



TITLE: Recombinant Human Bone Morphogenetic Protein-2
For Spinal Surgery and Treatment of Open Tibial Fractures

AUTHOR: Mitchell D. Feldman, M.D., M.Phil
Professor of Medicine
Division of General Internal Medicine
Department of Medicine
University of California San Francisco

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RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN-2 FOR SPINAL SURGERY AND TREATMENT OF OPEN TIBIAL FRACTURES

INTRODUCTION

The California Technology Assessment Forum has been asked to review the scientific literature on the safety and efficacy of rhBMP for spinal surgery and tibial fractures.

This review will focus on the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) for the promotion of bone fusion in spinal surgery and to accelerate healing and decrease the need for secondary interventions after a tibial fracture. Other bone morphogenetic proteins (BMP's), most notably BMP-7 commonly known as OP-1 have also been studied in these conditions, but are not included in this review because they have either not obtained FDA approval or, as is the case with OP-1, have received approval only under the Human Device Exemption (HDE).

BACKGROUND

Low back pain is a common disorder, ranking second only to upper respiratory tract infection as a reason for visits to physicians in the United States (Deyo and Weinstein, 2001). Back pain may originate from many spinal structures, including ligaments, facet joints, the vertebral periosteum, the para-vertebral musculature and fascia, blood vessels, the annulus fibrosus, and spinal nerve roots. Perhaps most common are musculo-ligamentous injuries and age-related degenerative processes in the intervertebral disks and facet joints, spinal stenosis, and disk herniation. It is often not possible to attribute the problem to any specific disease or pathologic lesion (Deyo and Weinstein, 2001) and the association between symptoms and imaging results is weak (Devereaux, 2003).

Treatment of chronic low back pain may consist of pharmacologic and/or non-pharmacologic approaches. Pharmacologic treatments generally include non-steroidal anti-inflammatory drugs and opioid or non-opioid analgesics and antidepressants. Nonpharmacologic techniques such as physical therapy, acupuncture, massage, and relaxation also may be helpful to the patient with chronic back pain. Epidural corticosteroid injections can provide short-term relief of sciatica but do not improve functional status or reduce the need for surgery. For the minority of patients with persistent pain that substantially limits their activity level, spinal fusion surgery may be recommended. Spinal fusion surgery is designed to stop the motion at a painful vertebral segment which in turn should decrease the pain generated from this joint. Fusion surgery is indicated for chronic lower back pain secondary to advanced degenerative disc disease that is generally limited to one or two levels of the lumbar spine. A recent multi center randomized trial of lumbar fusion vs. non-surgical treatment (physical therapy) for chronic low back pain found that back pain was reduced in the

surgical group significantly more than in the non-surgical group. Of the patients who underwent fusion, the majority (58%) were fused at a single level (Fritzell *et al.*, 2001).

Spine fusion surgery is quite common in the U.S. with over 250,000 procedures performed annually. Spinal fusions can be performed by an anterior or posterior approach. The majority of spinal fusion operations in the US have been by the posterior approach, which in turn is comprised of three main techniques: a posterior lumbar interbody fusion (PLIF), a posterolateral gutter fusion surgery and a transforaminal lumbar interbody fusion (TLIF). In these procedures, the paraspinal muscles must be detached, thus potentially leading to paraspinal muscle weakness and atrophy in some patients. The PLIF and TLIF allow for placement of bone or a cage in the disc space. There are two types of anterior fusion procedures: the anterior/posterior lumbar fusion and the anterior lumbar interbody fusion (ALIF). In both operations, the spinal column is accessed through an incision in the abdomen, with some procedures done with either a mini-laparotomy or via an endoscopic approach. The anterior approach preserves the paraspinal musculature and nerves. In addition, bone graft is placed in front of the spine and therefore receives more compression and may fuse more efficiently (Burkus, Gornet *et al.*, 2002). Risks of ALIF surgery include damage to large blood vessels, and in males, retrograde ejaculation in around 1% of cases (Fowler *et al.*, 1995).

