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Vancomycin versus Linezolid in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Meningitis

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Abstract

Background: Vancomycin is the mainstay of treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) meningitis. However, successful outcomes with linezolid have not been reported in a large series of patients. We conducted a single-center retrospective cohort study to compare vancomycin with linezolid in the treatment of MRSA meningitis.

Methods: We extracted data and outcomes for all adult patients (age >18 years) with culture-proved MRSA meningitis who received vancomycin or linezolid between January 2006 and June 2011. A definite diagnosis of meningitis was based on the isolation of MRSA in at least one cerebrospinal fluid (CSF) culture and findings in CSF that are typical of the infection. Linezolid was given intravenously (IV) at a dosage of 600 mg q12h and vancomycin IV at 500 mg q6h.

Results: A total of 8 patients with MRSA meningitis (5 male, 3 female; age [mean ± SD] 61.6 ± 13.2 years) received vancomycin and 9 patients (7 male, 2 female; age 59.1 ± 15.6 years) received linezolid. All isolated strains of MRSA were susceptible to both vancomycin and linezolid. The rates of microbiologic success with linezolid or vancomycin, in terms of clearance of MRSA from CSF on day 5, were 7/9 and 2/8 ($p = 0.044$, Fisher exact test). No severe adverse events occurred in either treatment arm of the study. One-month survival of the patients in whom treatment was successful microbiologically was 2/2 in the vancomycin-treated group and 4/7 in the linezolid-treated group. Minimum inhibitory concentration (MIC) data for vancomycin were available for 5/6 treatment failures with vancomycin, and vancomycin MIC values of these five strains were 2 mg/L.

Conclusion: Analysis of the findings in the limited cohorts in our study suggests that linezolid is superior to vancomycin for treating MRSA meningitis, especially in cases in which there is a high MIC (2 mg/L) for vancomycin. A clinical study involving larger cohorts may increase the evidence available in relation to this question.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a prominent gram-positive organism causing nosocomial bacterial meningitis in most parts of the world. Vancomycin is the mainstay of treatment for MRSA meningitis [1–6].

Linezolid is a drug in the oxazolidinone class of antibiotics. It is mainly a bacteriostatic antibiotic with relatively high cerebrospinal fluid (CSF) penetration and broad activity against gram-positive pathogens including MRSA. Although linezolid is a bacteriostatic antibiotic, several case reports describe its use in the management of severe infections related to gram-positive bacteria, such as meningitis and endocarditis, in which it is standard to use antibiotic drugs that exert bactericidal activity [4,5]. However, no clinical data have been reported for a comparison of vancomycin with linezolid in the management of meningitis. We conducted a single-center, retrospective cohort study to compare vancomycin with linezolid in the treatment of MRSA meningitis.

Patients and Methods

The study was done at a tertiary-care teaching hospital with an active neurosurgery ward containing 78 beds, 16 of which are in an intensive care unit. We extracted data and outcomes for all adult patients (age ≥18 years) with culture-proved MRSA meningitis who received vancomycin or linezolid between January 2006 and June 2011. Demographic, clinical, and laboratory findings and predisposing factors, and

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information about the response to treatment and the outcome of treated patients, were obtained prospectively.

A definite diagnosis of meningitis was based on the isolation of MRSA in at least one CSF culture. Typical CSF findings included leukocytosis with a predominance of polymorphonuclear cells, and classical clinical manifestations of meningitis. Nosocomial meningitis was defined as bacterial infection not present when the patient was admitted to the hospital, or as clinical evidence of infection within a short period after discharge from the hospital of a patient who had undergone an invasive procedure. Patients developing meningitis after neurosurgical procedures were defined as having post-neurosurgical infection [6].

