

# Efficacy of Moxifloxacin Compared to Teicoplanin in the Treatment of Implant-Related Chronic Osteomyelitis in Rats

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**ABSTRACT:** Treatment of implant-related chronic osteomyelitis is often difficult and usually consists of implant removal, extensive surgical debridement, and prolonged antibiotic use. This study was performed to assess the efficacy of moxifloxacin compared to a glycopeptide, teicoplanin in chronic implant-related methicillin-sensitive *Staphylococcus aureus* (MSSA) osteomyelitis. The left femoral medullar cavities of 60 Wistar male rats were contaminated with 100  $\mu$ l of  $10^8$  cfu/ml methicillin-sensitive *S. aureus* (ATCC 29213) and Kirschner wires were placed into the medulla of the femur. After 6 weeks, rats were randomly divided into five groups. In two groups, the Kirschner wires were removed. Experimental groups were as follows: group 1: contaminated, Kirschner wire inside, received teicoplanin; group 2: contaminated, Kirschner wire removed, received teicoplanin; group 3: contaminated, Kirschner wire inside, received moxifloxacin; group 4: contaminated, Kirschner wire removed, received moxifloxacin; group 5: contaminated, Kirschner wire inside, no antibiotics (control group). Groups 1 and 2 received teicoplanin (20 mg/kg once daily), whereas groups 3 and 4 received moxifloxacin (10 mg/kg twice daily) intraperitoneally for 28 days. At the end of the treatment, animals were sacrificed by inhalation anesthesia with ether and femora were retrieved and bacterial counts (cfu/g) were determined. Bacterial counts in all study groups were significantly reduced relative to the control. The decrease of bacterial counts was more prominent in group 4 compared to group 1 ( $p = 0.001$ ) and group 2 ( $p = 0.003$ ). Moxifloxacin therapy is an effective alternative to teicoplanin for chronic implant-related MSSA osteomyelitis. © 2010 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J. Orthop. Res. 28: 1368–1372, 2010

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Osteomyelitis is an infection of the bone and bone marrow, which may be caused by trauma, nosocomial infection, or orthopedic surgery.<sup>1,2</sup> *Staphylococcus aureus* is the most commonly detected pathogen in chronic osteomyelitis. Orthopedic metallic implants are known to promote the onset of infection,<sup>3</sup> and implant-related osteomyelitis is considered to be a disastrous complication in orthopedic surgery. Current management of these forms of osteomyelitis involves removal of all foreign materials followed by meticulous debridement of the necrotic and infected areas and long-term use of systemic antibiotics. This condition is associated with prolonged hospitalization, side effects of antibiotic therapy, and high economic costs.

The infection rate in orthopedic surgery is low, with a frequency between 0.7% and 4.2%.<sup>4–8</sup> These rates are related to surgery type, soft tissue status, general condition of the patient, and prophylactic antibiotic use.<sup>9–11</sup> In implant-related *S. aureus* osteomyelitis, bacteria adhere to the implant surface, and then reorganize and form a biofilm. More specifically, the bacterium produces an extracellular hexopolysaccharide matrix, or glycocalyx,<sup>12,13</sup> which provides protection against antibiotics and macrophages.<sup>14–17</sup>

Moxifloxacin is a fourth-generation quinolone with a broad spectrum of antibacterial activity that can reach high tissue concentrations. Moxifloxacin exhibits

enhanced activity against *S. aureus*<sup>18,19</sup> and has a low propensity for selecting resistant mutants in vivo and in vitro.<sup>20–24</sup> Teicoplanin is a glycopeptide antibiotic and has excellent bactericidal activity against *S. aureus*. Glycopeptide antibiotics are currently the gold standard in the treatment of implant-related chronic osteomyelitis. In recent years, however, resistance to these antibiotics has appeared,<sup>25</sup> necessitating the use of alternative antibiotics that are as effective and safe as glycopeptides.

The aim of this study was to evaluate the in vivo efficacy of moxifloxacin and teicoplanin in a rat chronic implant-related osteomyelitis model, both in the presence and after removal of the implants.