Most lumbar spinal fusion surgery involves the use of a bone graft, generally autologous bone taken from the patient's hip. The goal is to cause two vertebral bodies to grow together into one long bone. To harvest the graft generally requires an additional surgery with concomitant potential adverse consequences such as additional blood loss, infection, pelvic instability and pain (Damien and Parsons, 1991). Up to 37% of patients suffer donor site pain 10 years after the procedure (Polly *et al.*, 2003). Autologous bone graft has two essential properties: osteoconduction and osteoinduction. Osteoconduction is the process by which the bone graft supports the ingrowth of capillaries, perivascular tissues and osteoprogenitor cells into the structure of the implant or graft. Osteoinduction is a process attributed to BMP's and is one that supports the proliferation of bone marrow cells to become osteogenic (Vaccaro and Cirello, 2002). Specially prepared allogeneic bone may be used as a substitute for autogenous bone in some patients, but because of its lower osteogenic capability and the small but real risk of infection, it is considered a second choice. In addition to these complications, there is a risk of non-union with the use of bone grafting in spinal fusion surgery. Overall, fusion rates for autogenous bone graft procedures vary widely in the literature from around 60% - 95% (Christensen *et al.*, 1996; Burkus, 2003). Host factors that negatively impact a successful fusion include smoking, obesity, diabetes mellitus, osteoporosis, chronic steroid use, prior back surgery or fusion and malnutrition (Vaccaro and Cirello, 2002).

There are approximately 1.5 million long bone fractures in the United States each year; of these up to 2% - 10% will be compromised by delayed healing or non-union. Delayed union of tibial fractures is common, reportedly 16% to 60% for less severe fractures and 43% to 100% for more severe fractures (Govender *et al.*, 2002). When healing is delayed in long bone fractures, a second intervention is often required; these interventions are associated with high rates of patient morbidity and reduced quality of life (Govender *et al.*, 2002). Treatment options for nonunion tibial fractures include skeletal fixation with or without bone graft (Friedlander *et al.*, 2001).

A variety of strategies have been used to help facilitate the natural process of new bone formation after an operation or fracture. These include autogenic bone grafts, allogenic bone grafts, electrical stimulation and more recently bone morphogenetic proteins. These strategies are more frequently employed in situations where there is higher risk of inadequate or ineffective healing taking place.

Recombinant Human Bone Morphogenetic Protein-2

Unlike most other tissues that heal when injured by forming connective tissue, bone heals by the formation of new bone. There are a number of complex steps or processes that are involved in bone remodeling and healing including the proliferation of mesenchymal stem cells from the bone marrow, periosteum and surrounding soft tissue. These cells are transformed into osteoprogenitor cells by the locally produced bone morphogenetic proteins (Rengachary, 2002). Collectively, BMP's are part of a larger family of proteins called the TGF- β superfamily (so named because of their ability to transform cultured fibroblasts) that play a role in embryonic development and regeneration of skeletal tissue in adults (Valentin-Opran *et al.*, 2002). BMPs have been shown in both in vivo and in vitro studies to induce chemotaxis (stimulation of cell migration in response to a chemical signal), and cell proliferation. To date, seven potentially bone morphogenetic proteins have been isolated and cloned, and four have shown bone morphogenetic activity in animals: BMP-2, BMP-4, BMP-5 and BMP-7 (also known as OP-1) (Wolfe *et al.*, 1999).

The first implantations of purified BMP's were undertaken by Marshall Urist at the University of California, Los Angeles (UCLA) in the mid 1960's when he demonstrated that crude bone extracts induced new bone in an ectopic site in a rat model. He coined the term bone morphogenetic protein or "osteogenic protein" (Rengachary, 2002). The bone induced by these BMP's appears and functions normally by histological, biomedical and radiological criteria (Valentin-Opran *et al.*, 2002). Bone morphogenetic protein is produced by the kidneys and under normal circumstances is found only in trace amounts in the human body. Bone morphogenetic protein is water soluble and diffuses very easily in body fluids, so in order for it to maintain adequate concentration at the surgical or fracture site it is necessary to contain the BMP in a carrier. The

major categories of carriers include inorganic materials, synthetic polymers, natural polymers, and allograft bone. Bovine Type 1 collagen (from bone, tendons or ligaments) is currently used in the clinical setting.

