Linezolid Versus Vancomycin for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Keratitis in Rabbits

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Purpose: To compare the efficacy of topical linezolid (LZD) 1 mg/mL or 2 mg/mL to vancomycin (VA) 50 mg/mL for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) keratitis in rabbits.

Methods: One hundred colony-forming unit (CFU) MRSA bacteria were injected intrastromally into rabbit corneas. Sixteen hours after the injection, 24 rabbits were randomly divided into 4 groups. Rabbit eyes were treated with 1 drop of topical LZD 1 mg/mL, LZD 2 mg/mL, VA 50 mg/mL, or isotonic saline every 15 minutes for 5 doses and then every 30 minutes for 14 doses. Eyes were examined before and after the treatment using slit-lamp biomicroscopy by 2 observers blinded to the study for the determination of clinical severity. Then, corneas were harvested for the quantification of bacteria and histopathology.

Results: There were no differences in clinical severity among the groups before and after the treatment in each eye. The mean CFU × 10^6 of MRSA recovered from the LZD 1 mg/mL, LZD 2 mg/mL, and VA 50 mg/mL groups were significantly lower than that recovered from corneas treated with isotonic saline. There was no statistically significant difference among the treatment groups in terms of CFU × 10^6. Epithelial erosion in the VA 50 mg/mL group was significantly worse than that in the other groups. LZD 2 mg/mL group had the lowest mean epithelial erosion values.

Conclusions: Topical LZD showed activity against MRSA that was comparable to fortified VA in this experimental keratitis model.

Key Words: linezolid, vancomycin, MRSA keratitis

(*Cornea* 2013;32:1052–1057)

Infectious keratitis is a leading cause of corneal blindness, affecting more than 30,000 new individuals every year in the United States.[1] Even with the current standard of care, it is estimated that 25% of patients with microbial keratitis are left legally blind after appropriate treatment.[2] *Staphylococcus* species are among the most important and commonly isolated pathogens from corneal scrapings and cultures in patients with bacterial keratitis.[3,4] Recent reports have indicated that methicillin-resistant *Staphylococcus aureus* (MRSA) keratitis is a serious and increasingly prevalent complication after refractive surgery[5] and contact lens wear.[6]

The current gold standard topical therapy in MRSA keratitis is fortified vancomycin (VA), which is a drug of last resort for MRSA corneal infections.[7] Unfortunately, there is no commercially available topical VA form specifically for the treatment of eye infections.[8] Corneal epithelial erosions have raised serious discomfort about the use of VA because of its low pH in solution. Furthermore, *S. aureus* has recently been reported to have acquired resistance to VA in nonocular infections.[9,10] Given antibiotic resistance in *S. aureus* isolates from cases of keratitis, it was of interest to explore the potential utility of novel antibiotics.

Linezolid (LZD) is a synthetic antibiotic compound in a new class of oxazolidinones. Its mode of action has been shown to involve the inhibition of protein synthesis at the initial phase by binding to the 50S ribosomal subunit. In addition, the degree of cross-reactivity between LZD and other protein synthesis–inhibiting drugs seems to be low.[11] It has effect with low minimal inhibitory concentration (MIC) values against MRSA, isolated from bacterial ulcer/keratitis cases.[12,13] The studies have not detected in vitro LZD resistance in any *Staphylococcus* species isolated from keratitis specimens, including MRSA.[12,13] Topically applied 2 mg/mL of LZD seemed to penetrate well into the anterior ocular structures, including the conjunctiva, cornea, and aqueous humor.[14]

To date, the chemotherapeutic potential of topical LZD has not been studied in corneal infection models. In this study, we evaluated, for the first time, the comparative efficacy of different doses of topical LZD against VA in the treatment of experimental MRSA keratitis in rabbits.

MATERIALS AND METHODS

Animals

A total of 24 New Zealand white male rabbits, weighing approximately 2.5 to 3.0 kg, were used. Animals were treated in

Received for publication December 27, 2012; revision received March 2, 2013; accepted March 8, 2013.

