Osteoclastic bone resorption in chronic osteomyelitis

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ABSTRACT

Osteomyelitis is a common infectious disease characterized by progressive inflammation and bone destruction. Although the total number of osteomyelitis cases is high – as approximately 112,000 and 240 orthopedic device-related infections occur per year in the US and Denmark respectively, at an approximate hospital cost of $15,000-70,000 per incident – the infection rates for joint prosthesis and fracture-fixation devices have been only 0.3-11% and 5-15% of cases respectively over the last decade, which has resulted in a low interest in rigorous prospective clinical studies.

Since osteomyelitis induces osteolysis around the implant, which can lead to fractures and complicate revision surgery, orthopedists have anecdotally used anti-resorptive bisphosphonates in these patients to preserve bone stock without knowledge of their effects on chronic infection. Furthermore, in the recent years there has been an alarming increase in reports of osteonecrosis of the jaw, a condition that has been associated with bisphosphonate usage.

Although osteomyelitis remains a serious problem in orthopedics, progress has been limited by the absence of an in vivo model that can quantify the bacterial load, metabolic activity of the bacteria over time, immunity and osteolysis. To overcome these obstacles, we developed a murine model of implant-associated osteomyelitis in which a stainless steel pin is coated with *Staphylococcus aureus* and implanted transcortically through the tibial metaphysis.

We analyzed the animals using radiology, histology as well as serology. Bacterial load and activity was determined by real-time quantitative PCR (RTQ-PCR) and in vivo bioluminescence imaging (BLI) of *luxA-E* transformed *Staphylococcus aureus* (Xen29). Collectively, these studies demonstrate the first quantitative model of implant-associated osteomyelitis that defines the kinetics of microbial growth, osteolysis and humoral immunity following infection.

To better understand the effects of bisphosphonates on osteomyelitis, and shed light on the mechanism of osteonecrosis of the jaw, we investigated the interaction of anti-resorptive agents in our established murine model of implant-associated osteomyelitis. We investigated two distinct classes of anti-resorptive drugs: the most widely prescribed bisphosphonate alendronate and the biologic antagonist osteoprotegerin (OPG). Both agents caused an increase in severe infections. This finding coincided with a significant decrease in osteolysis and draining lymph node volume, suggesting that anti-resorptive agents decrease efflux of marrow lymph during the establishment of osteomyelitis that could lead to a dramatic increase in intraosseous pressure, infarction and bone pain.

Finally, we evaluated the use of colistin polymethyl methacrylate (PMMA) beads in treating *Acinetobacter baumannii* induced osteomyelitis. This was done by using our established murine osteomyelitis model and infecting animals with clinical isolates of multi-drug resistant *Acinetobacter baumannii*. To demonstrate efficacy of colistin prophylaxis in this model, mice were treated with either parenteral colistin or local colistin using PMMA beads. While parenteral colistin failed to demonstrate any significant effects vs. placebo, the colistin PMMA beads significantly reduced the infection rate.

ABSTRACT OF DISSERTATION

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