Most of the clinical trials to date that have used rhBMP-2 in spinal fusion have used the INFUSE® Bone Graft system. In this system, rhBMP-2 is hydrated with sterile water and placed on an absorbable collagen sponge made from Type 1 bovine collagen. The sponge is then placed into the LT-CAGE® Threaded Fusion Device and then inserted into the disc space. The InFUSE® Bone Graft/LT-CAGE® Lumbar Tapered Fusion Device is indicated for anterior lumbar interbody spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1, who may also have up to Grade I spondylolisthesis at the involved level (<http://www.spineuniverse.com>). In tibial fracture repair, the rhBMP-2/collagen mixture is formed into a paste and applied to the bones during surgery.

TA Criterion 1: The technology must have the appropriate regulatory approval.

On July 2, 2002, Medtronic Sofamor Danek, Inc. USA (Memphis, TN) received PMA approval for the InFUSE™ Bone Graft/LT-CAGE™ Lumbar Tapered Fusion Device. This device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L4-S1. In 2004 the levels of use were extended to L2-S1.

On April 30, 2004, Wyeth Pharmaceuticals, Inc. received PMA approval for INFUSE® Bone Graft. This device is indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management.

Other interbody fusion cages such as the BAK VISTA Fusion System (Centerpulse Spine-Tech, Mineapolis, MN) and the INTER FIX Threaded Fusion Device (Sofamar Danek, Inc.) have FDA approval for use in spinal fusion with autogenous bone graft.

TA criterion 1 is met

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

To date, there have been six randomized clinical trials of rhBMP-2 in single level lumbar spinal fusion published in peer-reviewed journals. There has been one published RCT of rhBMP-2 in cervical fusion and one randomized trial of rhBMP-2 for the treatment of open tibial fractures.

These trials have assessed clinical and radiographic outcomes, generally at three, six, 12 and 24 months. In the lumbar spinal fusion trials, the main clinical outcomes tracked include neurologic status, work status,

patient satisfaction, pain (back, leg and graft site) and Oswestry Low Back Pain Disability questionnaire. The Oswestry questionnaire is a self-administered evaluation of 10 domains scored from 0 (no pain or disability) to 5 (severe pain or disability) that has been well validated and is frequently used in low back pain research (Fairbank *et al.*, 1980).

Radiographs and computed tomography (CT) scans are used to assess fusion rates after surgery. In general, two blinded radiologists interpret the studies at regular intervals with disagreements adjudicated by a third radiologist. Fusion is defined as the absence of radiolucent lines covering > 50% of either implant, translation of ≤ 3 mm and angulation $< 5^\circ$ on flexion-extension radiographs, and continuous trabecular bone growth connecting the vertebral bodies on CT scan cut. Several trials take a conservative approach of rating the outcome a “fusion failure” if the patient underwent a second surgery for symptoms or suspected non-union even if the studies themselves indicated a successful fusion (Burkus, Gornet, *et al.*, 2002)

In the trial of rhBMP-2 and treatment of open tibial fractures, the main outcome measures included evidence of fracture healing (radiographic evidence of fracture union and fulfillment of clinical criteria including full weight bearing and lack of tenderness at the fracture site with palpation). In addition, recommendation for secondary intervention by the investigators and/or the performance of such an intervention to promote fracture union was considered a treatment failure (Govender *et al.*, 2002).

For rhBMP-2 in lumbar spinal fusion, there are sufficient well-done randomized clinical trials with appropriate outcome measures to permit conclusions regarding the effectiveness of the technology. Other uses of rhBMP-2 have too few trials on which to draw conclusions.

TA criterion 2 is met for rhBMP-2 in spinal fusion.

TA criterion 2 is not met for rhBMP-2 in tibial fracture.

Levels of Evidence: 1 and 5.

TA Criterion 3: The technology must improve the net health outcomes.

RANDOMIZED TRIALS:

Recombinant human BMP-2 in Lumbar Spinal Fusion

Boden *et al.* (2000) report on a prospective randomized controlled pilot trial of 14 patients with single-level lumbar degenerative disc disease refractory to non-operative management. The primary objective of the study was to compare experimental and control treatment with regards to efficacy in achieving fusion as demonstrated by CT scans. Secondly, they assessed the effectiveness of treatment regarding pain and function. Patients were randomized to receive a lumbar inter-body arthrodesis with a tapered cylindrical

threaded fusion cage filled with rhBMP-2/collagen sponge (N=11) or the fusion cage and autogenous iliac crest bone (N=3). Exclusion criteria included use of tobacco and non-steroidal anti-inflammatory medications. All eleven patients treated with rhBMP-2 had successful fusion as determined by thin cut CT as did two of the three control patients. There was no significant difference in Oswestry Disability Questionnaire scores at six months. None of the 14 patients had increased rhBMP-2 antibody titers following implantation of the device. Based on this pilot study, rhBMP-2 can induce interbody spinal fusion in humans without significant adverse consequences.

