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Osteogenic Protein-1 (Bone Morphogenetic Protein-7) in the Treatment of Tibial Nonunions:

A Prospective, Randomized Clinical Trial Comparing rhOP-1 with Fresh Bone Autograft*

GARY E. FRIEDLAENDER, MD
From the Department of Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, Connecticut

CLAYTON R. PERRY, MD
U.S. Center for Sports Medicine, St. Louis, Missouri

J. DEAN COLE, MD
Orlando Regional Medical Center, Orlando, Florida

STEPHEN D. COOK, PHD
Department of Orthopaedic Surgery, Tulane University Medical Center School of Medicine, New Orleans, Louisiana

GEORGE CIERNY, MD
Resurgens Orthopaedics, Atlanta, Georgia

GEORGE F. MUSCHLER, MD
Department of Orthopaedic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio

GREGORY A. ZYCH, DO
JASON H. CALHOUN, MD
Division of Orthopaedic Surgery, University of Texas Medical Branch at Galveston, Galveston, Texas

AMY J. LAFORTE, PHD
Stryker Biotech, Hopkinton, Massaschusetts

SAMUEL YIN, PHD
Stryker Biotech, Hopkinton, Massaschusetts

Abstract

Background: The role of bone morphogenetic proteins (BMPs) in osseous repair has been demonstrated in numerous animal models. Recombinant human osteogenic protein-1 (rhOP-1 or BMP-7) has now been produced and was evaluated in a clinical trial conducted under a Food and Drug Administration approved Investigational Device Exemption to establish both the safety and efficacy of this BMP in the treatment of tibial nonunions. The study also compared the clinical and radiographic results with this osteogenic molecule and those achieved with fresh autogenous bone.

Materials and Methods: One hundred and twenty-two patients (with 124 tibial nonunions) were enrolled in a controlled, prospective, randomized, partially blinded, multi-center clinical trial between February, 1992, and August, 1996, and were followed at frequent intervals over 24 months. Each patient was treated by insertion of an intramedullary rod, accompanied by rhOP-1 in a type I collagen carrier or by fresh bone autograft. Assessment criteria included the severity of pain at the fracture site, the ability to walk with full weight-bearing, the need for surgical re-treatment of the nonunion during the course of this study, plain radiographic evaluation of healing, and physician satisfaction with the clinical course. In addition, adverse events were recorded, and sera were screened for antibodies to OP-1 and type-I collagen at each outpatient visit.

Results: At 9 months following the operative procedures (the primary end-point of this study), 81% of the OP-1-treated nonunions (n = 63) and 85% of those receiving autogenous bone (n = 61) were judged by clinical criteria to have been treated successfully (p = 0.524). By radiographic criteria, at this same time point, 75% of those in the OP-1-treated group and 84% of the autograft-treated patients had healed fractures (p = 0.218). These clinical results continued at similar levels of success throughout 2 years of observation, and there was no statistically significant difference in outcome between the two groups of patients at this point (p = 0.939). All patients experienced adverse events. Forty-four percent of patients in each treatment group had serious events, none of which were related to their bone grafts. More than 20% of patients treated with autografts had chronic donor site pain following the procedure.

Conclusions: rhOP-1 (BMP-7), implanted with a type I collagen carrier, was a safe and effective treatment for tibial nonunions. This molecule provided clinical and radiographic results comparable with those achieved with bone autograft, without donor site morbidity.

Despite the remarkable intrinsic capacity of bone to regenerate and undergo repair, numerous musculoskeletal disorders require or benefit from the addition of an osteoinductive stimulus, traditionally in the form of autogenous bone graft. One such challenging clinical condition is nonunion of the tibia.

The estimated incidence of long bone fractures in the United States is nearly 1,500,000 per year[26]. A relatively small percentage of these injuries proceed to nonunion, while considerably more result in delayed healing[8]. The majority of long bone nonunions occur in the tibia, and they are responsible for substantial morbidity in the form of pain, loss of function, and interference with personal and vocational productivity[7,26]. Tibial nonunions are particularly recalcitrant to treatment, and consequently many alternative approaches to elicit their healing have been suggested. These options include various forms of skeletal fixation, with or without supplemental bone graft, usually autogenous in nature[34]. Additional treatment considerations include physical modalities, such as electrical stimulation[1,4] or the use of ultrasound[19]. Each approach offers advantages and disadvantages. None of these methods, however, has provided a rapid and uniformly reliable method of treatment to manage the pain, lost function, or morbidity associated with these injuries. Indeed, some morbidity may be attributed to the selected modality of treatment, such as pain at the bone graft donor site[35], pin track or surgically introduced infection, and muscle atrophy or joint stiffness secondary to immobilization.

