Ontario Health Technology Assessment Series 2005; Vol. 5, No. 6

Osteogenic Protein-1 for Long Bone Nonunion

An Evidence-Based Analysis

April 2005

Ontario

Medical Advisory Secretariat
Ministry of Health and Long-Term Care

Suggested Citation

This report should be cited as follows:

Medical Advisory Secretariat. Osteogenic protein-1 for long bone nonunion: an evidence-based analysis. *Ontario Health Technology Assessment Series* 2005; 5(6)

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ISSN 1915-7398 (Online)
ISBN 1-4249-0127-8 (PDF)

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The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

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Executive Summary

Objective

To assess the efficacy of osteogenic protein-1 (OP-1) for long bone nonunion.

Clinical Need

Although most fractures heal within a normal period, about 5% to 10% do not heal and are classified as delayed or nonunion fractures. Nonunion and segmental bone loss after fracture, reconstructive surgery, or lesion excision can present complex orthopedic problems, and the multiple surgical procedures often needed are associated with patient morbidity and reduced quality of life.

Many factors contribute to the pathogenesis of a delayed union or nonunion fractures, including deficiencies of calcium, vitamin D, or vitamin C, and side effects of medications such as anticoagulants, steroids, some anti-inflammatory drugs, and radiation. It has been shown that smoking interferes with bone repair in several ways.

Incidence of Nonunion and Delayed Union Cases

An estimated 5% to 10% of fractures do not heal properly and go on to delayed union or nonunion. If this overall estimate of incidence were applied to the Ontario population[1], the estimated number of delayed union or nonunion in the province would be between 3,863 and 7,725.

Treatment of Nonunion Cases

The treatment of nonunion cases is a challenge to orthopedic surgeons. However, the basic principle behind treatment is to provide both mechanical and biological support to the nonunion site.

Fracture stabilization and immobilization is frequently used with the other treatment modalities that provide biological support to the fractured bone. Biological support includes materials that could be served as a source of osteogenic cells (osteogenesis), a stimulator of mesenchymal cells (osteoinduction), or a scaffold-like structure (osteoconduction).

The capacity to heal a fracture is a latent potential of the stromal stem cells, which synthesize new bone. This process has been defined as osteogenesis. Activation of the stem cells to initiate osteogenic response and to differentiate into bone-forming osteoblasts is called osteoinduction. These 2 properties accelerate the rate of fracture healing or reactivate the ineffective healing process. Osteoconduction occurs when passive structures facilitate the migration of osteoprogenitor cells, the perivascular tissue, and capillaries into these structures.

[1] Based on the number of fee-for-service claims - fiscal year 2003/2004

Bone Grafts and Bone Graft Substitutes

Bone graft and bone graft substitutes have one or more of the following components:

- Undifferentiated stem cells
- Growth factors
- Structural lattice

Undifferentiated stem cells are unspecialized, multipotential cells that can differentiate into a variety of specialized cells. They can also replicate themselves. The role of stem cells is to maintain and repair the tissue in which they are residing. A single stem cell can generate all cell types of that tissue. Bone marrow is a source of at least 2 kinds of stem cells. Hematopoietic stem cells that form all types of blood cells, and bone marrow stromal stem cells that have osteogenic properties and can generate bone, cartilage, and fibrous tissue.

Bone marrow has been used to stimulate bone formation in bone defects and cases of nonunion fractures. Bone marrow can be aspirated from the iliac crest and injected percutaneously with fluoroscopic guidance into the site of the nonunion fracture. The effectiveness of this technique depends on the number and activity of stem cells in the aspirated bone marrow. It may be possible to increase the proliferation and speed differentiation of stem cells by exposing them to growth factor or by combining them with collagen.

Many growth factors and cytokines induced in response to injury are believed to have a considerable role in the process of repair. Of the many bone growth factors studied, bone morphogenetics (BMPs) have generated the greatest attention because of their osteoinductive potential. The BMPs that have been most widely studied for their ability to induce bone regeneration in humans include BMP-2 and BMP-7 (osteogenic protein). Human osteogenic protein-1 (OP-1) has been cloned and produced with recombinant technology and is free from the risk of infection or allergic reaction.

The structural lattice is osteoconductive; it supports the ingrowth of developing capillaries and perivascular tissues. Three distinct groups of structural lattice have been identified: collagen, calcium sulphate, and calcium phosphate. These materials can be used to replace a lost segment of bone.

Grafts Used for Nonunion

Autologous bone graft is generally considered the gold standard and the best material for grafting because it contains several elements that are critical in promoting bone formation, including osteoprogenitor cells, the matrix, and bone morphogenetic proteins. The osteoconductive property of cancellous autograft is related to the porosity of bone. The highly porous, scaffold-like structure of the graft allows host osteoblasts and host osteoprogenitor cells to migrate easily into the area of the defect and to begin regeneration of bone. Sources of cancellous bone are the iliac crest, the distal femur, the greater trochanter, and the proximal tibia. However, harvesting the autologous bone graft is associated with postoperative pain at the donor site, potential injury to the surrounding arteries, nerves, and tissues, and the risk of infection. Thus the development of synthetic materials with osteoconductive and osteoinductive properties that can eliminate the need for harvesting has become a major goal of orthopedic research.

Allograft is the graft of tissue between individuals who are of the same species but are of a disparate genotype. Allograft has osteoconductive and limited osteoinductive properties. Demineralized bone matrix (DBM) is human cortical and cancellous allograft. These products are prepared by acid extraction

of allograft bone, resulting in the loss of most of the mineralized component while collagen and noncollagenous proteins, including growth factors, are retained. Figures 1 to 5 demonstrate the osteogenic, osteoinduction, and osteoconduction properties of autologous bone graft, allograft, OP-1, bone graft substitutes, and bone marrow.

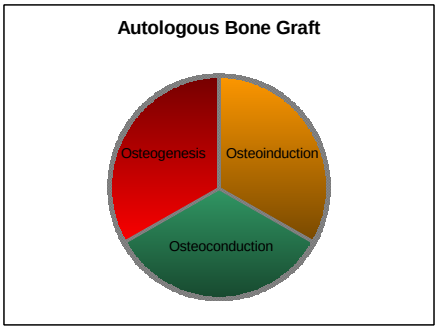

Figure 1. Autologous Bone Graft

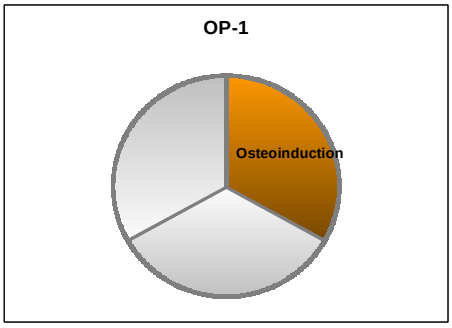

Figure 2. Osteogenic Protein-1

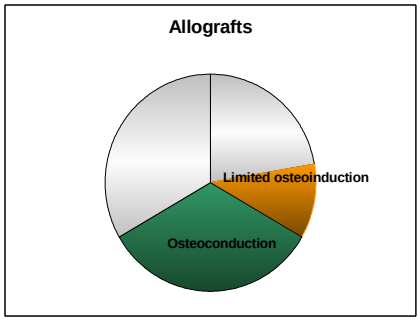

Figure 3. Allograft bone and Demineralized Bone Matrix

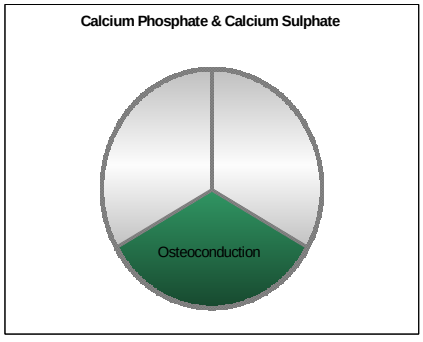

Figure 4. Bone Graft Substitutes

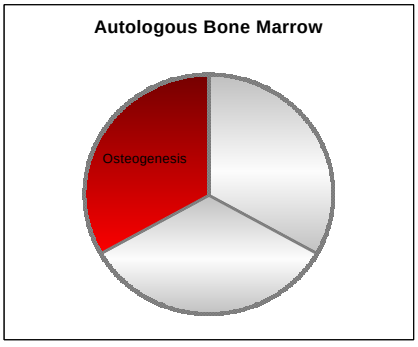

Figure 5. Autologous Bone Marrow Graft

New Technology Being Reviewed: Osteogenic Protein-1

Health Canada issued a Class IV licence for OP-1 in June 2004 (licence number 36320). The manufacturer of OP-1 is Stryker Biotech (Hapkinton, MA).

The United States Food and Drug Administration (FDA) issued a humanitarian device exemption for the application of the OP-1 implant as an "alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed." Regulatory agencies in Europe, Australia, and New Zealand have permitted the use of this implant in specific cases, such as in tibial nonunions, or in more general cases, such as in long bone nonunions.

According to the manufacturer, OP-1 is indicated for the treatment of long bone nonunions. It is contraindicated in the patient has a hypersensitivity to the active substance or collagen, and it should not be applied at the site of a resected tumour that is at or near the defect or fracture. Finally, it should not be used in patients who are skeletally immature (< 18 years of age), or if there is no radiological evidence of closure of epiphysis.

Review Strategy

Objective

- To summarize the safety profile and effectiveness of OP-1 in the treatment of cases of long bone nonunion and bone defects
- To compare the effectiveness and cost effectiveness of OP-1 in the treatment of long bone nonunions and bone defects with the alternative technologies, particularly the gold standard autologous bone graft.

Literature Search

International Network of Agencies for Health Technology Assessments (INAHTA), the Cochrane Database of Systematic Reviews and the CCTR (formerly Cochrane Controlled Trials Register) were searched for health technology assessments. MEDLINE, EMBASE, Medline In Process and Other Non-Indexed Citations were searched from January 1, 1996 to January 27, 2004 for studies on OP-1. The search was limited to English-language articles and human studies. The search yielded 47 citations. Three studies met inclusion criteria (2 RCTs and 1 Ontario-based study presented at an international conference.

Summary of Findings

Friedlaender et al. conducted a prospective, randomized, partially blinded clinical trial on the treatment tibial nonunions with OP-1. Tibial nonunions were chosen for this study because of their high frequency, challenging treatment requirements, and substantial morbidity. All of the nonunions were at least 9 months old and had shown no progress toward healing over the previous 3 months. The patients were randomized to receive either treatment with autologous bone grafting or treatment with OP-1 in a type-1 collagen carrier. Both groups received reduction and fixation with an intramedullary rod. Table 1 summarizes the clinical outcomes of this study.

Table 1. Outcomes in a Randomized Clinical Trial on Tibial Nonunions: Osteogenic Protein-1 versus Autologous Bone Grafting

Clinical Indicator at 9 months	Success by Procedure		
	OP-1 % (range)	Autograft % (range)	*P*
Weight-bearing*	86	85	not significant
Pain on Weight-bearing*	89	90	not significant
Bridging seen on radiograph (at least 1 view)	75	84	not significant
Bridging seen on radiograph (at least 3 views)	62	74	not significant
Repeated surgery*	5	10	not significant
Physician satisfaction	86	90	not significant
Mean operative time in minutes (range)	169 (58 – 420)	178 (58 – 420)	not significant
Mean operative blood loss in ml (range)	254 (10–1,150)	345 (35 – 1,200)	.049
Mean length of stay in days (range)	3.7 (0 – 18)	4.1 (1 – 24)	not significant
Pain at the donor site	N/A	80	N/A
At 6 months postsurgery		20	
At 12 months postsurgery		13	
Osteomyelitis % (number)	3 (2/61)	21 (13/61)	.002

*Clinical success was defined as full weight-bearing, loss of severe pain at the fracture site on weight-bearing, and no further surgical treatment to enhance fracture repair.

