[a], S. Uysal[a], H. Sipahi[h], S. Aydemir[i], S. Ulusoy[a]

[a] *Ege University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey*
[b] *Baskent University, Faculty of Med., Department of Infectious Diseases and Clinical Microbiology, Adana, Turkey*
[c] *Adana Numune Hospital, Infectious Diseases and Clinical Microbiology Clinic, Adana, Turkey*
[d] *Katip Celebi University, Faculty of Med., Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey*
[e] *Gazi University, Faculty of Med., Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
[f] *Eskisehir Private Umit Hosp., Eskisehir, Turkey*
[g] *Antalya Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Antalya, Turkey*
[h] *Bornova Health Directorate, Izmir, Turkey*
[i] *Ege University, Faculty of Medicine, Department of Microbiology and Clinical Microbiology, Izmir, Turkey*

ARTICLE INFO

Article history:
Received 10 October 2020
Received in revised form 10 January 2021
Accepted 15 January 2021
Available online 22 January 2021

ABSTRACT

Objectives: Daptomycin is highly effective against Gram-positive multidrug-resistant bacteria. Publications on daptomycin in osteomyelitis treatment are limited.
Patients and methods: In this multicenter retrospective cohort study, the aim was to evaluate the outcomes of osteomyelitis cases having received daptomycin or teicoplanin. This multicenter retrospective cohort study gathered data from seven centers located in five cities of Turkey. Study inclusion criteria were as follows: (a) magnetic resonance imaging and/or direct X-ray revealed osteomyelitis or biopsy pathologic examination results concomitant with osteomyelitis. Chi-squareand Student *t*-tests were used for statistical comparison.
Results: A total of 72 patients, 38 cases in the daptomycin group and 34 cases in the teicoplanin group diagnosed with osteomyelitis fulfilling the study inclusion criteria, were included in the study. Clinical success at the end of induction therapy was achieved in 32/38 cases in the daptomycin cohort vs. 30/34 cases in the teicoplanin cohort (p: 0.73).
Conclusion: Although this is a limited experience in a small but well-defined cohort, our data suggest that daptomycin may be a safe alternative to glycopeptides in osteomyelitis treatment. A randomized controlled clinical study involving larger cohorts may increase the available evidence.

1. Introduction

Notwithstanding developments in the quality of medical care, surgery and antimicrobial therapy, osteomyelitis remains associated with significant morbidity [1,2]. Staphylococci, as well as methicillin-resistant staphylococci, are the main causative agents in osteomyelitis [1–4]. Historically, vancomycin, teicoplanin or linezolid may be indicated in empirical and/or etiology-based treatment of osteomyelitis [1–4]. Despite these extended spectrum Gram-positive bacteria-oriented antibacterial agents, clinical as well as microbiological failure is not rare [5–10].

Daptomycin is a cyclic lipopeptide antibiotic with rapid, concentration-dependent bactericidal activity without cell lysis. It is highly effective against Gram-positive multidrug-resistant bacteria [11,12]. Publications on daptomycin in osteomyelitis treatment are limited [10–17]. In this multicenter retrospective cohort study, the aim was to evaluate the outcomes of osteomyelitis cases having received daptomycin or glycopeptide (although we asked all the study centers to include cases having used teicoplanin or vancomycin, many centers used only teicoplanin but not vancomycin as a glycopeptide; for this reason, we will continue reporting on the teicoplanin cohort in the rest of the manuscript).

* Corresponding author at: Ege University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Bornova, Izmir 35100, Turkey.
E-mail addresses: oguz.resat.sipahi@gmail.com, oguz.resat.sipahi@ege.edu.tr (O.R. Sipahi).

https://doi.org/10.1016/j.idnow.2021.01.009

2. Materials and methods

This multicenter retrospective cohort study gathered data from five cities (İzmir–Ankara–Adana–Antalya–Eskişehir) from three geographic regions of Turkey. The planned study was announced via the Infectious Diseases and Clinical Microbiology Specialty Society of Turkey (EKMUD) mail communication group and all sites having accepted the invitation were included in the study. The study comprised adult osteomyelitis cases having received daptomycin or teicoplanin including [(D) or (T)]. Clinical data including fever ($\geq 38\,^{\circ}C$), treatment, laboratory findings and outcomes for all cases fulfilling the study inclusion criteria were evaluated retrospectively by chart review and hospital databases.