In recent years, our knowledge of bone repair and regeneration, at both the cellular and molecular levels, has greatly improved[5,23]. This is particularly true with respect to the molecular signals responsible for regulating the recruitment, differentiation, and activity of macromolecules responsible for the bone remodeling cycle. Observations by Urist and Strates[31,32] and later by Sampath and Reddi[29] predicted and then demonstrated the properties and effects of the bone morphogenetic proteins (BMPs). Along with other members of the transforming growth factor-beta (TGF-β) superfamily and related growth and differentiation factors (GDFs), these molecules are directly involved in the processes of fracture repair and bone graft incorporation[3,11,22,27,28,30].

Human osteogenic protein-1 (OP-1 or BMP-7) has been cloned and reproduced with recombinant technology (rhOP-1)[24] and, when combined with a collagen carrier, has been shown to induce new bone formation in heterotopic sites as well as repair skeletal defects in a wide variety of animal models[9-13,18]. These extensive preclinical studies have also supported the safety of OP-1. On the basis of this biological success and safety profile, a prospective, randomized, partially blinded clinical trial was accomplished in which patients with established tibial nonunions were treated with intramedullary fixation and implantation at the fracture site of OP-1 in a collagen carrier or by bone autograft.

Materials and Methods

The Study Population

One hundred and twenty-two patients with 124 tibial nonunions (one patient had bilateral tibial nonunions and one patient had two nonunited fractures in the same tibia) were enrolled in a clinical study, under a Food and Drug Administration (FDA) approved Investigational Device Exemption (IDE), in which they were randomly assigned to one of two treatment groups (OP-1 or bone autograft). Each patient had a tibial nonunion, as based on a 1988 FDA guidance document definition requiring 9 months duration of the non-united fracture with no evidence of progressive healing over the previous 3 months[14]. Patients who, in the judgment of their treating orthopaedic surgeon, were candidates for internal fixation alone (generally reaming and an intramedullary rod), were excluded, as were patients with clinically apparent infection at the fracture site. Other contraindications to inclusion in this study are listed in Table I.

All patients were treated between February, 1992, and August, 1996, at one of 17 medical centers in the United States, after institutional review board approval had been obtained at the local health care facility and with the patient's informed consent. In each case, the involved orthopaedic surgeon had determined that the patient would best be treated by internal fixation and required a supplemental bone graft. Consequently, all 122 patients enrolled in this study underwent intramedullary (IM) rod fixation (the type of rod and the decision to lock the device were left to the discretion of each surgeon). A new rod was inserted at this time in more than 90% of fractures in each group (90.5%, 57 of 63 fractures in the OP-1-treated group, and 91.8%, 56 of 61 fractures in the autograft-treated group). In the remaining fractures, a previously inserted IM rod was left in place. One-half of the patients (61 patients with 63 tibial nonunions) were randomly assigned to receive an implant at the fracture site with OP-1 in a type I collagen carrier, and the other half (61 patients with 61 tibial nonunions) received bone autograft in a similar manner. Surgeons were aware of the treatment group to which each patient was assigned after the random selection process.

OP-1 Implant

The rhOP-1 implant was supplied by Stryker Biotech (Hopkinton, Massachusetts). Each sterile package (or unit) contained 3.5 milligrams of the rhOP-1 mixed with 1 gram of type I bovine bone-derived collagen (the total reconstituted volume was approximately 4 milliliters per unit). The volume of fracture gap present at the time of surgery (following debridement) determined the amount of rhOP-1 used in each patient, to a maximum of two units.

Methods of Clinical Assessment

Clinical assessment included the presence of pain at the fracture site (none, mild, moderate, or severe) and the ability to bear weight (none, partial, or full) on the involved extremity. These criteria were evaluated at 1, 2, 3, 6, 9, 12, and 24 months following surgery, and the primary end-point of the study was the 9-month visit. *Clinical success was defined as full weight-bearing, less than severe pain at the fracture site on weight-bearing, and no further surgical intervention for the purpose of enhancing fracture repair (i.e., re-treatment).* The operating surgeon's level of satisfaction with the healing process at this same time interval was also recorded. In addition, the time of the surgical procedure, estimated blood loss, and hospital length of stay were noted. For patients who received autograft, the degree of pain at the donor site (none, mild, moderate, or severe) was recorded.