Boden *et al.* (2002) report on a prospective randomized pilot study of rhBMP-2 to achieve posterolateral lumbar spine fusion in humans. In this study, 27 patients undergoing single level posterolateral lumbar arthrodesis for single level DJD with disc degeneration were randomized to one of three treatments: autogenous iliac crest bone graft with Texas Scottish Rite Hospital (TSRH) pedicle screw instrumentation; rhBMP-2 with the internal fixation provided by the TSRH; and rhBMP-2 with no instrumentation. In this trial, the carrier for the rhBMP-2 was biphasic calcium phosphate granules (BCP). There were no complications attributable to the rhBMP-2/BCP or the TSRH internal fixation. Two blinded radiologists assessed spinal fusion using "strict criteria" and determined that the fusion rate in both rhBMP-2 groups was greater (20 of 20 achieved fusion) than in the autograft/TSRH group (2 of 5 achieved fusion). In addition, patients in the rhBMP-2 arms had significantly faster and overall greater improvement in patient derived clinical outcomes.

Burkus, Gornet *et al.* (2002) report on a multi-center (16 sites), prospective, randomized trial of 279 patients with DJD. All patients underwent the ALIF procedure through an open approach. The experimental group (N= 143) was treated with the LT-Cage with INFUSE (rhBMP-2) for a single level anterior lumbar interbody fusion. The control group was treated with the same cage filled with iliac-crest autograft. All patients had symptomatic single level DJD and disabling low back and/or leg pain of at least six months duration. There were no significant differences between experimental and control patients in the use of tobacco (about one-third in each). The operative time and blood loss were significantly less in the investigational group. Surgical complications were not significantly different between the two groups (vascular events in 4.2% of experimental patients and 3.7% of controls and retrograde ejaculation in 4.1% of male patients) except for those related to the iliac crest graft site. In the control group, eight patients had adverse events related to harvesting of the iliac crest graft. In addition, by 24 months after surgery nearly one-third of patients still experienced donor site pain. There were no differences in Oswestry outcome scores between the experimental and control groups at any point in the follow up over 24 months, with all groups showing significant improvement. Similarly, ratings of back pain improved in both the experimental and control groups and were not significantly different, and the number of patients who returned to work was also comparable. Patient satisfaction results were also similar; at 24 months 81.2% of the 122 experimental

patients and 80.4% of the 108 controls said they were satisfied with their surgical outcomes. Radiographic outcomes were assessed by two radiologists blinded to the treatment with disagreements (which reportedly occurred less than 2% of the time) adjudicated by a third radiologist. The criteria for fusion were based on analysis of plain radiographs and thin-cut computed tomography scans. At six months, 97% of patients in the experimental group had evidence of interbody fusion compared with 95.8% in the control group. At 24 months, the fusion rate was 94.5% in the experimental group as compared with 88.7% in the control. No p values are provided by the authors with regards to this outcome but they imply that this was not a statistically significant difference. Fusion rates declined in part because patients who had radiographic evidence of fusion but who underwent further stabilizing surgery on the basis of symptoms were classified as fusion failures. This large study demonstrated that for patients with single-level DJD undergoing anterior inter-body spinal fusion, clinical and radiographic outcomes are similar with rhBMP-2 or autogenous bone graft with interbody cages. They do report a small number of adverse events related to the autograft harvest and that one-third of patients report pain at the graft site after two years; however patient satisfaction was comparable with the two procedures.

