Stem Cell Therapy for Osteogenesis Imperfecta: A Systematic Review and Meta-analysis of Preclinical Studies using Mouse Models

L. Battle, S. Yakar and A. Carriero

Osteogenesis imperfecta (OI) is a genetic collagen-related disease characterized by poor bone quality, osteopenia and increased fracture risk[1]. Bisphosphonates and other existing treatments can only partially correct the bone phenotype, providing symptomatic relief but not addressing the underlying genetic defect. Stem cell therapy is a promising treatment as it holds potential to correct the bone phenotype at the cellular level by utilizing genetically healthy cells early in their development to improve the quality and increase the quantity of OI bone. Here, we conduct a meta-analysis to investigate the efficacy of stem cell therapy on mouse models of OI.

A literature review was performed to identify studies treating mouse models of OI with stem cells, including bone marrow, mesenchymal stem cells, and human fetal stem cells. Effect size of fracture incidence, maximum load, stiffness, cortical thickness, BV/TV, and raw engraftment rates were pooled in a random-effects meta-analysis. Moderator analyses were run to estimate the influence of variables including cell type, cell number, injection route, mouse age, irradiation, anatomical bone, and follow-up time.

Consistent with clinical case studies[2], bone fracture incidence greatly decreased with stem cell therapy, although the small raw engraftment rate. Cell therapy had a beneficial effect on maximum load, with follow-up time and anatomical bone having an influence on it. Stiffness, cortical thickness and BV/TV were not affected by cell therapy in mouse models of OI.

This study demonstrates the promising potential of stem cell therapy to reduce fractures in OI despite the low cell engraftment. The mechanism of stem cell engraftment and its participation in bone modeling and remodeling is yet to be understood. Results support the hypothesis that transplanted cells produce beneficial effects by secreting paracrine factors and other soluble molecules[3]. It was not possible to investigate further parameters due to the lack of standards of investigation between the studies. Being bone fracture the primary symptom of OI, there is a critical need to measure the fracture toughness of OI bone treated with stem cells to assess the actual efficacy of the treatment to rescue OI bone brittleness. Understanding the mechanism of cellular therapy on bone (re)modeling as well as its actual efficacy on enhancing the strength and toughness of OI bone is crucial for the successful implementation of this therapy in the clinic.

1. Van Dijk FS, Sillence DO. *Am J Med Genet A*. 2014;164A(6):1470-1481.
2. Horwitz EM, Prockop DJ, Gordon PL, et al. *Blood*. 2001;97(5):1227-1231.
3. Prockop DJ. *Cytotherapy*. 2017;19(1):1-8.

Outcome	# of Studies	Effect Size (CI)
Fracture Incidence (RR)	5	0.27 (0.19, 0.38)*
Engraftment (Raw %)	6	6.35 (0.14, 12.55)
Maximum Load (SMD)	6	2.37 (0.43, 4.32)*
Stiffness (SMD)	6	2.09 (-0.45, 4.64)
Cortical Thickness (SMD)	5	0.72 (-0.79, 2.23)
BV/TV (SMD)	3	1.37 (-1.26, 4.00)

Table 1 Meta-analysis conducted on 5 outcomes common to the studies analyzed. The effect size, representing the magnitude of the observation, was considered significant (*) if the relative 95% confidence interval (CI) did not include 0. Risk ratio (RR) of fracture incidence was calculated as the total number of fractured long bones over the total number of long bones. Risk ratios lower than one signify a decrease in risk in the stem cell treated OI bone. Engraftment rate was expressed as the raw percentage of human cells to total (mouse) cells. Stem cell treated bones showed low and variable rates of engraftment. Standardized mean differences (SMD) were calculated for the other outcomes as the mean difference over the pooled standard deviation. Only Maximum Load was significantly higher in stem cell treated OI bone.