Samples of CSF were centrifuged routinely and the pellet was gram-stained. Isolates of *S. aureus* were identified through routine microbiologic methods. Antibacterial susceptibility tests were performed using the Kirby–Bauer disk-diffusion method and evaluated as described by the Clinical and Laboratory Standards Institute (CLSI) [7]. Minimum inhibitory concentrations of vancomycin or teicoplanin were measured with the Etest (AB BIODISK, Solna, Sweden). Microbiologic success was defined as the clearance of MRSA from CSF on day 5 of treatment with linezolid or vancomycin. The dosing for linezolid was 600 mg q12h and that for vancomycin was 500 mg q6h as 1-h intravenous (IV) infusions of each drug. Data were evaluated with the SPSS version 13.0 software package (SPSS Inc., Chicago, IL) using the Mann–Whitney *U*-test, and Fisher exact test. A value of $p < 0.05$ was considered significant.

Results

The vancomycin group in the study consisted of eight patients (five male, three female; age 61.6 ± 13.2 years) and the linezolid group consisted of nine patients (seven male, two female; age 59.1 ± 15.6 years) who fulfilled the inclusion criteria for the study.

Clinical presentation and diagnosis

Patients in both the linezolid and vancomycin groups were similar with respect to age, gender, and clinical presentation. They were also similar with respect to their CSF protein and glucose concentrations and the degree of pleocytosis in their CSF (Table 1).

Table 1. Gender, Age, and Clinical and Cerebrospinal Fluid Characteristics of Vancomycin and Linezolid Treatment Cohorts

	Vancomycin (n = *8*)	*Linezolid* (n = *9*)	p *value*
Male	5	7	> 0.05
Female	3	2	> 0.05
Age	61.6 ± 13.2	59.1 ± 11.2	> 0.05
Glasgow Coma Scale	13.5 ± 1.3	12.3 ± 2.1	> 0.05
Shunt infection	6	6	> 0.05
Fever	7	8	> 0.05
Disturbances in consciousness	5	7	> 0.05
Nausea	5	3	> 0.05
Neck stiffness	1	1	> 0.05
Cerebrospinal fluid protein	301.6 ± 127.0	291.6 ± 155.9	> 0.05
Cerebrospinal fluid glucose	24.2 ± 11.2	22.3 ± 11.3	> 0.05

All of the patients had hospital-acquired meningitis and had undergone neurosurgical operations. Seven of the patients had shunt infections, all of which were treated with shunt removal and external ventricular drainage. The reasons for neurosurgical operations in the other patients are shown in Tables 2 and 3. One patient in the linezolid group had MRSA and coinfection with methicillin-resistant coagulase-negative staphylococci (MRCNS). All of the other patients in both treatment groups had only MRSA as the etiologic agent of their infections. All of the strains of *S. aureus* in the patients' CSF were susceptible to vancomycin and linezolid according to CLSI criteria [7]. In the initial evaluation, gram staining gave negative results in all of the patients except for one patient in the linezolid-treated group (Table 2, Patient 2) and two patients in the vancomycin-treated group (Table 3, Patients 7 and 8).

Treatment of meningitis

Patient treatment regimens and the duration of treatment are summarized in Tables 2 and 3. Six of the patients had been given vancomycin and one patient had been given teicoplanin before receiving linezolid. The remaining two patients in the linezolid group received linezolid as their primary treatment during consultations for positive CSF cultures. During linezolid therapy, two patients received additional antibiotics for nosocomial pneumonia that were not active against MRSA (Table 2).

Microbiologic success

Microbiologic success rates on day 5 with linezolid and vancomycin were 7/9 and 2/8, respectively ($p = 0.044$, Fisher exact test). Vancomycin was replaced with linezolid in six patients in whom vancomycin failed to eradicate MRSA. Of these six patients, two died while receiving linezolid. In the first case of MRSA meningitis in which linezolid failed, daptomycin was added to linezolid. However, the patient died on the day 3 of this combined treatment. The second patient in whom linezolid failed died during treatment with the drug after the development of *Pseudomonas aeruginosa* meningitis (Table 2).