The results of this study demonstrated that recombinant OP-1 is associated with substantial clinical and radiographic success for the treatment of tibial nonunions when used with intramedullary rod fixation. No adverse event related to sensitization was reported. Five per cent of the patients in the OP-1 group had circulating antibodies against type 1 collagen. Only 10% of the patients had a low level of anti-OP-1 antibodies, and all effects were transient. Furthermore, the success rate with the OP-1 implant was comparable with those achieved with autograft at 9 and 24 months follow-up. Eighty-two per cent of patients were successful at 24 months follow-up in both groups.

Statistically significant increased blood loss in the group treated with the autograft was observed (P = .049). Patients treated with autograft had longer operation and hospitalization times. All patients in the autograft group had pain at the donor site after surgery, and more than 80% judged their postoperative pain as moderate or severe. At their 6-month visit, 20% of the patients in the autograft group had persistent pain, mild or moderate in nature, at the donor site. This number fell to 13% at 12 months.

All patients in each of the groups had at least 1 adverse event that wasn't serious, such as fever, nausea and vomiting, leg edema, discomfort, and bruising at the operative site. The incidence of these events was similar in both groups. Serious adverse events were observed in 44% of both groups, none of which were considered related to the OP-1 implant or autograft.

On the basis of this data, the FDA issued a humanitarian device exemption for the application of OP-1 implant as an alternative to autograft in recalcitrant long bone nonunions when the use of autograft is unfeasible and alternative treatments have failed.

Study on Fibular Defects

Geesink et al. investigated the osteogenic activity of OP-1 by assessing its value in bridging fibular defects made at the time of tibial osteotomy for varus or valgus deformity of the knee. This study had 2 phases and included 12 patients in each phase. Each phase included 12 patients (6 in each group). Patients in the first phase received either DBM or were left untreated. Patients in the second phase received either OP-1 on collagen type-1 or collagen type-1 alone.

Radiological and Dual Energy X-ray Absorptiometry (DEXA) evaluation showed that in patients in whom the defect was left untreated, no formation of bone occurred. At 12 months follow-up, new bone formation with bridging occurred in 4 of the 6 patients in DMB group, and 5 of the 6 patients in OP-1 group. One patient in OP-1 group did not show any evidence of new bone formation at any point during the study.

Ontario Pilot Study

A prospective pilot study was conducted in Ontario, Canada to investigate the safety and efficacy of OP-1 for the treatment of recalcitrant long bone nonunions. The study looked at 15 patients with complex, recalcitrant, long bone nonunions whose previous treatment had failed. The investigators concluded that this bone graft substitute appears to be safe and effective in providing sufficient biological stimulation in difficult to treat nonunions. Results of a more complete study on 70 patients are ready for publication. According to the principal investigator, OP-1 was 90% effective in inducing bone formation and bone healing in this sample.

Alternative Technologies

The Medical Advisory Secretariat conducted a literature search from January 1, 2000 to February 28, 2005 to identify studies on nonunions/bone defects that had been treated with alternative technologies. A review of these studies showed that, in addition to the gold standard autologous bone marrow grafting, bone allografts, demineralized bone matrices, bone graft substitutes, and autologous bone marrow have been used for treatment of nonunions and bone defects. These studies were categorized according to the osteoinductive, osteoconductive, and osteogenesis properties of the technologies studied.

A review of these studies showed that bone allografts have been used mostly in various reconstruction procedures to restore the defect after excavating a bone lesion. Two studies investigated the effectiveness of DBM in healing fracture nonunions. Calcium phosphate and calcium sulphate have been used mostly for repair of bone defects.

Several investigators have looked at the use of autologous bone marrow for treatment of long bone nonunions. The results of these studies show that method of percutaneous bone marrow grafting is highly effective in the treatment of long bone nonunions. In a total of 301 fractures across all studies, 268 (89%) healed with a mean healing time of 2.5 to 8 months. This healing time as derived from these case series is less than the timing of the primary end point in Friedlaender's study (9 months). Table 2 summarizes the results of these studies. Table 2 summarizes the results of these studies.

Table 2. Studies that used Percutaneous Bone Marrow Grafting for Treatment of Nonunions

Study	Study design	No. and type of bone	Success rate Number, (%)	Months to union
Goel et al. 2005	Prospective	20 tibia	15/20 (75)	3.5
Wilkins et al. 2003	Prospective	66 long bones (69 procedures)	61/69 (88)	8
Siwach et al. 2001	Prospective	72 long bones	68/72 (94)	3 – 6
Jean et al. 2001	Retrospective	14 tibia	12/14 (86)	6
Wang et al. 2001	Prospective	56 tibia	53/56 (95)	8
Matsuda et al. 1998	Prospective	7 femur		5 – 9
Non-infected			4/4 (100)	
Subsided infection				
Partial healing			1/1 (100)	
Infected			0/2 (0)	
Pan et al. 1996	Retrospective	12 tibia	10/12 (83)	5.4
Garg et al. 1993	Prospective	20 long bones	17/20 (85)	5
Sim et al. 1993	Retrospective	11 long bones	9/11 (82)	2.5 (median)
Connolly et al. 1989	Prospective	20 tibia		6.8
Intramedullary nail			10/10 (100)	
fixation			8/10 (80)	
Immobilization				

Economic Analysis

Based on annual estimated incidence of long-bone nonunion of 3,863 – 7,725, the annual hospitalization costs associated with this condition is between $21.2 and $42.3 million based on a unit cost of $5,477 per hospital separation. When utilized, the device, a single vial of OP-1, is approximately $5,000 and if adopted universally in Ontario, the total device costs would be in the range of $19.3 - $38.6 million annually. The physician fee for harvest, insertion of bone, or OP-1 is $193 and is $193 for autologous bone marrow transplantation. Total annual physician costs are expected to be in the range of from $0.7 million to $1.3 million per year. Expenditures associated with long-bone nonunion are unlikely to increase since incidence of long-bone nonunion is unlikely to change in the future. However, the rate of uptake of OP-1 could have a significant impact on costs if the uptake were large.

The use of OP-1 and autologous bone marrow transplantation may offset pain medication costs compared with those associated with autologous bone harvest given that the former procedures do not involve the pain associated with the bone harvest site. However, given that this pain is normally not permanent, the overall offset is likely to be small. There are likely to be smaller OHIP costs associated with OP-1 than bone-harvest procedures given that only 1, rather than 2, incisions are needed when comparing the former with the latter procedure. This offset could amount to between $0.3 million to $0.7 million annually.

No data on the cost-effectiveness of OP-1 is available.

Appraisal

OP-1

OP-1 is a Class IV device and is indicated for use as an alternative treatment when other options have failed or are not feasible. However, Friedlaender's study shows that the incidence of adverse events were similar when treating patients with OP-1 and autologous bone graft; therefore, using OP-1 does not impose additional risk to patients.

Alternative Technologies

Following reports by Connolly et al. and Healey et al. that showed percutaneous injection of autologous bone marrow successfully treated between 78% and 95% of long bone nonunions, a number of investigators were encouraged to study the use of autologous bone marrow grafting in their patients. All these investigators have reported that percutaneous injection of bone marrow is a simple, safe, and useful technique that can become the procedure of choice in many patients with delayed union or nonunion. In addition, they have indicated that this is a useful procedure for patients at high risk for anesthesia and surgery, and also those who are waiting for any definitive surgical procedures.

Autologous cancellous bone grafting is considered the gold standard in the treatment of long bone nonunions. Unfortunately, this procedure is associated with complications at the donor and recipient sites including infection, pain, bruising, scaring, wound problems, nerve injury, and fracture. Harvesting the graft requires an additional surgical procedure. This increases the risk of perioperative blood loss and infection, leading to a prolonged hospital stay and additional cost. The need to open the nonunion site also adds to the risk of devascularization at the fracture site where healing is already impaired.
An alternative technology must be equally successful in achieving union, as well as providing some increased benefit to justify its use. OP-1 and autologous bone marrow grafting both eliminate the risk of donor site morbidity. Autologous bone marrow grafting has the additional advantage of decreased cost and no hospital stay because the procedure is performed in an outpatient setting.

Three technologies that demonstrated positive clinical outcomes in the treatment of fracture nonunions were ranked according to 10 criteria. For each criterion, a score from 1 to 3 (1=the best outcome) was assigned to each technology. According to this schema, autologous bone marrow grafting has the lowest total score and the best ranking. (See the full report, page 48.)

Since the studies on autologous bone marrow grafting are case series in which the patients serve as their own control, it cannot be concluded whether this procedure is as effective as autologous bone grafting. A randomized comparative study is needed to clarify this issue.

Conclusions

Based on level 1 evidence (1 randomized controlled trial), OP-1 is a reasonable alternative to autologous bone grafting in the treatment of long bone nonunions.

Based on level 4 evidence (10 studies, a total of 301 patients), percutaneous autologous bone marrow

grafting is effective in the treatment of long bone nonunions in patients with no active infection at the fracture site.

Based on the above evidence and the fact that both procedures (percutaneous autologous bone marrow grafting and OP-1) eliminate the risk of donor site morbidity and reduce the risk of infection at the recipient site, the following questions should be considered in making decisions regarding these competing technologies:

- Should the effectiveness of percutaneous bone marrow grafting as a treatment modality for non-infected long bone nonunions be explored further?

- Should access to OP-1 be provided to the patients with long bone nonunions (according to the definitions set by FDA) when other methods of treatment have failed?

Objective

To assess the efficacy of osteogenic protein-1 (OP-1) for long bone nonunion.

Background

Clinical Need: Target Population and Condition

Although most fractures show normal bone healing, about 5% to 10% do not heal and are classified as delayed or nonunion fractures. (1) Nonunion and segmental bone loss after fracture, reconstructive surgery, or lesion excision can present complex orthopedic problems, and the multiple surgical procedures often needed are associated with patient morbidity and reduced quality of life. (2)

It has been over a decade since the first bone morphogenetic protein (BMP) gene was reported. A large variety of animal models have evaluated the therapeutic potential of these proteins, particularly BMP-2 and BMP-7. Of the many growth factors studied, BMPs have generated the most attention because of their osteoinductive potential. Osteoinduction is a process that supports the proliferation of undifferentiated mesenchymal cells and the formation of cells with the capacity to form bone. (2) More recently, the efficacy of BMPs in bone repair has been demonstrated in humans. BMPs have proven to be an important new area of developmental biology and have become an important tool in the field of tissue engineering.

The potential clinical application of OP-1 includes treatment of nonunion and segmental bone defects. The human OP-1 combined with a bioresorbable carrier matrix, when introduced at the fracture site, initiates the proliferation and differentiation of mesenchymal cells, leading to new bone formation.

Incidence of Nonunion and Delayed Union

An estimated 5% to 10% of fractures do not heal properly and go on to be delayed union or nonunion fractures. (1) If this overall estimate of incidence were applied to the Ontario population[2], the estimated number of delayed union or nonunions in the province would be between 3,863 and 7,725.

Bone Formation Process and Bone Healing

Bone fracture initiates an orchestrated series of events involving serial participation of different cells and factors. After a fracture, or an interruption of the blood supply, dead bone must be resorbed, and new bone reformed. Resorption of bone is carried out mainly by multinucleated cells called osteoclasts and formation of new bone is carried out by cells from mesenchymal origin called osteoblasts. Osteoblasts line the outer surface of the bones and are also present inside most of the bone cavities. These cells secrete a very strong protein matrix, made up mainly of collagen fibres, which gives the bone its toughness. The matrix is then mineralized, and osteoblasts become surrounded by the matrix and become osteocytes.