All perioperative and postoperative complications were reported and classified as severe (potentially life threatening and requiring treatment), moderate (non-life threatening but requiring therapeutic intervention), or mild (resolved without any treatment). Whether the complication was related to the OP-1 implant or the bone autograft was determined.

Retrospectively, all adverse events were classified as serious or non-serious according to International Conference of Harmonization (ICH) Guidelines[20].

Immunological Assessment

All of the patients were screened for antibodies to OP-1 and type I collagen by an enzyme-linked immunoabsorbent assay (ELISA) with sera collected at each follow-up visit. The specificity of the response was confirmed with use of Western blot analysis for those patients demonstrating positive anti-OP-1 or anti-collagen activity in the screening assay.

Radiographic Assessment

Standard radiographs were obtained in the anteroposterior, lateral, and two oblique projections. A panel of three musculoskeletal radiologists, blinded to treatment and time following the surgical procedure, independently *assessed whether bridging by new bone existed across the fracture site and on how many of the four views this bridging was apparent.* The final result reflected the consensus of at least two of these three radiologists.

Statistical Analysis

Analyses of efficacy outcomes were conducted with use of a chi-square test, and a p value of ≤ 0.05 was considered statistically different. Differences in the frequency of adverse events were evaluated by a two-tailed chi-square or Fisher's exact test, as appropriate. Comparison of the means of operative blood loss was performed with a Student *t* test. For the length of stay and operative time, Wilcoxon rank sum tests were performed, which are appropriate for variables that are not normally distributed. A p value of ≤ 0.05 for analysis of safety variable was considered significant.

Results

Demographics

The demographics of the study groups are presented in Table II. These two randomly assigned populations were similar in most respects, including age, sex ratio, duration of nonunion, and the number of prior surgical interventions. There was, however, a statistically higher prevalence of atrophic nonunions (41 compared with 25%, $p = 0.048$) and a strong trend toward more smokers (74 compared with 57%, $p = 0.057$) in the OP-1 group. There were also trends toward higher percentages of comminuted fractures at injury, prior failures of bone autografts, and prior use of intramedullary rods in the individuals in the OP-1 treated group.

The maximum number of units of OP-1 implants used in this study was two, and 47 of the 63 nonunion sites were treated with a single OP-1 implant. The volume of bone autograft used for each patient was left to the discretion of the surgeon and was not reported.

Treatment of 41% of nonunions was accompanied by a fibulectomy (40% of the OP-1 and 43% of the autograft-treated groups). Overall, 92% of the intramedullary rods were locked, including 94% in the OP-1 and 92% in the autograft-treated groups.

Clinical Outcomes

Length of stay, operative time, and operative blood loss are recorded in Table III. The trend toward longer operative and hospitalization times and the statistically significant increased blood loss ($p = 0.049$) in the autograft-treated group were imposed by the nature of a bone donor recovery site. In addition, all patients in the autograft group had pain at the donor site following the operative procedure, and more than 80% judged their postoperative pain as moderate or severe. Furthermore, more than 20% of patients had persistent pain, mild or

moderate in nature, at their 6-month visit, and approximately 13% had persistent pain at the donor site 12 months following the operative procedure.

All patients in each group had at least one adverse event, usually mild or moderate and non-serious in nature. Examples of these events included common postoperative sequelae such as fever, nausea and vomiting, leg edema, discomfort, and hematoma at the operative site. The incidence of these events was similar in both groups (Table IV). Forty-four percent of both groups had serious adverse events, none of which were considered related to the OP-1 implant or the bone autograft. Osteomyelitis was reported at the fracture site in 21% of patients (13 of 61, Table IV) following treatment with bone autograft but in only 3% (2 of 61; Table IV) of those receiving OP-1 ($p = 0.002$).

Clinical success in this study required a patient to be fully weight-bearing with less than severe pain at the fracture site (Table V). By these criteria, at 9 months following surgery, 81% (51 of 63) of the OP-1-treated group and 85% (52 of 61) of the autograft-treated group were considered to have successful outcomes ($p = 0.524$, not statistically different). This high level of satisfactory outcome remained present, with both groups demonstrating an 82% success rate after 24 months of observation (37 of 45 patients treated with OP-1 and 31 of 38 patients receiving autograft, $p = 0.939$).

By the 9-month follow-up visit, surgical re-treatment occurred in 5% of the OP-1-treated patients and in 10% of those receiving autograft. Physician satisfaction with the healing process at 9 months following surgery was favorable for 86% of those treated with OP-1 and 90% of the autograft-treated patients.