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Supported by Abant Izzet Baysal University Scientific Research Committee (Project 2012.08.01.571).

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accordance with the Association for Research in Vision and Ophthalmology statement for Use of Animals in Ophthalmic and Vision Research. The local ethics committee approved the study.

Preparation of the Infectious Isolate for the Keratitis Model

MRSA ATCC strain 43300 was used. The isolate was streaked on a blood agar plate and was incubated overnight at 37°C. At the end of incubation, several colonies were inoculated into sterile saline to form a density of 0.5 McFarland standard, meaning 1 to 2×10^8 colony-forming unit (CFU)/milliliter of bacteria. Serial 10-fold dilutions were made, and the 10^{-4} dilution, equivalent to approximately 100 CFU/10 μL, was used to infect the corneas of the rabbits. Accuracy of the inoculum was confirmed by inoculating each of the serial 10-fold dilutions onto blood agar plates in duplicate.

MIC Test

The MIC values of LZD and VA were determined using a BD Phoenix Automatized Microbiology System (BD; Diagnostic Systems, Sparks, MD), as described by the manufacturer, according to the Clinical and Laboratory Standards Institute criteria.

Corneal Infection of Rabbits

Each rabbit was systemically anesthetized with an intramuscular injection of 10 mg/mL of xylazine (Basilazin; Bavet, Bösensel, Germany) and 35 mg/kg of ketamine hydrochloride (Ketalar; Pfizer, Kirklareli, Turkey). One or 2 drops of 0.5% proparacaine hydrochloride were added to each eye for topical anesthesia. Each eye was held steady with clamping forceps, and 10 μL of MRSA containing 100 CFUs was injected directly to the corneal stroma using a 30-gauge needle on a 0.1-mL gas-tight syringe under a binocular microscope (Olympus SZ61, Tokyo, Japan; Fig. 1A).[15,16]

Examination and Scoring of Rabbit Eyes

Eyes were examined using slit-lamp examination by 2 observers blinded to this study 16 hours (pretreatment) and 25 hours (posttreatment) after the infection. Eight parameters were assessed to determine the severity of infection: conjunctival injection, chemosis, iritis, corneal infiltrate, corneal edema, fibrin, hypopyon, and epithelial erosion. Each parameter was given a grade of 0 (normal) to 4 (maximal severity) by each observer, and the 8 grades were added to achieve a total score with a theoretical maximum of 32.[15] The final score for each eye represented the average of the scores of the 2 observers.

Treatment Regimen

Treatment began immediately after the examination, and scoring began 16 hours after MRSA injection. The rabbits were randomized into 4 treatment groups (6 rabbits per group) by an investigator who was not involved in the examination and scoring. The treatment groups consisted of LZD 1 mg/mL (obtained from 0.5 dilution of LZD 2 mg/mL commercially available preparation), LZD 2 mg/mL (Zyvoxid; Pfizer, Istanbul, Turkey), VA 50 mg/mL (Vancomycin HCl 500 mg; Abbott, Istanbul, Turkey), and isotonic saline (control). One drop was