Burkus, Transfeldt *et al.* (2002) report on a randomized trial of InFUSE Bone Graft (BMP-2 in an absorbable collagen sponge) and threaded cortical allografts in patients undergoing anterior lumbar interbody fusion (ALIF). Patients with single level lumbar DJD and disabling symptoms for at least six months were included. Patients at 5 sites who underwent ALIF surgery were randomly assigned to one of two groups: the investigational group (N=24) received InFUSE Bone Graft used in conjunction with the MD-II threaded (allograft) cortical bone dowel (Regeneration Technologies, Inc., Alachua, FL); and the control group (N=22) who received a cortical bone dowel with autogenous iliac crest bone graft. Clinical outcomes included the Oswestry Low Back Pain Disability Questionnaire, SF-36, neurologic status, work status, patient satisfaction, and back, leg and graft site pain. Radiographs and CT scans were assessed by two radiologists blinded to the group assignment. The average blood loss was less in the investigational group ($p=.026$) though the average hospital stay was similar in both groups. Patients treated with InFUSE had significantly more improvement in Oswestry scores at three, six and 24 months ($P=.032$, $.039$ and $.039$ respectively). The trend was also seen at 12 months but did not reach statistical significance. At six months, 19 of 21 InFUSE treated patients had fusion, and by one year 24 of 24 patients had radiographic evidence of fusion in contrast with 17 of 22 patients in the control group. Thirty-nine percent (7/18) of control patients reported persistent donor-site pain two years following surgery.

Burkus, Dorchak *et al.* (2003) report on radiographic outcomes of patients who underwent single level anterior lumbar interbody fusion using cylindrical interbody fusion cages. Patients were randomized to receive ALIF with two tapered cylindrical cages plus rhBMP-2 on an absorbable collagen sponge or a

control group that received the cages plus autogenous iliac crest bone graft. Plain radiographs and CT scans were used to measure the pattern of osteoinduction in the interbody space. They found that new bone formation occurred more rapidly in the rhBMP-2 investigational group, but by 12 and 24 months there was not a statistically significant difference between the groups in bone density either within or outside of the interbody fusion device. In this small study, rhBMP-2 appears to be equally as effective as autogenous bone graft in promoting new bone formation in patients with an ALIF using a tapered cylindrical device. The lack of clinical outcome measures in this study makes it impossible to draw broader conclusions.

Haid *et al.*, (2004) report on a prospective randomized non-blinded multisite pilot study of 67 patients with symptomatic single level lumbar disc disease of at least 6 months duration who underwent a single level posterior lumbar interbody fusion using two paired cylindrical threaded titanium fusion devices (INTER FIX device; Medtronic Sofamor Danek, Memphis, TN). The authors report that this device was not FDA approved for this indication. The investigational group received rhBMP-2 on a collagen sponge carrier and the control received autogenous iliac crest bone graft. As in previous studies, they found no significant differences in fusion rates or back pain and functional outcomes between the two groups. At 2 years, 13% of control patients reported that the graft site still bothered them (pain scores averaged 5.5 out of 20), although 69% of the investigational group stated that they would undergo surgery again compared with 83% of the investigational group ($p=NS$). Of note is that new bone formation extending outside the disc space and into the spinal canal or neuroforamina was found in 28 patients (24 investigational and 4 control), though this finding did not seem to correlate with reported leg pain.

Recombinant human BMP-2 in Cervical Spinal Fusion

Baskin *et al.* (2003) report on a randomized clinical trial of rhBMP-2 (INFUSE) as compared with an autogenous iliac crest bone graft placed inside the CORNERSTONE-SR fibular allograft in anterior cervical discectomy and interbody fusion. Patients were randomized and underwent a single- or two-level anterior discectomy and fusion and were evaluated at three, six, 12 and 24 months post-operatively with radiographic and clinical outcomes. Eighteen patients were enrolled in the INFUSE arm; of these 10 underwent a single-level fusion and eight a two-level fusion. In the control arm, eight patients underwent single-level and seven a two-level fusion. At 24 months, investigational patients had mean improvement superior to the control group ($P<0.03$) with regards to the Neck Disability Index and overall neck pain ($p<0.055$). They found no differences in outcomes of the SF-36 and overall patient satisfaction with the procedures. Fusion rates in both groups were 100%. They report no device related adverse events. In this study, rhBMP-2 achieved similar clinical and radiographic outcomes compared with autogenous bone graft when combined with a fibular allograft in anterior cervical discectomy and interbody fusion.