The bone marrow contains mesenchymal (stromal) stem cells that have the capacity to transform into other cell types to repair the damaged tissue. In fractures in which the apposition of fragments is poor and motion exists at the fracture site, the progenitor stromal cells differentiate into cells with different functional capacities; therefore, varying amount of fibrous tissue and cartilage are formed. On the other hand, when there is good apposition with bone fixation and little motion at the fracture site, new bone forms without scar tissues.

[2] Based on the number of fee-for-service claims - fiscal year 2003/2004

Re-establishment of vascularity and formation of new vessels are early events in fracture healing. Blood vessels carrying the mineral elements are key contributors to the process of osteogenesis. (3) Inadequate or inappropriate bone vascularity is associated with decreased bone formation and bone mass. The importance of arterial integrity in tibial fracture healing, for example, has been demonstrated in a study of 114 patients who were treated for an open fracture of the tibia. In this study, the group of patients who had arterial occlusion had a significantly higher incidence of delayed unions or nonunions and notably more cases of osteomyelitis. (4) Fracture of bone may disrupt its circulation leading to acute necrosis and hypoxia of adjacent bone and marrow.

Nonunion Fractures

Some fractures take a long time to heal or fail to unite, most commonly with fibrous bridging of the fragments or persistence of the fracture gap. Occasionally a pseudoarthrosis with a fluid-filled cavity and fibrocartilaginous capping of the ends develops. (5) Many factors contribute to the pathogenesis of a delayed union or nonunion fractures, including deficiencies of calcium, vitamin D, vitamin C, and the adverse effects of medications such as anticoagulants, steroids, some anti-inflammatory drugs, (5) and radiation. It has been shown that smoking interferes with bone repair in several ways. (6) It is associated with a decrease in bone density in the axial skeleton (7), a decrease in parathyroid hormone, resistance to calcitonin, and it also interferes with osteoblastic function. (6) Furthermore, nicotine stimulates sympathetic vasoconstriction and results in reduced cellular metabolic processes. (6)

The tibia is one of the most commonly fractured long bones (8) Tibial fractures are also associated with a high incidence of delayed union and nonunion fractures (35% to 65% of all nonunion fractures). (4)

Segmental Bone Defects

In a variety of clinical circumstances such as trauma, infection, primary and metastatic tumours, or failed arthroplasty, a segment of the bone is lost or excised. (9) Large amounts of bone graft materials are used to aid healing of bone defects. The usefulness of autologous bone grafting to treat segmental bone defects is often limited by the amount that is available. The limited supply, additional surgical time required, and morbidity associated with autograft bone harvesting, has resulted in the use of various types of allograft bone. Patients with large segmental defects and bone loss require additional bone graft alternatives to augment bone regeneration. Allograft bone is attractive because it supports bone formation and its supply is less limited. (9) However, allograft bone has little osteoinductive capacity, (10) and in cases in which allograft bone is expected to sustain mechanical load, failure may occur if it is subjected to repetitive weight bearing. (9)

Treatment of Nonunion

The treatment of nonunion is a challenge to orthopedic surgeons. However, the basic principle behind treatment is to provide both mechanical and biological support to the nonunion site. Several biological and biophysical approaches have been introduced to treat delayed union and nonunions.

Biophysical Approach

Electrical and Ultrasound Stimulation

A number of physical modalities have been approved for the management of nonunion and delayed union fractures. Pulsed electromagnetic fields (PEMF) and capacitive coupling induce fields through the soft tissue, resulting in low-magnitude voltage and currents at the fracture site. Electrical signals can be delivered with an implantable direct current stimulator, or noninvasively with inductive or capacitive coupling to induce currents in the tissues. (11) The effectiveness of PEMF in promoting healing of delayed nonunions has been the subject of a comprehensive review. (12) Twenty-eight studies of non-union tibial fractures treated with PEMF were compared with 14 studies of similar fractures treated with bone graft with or without internal fixation. The overall success rate for the surgical treatment of 569 ununited tibial fractures was 82% (range, 70% – 100%) and the overall success rate of PEMF treatment of 1,718 ununited tibial fractures was 81% (range, 13% – 100%). Ito et al. (13) have shown that PEMF therapy is an effective treatment for ununited tibial fractures with good blood supply to the bone ends. Treatment failures occurred only among lesions with a poor blood supply, where there was radiological evidence of necrotic or defective bone. (13) Capacitive coupling appears to be effective both in extremity nonunions and lumbar fusions. (14)

Low-intensity pulsed ultrasound (frequency 1.5 MHz) transmitted transcutaneously was shown to accelerate fresh fracture healing both clinically and experimentally (15;16) A systematic review and meta-analysis of randomized controlled trials of low-intensity pulsed ultrasound therapy for healing of fractures showed that ultrasound therapy may be beneficial to fracture healing. (17) The conclusion of this review was that treatment with a low-intensity pulsed ultrasound signal may reduce healing time, and could yield substantial cost-savings and decreases in disability associated with delayed union and nonunion of fractures.

Biological Approach

Fracture stabilization and immobilization are frequently used with the other treatment modalities that provide biological support to the fractured bone. Biological support includes materials that could be served as a source of osteogenic cells, a stimulator of mesenchymal cells, or a scaffold-like structure. The biological processes involved in bone formation are osteogenesis, osteoinduction, and osteoconduction. The capacity to heal a fracture is a latent potential of the stromal stem cells, which synthesize new bone (osteogenesis). Activation of the stem cells to initiate an osteogenic response and to differentiate into bone-forming osteoblasts is called osteoinduction. These 2 properties accelerate the rate of fracture healing or reactivate the ineffective healing process. Osteoconduction occurs when passive structures facilitate the migration of osteoprogenitor cells, the perivascular tissue and capillaries into these structures.

Bone Grafts and Bone Graft Substitutes

Bone graft and bone graft substitutes have one or more of the following components: (18)

- Undifferentiated stem cells
- Growth factors
- A structural lattice

Undifferentiated Stem Cells

Undifferentiated stem cells are unspecialized, multipotential cells that can differentiate into a variety of specialized cells. They can also replicate themselves. The role of stem cells is to maintain and repair the tissue in which they are residing. A single stem cell can generate all cell types of that tissue. Stem cells have been derived from a variety of tissues including umbilical cord and placenta. Bone marrow is a source of at least 2 kinds of stem cells. Hematopoietic stem cells that form all types of blood cells, and bone marrow stromal stem cells that have osteogenic properties and can generate bone, cartilage, and fibrous tissue.

Bone marrow has been used to stimulate bone formation in bone defects and cases of nonunion fractures. (18) Bone marrow can be aspirated from the iliac crest and injected percutaneously with fluoroscopic guidance into the nonunion site. The effectiveness of this technique depends on the number and activity of stem cells in the aspirated bone marrow. Approximately 1 of every 100,000 nucleated cells aspirated from bone marrow is a stem cell. (18) It may be possible to increase the proliferation and speed differentiation of stem cells by exposing them to growth factor or by combining them with collagen. (19) Centrifugation of aspirated bone marrow can separate the marrow cells from plasma and decrease the volume of the material injected while preserving the osteogenic potential of the cells. (18)

Growth Factors

In 1965, Urist (20) discovered that the extracellular matrix of bone contains a substance that has the capacity to induce new bone formation when implanted into extraskeletal sites (osteoinduction). It was later shown that it was the protein contained within the matrix that was responsible for ectopic bone formation. (21) These proteins were named bone morphogenetic proteins and were shown to exist across all species and highly conserved in mammals. (22) Observation by Urist and later by Sampath and Reddi (23) provided a basis for the development of an assay for the purification of these proteins. In the 1980s, the inductive preparations were purified from bovine bone to provide amino acid sequence data. This further resulted in the identification and characterization of deoxyribonucleic acid (DNA) sequence encoding of these proteins. (23)

All of the BMPs are members of the transforming growth factor-β (TGF-β) superfamily of genes. (24) Members of the BMP subfamily play a critical role in regulating the growth, differentiation, and apoptosis of various cell types, including osteoblasts, chondroblasts, neural cells, and epithelial cells.

Structural Lattice

The structural lattice is osteoconductive and can be used to replace a lost segment of bone. Osteoconduction is a process that supports the ingrowth of developing capillaries and perivascular tissues. (25) Three distinct groups of structural lattice have been identified: collagen, calcium sulphate, and calcium phosphate.

Collagen is used as a bone graft substitute. In its most commonly used form, purified fibrillar collagen obtained from bovine dermis is mixed with hydroxyapatite, and tricalcium phosphate to form a paste or a sheet. The manufacturer recommends mixing of the collagen and hydroxyapatite with autologous bone marrow. (18)

The advantage of the calcium sulphate is that it can be absorbed by the osteoclasts, so that the osteoblasts can attach to it and deposit osteoid on its surface. (26)

The most common forms of calcium phosphate are coralline hydroxyapatite and tricalcium phosphate. Coralline hydroxyapatite is the exoskeleton of 2 marine corals, Porites and Goniopora. The dense material obtained from Porites has a pore diameter of 200μm and is used primarily for dental applications. (27) The less dense material obtained from Goniopora has a pore diameter of about 500μm and is used primarily for orthopedic applications. The potential advantages of tricalcium phosphate over the other calcium phosphates is its low crystallinity and smaller grain size. This makes it more absorbable by osteoclasts. (18) However, tricalcium is applied in a liquid state, and then hardens in situ. It acts as a cement to add mechanical stability to the construct, but it also may leak into the surrounding tissues.

Autologous Bone Graft

Autologous bone graft is generally considered the gold standard and the best material for grafting because it contains several elements that are critical in promoting bone formation, including osteoprogenitor cells, (18) (osteogenic component), the matrix (osteoconductive property), and bone morphogenetic proteins (osteoinductive property). (18;25;28) The osteoconductive property of cancellous autograft is related to the porosity of bone. The highly porous, scaffold-like structure of the graft allows host osteoblasts and host osteoprogenitor cells to migrate easily into the area of the defect and to begin regeneration of bone. Sources of cancellous bone are the iliac crest, the distal femur, the greater trochanter, and the proximal tibia. More graft can be obtained from the iliac crest than from the other sites, and evidence shows that bone of membranous origin (ilium) is more osteoinductive than bone of endochondral origin (tibia and femur). (29)

However, harvesting the autologous bone graft is associated with postoperative pain at the donor site, potential injury to the surrounding arteries, nerves and tissues, and the risk of infection. Thus the development of synthetic materials with osteoconductive and osteoinductive properties that can eliminate the need for harvesting has become a major goal of orthopedic research.

Vascularized Bone Transfer

In vascularized bone transfer, the transferred bone is living. Theoretically, living bone is more resistant to infection and will heal more quickly to the native bone (18). In reality, healing of transferred vascularized

bone segment to native bone is not reliable and frequently supplemental autogenous bone grafting is required. (18) The bone most frequently transferred is from the fibula, followed by that from the iliac crest. (18) A defect of 6cm is the minimum indication for vascularized bone transfer, and a prolonged immobilization and no weight bearing is a necessary part of the treatment. (18)

Allograft

Allograft is graft of tissue between individuals who are of the same species but are of disparate genotype. Allograft has osteoconductive and limited osteoinductive properties. (30) Allograft bone is used in small, morselized fragments or as a structural component for reconstruction of bony defect after tumour resection, trauma, and total arthroplasty. Active infection is an absolute contraindication for allograft implant. Infection and fracture may occur in allograft implant and complicate the results. Allografts have been used successfully in a variety of clinical circumstances, but there are concerns regarding immunological reactions and the potential transmission of infectious diseases.

