INTRODUCTION: Recent advances in molecular biology have allowed us to understand the molecular mechanisms of fracture healing better than ever and have provided possible new solutions for fracture healing. For example, bone morphogenetic proteins (BMPs) were discovered and cloned decades ago and now are available for human use. BMPs have been suggested as very promising molecular biology drugs in animal experimental models. However, higher animal studies using primates have raised concerns that higher concentrations and higher doses of BMPs may be necessary compared with lower animals and rodents. The difficulty also remains of finding a suitable carrier and delivery system. As suggested by these studies, the bone formation or fracture healing achieved by rhBMP was not as robust in human clinical trials as that in lower animal studies. The purpose of our study is to determine the therapeutic effect of rhBMPs in difficult nonunions.

MATERIALS AND METHODS: The present study was a prospective clinical trial of a consecutive series of ten patients who had congenital pseudarthrosis of the tibia (N=5) or allograft-host nonunions (N=5). The use of rhBMP and a prospective clinical study protocol were approved by the Western Institutional Review Board. There were six skeletally immature patients with open growth plate and four skeletally mature patients. An anterior midline skin incision was made over the nonunion site. 3.5 mg of rhBMP-7 mixed with a type I collagen carrier and corticocancellous allograft bone chips (N=7) or 1.5 mg of rhBMP-2 in a type I collagen sponge (N=3) were applied around the nonunion site after removal of dense fibrous tissues around the nonunion site. Postoperatively, all patients had plain radiographs at 4 week intervals for one year postoperatively. Six patients had follow-up 99mTc bone scan 6 months postoperatively. Healing of the nonunion site, incorporation of the OP-1-allograft composite, resorption of the allograft, radiographic changes of growth plate and limb length discrepancy were recorded and analyzed. Complications including infection, drainage and wound dehiscence were recorded.

RESULTS: Satisfactory union was achieved in only one patient at 9 months. The remaining nine patients did not demonstrate any new bone formation or healing at the nonunion site (Figure 1). Furthermore, most of the allograft bone grafts were gradually resorbed. Bone scan did not reveal any increased radio-isotope uptake. There were no side effects following the use of rhBMP-7 in skeletally immature children. There was no adverse effect on the growth plate on radiographs.

DISCUSSION: Although rhBMP-2 and rhBMP-7 demonstrated similar healing rate in tibial nonunions and open tibial fractures in comparison to autogenous iliac crest bone graft, rhBMPs were not sufficient to achieve healing in difficult types of nonunions such as congenital pseudarthrosis of tibia or allograft-host nonunions. One study has demonstrated successful healing of the allograft osteotomy sites by rhBMP-2 in rodents, but the results were not reproduced in humans. Difficult human nonunions may require coordinated action of multiple growth factors or other elements such as reparative cells that are necessary for healing. Finally, our study indicates that the results of small animal studies do not necessarily predict similar results in human.