2.1. Inclusion and exclusion criteria

Study inclusion criteria were as follows:

- magnetic resonance imaging and/or direct X-ray revealed osteomyelitis or biopsy pathologic examination results associated with osteomyelitis;
- at least seven days of daptomycin or teicoplanin up until November 2016.

Study exclusion criteria were as follows:

- cases aged < 18;
- cases who received daptomycin or glycopeptides fewer than seven days;
- cases with concomitant pneumonia;
- cases with prosthesis/prosthetic joint infection/fracture fixation with any foreign body.

Patients with the following criteria were considered to have chronic osteomyelitis; clinical or radiographic evidence of infection > 6 weeks, relapse or persistence of infection after appropriate antibiotic therapy, and infections associated with foreign bodies or vascular abnormalities [1]. Cases that had none of the chronic osteomyelitis criteria were considered as non-chronic osteomyelitis.

Bacteriological isolates were identified by standard techniques. Antimicrobial susceptibility testing of the isolates was performed with the VITEK 2 system (bio Merieux, La Balme-les-Grottes, France) in all centers. Results were interpreted according to the Clinical Laboratory Standards Institute criteria [18]. Vancomycin, teicoplanin or daptomycin Etest (bio Merieux, La Balme-les-Grottes, France) was used when the automated system result was "non-susceptible".

The primary efficacy outcome was clinical success (resolution of clinical signs including fever and purulent discharge and other symptoms) or negative culture reported at the end of induction therapy (induction therapy refers to period of teicoplanin or daptomycin including therapy), while the secondary efficacy outcome was maintenance of success through one month following completion of induction without any relapse. Infection-related mortality referred to death resulting from osteomyelitis. All-cause mortality referred to death resulting from any reason during the treatment and the 30-day follow-up period.

2.2. Statistical analysis

The objective of this study was to compare the clinical success rates of the daptomycin and teicoplanin cohorts. All analyses were performed by SPSS version 18.0 (Chicago, IL, USA). The significance of difference between groups was evaluated by Chi-square test and *t*-test as indicated. The significance level was accepted as $P < 0.05$. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

2.3. Ethical approval

This retrospective cohort study was approved by the Ege University Institutional Review Board (decision No. 15-6/14).

3. Results

A total of 72 patients, 38 cases in the daptomycin cohort and 34 cases in the teicoplanin cohort diagnosed according to the above-mentioned criteria, were included in the study. The clinical characteristics of the patients in the two treatment cohorts are shown in Table 1. Age, gender, number of patients with chronic renal failure, diabetes mellitus, previous diabetic foot infection, previous amputation, peripheric artery disease, peripheral neuropathy, insulin use, venous failure and immunosuppression were similar in both treatment arms (Table 1).

3.1. Clinical presentation and diagnosis

The main complaints at admission were back pain ($n = 20$) and purulent wound discharge ($n = 13$) in the daptomycin group and while back pain ($n = 15$) and purulent wound discharge ($n = 13$) in the teicoplanin group. Ten vs. eight cases had osteomyelitis secondary to spinal surgery: six vs. six had primary osteomyelitis, 17 vs. 17 had vertebral osteomyelitis whereas four vs. eight had long bone osteomyelitis in the daptomycin and glycopeptide groups, respectively ($P > 0.05$, Table 1).

Tissue biopsy cultures revealed the etiology in 20 vs. 23 cases ($P = 0.23$, Table 1) while other etiologic agents were isolated from abscess material or operation material (Table 1). The most common etiologic agent was *Staphylococcus aureus*. The number of cases diagnosed via X-ray, MRI and CT or via pathology; duration of osteomyelitis before daptomycin or teicoplanin; therapy; fever; mean blood leukocyte count; erythrocyte sedimentation rate; and CRP levels of the cohorts, are shown in Table 1 and were similar in the (D) and (T) groups.

3.2. Previous antibiotic therapy

Twenty-nine cases had received 1–5 (median 2) different antibiotics with failure (16 had received glycopeptides) before receiving daptomycin including regimens, while 9 had received daptomycin as primary treatment in the daptomycin cohort.