Radiographic Results

Seventy-five percent (47 of 63) of the nonunions in the OP-1-treated group demonstrated radiographic evidence of bone bridging on at least one view, compared with 84% of those treated with autograft ($p = 0.218$, not statistically significant) at 9 months following surgery (Table V). The use of more rigorous criteria—bridging in at least three of four views—resulted in lower radiographic healing rates in both groups: specifically, 62% of the OP-1 recipients and 74% of the autograft-treated group ($p = 0.158$, not statistically significant).

Influence of a Prior Autograft

Nineteen (31%) of the 61 nonunions treated with autografts in the present study and 27 (43%) of 63 nonunions in the OP-1-treated group had received autograft in the course of their previous treatment for the nonunion. Clinical success and radiographic outcomes in these subsets were not significantly different from the nonstratified results.

Immunological Results

Circulating antibodies against type I collagen were detected postoperatively in the sera of 5% of those patients receiving this matrix, and low levels of anti-OP-1 antibodies developed in 10% of those treated with OP-1. All of the anti-OP-1 antibody responses were transient, and all titres were low. No adverse events related to sensitization were reported. By 9 months, five of the six patients with an anti-OP-I antibody response had unions that were healed clinically and radiographically. The nonunion in the remaining patient went on to heal radiographically at 24 months.

Discussion

The results of this study demonstrate that rhOP-l is a clinically safe osteogenic implant and is associated with substantial clinical and radiographic success when used in conjunction with

intramedullary rod fixation for the treatment of tibial nonunions. Furthermore, these rates of success were comparable with those achieved with autograft, when evaluated at 9 and 24 months following surgery.

Tibial nonunions were chosen for this study because of their relatively high frequency, substantial morbidity, and challenging treatment requirements[26,34]. The incidence of fractures in the United States exceeds six million each year, of which approximately 25% involve long bones and more than one-third of these (more than 580,000 cases) are injuries of the tibia and fibula. Collectively, fractures result in greater than 3.5 million visits to emergency rooms and nearly 11 million outpatient visits on an annual basis. The socioeconomic impact of fractures further includes approximately 146 million restricted activity days, more than 36 million lost work days, more than 7.3 million lost school days, and nearly 6.5 million patient days each year.

Many prior clinical studies have been designed to evaluate treatment alternatives for tibial nonunions[1,4,8,19,21,34], but this is the first of a prospective, randomized, and partially blinded nature to assess a BMP or other osteogenic molecule. In these previous studies, there has been a lack of uniformity in the definition of nonunion and often a lack of rigor in terms of assessment criteria, particularly radiographic analysis[33].

As is true of other studies, radiographic analysis in the present circumstance raises important issues regarding the assessment of fracture repair. It is, for example, difficult to maintain "blinding" of the radiologists with respect to autograft, which is mineralized from the outset, when compared with the radiolucent nature of OP-1 and its collagen matrix. On the other hand, without the benefit of history and time frame since surgery for each set of radiographs, it becomes problematic to separate the presence of pre-existing mineral of bone autograft from induced new bone. Similarly, standardized plain radiographic views that adequately and reproducibly demonstrate the entire bone gaps of irregular fracture configurations, partially obscured by their associated internal fixation, are impractical if not impossible. In the final analysis, radiographic interpretation is subjective. The establishment of outcome criteria, such as the definitive time following treatment used for analysis and the percent of the circumferential gap (or number of cortices) that must be bridged to confer success, represent arbitrary decisions. Indeed, in clinical practice, the physician combines historical, clinical, and radiographic information to arrive at a conclusion regarding the status of fracture healing or outcome. It is this comprehensive perspective, as reported in the present study, that supports the conclusion of substantial clinical efficacy of OP-1 in the treatment of tibial nonunions, comparable with that achieved with the use of autogenous bone.

It is also important to keep in mind that OP-1 (BMP-7) is not a new molecule. Rather, this protein structure has been highly conserved in phylogeny since the introduction of the skeleton over 400,000,000 years ago. The availability of this molecule, in recombinant form, for the purpose of enhancing osseous repair is novel.

OP-1 has been evaluated extensively in preclinical studies in critical-sized defects of rabbit, canine, sheep, and nonhuman primates[9-13,18]. In each circumstance, OP-1 was associated with a high degree of success, comparable in frequency and completeness of repair with that seen with bone autograft. Importantly, all new bone induced by any bone graft material or osteogenic molecule, including OP-1, is of autogenous origin, and this bone continues to remodel in the same manner as is normal for the particular skeletal site and its biomechanical environment.

