Peri-Operative Zoledronic Acid Attenuates Peri-prosthetic Osteolysis Through a Reduction in Bone Turnover

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Disclosures: K Mann, M Miller, M Tatusko, J Kusler, A Biggs, M Oest: None.

INTRODUCTION: Progressive loss of cement-bone fixation can lead to clinical loosening in cemented knee arthroplasty. We previously reported that there was progressive periprosthetic osteolysis at the cement-bone interface using a using a hemiarthroplasty model in aged rats [1], and that peri-operative administration of Zoledronic Acid (ZA) substantially reduced the progression of gaps that formed at the cement-bone interface. In this study, the goals were to quantify morphologic, tissue mineral, and cellular measures of the response to ZA administration in the rat knee hemiarthroplasty model. We hypothesized that alterations in bone turnover would be responsible for the improved cement-bone fixation with ZA administration.

METHODS: Unilateral hemiarthroplasty surgeries using PMMA cement and PEEK implants (**Fig 1**) were performed on 46 9-month old female SAS Sprague-Dawley rats (with IACUC approval). Daily welfare observation and biweekly cage and bedding changes were performed in our AAALAC-accredited facility (PHS D16-00318). At the time of surgery, animals received either a saline injection (*Veh group*) or 0.1 mg/kg SC Zoledronic acid (*ZA group*). Animals were assigned to 2, 6, 12 week end points (n = 6-9/end point). Extended-release buprenorphine was administered at the time of surgery, and calcein green and alizarin complexone fluorochromes were administered 14 and 4 days before euthanasia for dynamic histomorphometry. Ex-vivo uCT scans (8 um/voxel) were performed on the proximal tibia to document morphology and tissue mineral density of bone. Histology with H&E staining was used to document bone viability (presence of nucleated or vacant osteocyte lacunae) and progression of fibrous tissue in the epiphyseal regions of the tibia. TRAP staining with ethyl green counterstain was used to document osteoclasts on the bone surface.

RESULTS: Progression of cement-bone gaps occurred predominantly in the epiphysis (**Fig 2A**) and administration of ZA reduced the rate of gap formation by 60% (p=0.0008), although gap formation increased with time in both groups (p<0.0001). The bone volume fraction (BV/TV) of peri-implant bone was greater in the metaphysis for the *ZA group* (p<0.0001) when compared to the *Veh group* suggesting that there was more distal support for the implant in the *ZA group*. Tissue mineral density was greater for the *ZA group* in both the epiphysis and metaphysis (p=0.0037). The amount of viable bone was diminished substantially in the epiphyseal regions following implantation for both groups, likely due to the surgical removal of bone and pressurization of cement in the region (**Fig 2B**). There was less viable bone in the epiphyseal region of the *ZA group* (p=0.0378), less active mineralizing bone surface (p=0.0035), and less bone formation (p=0.0132). There was not a reduction of osteoclasts in the *ZA group* in the epiphysis (p=0.102) and an increase in osteoclasts was found in the metaphysis (p=0.0011). The proportion of viable bone in the epiphysis increased with time in the *Veh group* (**Fig 3**). In contrast, the proportion of non-viable bone in the epiphysis was substantial and remained elevated in the *ZA group* when compared to the *Veh group*.

DISCUSSION: The reduction of new bone formation and enduring non-viable bone in the epiphysis for the *ZA group* is indicative of reduced bone turnover. Peri-operative administration of a single dose of ZA may suppress the early catabolic response caused by the surgical implantation thereby maintaining better cement-bone fixation in the epiphysis and supporting bone in the metaphysis. At the same time, metaphyseal fixation becomes more robust with ZA. The combination of improved cement-bone fixation in the epiphysis and metaphysis could minimize implant motion and associated motion-induced osteolysis. The elevated osteoclast count with ZA is consistent with other reports [2] which describe that nitrogen-containing bisphosphonates interfere with the mevalonic pathway, disturbing the osteoclast capability to digest bone.

SIGNIFICANCE/CLINICAL RELEVANCE: There are a number human clinical series [3] that report a reduction in revision rates for joint replacement patients that were prescribed bisphosphonates at the time of surgery, and there is an ongoing randomized/double-blinded clinical trial [4] using a single post-op dose of ZA to test efficacy. This work provides compelling cellular and morphologic data from a preclinical animal model to describe the ability of zoledronic acid (ZA) to mitigate early aseptic loosening of knee replacements.

REFERENCES: [1] JOR 39: 2352, 2021, [2] BoneKEy Reports 3, 529 (2014), [3] Arthoplasty Today 14:133, 2022, [4] BMJ Open 10(9): e040985, 2020.

ACKNOWLEDGEMENTS: Funded by NIH AR42017.

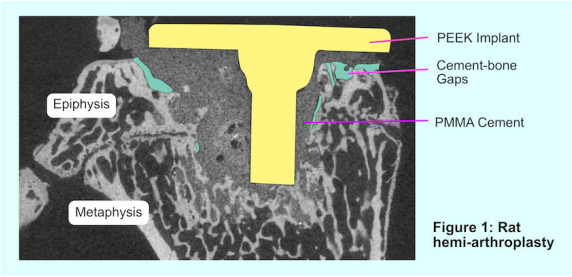

Figure 1: Rat hemi-arthroplasty

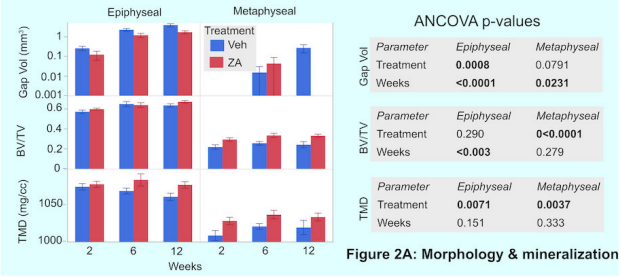

Figure 2A: Morphology & mineralization

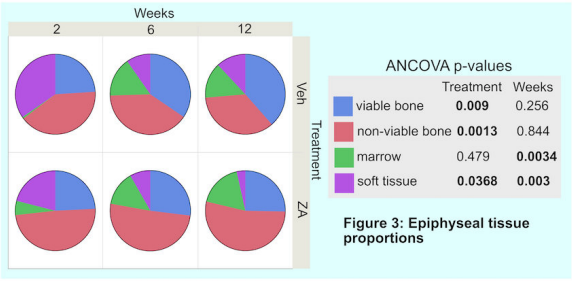

Figure 3: Epiphyseal tissue proportions

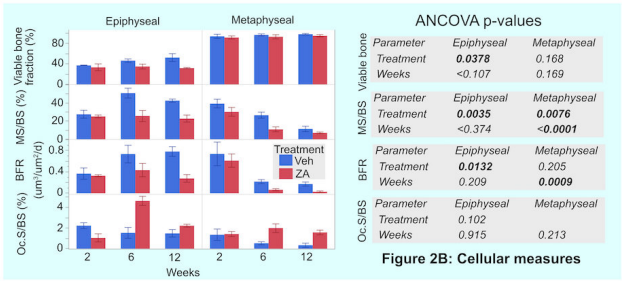

Figure 2B: Cellular measures