Demineralized bone matrix (DBM) is human cortical and cancellous allograft are prepared by acid extraction of allograft bone, resulting in the loss of most of mineralized component while collagen and noncollagenous proteins, including growth factors, are retained. (28) DBMs do not contain osteoprogenitor cells, but the osteoconductivity of their carrier complex may be an important factor in promoting the migration of osteoprogenitor cells to the bone defect site. (28) A growing number of bone alternatives are commercially available for orthopedic applications including segmental bone defects. Many bone banks supply various forms and preparations of DBMs. The content and activity of osteoinductive property of these products can range widely depending on the type of bone and tissue processing. In the United States, DBM is considered a transplantable tissue and is regulated primarily by the American Association of Tissue Banks. (31)

Gene Therapy

In gene therapy, the transfer of genetic information to a cell that either resides in the host or is derived from the host is another way to deliver proteins to a specific anatomic site. Different methods of gene transfer are being investigated for the purpose of bone repair; in the future, gene therapy may be one of the tools available to orthopedic surgeons to treat difficult bone loss cases. (32)

Figures 1 to 5 demonstrate osteogenic, osteoinduction, and osteoconduction properties of autologous bone graft, allograft, OP-1, bone graft substitutes, and bone marrow.

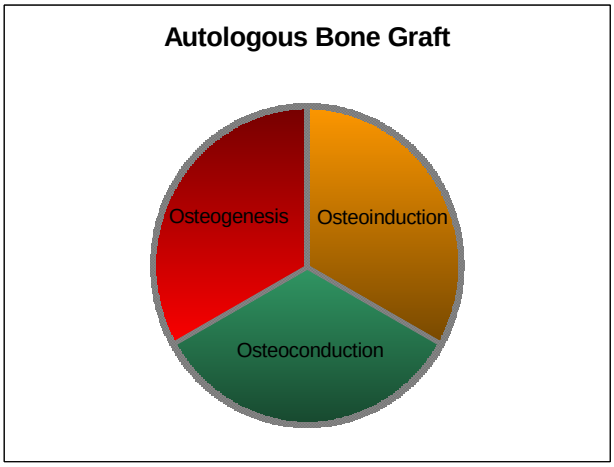

Figure 1. Autologous Bone Graft

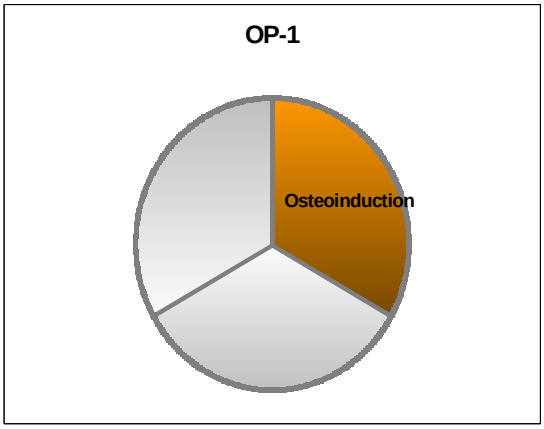

Figure 2. Osteogenic Protein-1

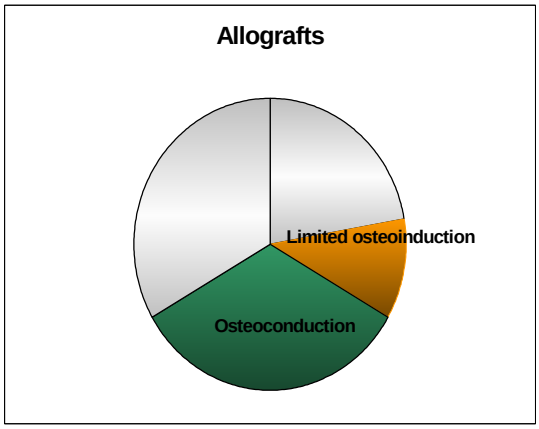

Figure 3. Allograft bone and Demineralized Bone Matrix (30)

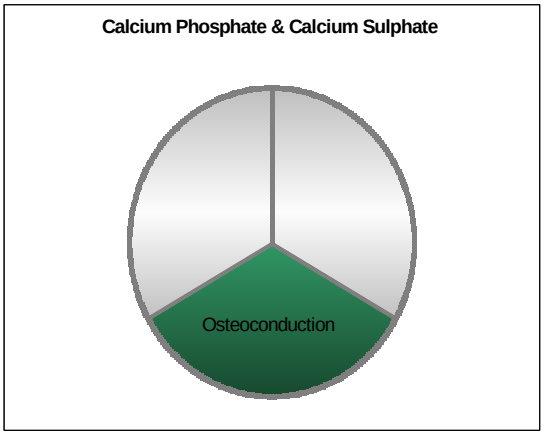

Figure 4. Bone Graft Substitutes (30)

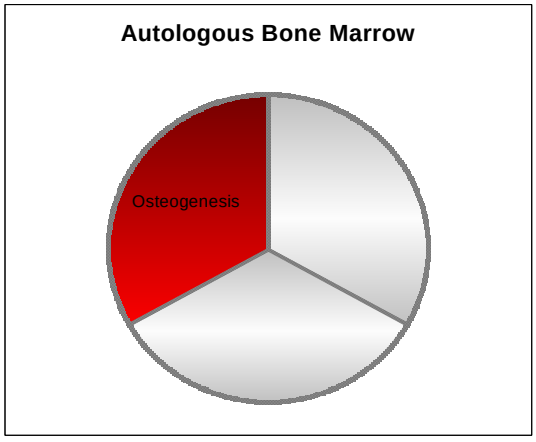

Figure 5. Autologous Bone Marrow Graft

New Technology Being Reviewed: Osteogenic Protein-1

The BMPs that have been most widely studied for their ability to induce bone regeneration in humans include BMP-2 and BMP-7 (osteogenic protein). (25) Human OP-1 has been cloned and produced with recombinant technology and is free from the risk of infection or allergic reaction. Preclinical and clinical research has demonstrated that OP-1 combined with a collagen carrier induces bone formation and healing of bone defects and accelerates fracture repair when it is surgically implanted. (33) The osteoinductive properties of recombinant human BMP (rhBMP) have been established in many animal models. (34)

OP-1 is typically applied in a carrier or matrix material. A carrier has several functions, including to providing a format for delivery of the osteoinductive protein, maintaining the material at the site of application long enough for the bone-inductive process to occur, and providing an environment in which bone formation can take place. (35) Currently, the available carrier and delivery system for OP-1 is type-1 collagen.

Many growth factors and cytokines induced in response to injury are believed to have a considerable role in the process of repair. (36) These include members of the fibroblast growth factor (FGF), transforming growth factor (TGF), insulin-like growth factor (IGF), and platelet-derived growth factor (PDGF) families (36), as well as vascular endothelial growth factor (VGEF). (37) These factors are produced by many cell types present at the fracture site. (37) BMPs are members of the TGF-β superfamily of growth factors. (38) composed of at least 14 proteins. (See Table 3.) Of the many bone growth factors studied, BMPs have generated the greatest attention because of their osteoinductive potential.

According to the manufacturer, OP-1 is indicated for the treatment of long bone nonunions. It is contraindicated if the patient has a hypersensitivity to active substance or collagen, and it should not be applied at the site of a resected tumour that is at or near the defect or fracture. Finally, it should not be used in patients who are skeletally immature (< 18 years of age), or if there is no radiological evidence of closure of epiphysis.

Table 3: Bone Morphogenetic Protein Family

BMP	Function
BMP-2	Osteoinductive osteoblast differentiation, apoptosis
BMP-3 (osteogenin)	Most abundant BMP in bone, inhibits osteogenesis
BMP-4	Osteoinductive, lung & eye development
BMP-5	Chondrogenesis
BMP-6	Osteoblast differentiation
BMP-7 (OP-1)	Osteoinductive, development of kidney & eye
BMP-8 (OP-1)	Osteoinductive
BMP-9	Nervous system, hepatic reticuloendothelial system, hepatogenesis
BMP-10	Cardiac development
BMP-11 (GDF-8, myostatin)	Patterning mesodermal & neuronal tissues
BMP-12 (GDF-7)	Induces tendon-iliac tissue formation
BMP-13 (GDF-6)	Induced tendon & ligament-like tissue formation
BMP-14 (GDF-5)	Chondrogenesis, enhances tendon healing & bone formation
BMP-15	Modifies follicle-stimulating hormone activity

Source: (39)

Regulatory Status

Health Canada issued a Class IV licence for OP-1 in June 2004 (licence number 36320). The manufacturer of OP-1 is Stryker Biotech (Hapkinton, MA).

The United States Food and Drug Administration (FDA) has issued a humanitarian device exemption for the application of the OP-1 implant as an "alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed." Regulatory agencies in Europe, Australia, and New Zealand have permitted the use of this implant in specific cases, such as in tibial nonunions, or in more general cases, such as in long bone nonunions.

Literature Review on Effectiveness

Objective

- To summarize the safety profile and effectiveness of OP-1 in the treatment of long bone nonunions and bone defects
- To compare the effectiveness and cost-effectiveness of OP-1 in the treatment of long bone nonunions and bone defects with the alternative technologies, particularly the gold standard autologous bone graft.

Questions Asked

- Is there any risk associated with the use of OP-1 for treatment of long bone nonunion and bone defects?
- How do outcomes of treatment with OP-1 in long bone nonunions and bone defects compare with those with alternative approaches, particularly autologous bone grafting.

Methods

Inclusion Criteria

- Studies reporting on the safety and effectiveness of OP-1 for the treatment of long bone nonunions and bone defects

- Studies comparing the clinical outcomes of treatment with OP-1 in long bone nonunions and bone defects with alternative approaches

Exclusion Criteria

- Studies investigating the clinical usefulness of OP-1 for the treatment of other conditions
- Studies focusing on technical aspects of OP-1

Literature Search

INAHTA, Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register were searched for health technology assessments. MEDLINE, EMBASE, Medline In Process and Other Non-Indexed Citations were searched from January 1, 1996 to January 27, 2004 for studies on OP-1. The search was limited to English-language articles and human studies.

Results of Literature Search

No health technology assessments were identified. A Technote report[3] (2002) provided by the Alberta Heritage Foundation for Medical Research was identified. The search yielded 47 citations. Three studies met inclusion criteria (2 RCTs and 1 Ontario-based study presented at an international conference). Levels of evidence were assigned according to the scale based on the hierarchy by Goodman (1985) and modified by the Medical Advisory Secretariat. An additional designation "g" was added for preliminary reports of studies that have been presented at international scientific meetings (Table 4).

The results of 1 RCT on fresh tibial fractures was reviewed and added to this document as additional information.

[3] The Alberta Heritage Foundation for Medical Research has defined "Technotes" as brief reports, prepared on an urgent basis, which draw on limited reviews and analysis of relevant literature and on expert opinion and regulatory status where appropriate. They are not subject to an external review process.

Table 4: Quality of Evidence of Included Studies

Study Design	Level of Evidence	Number of Eligible Studies
Large RCT,* systematic reviews of RCT	1	1
Large RCT unpublished but reported to an international scientific meeting	1(g)†	0
Small RCT	2	1
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	0
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modeling	4d	0
Case series presented at international conference	4(g)	1

*RCT refers to randomized controlled trial.
†g indicates grey literature.