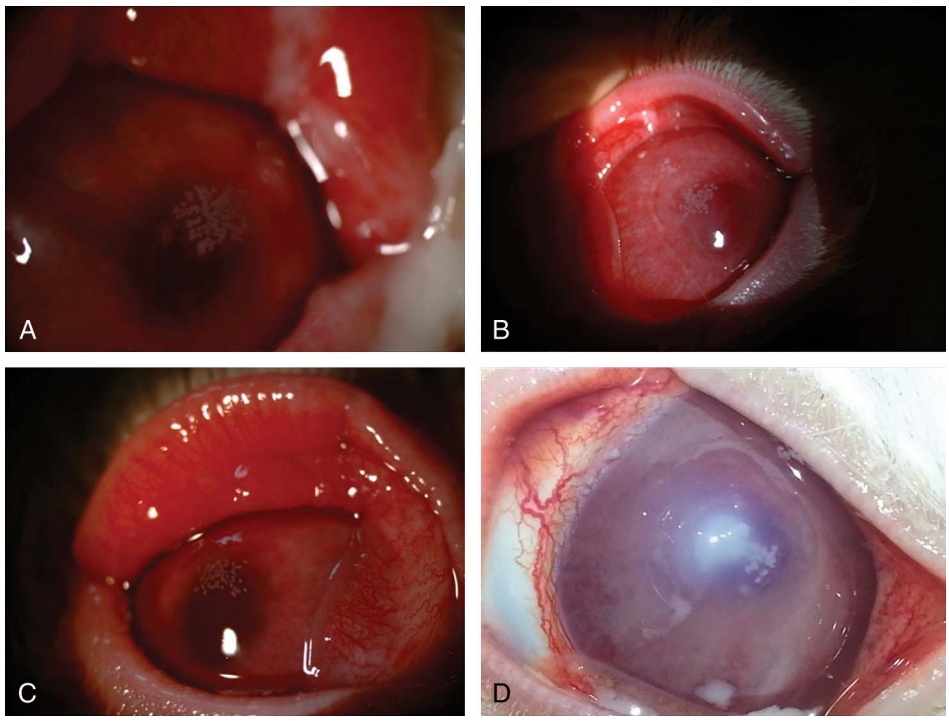

FIGURE 1. Representative images of infected eyes after treated with topical LZD 1 mg/mL (A), LZD 2 mg/mL (B), VA 50 mg/mL (C), and isotonic saline (D).

placed in each eye every 15 minutes for 5 doses and then every 30 minutes for 14 doses.[15]

Euthanasia and Tissue Harvest

Rabbits were euthanized with an intravenous overdose of sodium pentobarbital (100 mg/kg; Sigma-Aldrich, St Louis, MO) at 25 hours after the infection (after the treatments and final slit-lamp examination). Rabbit corneas were excised using a uniform sterile 7.5-mm Hessburg-Barron vacuum trephine (Altomed, England, United Kingdom). Left eyes were placed into a sterile container for microbiological evaluation. Right eyes were fixed in 10% formaldehyde solution for histopathological examination.

Bacterial Cultures From the Corneas

The cornea was fragmented with a sterile lancet, and 2 mL of sterile saline was added. The container was vortexed and 1, 10, and 100 μL of saline suspensions were inoculated onto the blood agar plates in duplicate. After an overnight incubation at 37°C, the colonies grown on the plates were counted and calculated as colony-forming unit per gram. One isolate from each group was identified as MRSA using the BD Phoenix Automatized Microbiology System again for confirmation.

Pathological Examination

Excised corneas in 10% buffered formalin were embedded in paraffin blocks. Tissue sections (4 μm thick) of all corneas were stained with hematoxylin and eosin and examined for corneal epithelial erosion, stromal edema, stromal polymorphonuclear leukocytes (PMNL) infiltration, and fibrin by a blinded observer using a light microscope. Epithelial erosion was determined as a percentage of the total length using an oculometer. The other parameters were given a grade of 0 (normal) to 3 (severe) for each cornea.

Statistical Analyses

Data analysis was performed using the SPSS software (version 11.5 for Windows; SPSS, Inc, Chicago, IL). Whether the distributions of continuous variables were normal was assessed using the Shapiro–Wilk test. The Levene test was used for the evaluation of homogeneity of variances. Data are shown as means ± standard deviations or medians (interquartile range, IQR), where appropriate. The mean differences among the groups were compared by 1-way analysis of variance. Otherwise, the Kruskal–Wallis test was used for comparisons of median values. When the P values from the 1-way analysis of variance or Kruskal–Wallis test statistics were statistically significant, a post hoc Tukey honestly significant difference or Conover nonparametric multiple comparison test were used to determine which groups differed from which others. The Wilcoxon sign rank test was used for intragroup comparisons. A P value <0.05 was considered to indicate statistical significance. The Bonferroni adjustment was used for all multiple comparisons, to control type I errors.