Geesink and colleagues[17] recently reported the first experience with rhOP-1 in humans. In the study, gaps were created in the fibula during high tibial osteotomy for degenerative disease of the knee. These segmental defects did not heal when implanted with the type I collagen carrier

alone but repaired completely in five of six patients in whom the OP-1 implant was placed in this gap.

At present, there are several alternatives to bone autografts. The choices include allogeneic bone processed fresh, deep-frozen, or freeze-dried and sometimes demineralized to varying degrees, as well as a variety of synthetic hydroxyapatite, tricalcium phosphate, and other ceramic preparations of a primarily osteoconductive nature[2,5,16]. Autogenous bone remains the standard to which other choices must be compared, reflecting its relatively high osteogenic potential and, by definition, its biocompatibility. Autograft has drawbacks, however, such as the need for an additional operative site with its associated perioperative morbidity (e.g., pain, potential infection, blood loss, and fracture)[35], and limits exist with respect to the size, shape, and quantity of bone autograft available. Donor site morbidity is eliminated with the use of allografts and synthetics, but the intrinsic osteoinductive capacity of these materials is absent or less than that of autograft. Biomechanical properties of these substances also vary, depending on the method of preparation, the structural characteristics of the product, or both[25]. Allografts are extremely safe in terms of disease transmission when acquired and processed according to established guidelines, but the remote possibility of contamination by clinically significant microorganisms remains[15].

The incidence of postoperative osteomyelitis at the nonunion site was significantly greater in the autograft-treated group (3% in patients implanted with OP-1 compared with 21% receiving autograft, $p = 0.002$). The reason or reasons for this difference were not addressed by this study, but a similar high rate of infection at the fracture site was reported by Chapman and colleagues[6]. This group compared autograft with a collagen-calcium phosphate graft material in the treatment of fresh fractures of long bones, and the autograft recipients had a significantly higher infection rate (13.0 compared with 4.9%, $p = 0.008$).

OP-1 in recombinant form and combined with a type-1 bovine bone-derived collagen offers the advantages of a highly inductive molecule, with an excellent safety profile and the lack of donor site morbidity. It has little intrinsic biomechanical strength, but OP-1 can be combined with other implants to achieve stability when necessary. Like all bone graft materials, OP-1 requires a healthy host bed, capable of providing the vascularity and cell populations necessary for osseous regeneration and repair. As such, OP-1 in an appropriate matrix provides a unique profile of clinical, biological, and biomechanical characteristics, which should be carefully considered by physicians and patients when making choices among available bone graft and graft substitutes used in the treatment of tibial nonunions. The efficacy of OP-1 in other formulations and clinical circumstances requiring an osteogenic stimulus, including various fracture sites, spinal arthodesis, total joint arthroplasty, and maxillofacial indications, is currently being explored.

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Gary E. Friedlaender, MD Department of Orthopaedics and Rehabilitation, Yale University School of Medicine, P.O. Box 208071, New Haven, CT 06520-8071. E-mail address: gary.friedlaender@yale.edu.

Clayton R. Perry, MD U.S. Center for Sports Medicine, 333 South Kirkwood Road, Suite 200, St. Louis, MO 63122

J. Dean Cole, MD 1118 South Orange Avenue, Suite 205, Orlando, FL 32856-8008. E-mail address: jdcmdpa@aol.com.

Stephen D. Cook, PhD Department of Orthopaedic Surgery SL32, Tulane University Medical Center School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112-2699. E-mail address: scook2@tulane.edu

George Cierny, MD Resurgens Orthopaedics, 5671 Peachtree Dunwoody Road NE, Suite 700, Atlanta, GA 30342. E-mail address: osteomyelitis@mindspring.com

George F. Muschler, MD Department of Orthopaedic Surgery, The Cleveland Clinic Foundation (A-41), 9500 Euclid Avenue, Cleveland, OH 44195-5029. E-mail address: muschlg@ccf.org

Georgory A. Zych, DO Department of Orthopaedics, University of Miami Medical Center, P.O. Box 106960, Miami, FL 33101. E-mail address: gzych@miami.edu

Jason H. Calhoun, MD Division of Orthopaedic Surgery, University of Texas Medical Branch at Galveston, Route G-92, 6.136 McCullough Building, Galveston, TX 77555-0792. E-mail address: jcalhoun@utmb.edu

Amy J. LaForte, PhD Stryker Biotech, 35 South Street, Hopkinton, MA 01748. E-mail address for A.J. LaForte: laforte.amy@strybio.com.