Summary of Medical Advisory Secretariat Review

Study on Tibial Nonunion

Friedlaender et al. (40) conducted a prospective, randomized, partially blinded clinical trial on the treatment of tibial nonunions with rhBMP-7 (OP-1). Tibial nonunions were chosen for this study because of their high frequency, challenging treatment requirements, and substantial morbidity. All of the nonunions were at least 9 months old and had shown no progress toward healing over the previous 3 months. The patients were randomized to receive either treatment with autologous bone grafting or treatment with OP-1 in a type-1 collagen carrier. Both groups received reduction and fixation with an intramedullary rod. Exclusion criteria included patients to whom the following applied:

- Were unable or unwilling to fulfil the follow-up requirements
- Were skeletally immature
- Had severely compromised soft tissue coverage at the nonunion site
- Had nonunion as a result of pathological fractures (neoplasia, metabolic bone disease)
- Were receiving radiation, chemotherapy, immunosuppression, or chronic steroids
- Were or could become pregnant during the study or were breastfeeding
- Had infection either systemically or at the site of nonunion
- Were under other investigational treatment
- Had congenital or synovial pseudoarthrosis of the tibia
- Had complete neuropathy that would interfere with walking or appreciation of pain
- Had nonunions of multiple bones (other than the tibia)
- Had a known autoimmune disease
- Were sensitive to collagen

A summary of the patient characteristics is shown in Table 5.

Table 5: Patient Characteristics in a Randomized Clinical Trial on Tibial Nonunions and Recombinant Human Osteogenic Protein (40)

Study design	RCT, partially blinded (surgeons were aware of the treatment group to which each patient was assigned, whereas radiologists assessing the postoperative x-rays for evidence of healing, were blinded to the original procedure) Multicentre (17 medical centres in the United States) Patients were randomly assigned to 1 of 2 treatment groups: • Group 1 received implant at the fracture site with OP-1 in a type 1 bovine bone-derived collagen carrier • Group 2 received autologous bone graft in a similar manner
Duration of nonunion in months	9 (with no evidence of progressive healing over the past 3 months)
Number of patients/implants	122 patients (124 tibial nonunions) • OP-1: 61 patients (63 implants) • Autograft: 61 patients
Mean age, years (SD) by type of treatment	OP-1: 38 (16) Autograft: 34 (11)
Male/Female	OP-1: 67/33 Autograft: 77/23
Intramedullary bone fixation	All 122 patients
Evaluation & follow-up in months	1, 2, 3, 6, 9, 12, and 24
Primary end-point in months	9
Outcome measures	• Presence of pain at fracture site • Degree of pain at the donor site (for autografts only) • Ability to bear weight • Additional surgical intervention • Time of the surgical procedure • Blood loss • Hospital length of stay
Laboratory assessment	All patients in OP-1 group were screened for antibodies to OP-1 and type 1 collagen at each follow-up visit
Radiographic assessment	A panel of 3 musculoskeletal radiologists, blinded to treatment and time following the surgical procedure, independently assessed whether bridging by new bone existed across the fracture site. The results were consensus of at least 2 of these 3 radiologists.
Demographics	• The 2 groups were similar on age, sex, weight, duration of nonunion, and number of prior surgical interventions. • The prevalence of atrophic nonunion was significantly higher in the OP-1 group: 41% vs. 25%, *P* = .048. • The prevalence of smokers was higher in the OP-1 group: 74% vs. 57%, *P* = .057. • There were trends toward a higher percentage of comminuted fractures at injury, prior failure of autografts, and prior use of intramedullary rods in the OP-1 group.

Clinical assessment included checking the presence of pain at the fracture site (none, mild, moderate, and severe), and the ability to bear weight (none, partial, or full) at the involved extremity. Clinical success was defined as full weight bearing, less than severe pain at the fracture site on weight bearing, and no further surgical intervention required to enhance fracture repair. Outcomes are shown in Table 6.

Table 6. Outcomes in a Randomized Clinical Trial on Tibial Nonunions: Osteogenic Protein-1 versus Autologous Bone Grafting

Clinical Indicator at 9 months	Success by Procedure		*P*
	OP-1 (% of patients)	Autograft (% of patients)	
Weight-bearing*	86	85	not significant
Pain on Weight-bearing*	89	90	not significant
Bridging seen on radiograph (at least 1 view)	75	84	not significant
Bridging seen on radiograph (at least 3 views)	62	74	not significant
Repeated surgery*	5	10	not significant
Physician satisfaction	86	90	not significant
Mean operative time in minutes (range)	169 (58 – 420)	178 (58 – 420)	not significant
Mean operative blood loss in ml (range)	254 (10–1,150)	345 (35 – 1,200)	.049
Mean length of stay in days (range)	3.7 (0 – 18)	4.1 (1 – 24)	not significant
Pain at the donor site, %	N/A	80	N/A
At 6 months postsurgery		20	
At 12 months postsurgery		13	
Osteomyelitis % (number)	3 (2/61)	21 (13/61)	.002

*Clinical success was defined as full weight-bearing, loss of severe pain at the fracture site on weight-bearing, and no further surgical treatment to enhance fracture repair.

The results of this study demonstrated that recombinant OP-1 is associated with substantial clinical and radiographic success for the treatment of tibial nonunions when used with intramedullary rod fixation. No adverse event related to sensitization was reported. Five per cent of the patients in the OP-1 group had circulating antibodies against type 1 collagen. Only 10% of the patients had a low level of anti-OP-1 antibodies, and all effects were transient. At 9 months following surgery, 81% of the OP-1 treated group and 85% of the autograft-treated group had successful outcomes. This difference was not statistically significant. Furthermore, the success rate with the OP-1 implant was similar with those achieved with autograft at 24 months follow-up. Furthermore, the success rate with the OP-1 implant was comparable with those achieved with autograft at 9 and 24 months follow-up. Eighty-two per cent of patients were successful at 24 months follow-up in both groups.

Statistically significant increased blood loss in the group treated with the autograft was observed (P = .049). Patients treated with autograft had longer operation and hospitalization times. All patients in the autograft group had pain at the donor site after surgery, and more than 80% judged their postoperative pain as moderate or severe. At their 6-month visit, 20% of the patients in the autograft group had persistent pain, mild or moderate in nature, at the donor site. This number fell to 13% at 12 months.

All patients in each of the groups had at least 1 adverse event that wasn't serious, such as fever, nausea and vomiting, leg edema, discomfort, and bruising at the operative site. The incidence of these events was similar in both groups. Serious adverse events was observed in 44% of both groups, none of which were considered related to the OP-1 implant or to the autograft.

Clinical success and radiographic outcomes in a subset of patients who had received autografts prior to the study (43% of the OP-1 group, and 31% of the autograft group) were not significantly different between the 2 groups.

This study was only partially blinded, because it is difficult to maintain blinding of the radiologists on the nature of autograft, which is mineralized, when compared with the OP-1, which has a radiolucent nature. However, without the benefit of history and period since surgery for each set of radiographs, it was impossible to distinguish the pre-existing mineral of bone graft from induced new bone.

On the basis of these data, the FDA issued a humanitarian device exemption for the application of OP-1 implant as an alternative to autograft in recalcitrant long bone nonunions when the use of autograft is unfeasible and alternative treatments have failed.

Study on Fibular Defects

Geesink et al. (34) investigated the osteogenic activity of OP-1 by assessing its value in bridging fibular defects made at the time of tibial osteotomy for varus or valgus deformity of the knee. A summary of the patient characteristics is shown in Table 7.

Table 7: Patient Characteristics in a Randomized Clinical Trial with Recombinant Human Osteogenic Protein in the Treatment of Fibular Defects (34)

Study design	Randomized controlled trial (2 phases) 6 patients were assigned to 1 of the 4 groups. Phase 1 study (12 patients) assessed whether the osteotomy would be suitable by comparing a group of patients in whom the gap had been left untreated with a group in which demineralized bone had been used to fill the defect. In phase 2 (12 patients), the ability of OP-1 within a collagen type 1 carrier to repair the defect was compared with the collagen alone. This part of the trial was double-blinded.
Reason for surgery	Fibular defect
Number of patients/implants	24
Evaluation & follow-up periods	1 weeks, 6 weeks 10 weeks, 4 months, 6 months, 12 months 3 patients missed 1 follow-up appointment. One at 1 week after surgery and 2 at 12 months.
Outcome measures	**Clinical outcomes** • Hospital for Special Surgical (HSS) Knee score • Pain at the fibular osteotomy site • Patient satisfaction **Radiography outcomes** Osseous response was classified as follows: • Bone formation that bridged the distal and proximal parts of the fibular defect • Bone formation, but not bridging the defect • No bone formation 2 orthopedic surgeons evaluated radiographs and were blinded to the intervention. Differences between the 2 assessors were resolved by discussion with a third orthopedic surgeon. **Dual energy x-ray absorptiometry (DEXA)** to determine bone mineral density within the fibular defect
Laboratory assessment	Immunological testing at 1 and 10 weeks. A minimum fourfold increase in antibody concentration was classified as an antibody reaction.
Radiographic assessment	2 orthopedic surgeons blindly and independently evaluated the radiographs. Differences between the 2 assessors were resolved by discussion with a third orthopedic surgeon.
Demographics of the study groups	Mean size of fibular defect: Untreated group: 15.6 mm DMB group: 13.4 mm OP-1 group: 16.4 mm Collagen group: 15.2 mm The preoperative values of bone mineral density varied among the treatment groups. This was adjusted in the statistical analysis phase.

Table 8: Severity of Pain on Fibular Osteotomy at Each Follow-up Period in a Randomized Clinical Trial of Fibular Defects and Recombinant Human Osteogenic Protein (34)

Follow-up period	Untreated		DMB		Collagen		OP-1	
	Pain level, #		Pain level, #		Pain level, #		Pain level, #	
1 week	None	0	None	0	None	6	None	2
	Mild/Moderate	5	Mild/Moderate	6	Mild/Moderate	0	Mild/Moderate	4
	Severe	1	Severe	0	Severe	0	Severe	0
6 months	None	5	None	4	None	5	None	1
	Mild/Moderate	1	Mild/Moderate	2	Mild/Moderate	1	Mild/Moderate	5
	Severe	0	Severe	0	Severe	0	Severe	0
12 months	None	6	None	6	None	6	None	3
	Mild/Moderate	0	Mild/Moderate	0	Mild/Moderate	0	Mild/Moderate	3
	Severe	0	Severe	0	Severe	0	Severe	0

Three patients were not satisfied with the results of surgery at 10 weeks and at 12 months follow-up (1 in untreated group, 1 in OP-1 group, and 1 in DMB group).

One patient in the OP-1 group had bruising on the lower leg at 1 week, which resolved spontaneously. One patient in the collagen group had an oozing fibular wound for 1 week, but required no intervention.

Radiological and DEXA (Dual Energy X-ray Absorptiometry) evaluation showed that in patients in whom the defect was left untreated, no formation of bone occurred. At 12 months follow-up, new bone formation with bridging occurred in 4 of the 6 patients in DMB group, and 5 of the 6 patients in OP-1 group. One patient in OP-1 group did not show any evidence of new bone formation at any point during the study. This observation shows that the size of the gap in fibular defect was such that it would require the use of an osteogenic agent. The results of the radiological evaluation are shown in Table 9.

Table 9: Radiological Evidence: Formation of New Bone and Bridging of the Fibular Defect in a Randomized Clinical Trial with Recombinant Human Osteogenic Protein (34)

Follow-up period	Untreated		DMB		Collagen		OP-1	
	Indicator, #		Indicator, #		Indicator, #		Indicator, #	
6 weeks	New bone formation	0	New bone formation	6	New bone formation	2	New bone formation	5
	With bridging	0	With bridging	1	With bridging	0	With bridging	4
6 months	New bone formation	2	New bone formation	6	New bone formation	2	New bone formation	5
	With bridging	0	With bridging	4	With bridging	0	With bridging	4
12 months	New bone formation	3	New bone formation	6	New bone formation	2	New bone formation	5
	With bridging	0	With bridging	4	With bridging	0	With bridging	5

During follow-up, the mean bone mineral density for the DBM and OP-1 groups increased by more than 80%. The difference between the untreated and DMB groups was significant (P = .001). The difference

between the OP-1 and collagen groups was also significant (P = .038). There was no difference between the OP-1 and DMB groups at any time. Similarly, no significant differences between the mean bone mineral density of the untreated and the collagen groups were observed.