## METHODS

### Pathogen

A methicillin-sensitive *S. aureus* (MSSA) strain (ATCC 29213) was used for bacterial contamination. A 0.5 McFarland suspension ( $1–2 \times 10^8$  cfu/ml) of the bacterium was prepared in tryptic soy agar.

### Antimicrobial Agents

Moxifloxacin (Avelox; Bayer, Istanbul, Turkey) and teicoplanin (Targocid; Aventis, Istanbul, Turkey) were used in the study. Solutions of the drugs were fresh on every day of assay.

### Animals and Operative Procedure

This study was approved by the ethics committee of School of Medicine, Duzce University, Turkey. Principles of laboratory animal care were followed in this study. Sixty Wistar rats weighing 300–350 g were used in the study. The animals

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**Figure 1.** The left femoral medullar cavities were infected and Kirschner wires were placed into the medulla of the femur.

were housed one per cage in a room with controlled temperature (23–25°C) and a light/dark cycle of 12:12 h. After a 1-week acclimatization period, each rat was anesthetized with an intraperitoneal injection of 1.5 mg of xylazine hydrochloride and ketamine HCl. An anterior longitudinal skin incision was made over the knee joint of the left hind leg, after first shaving and then disinfecting the area with povidone–iodine solution. After making a medial parapatellar incision, the patella was luxated medially. The knee was flexed and the intercondylar notch was fully exposed. The medullar cavity was exposed from the intercondylar notch to the medulla of the femur by drilling.<sup>26</sup> A 100- $\mu$ l aliquot of the MSSA strain ATCC 29213 ( $1 \times 10^8$  cfu/ml) was injected into the medullar cavity. The cavity was then filled with a Kirschner wire, and the joint was irrigated with saline solution (Fig. 1). The skin was closed with sutures and disinfected.

At the beginning of the study, all of the Kirschner wires were well fixed and none were loose. Six weeks after infection, the rats were randomly divided into five groups. In two groups, the animals were opened again and the Kirschner wires, which had become loose (likely due to infection), were removed after first exposing and enlarging the entrance of the cavity (Fig. 2). Abscess formation and cortical destruction were observed in all animals (Fig. 3). Limited debridement of the infection site



**Figure 2.** Six weeks after bacterial inoculum injection, Kirschner wires were removed and X-rays depict signs of osteomyelitis.



**Figure 3.** Clinical appearance of osteomyelitis. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

was performed. The cavity was drilled and washed with saline solution.

#### Study Groups

Experimental groups were as follows: (1) contaminated, Kirschner wire inside, received teicoplanin; (2) contaminated, Kirschner wire removed, received teicoplanin; (3) contaminated, Kirschner wire inside, received moxifloxacin; (4) contaminated, Kirschner wire removed, received moxifloxacin; and (5) contaminated, Kirschner wire inside, no antibiotic treatment (control group). Animals in groups 1 and 2 received teicoplanin at 20 mg/kg once daily, and those in groups 3 and 4 received moxifloxacin at 10 mg/kg twice daily via intraperitoneal injection for 28 days.

#### Follow-Up

Animals were monitored for 28 days. One animal in group 1 and two animals in group 5 died. The rest of the animals were sacrificed by inhalation anesthesia with ether 2 h after the final antibiotic treatment.

#### Microbiological Evaluation

The left femora of the left hind legs were harvested under sterile conditions. Specimens weighing 1 g were placed into tubes, numbered, and sent to the laboratory; the microbiologist was blinded to the treatment group. Samples were homogenized under sterile conditions and vortexed for 1 min in screw-capped sterile glass tubes containing 4 ml of 0.9% NaCl solution. Serial dilutions were made for colony counting. Aliquots of 10  $\mu$ l of the dilutions were cultured on tryptic soy agar. Colonies were counted after an incubation period of 37°C for 24 h.

#### Statistical Analysis

All calculations were carried out using the Statistical Package for Social Sciences 11.0 (SPSS 11.0; SPSS, Inc., Chicago, IL). Differences in bacterial concentrations among the five groups were analyzed using a nonparametric method (Kruskal–Wallis test) with Bonferroni's correction. The Mann–Whitney *U*-test was used to make between-group comparisons of bacterial concentrations. The level of significance for all analyses (except for Bonferroni's correction) was  $p < 0.05$ .

