THE EFFECT OF REGIONAL GENE THERAPY WITH BONE MORPHOGENETIC PROTEIN-2-PRODUCING BONE MARROW CELLS ON SPINAL FUSION IN RATS

Jeffrey C. Wang, M.D.
Jay R. Lieberman, M.D.

UCLA Department of Orthopaedic Surgery
Los Angeles, CA

Corresponding Author:
Jeffrey C. Wang, M.D.

UCLA Department of Orthopaedic Surgery
UCLA School of Medicine
Box 956902
Los Angeles, CA 90095-6902
Tel: (310) 206-8263
Fax:(310) 825-1311
ABSTRACT

BACKGROUND: Bone morphogenetic proteins (BMP) are now being used as bone graft substitutes for spinal fusion because of the high rates of pseudarthrosis and the morbidity associated with the harvesting of autogenous iliac crest bone grafts. However, the large doses of BMP required to induce a spinal fusion in humans suggests that the delivery of these proteins requires further optimization. We used ex vivo adenoviral gene transfer to create BMP-2 producing bone marrow cells and these autologous cells induced a posterolateral fusion of the spine in syngeneic rats.

METHODS: Intertransverse spinal fusion (L4-L5) was attempted in ten groups of Lewis rats with $5 \times 10^6$ BMP-2 producing rat bone marrow cells (Ad-BMP-2 cells) created via adenoviral gene transfer with guanidine hydrochloride extracted demineralized bone matrix as a carrier (eight spines, Group I); $5 \times 10^6$ Ad-BMP-2 cells on a collagen sponge carrier (seven spines, Group II); 10 micrograms of recombinant BMP-2 (rhBMP-2) on guanidine hydrochloride extracted demineralized bone matrix carrier (eight spines, Group III); 10 micrograms of rhBMP-2 on a collagen sponge carrier (seven spines, Group IV); autogenous iliac crest bone graft (fifteen spines, Group V); $5 \times 10^6$ beta-galactosidase producing rat bone marrow cells created via adenoviral gene transfer with guanidine hydrochloride extracted demineralized bone matrix as a carrier (eight spines, Group VI); decortication of the transverse processes alone (eight spines, Group VII); $5 \times 10^6$ uninfected rat bone marrow cells with a guanidine hydrochloride extracted demineralized bone matrix carrier (eight spines, Group VIII); guanidine hydrochloride extracted demineralized bone matrix only (eight spines, Group IX); or a collagen sponge alone
(eight spines, Group X). Each specimen underwent plain radiographs, manual palpation, and histological analysis.

RESULTS: All fifteen spines in Groups I and II (BMP-2 producing bone marrow cells) and all fifteen spines in Groups III and IV were fused four weeks post-operatively. In contrast, none of the fifty-five spines in the other groups fused at a minimum of eight weeks after implantation. Histological analysis of the specimens revealed that spines that had received BMP-2 producing bone marrow cells (Groups I and II) were filled with coarse trabecular post-operatively, whereas in those that had received rhBMP-2 (Groups III and IV) the fusion mass was thin and lace-like. Spines that had been treated with autogenous iliac crest bone (Group V), bone marrow cells producing beta-galactosidase (Group VI), decorticated transverse processes (Group VII), uninfected bone marrow cells (Group VIII), guanidine hydrochloride extracted demineralized bone matrix only (Group IX), or collagen sponge only (Group X) produced minimal or no bone formation.

CONCLUSION: This study demonstrated that BMP-2 producing bone marrow cells, created by adenoviral gene transfer, produce sufficient protein to induce an intertransverse fusion of the rat spine.

CLINICAL RELEVANCE: Regional gene therapy can be used to induce spinal fusion. This strategy using transduced bone marrow cells created via ex vivo gene transfer with a BMP-2 containing adenovirus could be adapted to enhance spinal fusions in humans.