Sclerostin Antibody Prevents Polyethylene Particle-Induced Implant Loosening in a Rat Model

1Liu, S; 1Virdi, A S; 2Sena K; 1Sumner D.R.

1Rush University Medical Center

Senior author: rick_sumner@rush.edu

INTRODUCTION

Peri-prosthetic osteolysis is one of the major causes of aseptic loosening, ultimately necessitating revision surgery in total joint replacement. The annual demand for hip and knee revision procedures in the US is expected to increase by 137% and 601%, respectively by 2030. Therefore, the prevention and treatment of peri-prosthetic osteolysis is of great concern. Currently, most studies have concentrated on anti-catabolic agents such as bisphosphonates and bone resorption cytokine inhibitors. Sclerostin inhibits the Wnt/β-catenin pathway and/or BMP activity and neutralizing antibodies to sclerostin represent a novel anabolic strategy. Sclerostin antibody enhances implant fixation in animal models, and also suppresses bone resorption. Therefore, in this study, we hypothesized that sclerostin antibody treatment prevents polyethylene particle-induced implant loosening in a rat model of intra-medullary implantation.

METHODS

Animal model: This study was approved by the local IACUC. 36 male Sprague Dawley rats (400-425g, Harlan, Madison, WI) received bilateral implantation of dual acid etched titanium rods (1.5 x 15mm, Goodfellow, Oakdale, PA) in the distal femur. The rats were randomly assigned to one of three groups (Table 1, n=12/group).

Table 1: Study Design

<table>
<thead>
<tr>
<th>Group</th>
<th>Knee Intra-articular Injection</th>
<th>Subcutaneous Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Control</td>
<td>Vehicle</td>
<td>Vehicle</td>
</tr>
<tr>
<td>2. PE Only</td>
<td>LPS-bound PE particles</td>
<td>Vehicle</td>
</tr>
<tr>
<td>3. PE/Scl Ab</td>
<td>LPS-bound PE particles</td>
<td>Sclerostin antibody</td>
</tr>
</tbody>
</table>

A 0.25mm wide gap was created around the distal 5 mm of the implant. Animals received weekly knee intra-articular injections and twice weekly subcutaneous injections beginning the first day after surgery for 12 weeks (Table 1). Polyethylene (PE) particle suspension (9.38x10^10 particles/ml in 6% rat serum) was treated with lipopolysaccharide (LPS, 0.7µg/ml Sigma-Aldrich, St. Louis, MO). Unbound LPS was removed by repeated washes. PE particles were injected into the knee joint once per week for the duration of the study at a dose of 4.69x10^6 per injection. Sclerostin antibody (Scl-AbIII, Amgen Inc., Thousand Oaks, CA) was given subcutaneously twice per week for the duration of the study at a dose of 25 mg/kg. At 12 weeks post-surgery, all animals were euthanized. The knee joint surfaces were examined grossly. Both femurs were contact radiographed (Faxitron MX-20 Specimen Radiography System) and scanned by microcomputed tomography (µCT). The left femurs were subjected to mechanical pull-out testing to determine implant fixation strength. µCT: Femurs were scanned perpendicular to the long axis of the implant at 70 kVp, 114 µA, integration 300 ms and 30 µm resolution (Scanco µCT 40, Wayne, PA). Three equably spaced ROIs (ROI I, II and III) were selected across the length of the implant from distal to proximal. Regular µCT bone architecture parameters were measured at all 3 ROIs. Mechanical pull-out testing: Implants were pulled out from the proximal end of the femur at a displacement rate of 0.25 mm/min to failure (Instron, Canton, MA, US). Pull-out strength (N/mm²) was calculated. Statistics: Data were evaluated by one way ANOVA with Bonferroni-corrected post-hoc tests (SPSS Inc., Chicago, IL, USA). P-values less than 0.05 were considered significant.

RESULTS

The joints of Group 1 animals were grossly normal while those of Group 2 and 3 animals had similar levels of cartilage damage, fibrosis and bone eburnation. Contact x-rays showed that Group 2 had reduced radiographic density at the distal peri-implant region compared to Group 1 and that Group 3 had higher radiographic density than either Group 1 or 2 (Fig. 1). µCT data showed that compared to Group 1, Group 2 had 57% lower BV/TV (p<0.001), 30% less Tb.N (p=0.007) and 36% greater Tb.Sp (p=0.001) at ROI I (Table 2, Fig. 2). Compared to Group 2, Group 3 had 313% greater BV/TV (p<0.001), 118% greater Tb.N (p=0.007), 58% smaller Tb.Sp (p=0.001), and 36% greater Tb.Th (p=0.001) at ROI I (Table 2, Fig. 2). In addition, compared to Group 1, Group 3 had 78% greater BV/TV (p<0.001), 53% greater Tb.N (p=0.001), 43% less Tb.Sp (p=0.001), and 36% greater Tb.Th (p=0.001) at ROI I (Table 2, Fig. 2). Compared to Group 1, Group 2 had a 40% reduction in pull-out strength (p=0.006, Fig. 3). Group 3 had 2.5-fold higher pull-out strength than Group 2 (p<0.001) and 1.5-fold higher pull-out strength than Group 1 (p<0.001, Fig. 3). Pull-out strength was significantly correlated with BV/TV (r=0.701, p<0.001).

DISCUSSION

We found that sclerostin antibody completely negated particle-induced implant loosening even though the antibody treatment did not suppress particle-induced joint damage. Thus, the protective mechanism of sclerostin antibody treatment was probably the treatment-induced increase in peri-implant bone volume. Our previous study in a similar rat model without LPS-PE particle-induced implant loosening showed 2-fold higher implant fixation strength at 8 weeks with sclerostin antibody treatment. In the present study the fixation strength in animals treated with LPS-PE particles and sclerostin antibody was nearly 3-fold higher than the animals with particles only. Thus the anabolic effect of sclerostin antibody is maintained even in the presence of the strong catabolic stimulus provided by the LPS-PE particles. Anti-catabolic agents, such as bisphosphonates, have been widely studied in the prevention and treatment of particle-induced osteolysis although their efficacy in clinical trials has not been demonstrated. As an alternative, the findings of the present study indicate that the Wnt signaling pathway is a potential target for prevention of particle-induced osteolysis and implant loosening.

REFERENCES


ACKNOWLEDGEMENT:

Grainger Foundation. Material (Scl-Ab) was provided by Amgen Inc. and UCB. Dr. Nadim Hallab provided access to the mechanical testing machine.