Twenty-one cases had received 1–5 (median 2) different antibiotics with failure before receiving teicoplanin including regimens, while 13 had received teicoplanin including therapy as primary treatment.

3.3. Treatment

Daptomycin was administered with a 500 mg q24h dose in 38 cases. In 20 cases, daptomycin was started in accordance with the results of the antibacterial susceptibility testing of tissue biopsy cultures, whereas in the remaining cases it was started empirically (Table 1). In the teicoplanin group, teicoplanin was given as a dose of 400 mg in 10 cases, 800 mg in 22 cases and 400 mg q72h in two cases. In 23 cases, teicoplanin was started in accordance with the results of the antibacterial susceptibility testing of tissue biopsy cultures, while it was started empirically in the remaining ones.

In the daptomycin cohort, daptomycin was used as monotherapy in 13 cases, and as part of combination therapy in 25 cases. No additional therapy was used after daptomycin in 21 cases, whereas 17 cases received further therapy. Glycopeptides were used as

Table 1
General characteristics of the daptomycin and glycopeptide groups.

	Daptomycin Total = 38 *n* (%)	Glycopeptides Total = 34 *n* (%)	*P*
Male	24 (63)	21 (62)	1
Female	14 (37)	13 (38)	1
Age	56.3 (± 14.7)	54.6 (± 15.4)	0.602
Duration of therapy, mean days	35.1 (± 22.7)	45.2 (± 27.4)	0.115
Diabetic foot infection	8 (21)	8 (24)	1
Long bone	5 (13)	8 (24)	0.359
Vertebral osteomyelitis	17 (45)	17 (50)	0.81
Posttraumatic osteomyelitis	2 (5)	4 (12)	0.41
Chronic osteomyelitis	31 (82)	24 (71)	0.405
Non-chronic osteomyelitis	7 (18)	10 (29)	0.405
Postsurgical osteomyelitis	15 (39.4)	10 (29.4)	0.45
Duration of the current infection (mean days)	183.68 ± 578.87	128.03 ± 199.73	0.581
Underlying disease			
Immunosuppression	4	1	0.36
Chronic renal failure	6	6	1
Diabetes mellitus	19	16	0.81
Peripheric neuropathy	5	2	0.43
Insulin therapy	15	15	0.81
Previous diabetic foot infection	5	4	1
Previous amputation	1	0	[a]
Peripheric artery disease	6	6	1
Venous failure	0	1	[a]
Fever	6	2	0.266
Leukocyte at the beginning of induction therapy (mean ± s.d./mm^3)	10,418 ± 4797	10498 ± 3826	0.937
Leukocyte at the end of induction therapy (mean ± s.d./mm^3)	8542 ± 2857	7833 ± 2146	0.252
CRP at the beginning of induction therapy (mean ± s.d. mg/dL)	8.87 ± 12.6	6.63 ± 5.42	0.314
CRP at the end of induction therapy (mean ± s.d. mg/dL)	2.78 ± 3.78	2.32 ± 2.28	0.753
ESR at the beginning of induction therapy (mean ± s.d. mm/h)	69.0 ± 30.2	66.8 ± 28.6	0.143
ESR at the end of induction therapy (mean ± s.d. mm/h)	41.9 ± 29.7	39.1 ± 25.5	0.710
Radiology			
X-ray performed	19	20	0.806
Osteomyelitis	17	17	0.81
CT performed	11	10	1
Osteomyelitis	1	0	[a]
Abscess	4	0	[a]
Septic arthritis	0	0	[a]
MRI performed	32	27	0.597
Osteomyelitis	22	21	0.81
Abscess	8	10	0.43
Septic arthritis	2	0	0.49
Pathology result compatible with osteomyelitis	13	15	0.47
Etiology	25	23	1
MRSA	9	10	0.60
MSSA	5	5	1
Enterococcus spp.	5	2	0.43
MRCNS	5	3	0.71
MSCNS	0	3	0.10
Streptococcus agalactiae	1	0	1
Fusobacterium nucleatum	0	1[b]	0.47
Other Gram-positive spp.	2	1	1
Debridement	12	10	1
Concomitant antibiotics with daptomycin or teicoplanin	25	26	0.437
3rd generation cephalosporin	5	4	0.859
Quinolones	7	11	0.172
Piperacillin/tazobactam	4	3	0.807
Carbapenems	6	6	0.833
Others	3	1	0.359