The MIC of vancomycin was available for five of the six patients in whom it failed, and was 2 mcg/L according to the Etest. Vancomycin was microbiologically effective on day 5 in only one of the six cases of MRSA meningitis in which the strains had a MIC value of 2 mg/L.

Rates of clinical success

One-month survival in the patients in whom treatment was microbiologically successful was 2/2 in the vancomycin group and 4/7 in the linezolid group, in the latter of which the three deaths were caused by reasons other than MRSA meningitis (two additional nosocomial infections and one sudden cardiac death) (Tables 2 and 3).

Adverse events

There was no severe hematologic, renal, or hepatic toxicity during treatment with either linezolid or vancomycin.

Table 2. Characteristics and Outcomes of Patients in Linezolid Treatment Group

Patient no.	*CSF leukocytes/blood leukocytes (blood polymorphonuclear leukocyte %)*	*Previous therapy*	*MIC (mg/L) vancomycin/ teicoplanin*	*Underlying condition*	*Treatment and duration*	*Morbidity*	*Result*
1	>1,000/16,700 (85)	Ceftizoxime, vancomycin	2/6	Surgery for normal-pressure hydrocephalus and shunt insertion*	Linezolid 600 mg IV q12h (28 d) piperacillin-tazobactam 4.5 g q8h (3 wks) after 5 d of linezolid	Cranial edema, decompression surgery, shunt removal, extraventricular drainage, reoperation for shunt	Microbiologic cure. Patient died 3 mo later from gastric bleeding
2	>1,000/14,100 (75.6)	Ceftizoxime, ceftriaxone	NA	Surgery for intracerebral hematoma	Linezolid (600 mg q12h (28 d) and imipenem-cilastatin 500 mg q6h (14 d) for *Pseudomonas aeruginosa* pneumonia*		Microbiologic cure Survived
3	>1,000/12,100 (90)	Ceftizoxime, cefepime, netilmicin, vancomycin	NA	Surgery for meningioma and shunt insertion	Linezolid 600 mg q12h (10 d)	Shunt removal and extraventicular drainage	Microbiologic cure but patient died from *Candida glabrata* meningitis on day 10 of therapy
4	>1,000/23,900 (92)	Ceftizoxime, ceftazidime, amikacin, teicoplanin	NA	Venticuloatrial shunt insertion for hydrocephalus developing after surgery for traumatic subarachnoid hemorrhage	Linezolid 600 mg q12h (12 d)	Shunt removal and insertion of venticuloperitoneal shunt	Microbiologic cure but patient died from sudden cardiac arrest on day 12 of therapy
5	>1,000/ 6,340 (58)	Ceftizoxime, ceftazidime, vancomycin	2/6	Surgery for degenerative lumbar stenosis	Linezolid 600 mg q12h (21 d)	Wound revision and lumbar drainage	Microbiologic cure Survived
6	250/20,500 (85)	Ceftizoxime, meropenem	2/3	Surgery for intracerebral hematoma	Linezolid 600 mg q12h (21 d)	Extraventricular drainage	Microbiologic cure but patient died from intracranial hematoma 2 mo later
7	>1,000/ 6,640 (76)	Ceftizoxime, vancomycin	2/4	Surgery for intracerebral hematoma and shunt insertion	Linezolid 600 mg × 2 10 days)	Shunt revision and extraventricular drainage	Microbiologic failure but patient died despite addition of daptomycin
8	>1,000/13,920 (78)	Ceftizoxime, imipenem-cilastatin vancomycin	2/6	Surgery for aneurysm and shunt insertion	Linezolid 600 mg q12h (21 d)	Shunt revision and extraventricular drainage	Microbiologic cure but patient died 1 mo later from *Pseudomonas aeruginosa* meningitis
9	>1,000/ 6,690 (77)	Ceftizoxime, vancomycin	2/3	Surgery for hydrocephalus developing after aneurysm and shunt insertion	Linezolid 600 mg q12h (5 d)	Shunt revision and extraventricular drainage	Microbiologic failure Patient died on day 5 of linezolid therapy from *P. aeruginosa* meningitis

CSF = cerebrospinal fluid; IV = intravenous; MIC = minimum inhibitory concentration; NA = not available.
*Meropenem was temporarily unavailable in the market.

