Examination of Transient Soft Tissue Edema Following Implantation of rhBMP-2 on an Absorbable Collagen Sponge (ACS) in a Rat Ectopic Model

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Introduction: Recombinant human bone morphogenetic protein-2 (rhBMP-2) is a powerful osteoinductive protein. When implanted with the appropriate carrier, rhBMP-2 can induce bone formation. However, in rare instances, rhBMP-2 on an Absorbable Collagen Sponge (ACS) has been associated with increased transient soft tissue swelling adjacent to the site of implantation. Furthermore, reports have indicated that high doses of rhBMP-2 may increase the possibility of this soft tissue phenomenon. The purpose of the current preclinical study was to examine: 1) the effects of increasing rhBMP-2 dose on peri-implant soft tissue edema, 2) the transient nature of the edematous response, and 3) whether rhBMP-2 solution alone can induce this soft tissue response.

Materials and Methods: Thirty (30) Lewis rats received intramuscular (IM) implantation of rhBMP-2 on ACS or IM injection of rhBMP-2 solution. Four sites were available per animal. Part I sites received 0.3 cc of 0, 0.1, 0.43, or 1.5 mg/mL of rhBMP-2/ACS. Due to the IM injections in Part II, a limit of 0.1 cc of 0.1 or 1.5 mg/mL rhBMP-2/ACS or rhBMP-2 solution was permitted by animal care. Animals were randomized to a two or seven day survival time. Treatment Groups included:

Part I - rhBMP-2/ACS at 0 μg (n = 12), 30 μg (n = 8), 129 μg (n = 8), and 450 μg (n = 8)

Part II - rhBMP-2/ACS or rhBMP-2 injection at 10 μg (n = 6 per) and 150 μg (n = 6 per)

Note that 10 μg of rhBMP-2/ACS is sufficient for bony healing in a rat. T2 Magnetic Resonance Imaging (MRI) with ANOVA analysis was used for edema volume measurements and comparisons. Histology was used to examine cellular response, vascularity, and ossification at each surgical site.

Results: Part I:

Quantitative MRI results demonstrated similar edema volumes between the buffer and low dose groups, a slight dose response in edema volume, and a significant decrease in edema volume from two to seven days. Histology demonstrated similar capillary density in all groups at two days. However, at seven days, the rhBMP-2 groups demonstrated chondroplasia/ossification, as expected with the higher dose groups demonstrating more ossification.

Part II:

Quantitative MRI results demonstrated a similar transient response for both implant groups. However, at two days, both rhBMP-2/ACS implant groups had significantly higher edema volumes compared to the rhBMP-2 injection sites.

Discussion: RhBMP-2 is both a chemotactic and angiogenic agent. As rhBMP-2 dose increases, more stem cells are attracted to the implantation site and the bone formation process is accelerated. This study demonstrates that rhBMP-2 used at the appropriate dose does not significantly increase peri-implant soft tissue edema and that rhBMP-2 solution apart from the carrier will not elicit a significant soft tissue edema response. Furthermore, increasing the overall rhBMP-2 dose to 4 and 15 times, while possibly accelerating bone formation, may increase the risk of peri-implant soft tissue swelling.