Introduction: Although the results of total hip replacement (THR) surgery are generally excellent in the short-to-medium term, with over 90% successful at 5-10 years, the long-term results are less satisfactory. The most common cause of failure in THR is loosening of the implant, which is associated with both biomechanical and biological factors. Particulate metallic and plastic debris, liberated from the articulating surfaces of the joint replacement prosthesis, appear to be the most important stimuli for the production of cytokines. Tumor necrosis factor-alpha (TNF-α) has been shown to be a potent stimulator of bone resorption in vitro and in vivo, but its effects on periprosthetic bone have not been determined. To address this issue, we developed a rabbit model in which a resorbable pellet containing a known amount of TNF-α was inserted adjacent to a polymethylmethacrylate (PMMA) implant in the distal femur. We hypothesized that local release of TNF-α adjacent to the implant would induce a dose-dependent increase in endosteal bone resorption.

Methods: 25 male New Zealand white rabbits were used in this IACUC-approved study. Animals were anesthetized with ketamine hydrochloride (40mg/kg, IM) and xylazine hydrochloride (5mg/kg, IM) and maintained on inhaled isoflurane (1.5-3% in oxygen) during the surgical procedure. A medial parapatellar incision was used to expose the distal femoral condyles. The intercondylar region was penetrated with an 18G needle and the hole enlarged by sequential drilling. A slow-release pellet (Innovative Research of America) containing 0, 420, 4200, 42000 or 420000pg/pellet of TNF-α (n=5 animals per dose level) was inserted into the drill hole. A cylindrical PMMA implant (20mm long by approximately 3 mm in diameter) was gently inserted into the drill hole and tapped into the femur until its distal end lay flush with the articular cartilage of the distal femur (Figure 1).

The joint was flushed with saline and the capsule closed with interrupted 6-0 Vicryl sutures. The skin was closed with subcuticular 6-0 Vicryl sutures. Animals were euthanized 42 days after surgery. The right femora were excised, radiographed, and processed for histology. Thick (200-300µm) sections through the pellet and proximal implant were prepared. These sections were ground to a final thickness of approximately 100µm and then stained with Sanderson’s Rapid Bone Stain or Giemsa. Digitized images of these sections were analyzed, and the following histomorphometric indices were measured: total tissue area; total cortical bone area; % cortical bone volume; % cortical porosity; % osteoid surface; % quiescent surface and % eroded surface. Data from control and treatment animals were compared with a one-way analysis of variance (ANOVA) using p<0.05.

Results: All of the animals recovered well after surgery. Radiographically, all of the implants appeared to be stable, with no evidence of linear or cystic osteolysis. Local delivery of TNF-α for 6 weeks had no effect on cortical bone area, volume or porosity. However, TNF-α stimulated bone resorption and decreased bone formation (p<0.05 for both) at the endosteal surface (Figures 2 and 3); these effects were not dose-dependent but were seen in all of the TNF-α groups.

Discussion: Our data provide direct evidence that intramedullary TNF-α is capable of inducing endosteal bone resorption in vivo. These findings are in direct contrast with our previous work with prostaglandin E2, which was found to be anabolic in this model [1]. The concentrations of TNF-α that were used in this study are in the range of those reported in interfacial tissues retrieved from patients with loose total joint replacements [2], so it is highly probable that our findings are of direct clinical relevance. Additional studies are now needed to determine the effects of other proinflammatory cytokines in this animal model. However, based on these results, it appears that targeted blockade of TNF-α release or activity may provide a rational therapeutic approach to osteolysis and aseptic loosening.


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