Table 3. Characteristics and Outcomes of Patients in Vancomycin Treatment Group

Patient no.	*CSF leukocytes/blood leukocytes (blood polymorphonuclear leukocyte %)*	*Previous therapy*	*MIC (mg/L) vancomycin/ teicoplanin*	*Treatment/underlying condition*	*Treatment and duration*	*Morbidity*	*Result*
1	>1,000/12,800 (82.6%)	Ceftizoxime	2/6	Surgery for normal pressure hydrocephalus, shunt insertion*	Vancomycin IV 500 mg q6h (5 d)	Cranial edema, decompression surgery, shunt removed, extraventricular drainage, reoperation for shunt	Microbiologic failure on day 5 of vancomycin
2	>1,000/ 7,000 (81.9)	Ceftizoxime, cefepime, netilmicin,	NA	Surgery for meningioma and shunt insertion	Vancomycin 500 mg q6h (5 d)	Shunt removal, extraventicular drainage	Microbiologic failure on day 5 of vancomycin
3	>1,000/ 4,780 (75)	Ceftizoxime	2/6	Degenerative lumbar stenosis	Vancomycin 500 mg q6h (5 d)	Wound revision, lumbar drainage insertion	Microbiologic failure on day 5 of vancomycin
4	>1,000/11,790 (92)	Ceftizoxime	2/4	Surgery for intracerebral hematoma and shunt insertion	Vancomycin 500 mg q6h (5 d)	Shunt revision and extraventricular drainage	Microbiologic failure on day 5 of vancomycin
5	300/14,150 (67)	Ceftizoxime, imipenem-cilastatin	2/6	Surgery for aneurysm and shunt insertion	Vancomycin 500 mg q6h (5 d)	Shunt revision and extraventricular drainage	Microbiologic failure on day 5 of vancomycin.
6	>1,000/ 6,690 (77)	Ceftizoxime	2/3	Surgery for hydrocephalus and shunt insertion	Vancomycin 500 mg q6h (5 d)	Shunt revision and extraventricular drainage	Microbiologic failure on day 5 of vancomycin
7	250/15,270 (82)	Ceftizoxime	2/2.5	Surgery for hematoma and shunt insertion	Vancomycin 500 mg q6h (19 d)	Shunt revision and extraventricular drainage	Cured, survived
8	170/12,100 (71)	Ceftizoxime	NA	Surgery for tethered cord syndrome	Vancomycin 500 mg q6h (14 d)	–	Cured, survived

CSF = cerebrospinal fluid; MIC = minimum inhibitory concentration; NA = not available.

Discussion

Methicillin-resistant *S. aureus* is an important cause of hospital-acquired meningitis [1,2,4,5]. Cases of the disease are usually associated with neurosurgical interventions, staphylococcal bacteremia, or a parameningeal focus of infection.

Despite the lack of a randomized controlled study of its clinical efficacy, vancomycin is the mainstay of treatment for MRSA meningitis. The evidence for this is confined to case series and experimental animal models. Vancomycin does not usually penetrate adequately into the CSF in the absence of inflamed meninges, but when meningitis develops, its penetration increases to a moderate degree [2,3]. Several treatment failures have been reported when IV vancomycin has been used alone, but many patients have been treated successfully with its intrathecal administration [2–4,8]. However, intrathecal vancomycin was not used in our study because of possible side effects. An additional strategy is treatment with vancomycin in combination with another antibiotic such as rifampicin. The activity of rifampin against *S. aureus* is excellent, with low MICs [2]. However, the strains of *S. aureus* in our two study cohorts were resistant to rifampin.

