Cationic Steroidal Antimicrobial-13 for the Prevention of Perioperative Device Related Joint Infections

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INTRODUCTION: More than 400,000 primary hip and knee replacements are performed each year in the United States. From these procedures, appropriately 2-3% will become infected and when considering revision surgeries, this number grows to 22%. Infection following total joint replacement (TJR) is difficult to diagnose and even more difficult to treat. This is especially true in cases where antibiotic resistant bacteria have been identified in persistent infections and present themselves in the form of methicillin-resistant Staphylococcus aureus (MRSA) or other similar resistant bacterial strains in humans.

Antibiotic resistant bacterial infections severely affect the patient’s quality of life. Preliminary studies with the silicone polymer released Cationic Steroidal Antimicrobial-13 (CSA-13) have exhibited rapid elimination of resistant bacterial strains in vitro. This translational experiment was done to determine the efficacy of CSA-13 when challenged with 5x10^6 MRSA in vivo. The study tested: the broad-spectrum polymer released CSA-13 antimicrobial for the prevention of planktonic MRSA infections and its biocompatibility with periprosthetic tissue when used as a surface coating on orthopedic devices. These studies were designed to model clinical conditions that are currently reported in patients. The following specific hypothesis was proposed: The CSA-13 antimicrobial (18% w/w) will prevent infection caused by MRSA in vivo when eluted from the silicone polymer coating on a porous coated titanium implant.

METHODS: Twelve titanium plugs received a commercially pure Pt^2 titanium porous coating (Thorite Inc., Portland, OR), applied to region II (Figure 1). Five titanium plugs (Group 1) had a novel blend of CSA-13 and a silicone polymer coating applied to the regions I and III (Figure 1) of the titanium plug. Group 2 (n=7) received the CSA-13/silicone polymer coating in the designated regions to assess biocompatibility, and Groups 3 and 4 did not receive the CSA-13/polymer coating. Group 3 was designated to demonstrate that an infection signal could be achieved and Group 4 was designated to examine the potential for infection due to the operation procedure. The bacteria used in this research, a clinical isolate acquired from a patient who underwent arthroplastic surgery for a confirmed MRSA infection, were acquired from ARUP Laboratories. Subsequent in vitro work has been conducted to verify the virulence of this strain. In order to select for planktonic cells of MRSA, colonies from a fresh agar culture of MRSA were inoculated into a brain heart infusion (BHI) broth solution and grown per our previous protocol. Bacterial cells used for inoculation into the sheep femur were drawn from the bulk solution of the BHI broth. Two hundred microliters of an experimentally relevant inoculum (5x10^6 colony forming units (cfu)) were added to the lumen of the plugs used in Groups 1 and 3.

RESULTS: Four of the five Group 1 (CSA-13/MRSA) animals thrived for the duration of the 12 week study. The first three days post-op were consistent with normal surgical trauma; however, beyond that point the animals presented normal. These clinical observations were confirmed with radiographic and microbiologic analysis which revealed no sign of infection. One of the five Group 1 animals encountered a spill of MRSA in the soft tissue during the surgery, became infected, and was euthanized 11 days post-op.

Group 2 animals (CSA-13) presented normal for the duration of the 12 week study. These clinical observations were confirmed with radiographic and microbiologic analysis which revealed no sign of infection.

Group 3 animals presented with clear signs of infection 3 days post-op. Two of the three animals were euthanized 6 days post-op and the third, with a modified analgesic regimen, was euthanized 10 days post-op. These clinical observations were confirmed with radiographic and microbiologic analysis which revealed clinical signs of infection. Radiographs of the animal euthanized 10 days post-op revealed evidence of early osteomyelitis. Microbiologic analysis revealed extensive colonization of the soft and hard tissue of these animals. The bacteria in question were confirmed to be the same as those used in the initial inoculum.

DISCUSSION: The objective of this work was to determine whether CSA-13 could be used to prevent periprosthetic device related infections. The novel broad-spectrum polymer released CSA-13 antimicrobial demonstrated the ability to eliminate 5x10^6 cfu of MRSA and prevent the onset of infection in the femoral condyle of the sheep model. Evaluation of the CSA-13 coating alone indicated good biocompatibility characterized by radiographic evidence of sound skeletal attachment within healthy bone. The virulence of the bacterial strain used in this work was confirmed within the control group (Group 3) where a rapid decline (6-10 days) was observed in the animal’s condition following the surgical procedure.

Future work will focus on histomorphologic evaluation to assess biocompatibility at the polymer/tissue interface, quantification of the mineral apposition rate and percent bone ingrowth, and additional studies will be designed to evaluate the effects of CSA-13 as a device coating when used within the joint capsule.

SIGNIFICANCE: The novel broad-spectrum polymer released CSA-13 antimicrobial demonstrated the ability to eliminate and prevent MRSA infection in the sheep model. Utilization of this combination device coating could significantly reduce the number of device related infections as well as reduce hospital and patient expenses.

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