CRP: C reactive protein; ESR: erythrocyte sedimentation rate; s.d.: standard deviation.
[a] *P*-value was not calculated since n was too small.
[b] Coinfected with methicillin-resistant coagulase-negative staphylococci.

monotherapy in eight cases, and as a part of combination therapy in the other 26 cases (*p*: 0.437). There was no significant difference between cohorts in terms of concomitant antibiotics used as combination therapy (Table 1). No additional therapy was used after glycopeptides in 20 cases, whereas 13 cases received further therapy. Twelve and 10 cases (Table 1) underwent additional surgery/debridement for osteomyelitis during the daptomycin and teicoplanin therapy periods, respectively (*P* = 1).

3.4. Clinical efficacy

Clinical success at the end of treatment was achieved in 32/38 cases in the (D) cohort vs. 30/34 cases in the teicoplanin cohort (*P* = 0.73), including a decrease in inflammatory parameters and relief of the clinical findings at the conclusion of induction therapy. Mean CRP and ESR level after the end of induction therapy were 2.78 ± 3.78 mg/dL in daptomycin, 2.32 ± 2.28 mg/dL in

Table 2
Clinical outcomes.

	Daptomycin cohort	Glycopeptide cohort	*P*
Clinical success at the end of induction therapy	32/38 (84.2)	30/34 (88.2)	0.73
Monothrapy with daptomycin or tericoplanin	13/13 (100)	8/8 (100)	
Daptomycin or teicoplanin + any concomittant antibiotic therapy during induction therapy	19/25 (76)	20/26 (76.9)	
No etiology	11/13 (84.6)	11/11 (100)	0.48
MRSA	8/9 (88.9)	9/10 (90)	1
MSSA	5/5 (100)	4/5 (80)	1
MRCNS	3/5 (60)	2/3 (66.7)	[a]
MSCNS	0	2/3 (66.7)	[a]
Any methicillin-resistant staphylococci	11/14 (78.6)	12/14 (84.6)	1
Any methicillin-sensitive staphylococci	5/5 (100)	6/8 (100)	0.487
Enterococcus spp.	5/5 (100)	2/2 (100)	[a]
Streptococcus agalactiae	0/1 (0)	0	[a]
Fusobacterium nucleatum	0	1/1[b]	[a]
Other Gram-positive spp.	½ (50)	1/1 (100)	[a]
Long bone	4/5 (80)	8/8 (100)	0.386
Vertebral osteomyelitis	14/17 (82.3)	14/17 (82.3)	1
All other osteomyelitis excluding vertebral osteomyelitis	18/21 (85.7)	16/17 (94.1)	0.613
Primary osteomyelitis	5/6 (83.3)	6/6 (100)	1
Postsurgical osteomyelitis	15/15 (100)	9/10 (90)	0.40
Diabetic foot osteomyelitis	7/8 (87.5)	7/8 (87.5)	1
Chronic osteomyelitis	25/31 (80.6)	20/24 (83.3)	1
Non-chronic osteomyelitis	7/7 (100)	10/10 (100)	1
Debridement	12/12 (100)	10/10 (100)	1
No debridement	20/26 (76.9)	20/24 (83.3)	0.727
All cause mortality	1/38 (2.6)	1/34 (2.9)	1

MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRCNS: methicillin-resistant coagulase-negative staphylococci.
[a] *P*-value was not calculated since *n* was too small.
[b] Coinfected with methicillin-resistant coagulase-negative staphylococci.

teicoplanin and 41.9 ± 29.7 mm/h in daptomycin, 39.1 ± 25.5 mm/h in teicoplanin cohorts. There was no significant difference in terms of clinical success in any subgroup analysis including monotherapy, daptomycin or teicoplanin + any combination therapy, methicillin-sensitive or resistant staphylococci, vertebral osteomyelitis, vertebral osteomyelitis, long bone osteomyelitis, primary osteomyelitis, postsurgical osteomyelitis, diabetic foot osteomyelitis, chronic osteomyelitis, non-chronic osteomyelitis, and with or without debridement (Table 2).