RESULTS

Clinical Scores

The mean [median (IQR)] pretreatment clinical scores of the right versus left eyes of the rabbits in the LZD 1 mg/mL, LZD 2 mg/mL, VA 50 mg/mL, and control groups were 7.0 (4.37) versus 8.7 (4.50), 8.2 (4.37) versus 9.0 (6.12), 9.5 (5.25) versus 11.5 (3.12), and 9.2 (2.50) versus 10.5 (2.75), respectively. The respective posttreatment scores were 11.5 (4.12) versus 10.0 (4.00), 9.7 (6.00) versus 11.0 (3.12), 11.2 (1.62) versus 14.2 (3.62), and 12.5 (2.50) versus 15.0 (4.37). The mean clinical scores between the pre- and posttreatment periods within the groups in each eye were not statistically significantly different. The mean pre- and posttreatment period clinical scores in each eye among the groups were also not statistically significantly different. Table 1 summarizes the pre- and posttreatment mean clinical scores and significance levels of the groups. Figure 1 shows representative images of the infected eyes at 25 hours after the infection after being treated with 19 doses of LZD 1 mg/mL, LZD 2 mg/mL, VA 50 mg/mL, and isotonic saline.

Microbiological Evaluation

MRSA was found in the corneal cultures of all rabbits except 1 in the LZD 1 mg/mL group. A marked decrease in bacterial load was observed in all treatment groups compared with the control group ($P = 0.029$). The mean [median (IQR)] bacterial loads (CFU × 10^6) in the LZD 1 mg/mL, LZD 2 mg/mL, VA 50 mg/mL, and control groups were 2.8 (5.08), 1.6 (4.76), 0.3 (6.60), and 20.0 (14.6), respectively. There was no statistically significant difference in terms of bacterial load among the treatment groups. However, the VA 50 mg/mL group showed the greatest decrease. The MICs against the MRSA strain were 2 mg/L for the LZD groups and 0.25 mg/L for the VA 50 mg/mL group. Table 2 shows the CFU × 10^6 and bacterial growth rates of the groups in detail.

Histopathological Examination

There was a statistically significant difference in terms of stromal edema and epithelial erosion among the groups ($P = 0.003$ and $P < 0.001$, respectively). However, there was no significant difference in other parameters, including fibrin and stromal PMNL infiltration. Table 2 shows the epithelial erosion, stromal edema, fibrin, and stromal PMNL infiltration characteristics of the groups and significance levels.

Mean ± [median (IQR)] percent epithelial erosion values were 37 ± 16.06 in the LZD 1 mg/mL group, 22.3 ± 6.98 in the LZD 2 mg/mL group, 66.8 ± 12.45 in the VA 50 mg/mL group, and 46.0 ± 16.77 in the control group. The mean percent epithelial erosion ratio was lower in the LZD 2 mg/mL group than in all other groups. There was no statistically significant difference between the LZD 1 mg/mL group and the LZD 2 mg/mL group in terms of epithelial erosion; however, percent epithelial erosion was significantly lower in the LZD 1 mg/mL and LZD 2 mg/mL groups than in the VA 50 mg/mL group ($P < 0.01$ and $P < 0.001$, respectively).

TABLE 1. Clinical Scores of the Eyes Before and After Treatment

Groups	Before Treatment	After Treatment	*P**	Difference	*P*†
LZD 1 mg/mL					0.112
Right eye	7.0 (4.37)	11.5 (4.12)	0.116	4.0 (7.00)	
Left eye	8.7 (4.50)	10.0 (4.00)	0.173	2.0 (4.62)	
LZD 2 mg/mL					0.588
Right eye	8.2 (4.37)	9.7 (6.00)	0.276	0.5 (2.62)	
Left eye	9.0 (6.12)	11.0 (3.12)	0.144	0.7 (3.12)	
VA 50 mg/mL					0.750
Right eye	9.5 (5.25)	11.2 (2.62)	0.058	3.0 (3.50)	
Left eye	11.5 (3.12)	14.2 (3.62)	0.027	2.0 (2.62)	
Control					0.075
Right eye	9.2 (2.50)	12.5 (2.50)	0.027	3,0 (3.12)	
Left eye	10.5 (2.75)	15.0 (4.37)	0.027	5,2 (2.75)	
P					
Right eye	0.683‡	0.092‡	—	0.161§	—
Left eye	0.477‡	0.031‡	—	0.029§	—

Values are represented as median (IQR).