NON-RANDOMIZED TRIAL: Recombinant human BMP-2 in Lumbar Spinal Fusion

Kleeman *et al.* (2001) report on results from a prospective nonrandomized study of laparoscopic anterior lumbar inter-body fusion with rhBMP-2 on a collagen sponge placed in NOVUS LT cage (Sofamor Danek, Memphis, TN). Surgical indications included refractory low back pain from single level degenerative disc disease or low-grade spondylolisthesis. There were eight male and 14 female patients with an average age of 38. At six months, all patients available for follow up (21 of 22) were reported to have solid spinal fusion. In addition, all patients reported significant improvement in pain and function at six and 12 months. No adverse events related to the rh-BMP-2 were reported. The small size and non-randomized design make it difficult to draw definitive conclusions from this study.

Lanman and Hopkins (2004) report on the use of rhBMP-2 with HYDROSORB Telamon (Medtronic Sofamor Danek) as an interbody spacer in 43 patients (79% had discogenic pain). Most patients (70%) underwent one level fusion. At 6 months, 98% of patients had evidence of interbody fusion including all 13 patients who underwent 2 level fusion. By 12 months, Oswestry scores were improved in 67% and worse or the same in 33% of patients.

Recombinant human BMP-2 for treatment of open tibial fractures

Govender *et al.*, (2002) report on a prospective, randomized multi-site study of 450 patients that evaluated the safety and efficacy of the use of rhBMP-2 to accelerate healing of open tibial shaft fractures and reduce secondary interventions. Patients were randomized to one of three groups: 1) Standard of care consisting of intramedullary nail fixation and routine soft tissue management (control group), 2) Standard of care plus an implant of 0.75 mg/mL of rh-BMP-2, or 3) standard of care and an implant containing 1.50 mg/mL of rhBMP-2. In addition, patients were stratified according to fracture severity to ensure a balanced distribution across the groups. Four hundred and fifty patients with open tibial fractures were enrolled. The median age was 32, most patients were male and 49% had a history of recent tobacco use. Most patients underwent definitive fracture fixation with an intramedullary nail within 48 hours after the injury. Reamed intramedullary nailing (enlargement of the intramedullary canal with a reamer to facilitate insertion of a larger nail) was used more often in the 1.50 mg/mL rhBMP-2 group (41% or 59 patients) than in the control group (27% or 39 patients) ($p=0.013$). An absorbable collagen sponge was used to deliver the rhBMP-2, which was then placed over the fracture site bridging the area of comminution. Four hundred twenty-one patients were followed for at least twelve months. An intent-to-treat analysis was used for patients who did not receive the randomized treatment. Patients in the high dose rhBMP-2 group required significantly fewer and less invasive interventions to promote fracture union than control patients. Overall, patients who received the 1.50 mg/mL rhBMP-2 had a significant 44% reduction in the risk of secondary intervention to promote fracture healing

compared with the control patients. There was a consistent increase in the rate of healing in the rh-BMP-2 groups at all visits, starting at 10 weeks after definitive wound closure. At six months, the healing rate in the 1.50 mg/mL group was 21% higher than that in the control group ($p=0.008$). There was no overall difference in the rate of fracture site infection across treatment groups. One patient died in each study group but none of the deaths were considered to be related to the study treatment. Antibodies to BMP-2 were observed in one, three and nine patients in the control, 0.75 mg/mL, and 1.50 mg/mL groups respectively. Overall, 35% of patients in the high- dose rhBMP-2 group were considered treatment failures compared with 46% in the low-dose BMP-2 group and 53% of the control group. Failure was defined as fracture not united and/or need for secondary intervention. There is no discussion of this failure rate by the study authors.