## RESULTS

Quantitative culture yielded median bacterial concentrations of  $5.6 \times 10^5$  cfu/g (lower quartile [LQ]/upper quartile [UQ],  $1.5 \times 10^5/8.1 \times 10^5$ ) in group 1,  $3.2 \times 10^5$  cfu/g (LQ/HQ,  $6.0 \times 10^4/6.0 \times 10^5$ ) in group 2,  $1.1 \times 10^5$  cfu/g (LQ/HQ,  $1.6 \times 10^4/2.0 \times 10^5$ ) in group 3,  $4.0 \times 10^4$  cfu/g (LQ/HQ,  $1.2 \times 10^4/2.6 \times 10^5$ ) in group 4, and  $6.4 \times 10^6$  cfu/g (LQ/HQ,  $8.1 \times 10^5/6.2 \times 10^7$ ) in group 5. The Kruskal–Wallis test revealed a highly significant difference in bacterial concentration among the five groups ( $p < 0.001$ ;  $p < 0.005$  after the Bonferroni's correction). Furthermore, significant differences were detected between groups 1 and 4 ( $p = 0.001$ ), groups 1 and 5 ( $p = 0.003$ ), groups 2 and 4 ( $p = 0.003$ ), groups 2 and 5 ( $p = 0.001$ ), groups 3 and 5 ( $p < 0.001$ ), and groups 4 and 5 ( $p < 0.001$ ) using the Mann–Whitney *U*-test. However, no significant difference was detected between groups 1 and 2 ( $p = 0.388$ ), groups 1 and 3 ( $p = 0.038$ ), groups 2 and 3 ( $p = 0.129$ ), or groups 3 and 4 ( $p = 0.285$ ), according to the Mann–Whitney *U*-test.

## DISCUSSION

In this study, a chronic implant-related osteomyelitis model was produced using a MSSA strain and then treated with moxifloxacin or teicoplanin. After 6 weeks, the implants were removed in groups 2 and 4 and antibiotic treatment was initiated in all groups. After 4 weeks, bacterial counts in all study groups (moxifloxacin/teicoplanin treatment) decreased significantly compared to the untreated control group. Bacterial counts decreased significantly in group 4 compared to both group 1 ( $p = 0.001$ ) and group 2 ( $p = 0.003$ ). These results demonstrate that, after removal of the implants, moxifloxacin therapy significantly reduced bacterial counts in comparison to teicoplanin therapy. Between groups 1 and 2 and groups 3 and 4, bacterial counts also decreased, but the differences were not statistically significant ( $p = 0.388$  and  $0.285$ , respectively). Possible requirement for a longer period of antibiotic therapy and lack of aggressive and repetitive debridement may be reasons for the latter results.

Kalteis et al.<sup>26</sup> evaluated the efficacy of moxifloxacin and another glycopeptide, vancomycin, in implant-related acute osteomyelitis. Similar to the results of our study, the authors reported that moxifloxacin treatment showed superior bacterial reduction compared to vancomycin therapy. However, in contrast to our study, antibiotic efficacy was evaluated in acute implant-related osteomyelitis and the implants were preserved.

In many previous studies, the treatment of osteomyelitis was evaluated without first inserting implants, or without removing the implants.<sup>3,27–32</sup> However, removal of the implant is essential to obtain a permanent satisfactory result in the treatment of chronic implant-related infections.<sup>33,34</sup> Because *S. aureus* forms a biofilm at the surface of metallic implants, antibiotic sensitivity is reduced, macrophage activity is obstructed, and the infection tends to become chronic.<sup>14–17</sup> Thus, the efficacy of antibacterial agents

cannot be evaluated reliably in implant-related experimental osteomyelitis studies without removal of the implants. For this reason, our experimental design included two groups (2 and 4) in which the implants were removed 6 weeks after *S. aureus* inoculation.

