Bone Ingrowth Performance Evaluation of a Novel Additive Manufactured Porous Titanium Interbody Spinal Fusion Cage using an Ovine Model

Michel Assad[1], Diane Beaudry[1], Britta Knight[1], Yannick Trudel[1], Annie Reza[2]
[1]Charles River Laboratories, Boisbriand, QC, Canada; [2]Stryker Spine, Allendale, NJ, USA
michel.assad@crl.com

Disclosures: Michel Assad (N), Diane Beaudry (N), Britta Knight (N), Yannick Trudel (N), Annie Reza (3A-Stryker Spine; 4-Stryker Spine)

INTRODUCTION: Additively manufactured porous titanium (Ti) biomaterials have gained interest in the spinal field as an alternative to traditional interbody devices (IBDs), such as allograft or those comprised of machined titanium or PEEK. 3D printing allows for the creation of unique configurations of randomized pore size distributions and interconnected void volumes similar to those seen in cancellous bone and thus, may promote osseointegration and early biological fixation [1]. The resulting porosity with capillary effects is expected to stimulate osteoblast proliferation and consequent bony integration within the porous matrix [2]. This study evaluated biological fixation as well as the safety and efficacy of porous Ti compared to cortical allograft IBDs following implantation into the lumbar spine. The specific objective was to histologically evaluate new bone ingrowth and the tissue response in a 16-week ovine lumbar intervertebral spinal fusion implantation study by assessing osseointegration via bone-implant contact (BIC) and intervertebral bone bridging via histopathology.

METHODS: Three (3) skeletally mature female sheep (Rideau Arcott Hybrids; ≥ 21-month old; 53-78 kg) underwent lumbar spinal fusion procedures at two non-contiguous sites (L2-L3 and L4-L5) using a retroperitoneal approach. All surgical procedures and animal husbandry adhered to protocols approved by the IACUC of an AAALAC- and CCAC-certified preclinical testing facility. First, a longitudinal 15-cm incision was made on the ovine flank from L1 to L5. A discectomy was performed at the L2-L3 and L4-L5 sites. Then, laser rapid manufactured (LRM) porous Ti [12×14×7mm (W×L×H), 0° lordosis; 55-65% porous; 400-500µm mean pore size; Group 1] or cortical allograft (AG) IBDs [12×14×7mm, 0° lordosis; Group 2] packed with iliac crest autograft were inserted. Supplemental fixation was placed at adjacent vertebral bodies with polyaxial pedicle screws joined by a titanium rod. Sheep were then allowed to recover for 16 weeks postoperatively.

At termination, rods and screws were removed, then the L1-L6 spinal segment was harvested *en bloc*, excising transverse processes and soft tissues, and immersed in 10% NBF. Microradiographs were performed using high-resolution radiography (Faxitron MX-20; Fig. 1a,b). Lumbar L2-L3 and L4-L5 units were isolated using a diamond saw, transferred to 70% ethanol, infiltrated with PMMA, then microground (Exakt 400 CS) in order to produce two (2) non-decalcified histological sections (≤60µm thickness) per explant in the sagittal plane, which were stained with Stevenel's Blue or H&E. Histomorphometry was used to quantify BIC, periprosthetic bone formation, as well as intervertebral bone bridging parameters. In parallel, histopathology evaluated the presence of inflammatory cells, necrosis/osteolysis, neovascularization, fibrous tissue, new bone formation, and bone bridging scores. One-way ANOVA was used with Dunnett's *post-hoc* test for multiple comparisons with a value of $p \leq 0.05$ to determine statistical significance for continuous histomorphometry data. The Mann-Whitney test was used to determine statistical significance ($p \leq 0.05$) for ordinal, non-continuous, histopathology scoring data.

RESULTS: All animals survived until scheduled termination and necropsy results revealed no macroscopic abnormalities. Due to its irregular porosity, porous Ti obtained a higher mean BIC compared to cortical allograft (48.35mm and 19.27mm, respectively), and showed bony ingrowth within its interconnected porosity (Fig. 1c). However, once normalized to implant perimeter, the BIC% was similar between porous Ti and cortical allograft (37.7% and 34.8%, respectively). Both groups demonstrated extensive new bone formation in the central graft window (Fig. 1c,d), with two of three porous Ti implants and one of three allografts exhibiting bone bridging in >70% of the graft window. Qualitative histological observations showed less fibrous tissue surrounding the porous Ti group, whereas the allograft group exhibited greater amounts of fibrous tissue surrounding the implant (Fig. 1d, black arrows); this was corroborated radiographically by peri-implant radiolucencies (Fig. 1b, white arrows). The porous Ti group showed a less pronounced inflammatory response versus the cortical allograft group, which was characterized by a greater presence of macrophages (Fig. 1e) and a statistically significant higher cumulative inflammation score, which was calculated based on the sum of scores of polymorphonuclear cells, lymphocytes, plasma cells, macrophages, and giant cells (Fig. 1f).

DISCUSSION: Despite being limited by a small sample size, this study revealed positive safety and biocompatibility of 3D printed porous Ti IBDs, as evidenced by bony ongrowth and ingrowth, accompanied by only a slight tissue reaction. While the porous Ti and cortical allograft implants demonstrated extensive new bone formation through the graft window over the course of this 16-week study, more variation in response was observed in the cortical allograft group and a considerable tissue reaction was noted. It is hypothesized that this tissue response may be associated, at least in part, with the allograft resorption process. Though cortical allograft IBDs were anticipated to elicit direct bony ongrowth [3], the allograft response in this study showed a tendency for fibrous tissue formation and peri-implant radiolucencies at the implant interface, accompanied by an increased inflammatory response. In contrast, histology of the porous Ti implants showed a high mean BIC along the roughened Ti surfaces indicating direct bony ongrowth as well as bony ingrowth into Ti pores, which aligns with the favorable osseointegration that is anticipated in scaffolds mimicking the randomized porous structure of bone [2].

SIGNIFICANCE/CLINICAL RELEVANCE: Interbody fusion is a well-established technique to treat degenerative disc disease. 3D printed randomized porous Ti is a promising interbody material, resulting in extensive bony apposition expressed as high BIC, which may help to achieve fusion.

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IMAGES:

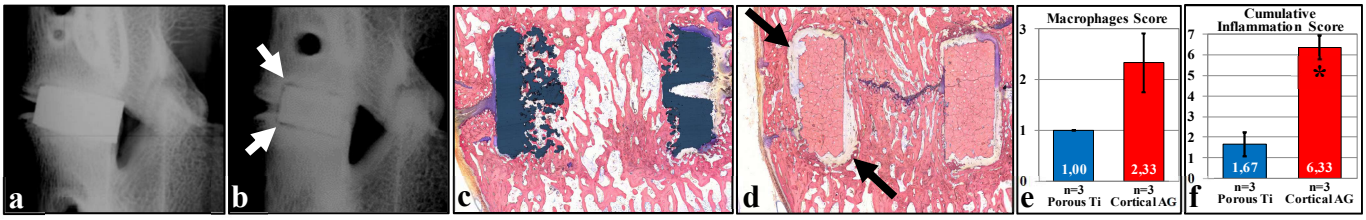

Figure 1: High-resolution lateral radiographs of Porous Ti (a) and allograft IBDs (b) at 16 weeks (white arrows denote radiolucency with allograft); Stevenel's Blue stained microground histology sections showing bone bridging with bony apposition observed for porous Ti (c) and notable fibrosis in the cortical allograft group as indicated by black arrows (d); selected histopathology scores characterizing inflammatory response (e, f; *$p \leq 0.05$).