Samuel Yin, PhD Stryker Biotech, 35 South Street, Hopkinton, MA 01748. E-mail address for S. Yin: yin.sam@strybio.com.

The sites (and principal investigators at these locations) are as follows: Cleveland Clinic Foundation, Cleveland, Ohio (George F. Muschler, M.D.); Barnes Hospital, Washington University Medical Center, St. Louis, Missouri (Clayton R. Perry, M.D.); Evans Army Community Hospital, Fort Carson, Colorado (Edward J. Lisecki, M.D., and John T. McBride, Jr., M.D.); Henry Ford Hospital, Detroit, Michigan (J. Tracy Watson, M.D.); Hospital for Joint Disease, Orthopaedic Institute, New York, New York (Kenneth J. Koval, M.D.); Hospital of University of Pennsylvania, Philadelphia, Pennsylvania (John L. Esterhai, M.D.); Memorial Hospitals Association, Modesto, California (David L. Samani, M.D.); Orlando Regional Medical Center, Orlando, Florida (J. Dean Cole, M.D.); Presbyterian-St. Luke's Medical Center, Denver, Colorado (Ross M. Wilkins, M.D.); St. Joseph's Hospital, Atlanta, Georgia (George Cierny, III, M.D.); Stanford University Medical Center, Stanford, California (George E. Sims, M.D.); Texas Tech University Health Sciences Center, Lubbock, Texas (Andrew F. Brooker, M.D.); Tulane University Medical Center, New Orleans, Louisiana (Stephen D. Cook, Ph.D.); University of California, San Diego Medical Center, San Diego, California (Wayne H. Akeson, M.D.); University of Miami School of Medicine, Miami, Florida (Gregory A. Zych, D.O.), University of Texas Medical Branch at Galveston, Galveston, Texas (Jason H. Calhoun, M.D.); and Valley Lutheran Hospital, Mesa, Arizona (Dennis Armstrong, M.D.).

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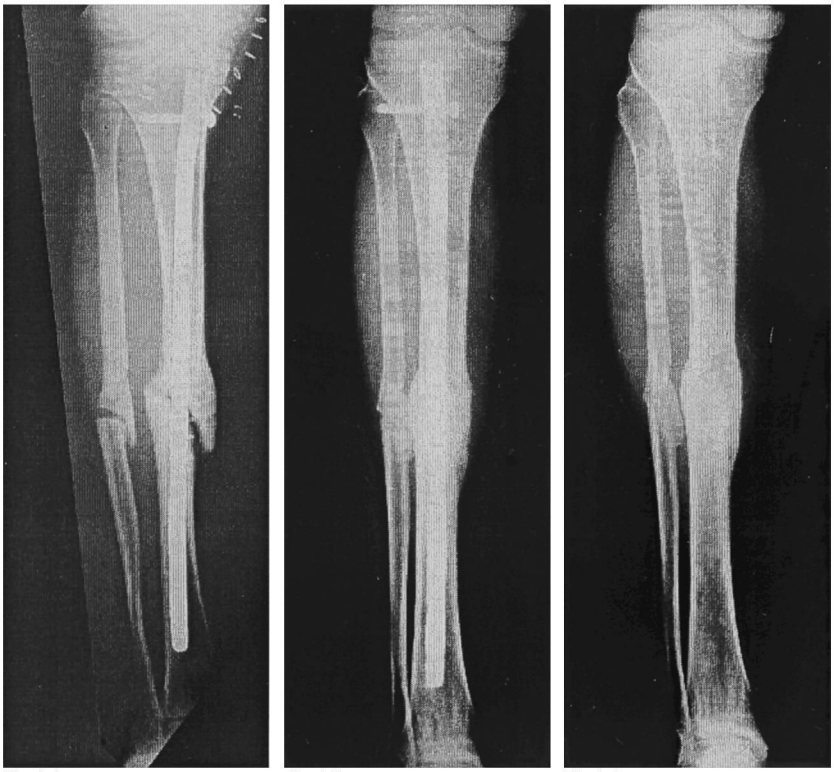

Fig. 1-A Fig. 1-B Fig. 1-C

Fig. 1.