Low levels of anti-OP-1 antibodies developed in 10% of those treated with OP-1, but all titres were low and transient. No allergic reaction was reported. Circulating antibodies against type 1 collagen was observed in 5% of those who received this matrix, but no adverse events were reported.

One patient treated with OP-1 developed pain at the implantation site. A local resection was performed and histological examination confirmed the presence of active bone remodelling. It was presumed that the localized discomfort reflected an increased bulk of bone at the gap site, which caused mechanical irritation in adjacent soft tissues. The symptoms were relieved by excision of the bony response. The authors concluded that the dose of human OP-1 could have been too high. They suggested that concentrations of OP-1 needed in vivo might be lower than in vitro especially when dealing with normal bone. The authors suggested that the dose – response profiles, the effects of different carriers, and the biological and mechanical characteristics of new bone should be investigated in future trials.

Ontario-Based Pilot Study

A prospective pilot study (41) was conducted in Ontario, Canada to investigate the safety and efficacy of OP-1 in the treatment of recalcitrant long bone nonunions. Fifteen patients with complex, recalcitrant, long bone nonunions whose previous treatment had failed were identified and included. A summary of the patient characteristics and outcomes are shown in Table 10.

Table 10: Patient Characteristics and Clinical Outcomes of Study on Complex, Recalcitrant, Long Bone Nonunions (41)

Study design	Prospective pilot study
Number of patients	15
Mean age (range)	52.8 (38 – 76)
Sex	Male: 9 Female: 6
Fracture site	Tibia (5), humerus (4), femora (2), clavicle (4)
Prior autograft	11 patients
Surgical method	Removal of any previously implanted hardware Debridement of nonunion Correction of deformity Internal fixation Use of OP-1
Mean follow-up in months (range)	22 (6 – 52)
Clinical outcomes	The nonunion of 13 patients (87%) healed at a mean of 11 weeks postoperatively. 1 patient with clavicular defect had delayed radiographic union at 6 months follow-up but had progressive bone formation and was clinically stable. The tibia of 1 patient developed recurrence of deep infection and required amputation. No adverse events were reported.

The investigators concluded that this bone graft substitute appears to be safe and effective in providing sufficient biological stimulation in difficult-to-treat nonunions. Results of a more complete study on 70 patients are ready for publication. According to the principal investigator, OP-1 was effective in inducing bone formation and bone healing in this sample and had a success rate of about 90%.

Study on Fresh Tibial Fractures

Recent laboratory experiments have suggested that BMPs may be injected to enhance the treatment of fractures that do not require operative treatment. Maniscalco et al. (42) did a clinical study to verify the potential of OP-1 in fresh tibial closed fractures. The aims of the study were to standardize the surgical technique; to evaluate tolerance and toxicity; to study the advantages and disadvantages of OP-1 in terms of bone healing and functional therapy; and to identify the types of fractures that could benefit from this therapeutic protocol.

Fourteen patients with closed fractures of the tibial shaft were randomly assigned to 2 groups. Each had 7 patients. Patients with open fractures, pathologic fractures, and vascular and/or nerve lesions were excluded. In the control group, only external fixation was applied. In the OP-1 group, after external fixation, a 1-cm incision was made above the fracture site, and the protein was inserted by a custom-designed system. A hole was created in the fracture site with a drill, and the liquid fluid protein was applied a pusher. In the immediate postoperative period, the leg was placed in a non weight-bearing position, and ankle movement was permitted immediately. All patients had prophylactic antithrombosis therapy with heparin. The same standardized rehabilitation program was applied to both groups. A summary of the patient characteristics is shown in Table 11.

Table 11: Randomized Clinical Trial with Recombinant Human Osteogenic Protein in the Treatment of Fresh Tibial Fractures: Maniscalco et al. (42)

Characteristic	OP-1 Treatment	Controls
Number of patients/implants*	7	7†
Mean age, years (range)	47 (26 – 68)	40 (21 – 53)
Sex, male/female	6/1	7/0
Mean time since injury, days	6.0	6.7
Mean time from injury to surgery, days (range)	6 (3 – 8)	6.7 (3h – 19d)
Mean follow-up period, days (range)	219 (156 – 329)	174 (140 – 234)

*2 patients had comorbidities, 0 patients had comorbidities; †external fixation only

Fracture union was confirmed by the presence of the callus bridging at the fracture site on the anteroposterior and lateral radiographs. Radiological evaluation was done postoperatively, and at 1 month, 2 months, 4 months, and 5 months to check for the presence of the callus bridging the fracture site. In addition, in the OP-1 group, an ultrasound was done immediately after surgery and at 1 month, 2 months, and 4 months after to evaluate the progressive formation of bone callus.

In the OP-1 group, all of the patients had blood and urine tests at baseline and 1 month, 2 months, and 3 months. This was to measure calcium, phosphate, alkaline phosphatase, serum nitrogen, and creatinine. Table 12 shows the result of this study.

Table 12: Clinical, Radiological, and Laboratory Results of Treatment of Fresh Tibial Fracture with OP-1: Maniscalco et al. (42)

Outcome measure	Results	
	OP-1 Treatment	Controls
Clinical and radiological signs of fracture union, mean days (range)	135, (120 – 165)	131, (134– 164)
External fixator was removed, mean days (range)	169, (130 – 170)	151, (97 – 175)
Consolidation with no intraoperative or postoperative complications, number of patients	6	7
Hospital stay, mean days, (range)	11.7 (5 – 21)	12.0 (5 – 26)
Laboratory tests		N/A
calcemia	No significant change	
calciuria	No significant change	
phosphatemia	No significant change	
phosphaturia	No significant change	
alkaline phosphatase	Progressive rise in 6 patients	

The consistency of OP-1 used for this study was different from that in the other 2 RCTs, and the injection of OP-1 necessitated excessive fluidity of the solution. The investigators concluded that OP-1 is not indicated for fresh shaft fractures of tibia. However, the study was not sufficiently powered to justify this conclusion.

Summary of Findings: OP-1

- OP-1 is an osteoinductive bone graft material. It contains human osteogenic protein and bovine bone derived collagen (3.5 mg OP-1 and 1 g collagen).
- So far, evidence for safety and effectiveness of OP-1 is based on 1 large RCT, 1 small RCT, and 1 pilot case series.
- There is level 1 evidence that OP-1 is as effective as autologous bone graft in the treatment of tibial nonunion. The rate of clinical success in tibial nonunions was similar to that for the autologous bone graft when used with intramedullary rod fixation.
- None of the studies using OP-1 documented any adverse systemic effects.

- The major advantages of using OP-1 rather than harvesting bone for autograft is the avoidance of pain and infection at the donor site associated with autograft procedures.
- Reconstruction of a bone defect with a large gap between the 2 ends requires the use of an osteogenic agent. Based on level 2 evidence, OP-1 may be used in the treatment of segmental bone defect, but this evidence is based on a small-sized trial; therefore, OP-1 can be considered still investigational in this area.
- There is level 2 evidence that OP-1 is not indicated for fresh shaft fractures of tibia.
- The dose – response profile and biological and biomechanical characteristics of new bone needs further evaluation.
- The FDA has limited the use of OP-1 to long bone nonunions when the use of autograft is unfeasible and alternative treatments have failed.
- According to the FDA, OP-1 should not be used in the presence of the following conditions:

    - Hypersensitivity to the active substance or to collagen
    - Pregnancy
    - Skeletal immaturity (e.g., in patients < 18 years of age)
    - At the site of a resected tumour that is at or near the defect or fracture

Alternative Technologies

The Medical Advisory Secretariat searched the literature from January 1, 2000 to February 28, 2005 to identify studies on nonunions and bone defects that used alternative technologies. A review of these studies showed that in addition to the gold standard autologous bone marrow grafting, bone allografts, demineralized bone matrices, bone graft substitutes, and autologous bone marrow have been used for treatment of nonunion and bone defects. These studies were categorized according to their osteoinductive, osteoconductive and osteogenesis properties.

Materials with Osteoconductive and Limited Osteoinductive Properties

Bone Allografts

Bone allografts have been used mostly in various reconstruction procedures to restore the defective bone after excavating a bone lesion. Table 13 shows a summary of these studies.

Table 13. Studies on the use of Allografts in Nonunions and Bone Defects (2000 – 2005)

Study	Level of evidence	Bone graft	Condition
Weng 2004 (43)	Case series, retrospective	Cortical strut allograft & autologous bone graft	Femoral nonunion
Muscolo 2004 (44)	Case series, prospective	Fresh deep frozen allograft	Bone tumour
DeGroot 2004 (45)	Case series, retrospective	Osteoarticular allograft	Bone tumour in humerus
Manfrini 2004 (46)	Case series, prospective	A combination of bone allograft and vascularized fibular autograft	Bone tumour in tibia and femur
Shasha 2003 (47)	Case series, prospective	Osteochondral allograft	Fracture of tibial plateau
Dudkiewicz (48) 2003	Case series, prospective	Composite massive allograft	Osteosarcoma of the proximal humerus
Mohler 2003 (49)	Case series, prospective	Allograft plus autologous bone graft in some cases	Resection of tibial sarcoma
Donati 2002 (50)	Case series, retrospective	Allograft arthrodesis	Knee arthrodesis
Rodl 2002 (51)	Case series, prospective	Osteoarticular allograft	Bone tumour of humerus
Shih 2002 (52)	Case series, retrospective	Intramedullary Cortical Allograft Strut	Bone tumour of humerus
Gao 2001 (53)	Case series, prospective	Vascularized bone transfer	Bone tumour of upper extremity

Two studies investigated the effectiveness of DBM in healing fracture nonunions. However, in these studies, autologous bone marrow grafting has also been used to stimulate healing. A summary of the patient characteristics, procedures, and results of these studies is shown in Table 14.

Table 14. Studies on the use of Demineralized Bone Matrix in Nonunions and Bone Defects (2000 – 2005)

	Ring 2004 (54)	Wilkins 2003 (55)
Study design	Case series, retrospective	Case series, retrospective
Patients	24	76
Mean age (range)	72 (52 – 86)	45 (18-76)
Condition, number (%)	Osteoporotic nonunions (diaphyseal humerus) Nonunion: 15 (63) Delayed union: 9 (38)	Long bone non-union: 41(46) Removal of benign bone tumour: 35 (54)
Procedure, number of patients	DBM: 13 Autologous bone graft: 12 Local graft: 2	DBM (allomatrix injectable putty) alone: 74 DBM with bone marrow aspirate: 3 tibial nonunions DBM with adjunctive strut allograft: 3 with humeral nonunions
Method of fixation	Locking compression plates	No change was made in the patients' immobilization or weight bearing status
Follow-up, months	12 (minimum)	Nonunion: 6 Benign tumour: 7
Results	All the fractures eventually healed; 2 healed after a second procedure for autologous bone grafting in patients who initially received DBM Since the study was designed to investigate the use of locking compression plate, the details in regards to the outcomes of DMB and autologous bone grafting are not reported.	Healing for nonunion: 85% Benign tumour group: 93%
Complications* • continued pain • refracture • hardware failure delayed union • postoperative neuroma over scar area • decreased range of motion • recurrent infection	9	2 (1 femur, 1 tibia) 1 1 1 1 1

*Refers to complications in non-union group in the Wilkins study

No definite conclusion can be made from the studies on DBMs. The objective of Ring's study was to investigate the usefulness of a fixation technique for treatment of osteoporotic nonunions. In the study by Wilkins et al., (56) some patients had also received bone marrow aspirate or strut allograft. These

investigators were contacted for additional information and updates. According to the investigators, about one third of the patients in their current database have also received either bone marrow aspirate or allograft.