*Comparison of clinical scores of the eyes before and after the treatment among the groups, using Wilcoxon signed rank test, according to Bonferroni adjustment of $P < 0.00625$, which was considered to be statistically significant.

†Comparison of clinical score changes of the right and left eyes within the groups after the treatment compared with baseline, using Wilcoxon signed rank test, according to Bonferroni adjustment of $P < 0.0125$, which was considered to be statistically significant.

‡Comparison of clinical scores of the eyes after the treatment compared with baseline among the groups according to laterality, Kruskal–Wallis test, according to Bonferroni adjustment of $P < 0.0125$, which was considered to be statistically significant.

§Comparison of clinical score changes of the eyes after the treatment compared with baseline among the groups according to laterality, Kruskal–Wallis test, according to Bonferroni adjustment of $P < 0.025$, which was considered to be statistically significant.

The level of corneal stromal edema was lower in the LZD 2 mg/mL and VA 50 mg/mL groups than in the control group. Stromal edema in the LZD 1 mg/mL group was significantly higher than in the LZD 2 mg/mL and VA 50 mg/mL groups ($P < 0.001$ and $P < 0.01$, respectively) but equal to the control group ($P > 0.05$).

DISCUSSION

The successful treatment of bacterial keratitis depends on identifying the causative agent and selecting the most appropriate antimicrobial agent. However, a limited number of antibiotics is available to treat MRSA keratitis. Therefore, new antimicrobials with an improved activity against emerging or resistant MRSA strains are of crucial importance.[17–19] This study provides the first reported evidence that LZD has the therapeutic potential for the treatment of keratitis caused by MRSA. We found that topical LZD was as effective in reducing CFUs as topical VA. Another interesting finding of the present study is that the epithelial toxicity of LZD was less than that of VA. Overall, in this pilot study, LZD seemed to be better tolerated than VA topically, although no statistically significant differences were found on clinical scores.

Second-generation fluoroquinolones were valuable agents in treating susceptible strains of MRSA; however, *S. aureus* has also become increasingly resistant to fluoroquinolones through mutations in the genes for DNA gyrase and topoisomerase IV.[20–22] Therefore, topical VA remains the

TABLE 2. Mean CFU Counts, Microbial Growth Counts and Histopathological Examination Characteristics of the Groups

Parameters	LZD 1 mg/mL	LZD 2 mg/mL	VA 50 mg/mL	Control	*P*
Microbial growth, n (%)	5 (83.3)	6 (100)	6 (100)	6 (100)	—
CFU x10^6, median (IQR)	2.8 (5.08)*	1.6 (4.76)†	0.3 (6.60)‡	20 (14.6)*†‡	0.029§
Fibrin, median (IQR)	0.5 (1.25)	0.0 (0.50)	0.0 (0.25)	0.0 (1.25)	0.590§
Epithelial erosion (%) (mean ± SD)	37.0 ± 16.06¶	22.3 ± 6.98†‖	66.8 ± 12.45¶‖	46.0 ± 16.77†	<0.001**
Stromal PMNL, median (IQR)	1.5 (1.25)	1.0 (1.00)	1.0 (0.25)	1.0 (1.00)	0.190§
Stromal edema, median (IQR)	2.0 (0.25)*¶††	1.0 (0.50)†††	1.0 (0.25)‡¶	2.0 (1.00)*†‡	0.003§

*There was a statistically significant difference between the LZD 1 mg/mL group and the control group ($P = 0.003$).

†There was a statistically significant difference between the LZD 2 mg/mL group and the control group ($P < 0.05$).

‡There was a statistically significant difference between the VA 50 mg/mL group and the control group ($P < 0.001$).

§Kruskal–Wallis test.

¶There was a statistically significant difference between the LZD 1 mg/mL group and the VA 50 mg/mL group ($P < 0.01$).