Radiographs of a 34-year-old male patient treated with osteogenic protein-1 (OP-1) and 33 months following a closed, comminuted tibial fracture sustained in a motor vehicle accident. Prior treatment included intramedullary rod fixation, fresh bone autograft, a fibulectomy, and external electrical stimulation. The clinical and radiographic results were considered successful at both 9 and 24 months following treatment with an intramedullary rod and OP-1. **A:** Immediate postoperative radiograph. **B:** Radiograph 9 months following treatment with OP-1. **C:** Radiograph 24 months following treatment with OP-1.

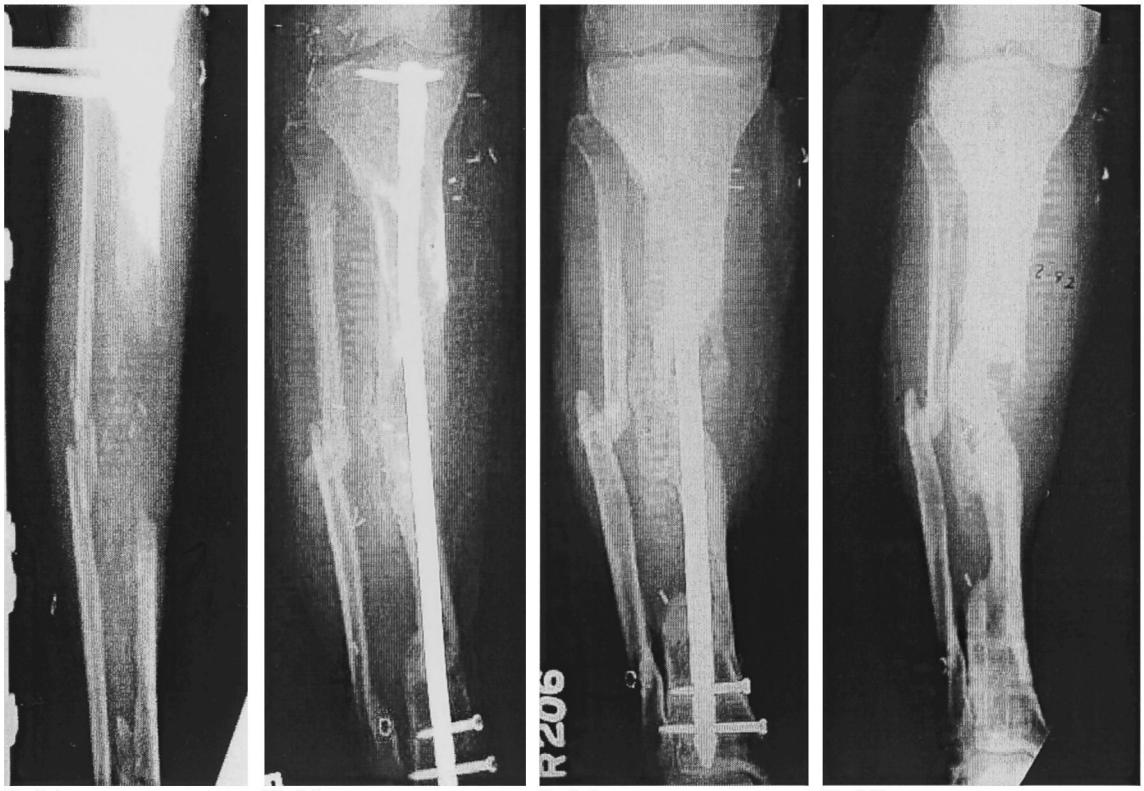

Fig. 2-A Fig. 2-B Fig. 2-C Fig. 2-D

Fig. 2.

Radiographs of a female patient, 34 years old at entry into this study, who sustained an open, comminuted, grade III-B tibial fracture as a result of a motor vehicle accident. Prior treatment include multiple debridements, implantation of antibiotic impregnated beads, a vascularized free soft-tissue flap, external fixation and, on two occasions, fresh bone autografts. The patient was treated by re-debridement, intramedullary fixation, and implantation of osteogenic protein-1 (OP-1) 14 months following the original injury. Despite abundant new-bone formation and mild pain during full weight-bearing at 9 and 31 months, this patient was considered a treatment failure because of incomplete bone bridging. **A:** Preoperative radiograph. **B:** Radiograph 3 months following treatment with OP-1. **C:** Radiograph 9 months following treatment with OP-1. **D:** Radiograph 31 months following treatment with OP-1.