Linezolid is indicated in the treatment of pneumonia and complicated soft tissue and skin infections. Nevertheless, it has excellent penetration into CSF (CSF:blood ratio >1) [4,5]. Faella et al. [9] used ceftriaxone plus linezolid in seven patients with meningitis caused by penicilin-resistant pneumococci and reported one death, two sequelae (one hearing loss and one severe disability), and four full recoveries. Recently Calik et al. [10] compared linezolid 10 and 20 mg/kg q 12 h with 20 mg/kg vancomycin q 12 h for 24 h in a rabbit MRSA meningitis model. At the end of treatment the decrease in bacterial counts in the vancomycin group was approximately two logs higher than the linezolid-20 group ($p > 0.05$) and approximately four logs higher than in the linezolid-10 group (p: 0.037). Ntziora and Falagas [5] reviewed 20 published cases of meningitis (four caused by MRCNS and three by MRSA) treated with linezolid by the end of October 2006. The duration of treatment in these cases ranged from 14 to 84 days. In the presented study, three of the patients received linezolid for 21 d and two others received it for 28 d. The fact that the three cases treated with 21 days of linezolid had microbioogic clearance, suggests that this duration of treatment may also be successful.

The recommendations of the CLSI for susceptibility testing of *S. aureus* to vancomycin have changed several times during the period of investigation of vancomycin [7]. The breakpoint of susceptibility of *S. aureus* to vancomycin in terms of the MIC of the drug decreased to ≤2 mg/L from ≤4 mg/L in 2006. After 2009, when the disc-diffusion test was withdrawn from susceptibility testing, both of the two cases of MRSA meningitis in our study had MICs that indicated susceptibility to vancomycin. All of the patients in our study had pathogens susceptible to vancomycin in terms of the disc diffusion test. In 2010, when the disc diffusion test was withdrawn from susceptibility testing, both of the two cases of MRSA meningitis in our study had MICs that indicated susceptibility to vancomycin.

The MIC of vancomycin is related closely to the rate of its microbiologic eradication in *S. aureus* bacteremia. According to findings by Moise et al. its MIC values of 0.5 mg/L, 1 mg/L, and 2 mg/L were marked by microbiologic success rates of 77%, 71%, and 21%, respectively [11]. Unfortunately, MIC data were not available in our study for all strains of the organism, and strains of MRSA for which the MIC of vancomycin was 2 mg/L might also have been heterogeneous, intermediate-level vancomycin-resistant *S. aureus*. Nevertheless, the MIC of vancomycin was 2 mg/L in all cases in which linezolid was used as secondary therapy after the failure of glycopeptides.

All strains of MRSA were sensitive to linezolid in terms of the disc diffusion test. However, relatively high MICs of linezolid, but that were still in the range of susceptibility, might theoretically have been effective in the two cases in which it failed, but we do not have data for the MIC of linezolid for any strain of MRSA. In two cases in our study, linezolid was used as the primary treatment for MRSA meningitis. Recent guidelines for treating meningitis from the European Federation of Neurological Sciences suggest linezolid as the first-line treatment option for methicillin-resistant staphylococcal meningitis [12].

The major weakness of our study was its relatively small number of subjects. In addition, although the data were collected prospectively, the study was retrospective. Another main disadvantage is the heterogeneity of the study group. Despite all of the patients having had post neurosurgical nosocomial meningitis, two received linezolid as primary therapy for the disease and seven received it as secondary therapy after the failure of glycopepties. Hence, six of the patients in the study were in both the linezolid and vancomycin cohorts. However, to our knowledge the present study is the first to compare linezolid with vancomycin in the treatment of human meningitis.

In conclusion, vancomycin is the main treatment option in staphylococcal meningitis. However, although our sample size is inadequate for providing a general conclusion, our data suggest that linezolid may be superior to vancomycin for such meningitis, especially in cases with high MICs of vancomycin. A clinical study involving larger cohorts may increase the evidence related to this question.

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