‖There was a statistically significant difference between the LZD 2 mg/mL group and the VA 50 mg/mL group ($P < 0.001$).

**One-way analysis of variance.

††There was a statistically significant difference between the LZD 1 mg/mL group and the LZD 2 mg/mL group ($P < 0.001$).

mainstay of treatment of MRSA keratitis because of the relative absence of antibiotic resistance. However, topical VA drops are not commercially available, necessitating the preparation in an inpatient pharmacy, and require refrigeration to maintain stability, and are toxic to the corneal epithelium, which may delay wound healing.[9] In addition to these drawbacks, the recent emergence of rare mutant MRSA strains are also no longer susceptible to VA.[10] Thus, there is a continuing need to search for new antimicrobial agents.

In vitro studies have found LZD to be active against most clinically significant gram-positive pathogens, including the difficult to eradicate VA-resistant *Enterococcus faecium*[23] and MRSA.[24] LZD levels in the aqueous humor, conjunctiva, and cornea exceeded the MIC of most gram-positive bacteria that cause keratitis after topical administration.[14] In the face of increasing resistance to VA, LZD could become a precious alternative in ocular infections caused by gram-positive organisms. The present study tested the efficacy of 2 different concentrations of topical LZD in comparison to fortified VA and a saline control in the treatment of MRSA keratitis. None of the treatments reduced the clinical scores of rabbit eyes at 25 hours after the infection; however, both LZD concentrations significantly reduced the CFU of bacteria recovered from corneas, which was comparable with VA. In accordance with our results, Ekdawi et al[25] found that topical LZD 4 mg/mL is at least as effective in reducing CFUs as VA in a rabbit model of keratitis caused by *Streptococcus pneumoniae*. They also reported markedly improved discharge, tearing, and corneal exudates in the LZD group compared with VA group and speculated that LZD is better tolerated than VA topically.

Topical instillation of an antibiotic to the ocular surface may achieve a very different concentration and bioavailability in the tissue. Because there are no in vitro susceptibility standards for interpreting ocular bacterial susceptibility, the MIC and disc susceptibility criteria after systemic administration are used to choose the antimicrobial for the treatment of microbial keratitis.[26,27] However, there is some evidence[28,29] that demonstrated the relationship between the MIC of topically applied agents and clinical outcomes in cases of bacterial keratitis. Therefore, the MIC is an important measure in the treatment of bacterial keratitis for evaluating the effectiveness of topically applied antimicrobials. In the present study, the MICs against the MRSA strain were 2 mg/L for the LZD groups and 0.25 mg/L for the VA mg/mL group. Although the LZD MIC was 4 times greater than the VA MIC for this MRSA strain, we noted no significant differences between the drugs in effectiveness. LZD 1 mg/mL and LZD 2 mg/mL were able to reduce the median colony counts by 7 and 12.5 folds when compared with control, a statistically significant effect.

In cases of keratitis, stromal edema and epithelial erosion may be observed in the natural course of the disease, regardless of the causative pathogen. In the present study, the epithelial erosion rate in both the LZD groups was significantly lower than that in the VA group. In particular, the epithelial erosion rate in the LZD 2 mg/mL group was significantly lower than that in either the VA group or the control group. These findings should not be considered as a surprise because the corneal epithelial toxicity of topical fortified VA is well-known, which may necessitate the discontinuation of the drug.

In conclusion, although this is a preliminary study and further studies are necessary, LZD may be an alternative to VA for the treatment of MRSA keratitis. The epithelial toxicity of VA can apparently be avoided with the use of LZD. LZD compared with VA reduces the bacterial load at a similar rate. Moreover, because LZD has activity against the entire major gram-positive organisms better than VA, it may be a good choice for empiric combined therapy in bacterial keratitis, offering broad spectrum cover against gram-positive microorganisms. Besides this, LZD is a bacteriostatic agent, which acts by inhibiting protein synthesis. New-generation bactericidal agents against MRSA, like daptomycin, may have a role in the treatment of keratitis. However, future studies are necessary to address this issue further.

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