Patient Risks

There are several theoretical concerns related to the use of rhBMP. The effects of high doses of BMP on a developing embryo are unknown, so its use during pregnancy is not advised. Development of an osteogenic sarcoma is theoretically possible but has not been seen in animal studies. Bone growth in the vicinity of neural structures is of concern and has been attempted to be minimized through the use of appropriate carriers and by placing the BMP inside a protective cage so it is not disrupted by an axial load (Rengachary, 2002). In the Haid (2004) study with a tapered titanium fusion cage, new bone formation was found in 84% of patients extending into the spinal canal. Although the authors report no adverse clinical consequences as a result, this phenomenon would seem to have the potential to lead to patient morbidity in the future. In the clinical trials, formation of antibody against rhBMP-2 occurs in about 0.7% of patients, a rate similar to that for control subjects (Poynton and Lane, 2002). There does not appear to be any correlation with the development of these antibodies and adverse outcomes (Valentin-Opran *et al.*, 2002). The risk of multiple uses of BMP (e.g. in repeat spinal surgery) is unknown. In light of the available data, rhBMP-2 appears to be safe provided that it is placed accurately and not allowed to come into contact with decompressed areas, is contained in the region of fusion, and is used with caution in the presence of dural defects (Poynton and Lane, 2002).

TA criterion 3 is met for rhBMP-2 in spinal fusion.

TA criterion 3 is not met for rhBMP-2 in tibial fracture.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

Autologous (or autogenous) bone graft, the procedure in which bone is taken from one anatomic site and transplanted to another site, is the current gold standard for spinal arthrodesis and to enhance fracture healing. Autologous bone graft has two essential properties: osteoconduction and osteoinduction.

Osteoconduction is the process by which the bone graft supports the ingrowth of capillaries, perivascular tissues and osteoprogenitor cells into the structure of the implant or graft. Osteoinduction is a process attributed to BMP's and is one that supports the proliferation of bone marrow cells to become osteogenic (Vaccaro and Cirello, 2002). Autografts have superior osteoconductive properties compared with bone graft substitutes such as demineralized bone matrix and bone substitutes such as calcium phosphate, hydroxyapatite and tricalcium phosphate.

Although bone grafts are effective treatments for spinal fusion and nonunion fractures, the problems with autogenous bone may at times outweigh the benefits (Damien and Parsons, 1991). To harvest the graft requires an additional surgical procedure, generally at the iliac crest which adds to the overall length of the operation and usually entails additional blood loss and occasional massive bleeding, infection, and pain (Fowler *et al.*, 1995). Some patients complain of pain at the harvest site for at least two years following the procedure (Burkus *et al.* 2002; Summers and Eisenstein, 1989). Other post-surgical complications include pelvic instability, fatigue fracture, iliac hernia, fistula, ureteral injury, nerve injury and heterotopic bone formation (Fowler *et al.*, 1995; Kurz *et al.*, 1989).

Allograft bone, or bone transferred between different persons, is another alternative to autograft. In adults, autografts are generally superior to allografts for achieving bone fusion (Janssen *et al.*, 2001). Allograft is the most commonly used alternative to autograft bone for reconstructive spinal surgery. It is used primarily when there is insufficient autograft. Age and size of the patient, prior surgery or bone harvesting in the area and other donor morbidities may lead to insufficient autograft (Vaccaro and Cirello, 2002). Allograft bone is available in different forms such as strips, wedges, shafts or machined dowels. While autogenous bone has osteoinductive, osteoconductive, and osteogenic properties, allogenic bone is not osteogenic (Vaccaro and Cirello, 2002). Different types of allograft bone will produce a spectrum of immunogenic responses from the host. The use of fresh-frozen allograft bone reduces this immunogenicity (Vaccaro *et al.*, 2002) and fresh allograft is not currently used. In the preparation of fresh-frozen allograft, however, BMP is destroyed which accounts for its lack of osteogenesis (Vaccaro and Cirello, 2002). Allograft bone has advantages over autograft in that it is available in a variety of shapes and sizes and avoids the host morbidity seen with bone harvesting. However, disadvantages of allograft, including longer initial fusion times, decreased vascular penetration and the potential of immunologic rejection by the host and the rare transmission of disease by the donor lead most experts to conclude that allograft is not recommended as a first line option in spinal fusion surgery (Vaccaro and Cirello, 2002).

Invasive and non-invasive electrical stimulation of the spine has been shown to be a useful adjunct in spinal fusion procedures. Invasive devices use direct current and require surgical implantation of a current generator while an electrode is implanted within the fragments of the bone graft at the fusion site. Non-

invasive electrical bone growth stimulators generate a weak electrical current delivered through a variety of mechanisms such as skin pads or a back brace. Data from randomized clinical trials support the use of electrical bone stimulation as an adjunct to spinal fusion surgery or as a treatment of failed spinal fusion surgery (Goodwin *et al.*, 1999; Mooney, 1990). Likewise, noninvasive electrical bone growth stimulation has been used to treat tibial fractures with delayed union. Data from clinical trials suggest that electrical stimulation is associated with higher healing rates but did not result in clearly improved overall clinical outcomes (de Haas *et al.*, 1986).