TABLE I

Study Exclusion Criteria

1.	Patients who do not meet the study inclusion criteria.
2.	Patients who are skeletally immature.
3.	Patients unable or unwilling to fulfill the follow-up requirements.
4.	Patients with severely compromised soft-tissue coverage at the nonunion site, sufficient to impair bone healing.
5.	Patients with nonunions resulting from pathological fractures (neoplasia, metabolic bone disease).
6.	Patients receiving radiation, chemotherapy, immunosuppression, or chronic steroids.
7.	Patients who are or could become pregnant during the study or who are breastfeeding.
8.	Patients with active infection systemically or at the site of nonunion.
9.	Patients receiving other investigational treatment.
10.	Patients with congenital or synovial pseudarthrosis of the tibia.
11.	Patients with complete neuropathy that would interfere with walking or appreciation of pain.
12.	Patients with nonunions of multiple bones (other than the tibia).
13.	Patients with a known autoimmune disease.
14.	Patients with known sensitivity to collagen.

TABLE II

Demographics of the Study Groups

	OP-1 implant (n = 63)*	Autograft (n = 61)*	P value
Nonunion duration (months)			
Median	17	17	0.858
Median ± S.D.	27 ± 26	33 ± 46	
Atrophic nonunion (%)	41	25	0.048[s]
Comminuted fracture at injury (%)	67	56	0.212
Open fracture at injury (%)	58	57	0.876
Grade III, IIIa, IIIb, or IIIc fracture at injury (%)	30	36[†]	0.480
Prior autograft (%)	43	31	0.177
Prior IM rod (%)	54	44	0.280
Tobacco/nicotine use (%)**	74	57	0.057
Age** (years, mean ± S.D.)	38 ± 16	34 ± 11	0.071
Weight** (pounds, mean ± S.D.)	171 ± 47	187 ± 40	0.060
Gender (%male/%female)**	67/33	77/23	

OP-1 = osteogenic protein-1, and IM = intramedullary rod.

*Based on the number of nonunions, except where noted by **.

**Based on the number of patients.

[s]= significant.

[†]Does not include patients with open fractures of unknown grade.

TABLE III

Comparison of Operative Time, Blood Loss, and Hospital Length of Stay

	OP-1 Implant mean range (n = 61)	Autograft mean (range) (n = 61)
Operative Blood Loss (ml)*	254 (10-1,150)	345 (35-1,200)
Length of Stay (days)	3.7 (0-18)	4.1 (1-24)
Operative Time (minutes)**	169 (58-420)	178 (58-420)

OP-1 = osteogenic protein-1.

* Statistically different, p = 0.049.

** Based on number of nonunions (otherwise based on number of patients).

TABLE IV

Adverse Events Most Frequently Reported in the Study Groups

Adverse Event	OP-1 Implant (n = 61) # (%)	Autograft (n = 61) # (%)	Total (n = 122) # (%)
Arthralgia, lower leg	8 (13)	5 (8)	13 (11)
Pain, multiple sites	8 (13)	9 (15)	17 (14)
Acute or sub-acute osteomyelitis lower leg	2 (3)	13 (21)*	15 (12)
Pyrexia	31 (51)	28 (46)	59 (48)
Vomiting	18 (30)	19 (31)	37 (30)
Edema, leg	5 (8)	7 (11)	12 (10)
Mechanical complication of internal orthopaedic device	25 (41)	34 (56)	59 (48)
Hematoma complicating a procedure	5 (8)	8 (13)	13 (11)
Postoperative infection	14 (23)	12 (20)	26 (21)

OP-1 = osteogenic protein-1.

* Statistically different, p = 0.002.

TABLE V

Clinical and Radiological Outcomes at 9 Months Following Treatment

Criteria	OP-1 Implant (n = 63)		Autograft (n = 61)		P Value*
	N	Success	N	Success	
Weight-bearing criterion	54	86%	52	85%	0.941
Pain (on weight-bearing) criterion	56	89%	55	90%	0.817
Combined Clinical Criteria	51	81%	52	85%	0.524
Radiographic bridging (in at least 1 view)	47	75%	51	84%	0.218
Radiographic bridging (in at least 3 views)	39	62%	45	74%	0.158
No surgical re-treatment	60	95%	55	90%	0.276
Physician satisfaction	54	86%	55	90%	0.447

As described in the Materials and Methods section, clinical success is defined as full weight-bearing, less than severe pain at the fracture site on weight-bearing, and no further surgical treatment to enhance fracture repair. OP-1 = osteogenic protein-1.

* Chi-square test where $p > 0.05$ indicates no significant difference between groups.