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Efficacy and Toxicity Combined Study of Human Adipose Tissue-derived Mesenchymal Stem Cells in a Rat Femoral Segmental Bone Defect Model

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Human adipose tissue-derived mesenchymal stem cells (hATMSC) have the potential to differentiate into multiple lineages ofmesenchymal tissues. The treatment of critical size bone defects is still a challenging problem in orthopaedics. This study was performed to evaluate efficacy of bone regeneration and toxicity of hATMSC for 16 weeks in a femoral bone defect model with athymic nude rats (Hsd:RH-Foxn1rnu).A critical-sized segmental bone defect, 5mm in length, was created in the femoral diaphysis of 60 rats under general anesthesia using zoletil/xylazine. Six groups were assessed over 16 weeks: empty defects (control: cell media), hydroxyapatite-tricalcium phosphate (HA-TCP) scaffold (group I), hATMSC (group II; 7.5x107 cell suspension), hATMSC-loaded HA-TCP scaffold(group III; 7.5x105, group IV; 7.5x106, group V; 7.5x107 cells/ml). The hATMSC were loaded onto a HA/TCP scaffold and observed under SEM to confirm attachment of cells on HA/TCP. The healing response was evaluated radiographically at postoperative, 2, 4, 8, 12, 16 weeks after implantation at the defects and by micro-computed tomography from representative samples at 16-week. To evaluate toxicological effect of hATMSC for 16 weeks, we assessed systemic response according to guidelines for Nonclinical Laboratory Studies issued by Korea Food & Drug Administration.SEM studies revealed that hATMSC were filled the pores and surfaces of HA/TCP scaffolds depending on cell-loading density. In vivo osteogenesis was characterized by almost bridged defects with newly formed bone after 16 weeks in group III, IV and V compared with group control, I, II. In that groups, paraffin section showed bone trabecules formed at the site of the defect. On comparing low cell-seeding density with the high that on HA/TCP, bone regeneration reached similar levels at 16 weeks. In toxicity study, no significant hATMSC-related changes were found in body weights, clinical signs, hematological/biochemical values, organ weights, histopathological findings. And we revealed no inflammation, or lymphocytic infiltration at the site of transplantation.The results of this study demonstrated that hATMSC loaded on HA/TCP implants enhanced the repair of a critical-sized femoral bone defect in nude rats. And no test article-related toxicity was observed in this model.