Materials with Osteoconductive Property

Calcium phosphate and calcium sulphate are osteoconductive materials that have been used mostly for repair of bone defects (See Table 15).

Table 15. Studies on the use of Calcium Phosphate and Calcium Sulphate in Nonunion/Bone Defects (2000 – 2005)

Study	Study design	Bone graft substitute	Condition
Arai 2005 (57)	Case series, prospective	Beta-tricalcium phosphate	Fibular defect due to harvesting
Matsumine (58) 2004	Case series, prospective	Calcium hydroxyapatite	Bone defects due to benign bone tumours
Hatoko 2004 (59)	Case series, prospective	Calcium phosphate cement	Radial defect due to harvesting
Borrelli 2003 (60)	Case series, retrospective	Calcium sulphate & Autologous bone graft	Nonunions and bone defects
Welkerling 2003 (61)	Case series, prospective	Calcium phosphate	Bone defect due to enchondroma
Dickson 2002 (62)	Small RCT (Hydroxyapatite vs autologous bone graft)	Hydroxyapatite	Bone defects due to trauma
Petruskevicius 2002 (63)	Small RCT (Calcium sulphate vs no filling)	Calcium sulphate	Tibial defects
McKee 2002 (64)	Case series, prospective	Calcium sulphate	Infected long bone defects
Hinz 2002 (65)	Case series, prospective	Beta-tricalcium phosphate	Bone defect due to traumatic injuries
Kelly 2001(66)	Case series, prospective	Calcium sulphate	Bone defects
Werber 2000 (67)	Case series, prospective	Hydroxyapatite ceramic	Radial defect due to fracture
Yamamoto 2000 (68)	Case series, prospective	Hydroxyapatite	Bone defects due to tumour excision

Material with Osteogenic Property

Bone Marrow Grafting

Several investigators have investigated the use of autologous bone marrow for treatment of long bone nonunions. A summary of the patient characteristics, procedures, and results of these studies is shown in Tables 16A to 16D.

Table 16A. Studies that used Percutaneous Injection of Bone Marrow for Treatment of Nonunions and Bone Defects

	Goel et al. 2005 (69)	Wilkins et al. 2003 (56)	Siwach et al. 2001 (70)
Study design	Case series, prospective	Case series, prospective	Case series, prospective
No. of patients (no. of procedures)	20	66 (69)	72
Mean age years (range)	37.5 (24 – 60)	42.0 (15 – 81)	41.2 (26 – 56)
Site, number of patients			
tibia	Tibial nonunion who were on the waiting list for open bone grafting	36	42
femora	N/A	16	8
humerus	N/A	4	12
ulna	N/A	4	3
radius	N/A	2	5
ulna and radius	N/A	N/A	2
fibula	N/A	1	N/A
ankle (failed fusion)	N/A	6	N/A
Conditions*, number of patients			
unspecified nonunion	N/A	N/A	22
delayed unions	N/A	N/A	38
atrophic nonunion	10	N/A	N/A
hypertrophic nonunion	10	N/A	N/A
open fracture	3	27	
failed ankle fusion	N/A	6	N/A
poor regenerates in segmental bone transportation and limb lengthening	N/A	N/A	5
iatrogenic causes	N/A	N/A	7
Definition of nonunion	Persisting pain and mobility at the fracture site for a minimum period of 6 months from injury and no progression on 3 monthly serial radiographs	Established nonunion more than 6 months after injury with no evidence of progressive healing for the previous 3 months	Not indicated
Mean time from fracture to diagnosis of nonunion, months (range)	12 (6 – 36)	21 (0.5 – 16)	11.6 (5 – 36)
Operative/anesthesia technique	Outpatient procedure under local anesthesia	Outpatient procedure under general or spinal anesthesia Aspirated bone marrow was mixed with a DBM composite	Outpatient procedure under local anesthesia
1 injection 2 injections 3 injections	2 patients 9 patients 4 patients	61 sites 8 sites	A second injection was performed after 4 – 6 weeks. The third injection was given to selected patients (total of 164 injections)
Method of fixation	Cast Patients encouraged to mobilize full weight bearing	No changes in fixation or other variables were made	Cast
Mean follow-up period, months (range)	Until definite union or failure The procedure was considered a failure if there was no clinical and radiological union at 6 weeks following the third injection	21.7 (3 – 54)	48
Results, number of patients (%)			Bony union occurred in 68 of 72 patients (94%)
success	15/20 (75)		
healed sites		61/69 (88)	
excellent results			52/72 (72.0)
good results			8/72 (11.0)

	Goel et al. 2005 (69)	Wilkins et al. 2003 (56)	Siwach et al. 2001 (70)
failure lost to follow-up	1		4/72 (5.5)
Mean time to union (range)	14 (6 – 22) weeks	8.1 months (2 months to 3 years)	Not indicated
Complications	None	None	Not indicated

***** Patients in the Siwach et al. study had poor soft tissue coverage

Table 16B: Studies That used Percutaneous Injection of Bone Marrow for Treatment of Nonunions and Bone Defects

	Jean et al. 2001 (71)	Wang et al. 2001 (72)	Matsuda et al. 1998 (73)
Study design	Case series - retrospective	Case series - prospective	Case series - prospective
Patients	14	56	7
Age (mean, range)	26.5 (21 – 62)	32 (19 – 72)	53.4
Nonunion site/condition	Site: Tibia Atrophic: 12 Hypertrophic: 2 Infection: 2	Site: Tibia Open: 37 Closed: 19	Site: Femora 4 non-infected 2 with active infection 1 with bone defect
Definition of nonunion/average time from initial treatment (months)	If the fracture had failed to demonstrate clinical and radiological healing, had persistent motion, and caused pain at the fracture site for 7 months or longer after injury	Not reported	If the fracture had not demonstrated radiographic healing and had caused pain and movement for more than 7 months after the initial treatment
Time from fracture to diagnosis of nonunion (mean, range) months	12 (12 – 26)	Not reported	17 (9 – 34)
Operative/anesthesia technique	General or spinal anesthesia	Not reported	Spinal anesthesia: 4; general anesthesia in 2 patients with infected nonunions, and 1 patient who underwent nail replacement
Frequency of injections	1 injection: 10 2 injections: 4	2 or 3 injections	Non-infected: 1 injection
Method of fixation		Suitable fixation materials	Intramedullary nail fixation
Follow-up (mean, range)	20 (12 – 48 months)	2.8 years (4 – 50 months)	37.8 (15 – 47) months
Results	Fractures healed in 12 of 14 cases (86%) 2 cases with initial infection failed to unite	Fracture healed in 53 of 56 patients (95%)	4 non-infected nonunion completely united 1 bone defect partially united (100%) 2 infected nonunions did not heal (1 was avascular)
Time to union (mean, range), months	6 (3 – 10)	8 (5 – 10)	5 – 9
Complications	None	None	None

Table 16C. Studies that used Percutaneous Injection of Bone Marrow for Treatment of Nonunions/Bone Defects

	Pan et al. 1996 (74)	Garg et al. 1993 (75)	Sim et al. 1993 (76)
Study design	Case series - retrospective	Case series - prospective	Case series - retrospective
Patients	12	20	10 patients with delayed union and nonunion (11 fractures)
Mean age, y (range)	35 (17 – 55)	35 (18 – 65)	38 (median)
Nonunion site/condition	Site: Tibial (7 open, 5 closed) Atrophied: 6 Hypertrophied: 6 Osteomyelitis: 1 Pin track infection: 3	Site: tibia: 15; Humerus: 3; Ulna: 2 Poor skin: 5	Site: Tibia: 8 (7 open; 2 had bone gaps 2 – 3 cm) Humerus: 1 Femur: 1 (1 had 1 cm bone gap) Radius/ulna: 1 open
Definition of nonunion		Not reported	Delayed union: Clinical: time to unite unduly prolonged, in excess of prediction by Perkin's timetable, pain and tenderness when stressed Radiological: Fracture sire clearly visible and ends not sclerosed Nonunion: Clinical: movement elicited at fracture site, painless unless excessive Radiological: fracture site visible, ends may be sclerosed and hypertrophica or atrophic
Time from fracture to diagnosis of nonunion/intervention (mean, range), months	8 (5 – 13)	10 (6 – 18)	4 (3 had 1 – 3 cm bone gaps)
Operative/anesthesia technique	General anesthesia	General anesthesia	
Frequency of injection	1 injection	Injection was repeated after 3 weeks for all cases	I injection
Method of fixation	The nonunion site was not internally or externally fixed	Plaster cast	Patients had plate or external fixator as their initial treatment
Follow-up (mean, range)	Not reported	Not reported	Until union or otherwise
Results	10 of the 12 nonunion that were treated with bone marrow graft achieved clinical union (83%)	17 of 20 nonunions healed (85%) Failures: 2 compound tibial fracture with bone loss; 1 closed ulnar fracture	9 of the 11 fractures healed (82%)
Time to union (mean, range), months	5.4 (1.5 – 12)	5 (3 – 7)	2.5 (1 – 6)
Complications	None	None	There was 1 case of post injection infection

Table 16D. Studies that used Percutaneous Injection of Bone Marrow for Treatment of Nonunions/Bone Defects

	Connolly et al. 1989 (77)
Study design	Case series - prospective
Patients	20 (10 received intramedullary nail fixation, 10 cast immobilization)
Age (median, range)	30 (18 – 82)
Nonunion site/condition	Site: Tibia (19 open; 1 closed) 10 with infection
Definition of nonunion	If the fracture had failed to demonstrate clinical and radiographic healing and had persistent motion and pain at the fracture site for 7 months or more after injury
Time from fracture to intervention (median, range), months	14 (7 – 36)
Operative/anesthesia technique	General anesthesia In 3 cases, because of a large defect in an infected nonunion, the marrow was mixed with DBM
Frequency of injection	I injection: 18 2 injections: 2
Method of fixation	Intramedullary nail fixation: 10 Cast immobilization: 10
Follow-up (mean, range)	Not reported
Results	18 of the 20 tibial nonunions healed (90%); 10 in intramedullary nail fixation group, 8 in cast immobilization group 2 cases did not heal (1 had infection before bone marrow injection)
Time to union (mean, range), months	6.8 (5 – 10)
Complications	None In 1 patients the use of a large bone biopsy needle for the injection caused persistent pain at the injection site

These case series show that percutaneous bone marrow grafting is highly effective in the treatment of long bone nonunions. In a total of 301 fractures across all studies, 268 (89%) healed with a mean healing time of 2.5 to 8 months. This healing time as derived from these case series is less than the timing of the primary end point in Friedlaender's study (9 months). Table 2 summarizes the results of these studies.

Reports show that cases with atrophic nonunions were successfully treated with percutaneous bone marrow grafting. (56;69;74). Jean et al. (71) and Matsuda et al. (73) reported that cases with initial infection failed the treatment. These investigators have indicated that active infection is a contraindication for this technique.

Summary of Findings: Bone Marrow Grafting

- Bone marrow grafting is a minimally invasive, simple, and inexpensive technique that has successfully treated long bone nonunions.
- None of the studies of autologous bone marrow grafting documented any adverse systemic effects.
- So far, evidence for effectiveness of bone marrow grafting is based on 10 case series in which clinical outcomes were compared with the patients' baseline conditions. No RCT has been conducted to compare the effectiveness of this technique with the gold standard, autologous bone grafting.