One out of the 30 teicoplanin cases (a case with MSCNS osteomyelitis) and none of the 32 (D) cases with a successful outcome at the end of induction therapy developed relapse during one month follow-up ($P = 0.48$). In the teicoplanin cohort, dosage did not change the primary outcome (400 mg q24h: 9/10, 400 mg q12h 12/14, 400 mg q72h: ½, $P = 1$ for q12h vs. q24h). One case in each arm died during therapy ($P = 1$) (Table 2).

3.5. Adverse events

The most common severe adverse event was elevated creatine phosphokinase (CPK) value; one in daptomycin arm and one in teicoplanin arm. In both cases, the treatment was switched to another therapy due to increased CPK ($P = 1$). There was no significant change among the two cohorts in terms of any adverse event.

4. Discussion

Despite extended developments in antimicrobial therapy, osteomyelitis is rarely associated with significant morbidity and mortality. The diagnosis of osteomyelitis depends on clinical and laboratory findings, as well as MRI and microbiology or pathology [1–4,19]. In our cohorts, the diagnosis was supported by radiology (MRI and/or X-ray) and microbiological evidence and/or pathological findings associated with osteomyelitis.

Vancomycin and teicoplanin have been the two glycopeptides used as the principal antibacterial agents in treatment of Gram-positive multidrug-resistant bacterial infections including osteomyelitis vs. MRSA and MRCNS since the 1960s and 1980s [3–10]. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) for the Treatment of MRSA Infections in Adults and Children [3] suggest IV vancomycin (B-II) and daptomycin 6 mg/kg/dose IV once daily (B-II) in cases of osteomyelitis. Some experts advise the addition of rifampin 600 mg daily or 300–450 mg PO twice daily to vancomycin or daptomycin (B-III). More recent IDSA native vertebral osteomyelitis guidelines [4] suggest vancomycin or daptomycin. Probably because teicoplanin is not licensed in the United States, it is not mentioned in the guidelines.

Randomized controlled data on glycopeptides vs osteomyelitis are scarce. In the only randomized controlled study comparing vancomycin and teicoplanin, cure rates were 7/12 in the teicoplanin group and 6/9 in the vancomycin group, respectively [5]. Weinberg reported a series of 60 cases treated with teicoplanin with a microbiological cure rate of 86% (37/43) [6]. Clinically, 45 patients infected with staphylococci (including methicillin-susceptible and MRSA and coagulase-negative staphylococci) met the predetermined criteria for complete and adequate therapy. Among them, 39 (87%) responded favorably and became free of all signs of infection. Similarly, Testore et al. [8] reported 92% (70/76) and LeFrock et al. [9] reported a 90% clinical success rate with teicoplanin in osteomyelitis. The above-mentioned studies suggest that vancomycin and teicoplanin have similar success rates in osteomyelitis, which also means similar failure rates. Our success rate in (T) cohort (29/34, 85%) was also compatible with the published data. Furthermore, teicoplanin dosage (400 mg q24 or q12h) did not affect the outcomes.

Daptomycin, tigecycline and linezolid are the major alternatives available in Turkey for treatment of MDR Gram-positive bacteria [20]. Although there exist clinical data on linezolid in osteomyelitis, it has the disadvantages of being bacteriostatic and having hematologic or neuropathic toxicity in long-term use [3,4]. Tigecycline has the advantage of covering susceptible *Acinetobacter* spp and *Enterobacteriaceae* infections but also the disadvantage

