Introduction: Particulate wear debris from total joint replacements incites an inflammatory response that results in osteolysis and has been implicated as a major cause of implant failure (Harris 1994; Maloney and Smith 1995). The 1994 NIH consensus statement on total hip replacement recognized that osteolysis and the biological response to wear particles are significant areas of concern. Currently there are no approved prophylactic drugs for the treatment or prevention of aseptic loosening. Osteoclasts resorb bone, and alendronate, a new bisphosphonate, inhibits osteoclastic bone resorption. We hypothesize that alendronate might be useful not only to treat but also to prevent particulate-induced bone loss. Our aim, therefore, is to test this hypothesis in an established animal model of osteolysis.

Materials and Methods: The study was approved by the IACUC. The design can be conceptualized as a randomized, prospective, mixed-model experiment with two arms: a prevention arm and a treatment arm. In the prevention arm, alendronate was given concomitantly with particles. In the treatment arm, osteolysis was established, and alendronate was subsequently administered to determine whether the bone loss could be reversed.

The Cambridge osteolysis model was used (Allen 1996). Seventy-two adult male Sprague-Dawley rats (300g) underwent right knee hemiarthroplasties, and joint, and the implant was inserted in a press-fit fashion. The patella was reduced, and the wound closed in layers.

At 4, 6, and 8 weeks postop, 200μl of particulate high molecular weight polyethylene (experimental) or saline/sodium (control) was injected into the operated knee. The particle size distribution was determined by a laser particle sizer with a mean particle size of 2 microns and all particles less than 10 microns. Particles were in suspension at a concentration of 3x10^10 particles/ml.

At 4 wk in the prevention arm and 10 wk in the treatment arm, alendronate (0.01mg/kg/day) was administered to test animals via miniosmotic pump (Alzet, Palo Alto, CA).

Experimental groups:
Group A: control animals euthanized 4 weeks postop
Group B: control animals euthanized at 10 weeks
Group C: control animals euthanized at 16 weeks

Prevention arm
Group D: saline injections at 4, 6, and 8 weeks postop.
Group E: particle injections at 4, 6, and 8 weeks postop with concurrent, drug administration.

At 10 weeks, animals in this arm (groups B, C, D) were euthanized.

Treatment Arm
Group G: salino only at 4, 6, and 8 weeks postop.
Group H: intraarticular particle injections at 4, 6, and 8 weeks postop. Group I: intraarticular particle injections at 4, 6, and 8 weeks postop. Then, weeks 10-16, continuous drug treatment.

At 16 weeks animals in this arm (groups E, F, G) were euthanized.

Post-mortem specimens were deburred of soft tissues. Tibiae were fixed in neutral buffered formaldehyde, dehydrated through a graded series of alcohols and embedded in methylmethacrylate. Sections of calcified tissues were collected, 5-8 microns thick, using a Reichart-Jung sliding microtome and tungsten carbide knife. Sections were stained with H&E and trichrome. Total calcified area was determined by von Kossa stain.

The image processing and analysis system was used to analyze light microscopic images of the bone-implant interface and periimplant tissues. A Nikon Microphot light microscope attached to a Sony video-camera was used for image analysis. The collected images were processed through Metamorph (Universal Imaging Corp) Slides were further examined under polarized light for polyethylene particulate debris. Standard histomorphometric measurements between test and control specimens were made and compared.

Results: A rim of bone formed around the implants at a distance of approximately 1mm by 4 weeks (group A) and remained present throughout (groups B and C). In all control animals, a fibrous membrane formed around the prosthesis. Osteolysis was produced in the positive control groups (groups E and H). It was characterized by thinning of the bony trabeculae with an intense inflammatory response. Foreign body giant cells were present around the implant, and polyethylene debris could be seen within them. The process was progressive between weeks 10 and 16. By 16 weeks, many of the implants were only surrounded by fluid and were no longer surrounded by a membrane. Many were grossly loose at autopsy. Polyethylene particles, which could be easily seen under polarized light, were present in the periimplant tissues. Over time they migrated away from the implants and were found more dispersed throughout the proximal tibial metaphyses.

There were distinct differences noted in the bone of the alendronate test groups (groups F and I). The bony trabeculae were both quantitatively and qualitatively different. With alendronate, the trabecular bone was noticeably thicker and were present in a greater number per cross section. The bone quality was better at 10 weeks (group F) than at 16 weeks (group I). The fibrous membrane surrounding the implants was more developed than in the corresponding control groups. Furthermore, there was less migration of the particulate polyethylene away from the periprosthetic tissues.

Conclusions: In this osteolysis model, particulate polyethylene incites an inflammatory response that results in loss of bone around the implant. The process is progressive with particles migrating away from the implants into the proximal tibial metaphysis over time.

Alendronate had protective effects on periprosthetic bone that prevented or at least retarded the process of osteolysis. Furthermore, our data supports the hypothesis that alendronate may in fact reverse the process of osteolysis. The clinical implications are obvious, however caution is encouraged, as long-term effects of alendronate on periprosthetic tissues remain unknown.

References:

Supported by a Resident Research Grant from the Orthopaedic Research and Education Foundation.

54th Annual Meeting, Orthopaedic Research Society, February 1-4, 1999, Anaheim, California