Injury, Int. J. Care Injured (2005) **36S**, S51—S59

ELSEVIER

INJURY
INTERNATIONAL JOURNAL OF THE CARE OF THE INJURED

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Application of recombinant BMP-7 on persistent upper and lower limb non-unions

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KEYWORDS
Recalcitrant non-unions;
BMP-7;
Growth factors

Summary The purpose of this study was to evaluate the efficacy and safety of recombinant bone morphogenetic protein 7 (rhBMP-7 or OP-1) as a bone-stimulating agent in the treatment of persistent fracture non-unions.

Twenty-five consecutive patients [19 males, mean age 39.4 years (range: 18—79)] with 26 fracture non-unions were treated with rhBMP-7. There were 10 tibial non-unions, eight femoral, three humeral, three ulnar, one patellar, and one clavicular non-union. The mean follow-up was 15.3 months.

The mean number of operations performed prior to rhBMP-7 application was 3.2, with autologous bone graft and bone marrow injection being used in 10 cases (38.5%). Both clinical and radiological union occurred in 24 (92.3%) cases, within a mean time of 4.2 months and 5.6 months, respectively. Of the remaining two cases, one patient ultimately underwent a below knee amputation, secondary to recurrence of deep sepsis. The other patient with recalcitrant ulnar non-union although the radiological union was incomplete, declined further intervention, as he was asymptomatic. No complications or adverse effects from the use of rhBMP-7 were encountered. This study supports the view that the application of rhBMP-7 as a bone-stimulating agent is safe and a power adjunct to be considered in the surgeon's armamentarium for the treatment of these challenging clinical conditions.

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doi:10.1016/j.injury.2005.10.010

Introduction

Despite the intrinsic regenerative and reparative capacity of bone and the ongoing advances in the treatment of fractures and understanding of the fracture repair processes, impaired healing continues to be one of the severe complications of fractures. Approximately 5—10%, of the 6.2 million fractures occurring annually in the United States, are associated with impaired healing.[38] These complications are challenging for the orthopaedic surgeon, as they are difficult to treat, often requiring a lengthy treatment, but, most importantly, they represent chronic clinical conditions, difficult for patients to endure, as they are associated with pain and functional and psychosocial disability.

The standard treatment of the majority of aseptic non-unions is mechanical stabilization including various forms of internal or external fixation, with or without biological stimulation, depending on the accurate assessment and classification of the non-union.[7] Autogenous cancellous bone grafting remains the gold standard biological method used to promote union by stimulating the local biology at the non-union site. However, its limited available quantity, as well as the donor site morbidity and complications,[1,14,45] dictated the need for the development of alternative methods of biological stimulation.

Such alternatives, used either alone or in combination for the treatment of non-unions, are the allogenic cancellous bone grafting, bone marrow injections, the use of electrical, ultrasound, and shockwave stimulation, and a variety of bone graft substitutes, with either osteoconductive or both osteoconductive and osteoinductive properties.[2,5,6,22,29,32,34,36,42,44] Biological response modifiers such as bone morphogenetic proteins (BMPs) and platelet-derived growth factors, also, appear to be safe and efficacious alternatives in the management of non-unions.[15,23,24,26,30]

BMPs are proteins, members of the transforming growth factor-beta superfamily, and they possess great osteoinductive potential. They induce a sequential cascade of events for chondro-osteogenesis during bone formation and ultimately fracture healing, including chemotaxis, proliferation of mesenchymal and osteoprogenitor cells and their differentiation into a chondrogenic or osteogenic lineage.[39,40] Knowing the osteoinductive properties of BMPs and having identified their genetic sequences,[35] recombinant gene technology has been utilized to produce BMPs for their clinical application as alternatives or adjuncts in the treatment of cases where bone regeneration is not anticipated. Currently, recombinant (rh)BMP-2 and rhBMP-7 (or osteogenic protein-1, OP-1) are commercially available and used in such cases.

The purpose of this study was to present our institutional experience from the application of human recombinant osteogenic protein-1 (rhBMP-7) for the treatment of upper and lower limb fracture persistent non-unions and to evaluate its safety and efficacy.

Patients and methods

Between October 2001 and December 2004, 25 patients with 26 persistent upper and lower limb non-unions were treated with recombinant BMP-7 (3.5 mg of rhOP-1 in each sterile vial) in our institution. Details such as demographic data, the location of non-union, initial and subsequent procedures performed, the type of stabilisation, the method of mobilisation, the application or not of autologous bone graft (ABG) and post-operative complications were recorded and computerised (Table 1, Figs. 1and 2).

The mean age of the 25 (19 males) patients was 39.4 years (range: 18—79). Ten were tibial non-unions, eight were femoral, three humeral, three ulnar, one patellar, and one clavicular non-union. In 24 patients, the non-union was the result of a previous fracture sustained either as an isolated injury (in 15 patients) or as part of multiple injuries (eight polytrauma patients). Eleven (44% of all fractures) were open fractures (seven tibial fractures, two femoral, one humeral and one ulnar fracture). In one patient, non-union occurred after a second elective lengthening procedure for congenital short femur, which was complicated by deep infection. Four patients (15.4% of all cases) had been diagnosed with infected non-unions. However, prior to administration of BMP-7 there was no evidence of ongoing deep sepsis.

The mean number of operations relating to fracture treatment performed prior to the application of rhBMP-7 was 3.2, with a range of 0 (when fractures treated conservatively) to 20. Prior to rhBMP-7 application, autologous iliac crest bone graft was had been used in nine cases and bone marrow injection in one case in an attempt to promote fracture union.

Following discharge from the hospital, patients were followed up in the outpatient orthopaedic department having routine clinical and radiological assessment. Successful completion of treatment was defined as the accomplishment of both clinical and radiological union. Clinical union was defined as painless full weight bearing and radiological union