of being bacteriostatic [2–4]. In clinical practice, daptomycin is a major alternative antibacterial agent in treatment of MDR Gram-positive bacterial infections, especially those involving glycopeptide MIC > 1 mg/dL [7] and vancomycin-resistant enterococci. In the only randomized controlled study comparing daptomycin with standard-of-care therapy (vancomycin, teicoplanin, or semisynthetic penicillin for prosthetic joint infection), there was no significant difference. Overall clinical success rates were 58.3% (14/24) and 60.9% (14/23) in the daptomycin 6- and 8-mg/kg groups, respectively, and 8 out of 21 (38.1%) in the comparator group [10]. Lalani et al. evaluated the clinical characteristics, treatment and outcomes of patients with osteoarticular infections associated with *S. aureus* bacteremia. In this phase 3 study subgroup analysis, at six weeks following the end of therapy a successful outcome was documented in 14 out of 21 (67%) patients with osteoarticular infections in the daptomycin group and 6 out of 11 patients (55%) treated with standard therapy ($P > 0.05$) [14]. Moenster et al. compared 17 osteomyelitis cases treated with daptomycin with a matched cohort of 34 cases having received vancomycin, and reported less recurrence in the daptomycin arm (5/17 vs. 21/34 $P < 0.05$) during six-month follow-up [17]. In another nested case-control study, 20 patients with MRSA osteoarticular infections treated with daptomycin were matched to 40 patients treated with vancomycin. Clinical success rates were similar between daptomycin and vancomycin at three months [15 (75%) vs. 27 (68%); $P = 0.8$] and six months [14 (70%) vs. 23 (58%); $P = 0.5$] [15]. Lastly, in a very recent industry-sponsored multicenter registry study, which comprised a total of 11,557 cases, the clinical success rate was 77.7% in the osteomyelitis subgroup (994 cases) [16]. In a recent systematic review, Telles et al. analyzed daptomycin as treatment for bone and joint infections and prosthetic joint infections. They reported considerable heterogeneity in different studies regarding device-related infections, surgical procedures, and daptomycin regimens (ranging from 4 mg/kg to 10 mg/kg). A total of 299 patients had been included in all studies (184 infections associated with orthopedic disposal, and 115 with osteomyelitis/septic arthritis). Two hundred and thirty-three patients were treated with daptomycin. The clinical cure rates on device-related and non-device-related infections (i.e. osteomyelitis) were 70% and 78%, respectively. In our study, the success rate of 84.2% was slightly higher; this may be due to the facts that prosthetic infections were excluded and that follow-up time was one month after induction therapy.

Montage et al reported bone penetration of daptomycin as 9.0% (interquartile range [IQR], 4.4 to 11% in 16 cases) [20]. Garazzino et al. analyzed bone penetration of glycopeptides. The bone penetration rates of vancomycin were numerically higher than those of teicoplanin (mean 20.67% and 89.39% vs. 12.35% and 48.6%, respectively), but the difference was not statistically significant ($P = 0.071$) [21].

Daptomycin is associated in time kill assays against staphylococci with a faster in vitro killing rate than glycopeptides [10]. However, in vitro speed did not result in a better outcome in clinical trials and our cohorts [10]. This is probably due to our study's long treatment period (mean 35.1 days in daptomycin and 45.2 days in glycopeptide cohort), which gave glycopeptides time to kill in vivo as much as daptomycin and/or better bone penetration of glycopeptides over longer periods. Since ours was a retrospective cohort study, we are lacking in bone penetration data on the cohorts.

Our study has several limitations. Although multicenter, it was a retrospective case-control study. If we kept follow-up time at one month, it was because the results of longer follow-up would have been affected by additional oral therapy. Even though the baseline characteristics of the daptomycin and glycopeptide cohorts were similar in all parameters we checked, this was not a randomized controlled study. Hence, we cannot exclude a selection bias. Despite these disadvantages, to our knowledge, this is the largest independent study and dataset comparing daptomycin with glycopeptides in adult osteomyelitis.

5. Conclusions

Although this is a limited experience in a small but well-defined cohort, our data suggest that daptomycin may be at least a salvage therapy option, a safe alternative to glycopeptides in the treatment of adult osteomyelitis.

Financial support

No funding was used for this study.

Disclosure of interest

The authors declare that they have no competing interest.

Authors' contributions

ORS-HAE and HK designed and performed the study, acquired and interpreted the clinical and laboratory data, and wrote the article and final version for publication. MM designed the research and helped write the final article. EK, BMS, TD, SAE, MD, MU, NÖT, BA, GQ, MT, SU, SA and SU contributed to the acquisition and interpretation of clinical data and approved the final version for publication. HS performed the statistical analysis and interpreted the data. ORS coordinated the entire project and gave final approval for the article to be published. All authors critically reviewed the article and approved the final version.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Acknowledgement

A part of this study was presented as an oral presentation in the European Conference on Clinical Microbiology and Infectious Diseases, Madrid – 2018.

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