Economic Analysis

Results of Literature Review on Economics

One published poster on the economic aspects of OP-1 for long bone nonunion was identified (78). This study compared the efficacy of OP-1 with autogenous bone graft in the management of tibial nonunions. Forty-one patients with nonunions amenable to intramedullary nailing were prospectively randomized into the OP-1 group or the autograft group. All patients underwent open intramedullary nailing and placement of either OP-1 or autograft. All patients were followed clinically and radiographically for a minimum of 1 year. Both groups were similar in respect to the duration of the nonunion, number of prior surgeries, and smoking history. Nineteen of 20 nonunions in the OP-1 group and 17 of 21 nonunion in the autograft group were consolidated. The cost of treatment with OP-1 was compared with the cost of treatment with autograft in 1 hospital (18 patients, 9 in each group). Table 17 shows the cost of treatment with OP-1 and autograft in these patients.

Table 17: The Cost Comparison Between Osteogenic Protein-1 and Autograft for the Treatment of Tibial Nonunion

Treatment	Mean cost, $ (US)	Range of cost, $ (US)
OP-1	12,468	10,279 – $15,097
Autograft	12,755	7,236 – $19,395

Ontario-Based Economic Analysis

Disclaimer: This economic analysis represents an estimate only, based on assumptions and costing methodologies that have been explicitly stated. These estimates will change if different assumptions and costing methodologies are applied for the purpose of developing implementation plans for the technology.

Hospitalization Costs

In 2003, an estimated total of 6,150 hospital separations were identified from the discharge abstracts database (DAD) that could have been associated with long bone nonunion. (A combination of ICD-10 diagnosis codes and CCI procedure codes were used.) An estimated total of 6,630 hospital separations were identified in 2002. Both figures are within the range of the incidence figures for long bone nonunion used in this report, i.e., 3,863 – 7,725 per year. Therefore, these discharge data are considered to be a valid depiction of the situation in Ontario. To determine the cost per case, the prospectively adjusted for complexity resource intensity weights (PAC-10 weights) were used based on a weight of 1.0 having a dollar value of $3,809 during 2003 (Personal Communication: Finance and Information Management Branch, MOHLTC). The mean PAC-10 weight in 2003 was 1.4, and since the 2002 average weight was within 0.1 of this figure, this was considered to be the overall average with an associated cost of $5,477 per hospital separation. Based on the range of annual incidence, the current annual hospitalization cost is between $21.2 million and $42.3 million.

Device Costs

A single vial of OP-1 is normally used per case of long bone nonunion. Given that the cost of a single vial is approximately $5,000 (Cdn) (according to figures provided by an Ontario hospital), the annual total cost of OP-1, if it were used universally for the treatment of long bone nonunion, would be in the range of $19.3 million to $38.6 million. There are no device costs associated with autologous bone marrow transplantation.

Professional (OHIP) Costs[4]

OP-1

The course of treatment for OP-1 is similar to that of autologous bone harvest except that a separate incision for harvesting bone from the iliac crest is not necessary when using OP-1. Therefore, it is assumed that similar FSC codes would be used for both procedures.

The physician fees for harvest, insertion of bone, or OP-1 is $193 (FSC E551 and E552 or Z279—we assume the latter is more common).

Autologous Bone Marrow Transplantation

The course of treatment for autologous bone marrow transplantation normally involves 2 procedures 6 weeks apart. The total physician costs are therefore doubled to reflect this normal course of treatment.

The cost for autologous bone marrow transplantation is $193 (FSC Z403 and Z426).

Based on annual incidence figures, total annual physician billings regardless of procedure—autologous bone harvest, OP-1, or autologous bone marrow transplantation—would be in the range of $0.7 million to $1.3 million per year.

Diffusion Pressure

Given that long bone nonunion is a definitive diagnosis that is unlikely to increase over time, the long-term prospects for diffusion beyond existing incidence figures is unlikely. However, the uptake is difficult to assess since annual sales data in the United States for the OP-1 product were not made available by the manufacturers.

Downstream Cost Savings

There may be pain medication cost offsets by using OP-1 and autologous bone marrow transplantation instead of autologous bone harvest, given that the former procedures do not involve the pain associated with the bone harvest site. However, given that this pain is normally not permanent, the overall offset is likely to be small. There are likely to be smaller OHIP costs associated with OP-1 than bone-harvest procedures given that only 1, rather than 2, incisions are needed in the former procedure. This offset could amount to between $0.3 million to $0.7 million annually.

Cost-Effectiveness

Given the recent development of OP-1, no cost-effectiveness data is available regarding this product. Though autologous bone-marrow transplantation has been used in jurisdictions outside Canada for some time, no cost-effectiveness data regarding the treatment of long bone nonunion were found regarding this technology.

[4] All physician billings are adjusted upward by 2% to reflect the 2005 OMA agreement.

Appraisal/Policy Development

OP-1 is a Class IV device and is indicated for use as an alternative treatment when other options have failed or are not feasible. However, Friedlaender's (40) study shows that the incidence of adverse events were similar when treating patients with OP-1 and autologous bone graft; therefore, using OP-1 does not impose additional risk to patients.

Patient Outcomes — Medical, Clinical

In patients with nonunion fractures in which harvesting autograft is deemed unfeasible, OP-1 can be considered as a reasonable alternative. These cases may include the following patient conditions:

- Insufficient bone tissue
- Infection at the donor site
- Discomfort or pain at the donor site
- Lesion/pathology at the donor site
- Poor quality of bone at the donor site
- Osteoporosis
- Comorbid conditions that increase the risk of harvesting autograft
- Extreme obesity
- Elderly

The cost of a vial of OP-1 is $5,000 to $5,500 (Cdn). Typically, 1 vial of OP-1 is used per treatment. Medical resources are among the other cost components and include surgical time, hospitalization, drugs, laboratory tests, and diagnostic imaging tests. However, in an analysis from a patient or social perspective, loss of productivity due to postoperative pain and infection following autograft may influence the analysis.

Diffusion — International, National, Provincial

Over the past few years, 15 to 20 hospitals in Ontario have used OP-1 for long bone nonunions. The manufacturer, Stryker Biotech, provides on-site training to the orthopedic surgeons. A package of inactive samples identical to OP-1 is used for training purposes. The manufacturer also supplies surgical techniques and videos demonstrating how the product is to be used.

FDA issued a humanitarian device exemption to authorize the marketing of OP-1. This exemption is applied when a device is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year. These devices bypass the premarket approval application process. However, humanitarian device exemption application must include sufficient data to show the probable benefits outweigh the risks.

Policy Considerations

Following reports by Connolly et al. (77) and Healey et al. (79) that showed percutaneous injection of autologous bone marrow successfully treated between 78% and 95% of long bone nonunions, a number of investigators were encouraged to study the use of autologous bone marrow grafting in their patients. All these investigators have reported that percutaneous injection of bone marrow is a simple, safe, and useful technique that can become the procedure of choice in many patients with delayed union or nonunion. In

addition, they have indicated that this is a useful procedure for patients at high risk for anesthesia and surgery and also for those who are waiting for any definitive surgical procedures.

Autologous cancellous bone grafting is considered the gold standard in the treatment of long bone nonunions. Unfortunately, this procedure is associated with complications at the donor and recipient sites including infection, pain, bruising, scaring, wound problems, nerve injury, and fracture. Harvesting the graft requires an additional surgical procedure. This increases the risk of perioperative blood loss and infection, leading to a prolonged hospital stay and additional cost. The need to open the nonunion site also adds to the risk of devascularization at the fracture site where healing is already impaired.
An alternative technology must be equally successful in achieving union, as well as providing some increased benefit to justify its use. OP-1 and autologous bone marrow grafting both eliminate the risk of donor site morbidity. Autologous bone marrow grafting has the additional advantage of decreased cost and no hospital stay because the procedure is performed in an outpatient setting.

Other advantages of autologous bone marrow graft include the following:

1. The use of autologous cells is facilitated by less stringent ethical and regulatory issues and does not require the patient to be immunologically suppressed. (80)

2. The procedure does not jeopardize any future procedure that may have to be done because bone marrow is a restorable source.

Three technologies that demonstrated positive clinical outcomes in the treatment of fracture nonunions were ranked according to 10 criteria. For each criterion, a score from 1 to 3 (1=the best score) were assigned to each technology. Ranking scores are shown in Table 18. According to this schema, a low total score would be associated with a better ranking.

Table 18: Ranking Scores for Technologies used for Long Bone Nonunions

	Autologous bone graft		OP-1		Autologous bone marrow graft	
Characteristic		**Score**		**Score**		**Score**
Invasiveness	More invasive	**3**	Less invasive	**2**	Minimally invasive	**1**
Operative procedure	Open surgery, 2 sites	**3**	Open surgery, 1 site	**2**	Closed	**1**
Need for hospitalization	Inpatient	**2**	Inpatient	**2**	Outpatient/short hospital stay	**1**
Anesthesia	General	**2**	General	**2**	Local/regional/ general	**1**
Donor site morbidity	Yes	**2**	No	**1**	No	**1**
Risk of infection at the fracture site	21%	**3**	3%	**2**	No	**1**
Perioperative blood loss	More	**3**	Less	**2**	No	**1**
Success rate (%)	85	**1**	81	**1**	75 – 95	**1**
Need for retreatment and feasibility to repeat the same procedure (%)	10, not easy	**3**	5, not easy	**2**	0, easy	**1**
Cost of treatment	Surgery + hospitalization	**2**	Surgery + hospitalization + device	**3**	Minimum cost	**1**
Total scores		**24**		**19**		**10**

10=best score

The method of percutaneous aspiration and injection of autologous bone marrow offers the advantages of treating long bone nonunions without exposing the patients to the risk of surgery and the complications of graft harvesting. The bone marrow is harvested by needle aspiration from the patient's pelvic bone and is then injected percutaneously into the fracture site under fluoroscopic control.

Autologous bone marrow grafting can heal a fracture because it has the key element in the process of bone generation (osteogenesis). Bone marrow contains stem cells, which are unspecialized cells that can produce mature osteoblasts and regenerate bone. Clinical use of stem cell transplants for hematopoietic conditions, such as various blood cell cancers, has been established over a decade ago.

Since the studies on autologous bone marrow grafting are case series in which patients serve as their own control, it cannot be concluded whether this procedure is as effective as autologous bone grafting. A randomized comparative study is needed to clarify this issue.

Conclusions

Based on level 1 evidence, (1 RCT, 124 patients) OP-1 is a reasonable alternative to autologous bone grafting in the treatment of long bone nonunions.

Based on level 4 evidence, (10 studies, a total of 301 patients), percutaneous autologous bone marrow grafting is effective in the treatment of long bone nonunions in patients with no active infection at the fracture site.

Based on the above evidence and the fact that both procedures (percutaneous autologous bone marrow grafting and OP-1) eliminate the risk of donor site morbidity and reduce the risk of infection at the recipient site, the following would form some of the important considerations in making decisions regarding these competing technologies:

- Should the effectiveness of percutaneous bone marrow grafting as a treatment modality for non-infected long bone nonunions be explored further?

- Should access to OP-1 be provided to the patients with long bone nonunions (according to the definitions set by FDA) where other methods of treatment have failed?

Glossary

Allograft	A graft of tissue between individuals of the same species but of disparate genotype
Apoptosis	Programmed cell death - a mechanism for cell destruction
Autogenous	Autologous
Autologous	Related to self
Cancellous bone	Spongy bone
Chondroblast	A cell that forms cartilage
Comminuted fracture	Broken or crushed into small pieces
DNA	Deoxyribonucleic acid
Osteoblast	Cell that produces bone
Osteoclast	A large multinucleated cell responsible for bone resorption
Osteoconduction	A process that supports ingrowth of developing capillaries and perivascular tissue
Osteoinduction	The process of stimulating osteogenesis
Osteoprogenitor cells	Precursor cells

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