Moxifloxacin is an 8-methoquinolone that shows increased efficacy against both MSSA and methicillin-resistant *S. aureus* (MRSA) isolates compared to previously developed quinolones.<sup>22,35–38</sup> Both oral and intravenous application of moxifloxacin result in similar tissue concentrations.<sup>26</sup> Moxifloxacin shows good bioavailability and penetration into both cortical and cancellous bone.<sup>39</sup> Moxifloxacin also diffuses well in inflammatory fluids and has a similar pharmacokinetic profile to that in human serum after a single oral dose.<sup>40,41</sup>

Teicoplanin has a similar antibacterial spectrum similar to that of vancomycin, but a longer half-life and a lower risk of serious side effects.<sup>42–46</sup> Atahan et al.<sup>47</sup> reported that teicoplanin shows superior effects in vascular graft infection with MSSA and MRSA compared to vancomycin.

The osteomyelitis model described by Kalteis et al.<sup>26</sup> was used in this study. However, in the present study, after bacterial inoculum injection the intramedullary implant was placed into the medulla of the femur. The distal end of the implant was at the level of the intercondylar notch, which was done to allow removal of the implants in groups 2 and 4 before starting antibiotic therapy.

Despite statistically significant decreases in all antibiotic treatment groups relative to the control group, no sterile bone was detected in any group. The failure to eradicate the pathogen, especially in the implant-removed groups, is likely the lack of aggressive and repetitive debridement. Similarly, complete eradication of the pathogen was not achieved in many previous experimental osteomyelitis studies.<sup>26,28,48</sup>

A prolonged period of antibiotic therapy (i.e., 4–6 weeks) is essential for the successful treatment of osteomyelitis,<sup>49</sup> although this may result in longer hospitalization time, increased treatment costs, risk of secondary infection, patient inconvenience, and the risk of systemic drug toxicity. The relatively poor antibiotic effect (moderate to no effect) observed in previous MSSA-induced osteomyelitis models treated with a single oral agent was likely due to the inability of most oral antibiotics to achieve concentrations in the bone significantly above their respective minimum inhibitory concentrations (MIC).<sup>30</sup> However, double-dose oral administration of moxifloxacin produces mean plasma and bone concentrations of  $>2.5$  mg/L, which were higher than the MIC<sub>90</sub> values for moxifloxacin in MSSA and MRSA models.<sup>39</sup>

As both oral and intravenous moxifloxacin administration produce similar tissue concentrations, osteomyelitis therapy may begin with oral moxifloxacin or be converted to oral therapy after a period of intravenous application. In this study, moxifloxacin was

injected intraperitoneally to facilitate simultaneous drug administration in equal doses to all animals.

Antibiotics may be given locally by various methods such as implantable antibiotic pumps,<sup>50</sup> polymethylmethacrylate beads,<sup>51</sup> hydroxyapatite cement,<sup>52</sup> biodegradable microspherical implants (microspheres prepared with chitosan,<sup>53</sup> polylactide glycolide microspherical implants<sup>54</sup>). Osteomyelitis treatment requires a long period of antibiotic therapy with high serum concentrations. High concentration of antibiotherapy may result in nephrotoxicity, hepatotoxicity, and gastrointestinal side effects. The main differences of the treatment with local delivery systems compared to the systemic antibiotherapy are lower serum concentrations. Therefore, local delivery systems provide patient friendly treatment options related to the minimal side effects and excellent patient compliance.

Glycopeptides show consistent antibacterial activity against all *S. aureus* strains and there have been a number of studies of these agents. However, resistance to these antibiotics was reported in the treatment of Gram-positive pathogens,<sup>25</sup> which may be the result of the increased use of these antibiotics in response to the rising frequency of Gram-positive bacterial infections. Therefore, alternative antibiotics should be considered for the treatment of staphylococcal infections. The long-term use of fluoroquinolones combined with adequate debridement for the treatment of osteomyelitis was reported as a safe and effective form of therapy.<sup>30</sup> In contrast to other quinolones, moxifloxacin shows better antibacterial activity against MSSA and MRSA strains<sup>18,19,55</sup> and a lower risk of the development of resistance in comparison to other quinolones.<sup>21,22</sup>

In conclusion, moxifloxacin is a good alternative to glycopeptide antibiotics, especially in the treatment of implant-related chronic osteomyelitis.

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