Demineralized bone matrix (DBM) has been used to augment autogenous bone grafts for fracture healing as well as for tibial and femoral non-unions. DBM is produced by the acid extraction of bone; the components that remain behind include the BMP's, other proteins and type 1 collagen (Ludwig *et al.*, 2000). To date, DBM's have not been studied in randomized clinical trials as an alternative to autologous bone graft or compared with BMP's in spinal fusion surgery.

More recently, research has been conducted to develop a gene therapy approach to achieve bone formation in spinal fusion, among other applications. The concept of local gene therapy involves the delivery of the gene for an osteoinductive factor rather than the protein itself. There are few published studies to date on this novel approach (Yoon and Boden, 2004; Sandhu *et al.*, 2002).

In sum, effective treatments are currently available to promote improved clinical outcomes in lumbar spinal fusion surgery. These include the current "gold standard" in spinal fusion, autogenous bone graft with or without electrical stimulation, as well as allogeneic bone graft. To date, there have been several randomized clinical trials that conclude that in selected patients undergoing spinal fusion treated with rhBMP-2, clinical and radiological outcomes are comparable to those seen with autogenous bone graft. In contrast, there is insufficient data to conclude that rhBMP-2 is as beneficial as current standard of care for the treatment of open tibial fracture or cervical spinal fusion.

TA criterion 4 is met for rhBMP-2 in spinal fusion.

TA criterion 4 is not met for rhBMP-2 in tibial fracture.

TA Criterion 5: The improvement must be attainable outside the investigational settings.

The use of rhBMP-2 in spinal fusion and open tibial fracture is attainable outside of investigational settings.

TA criterion 5 is met for both indications.

CONCLUSION

Spinal fusion surgery is common in the U.S. with over 250,000 procedures performed annually. Most spinal fusion surgery involves the use of a bone graft, generally autologous bone taken from the patient's hip. This additional procedure can lead to significant co-morbidities such as blood loss, infection, pelvic instability and pain, the latter sometimes for years after the initial procedure (Damien and Parsons, 1991). In addition to these adverse effects, some spinal fusions result in non-union or delayed union and may result in secondary procedures for the patient. Autologous bone graft may also be used in the repair of long bone fractures. Delayed union of tibial fractures is common, reportedly 16% to 60% for less severe fractures and 43% to 100% for more severe fractures (Govender *et al.*, 2002). When healing is delayed in long bone fractures, a second intervention is often required; these interventions are associated with high rates of patient morbidity and reduced quality of life (Govender *et al.*, 2002).

As a consequence of these problems with autologous bone graft and other bone graft substitutes, attention has focused on bone morphogenetic proteins as an alternative to bone grafting. To date, most human trials have examined recombinant human bone morphogenetic protein-2 (rhBMP-2) for promotion of bone fusion in lumbar spinal surgery. This review has addressed the following questions: 1) How does rhBMP-2 compare with autogenous bone graft in spinal fusion surgery and in treatment of open tibial fractures? 2) For which patients is rhBMP-2 a viable alternative? 3) Is it safe?

1. How does rhBMP-2 compare with autogenous bone graft in spinal fusion surgery and in treatment of open tibial fractures? Evidence from four randomized clinical trials suggests that rhBMP-2 promotes spinal fusion rates that are comparable to those obtained with autologous bone graft (Burkus, Gornet *et al.*, 2002; Boden *et al.*, 2000; Boden *et al.*, 2002; Baskin *et al.*, 2003). Three of these trials were in the lumbar spine and one in the cervical spine. An additional trial compared rhBMP-2 and cortical allograft dowels with autogenous iliac crest graft (Burkus, Transfeldt *et al.*, 2002). It is difficult to draw specific conclusions from this trial because of its use of allograft instead of an interbody fusion cage.

The largest of these trials (Burkus, Gornet *et al.*, 2002) report on a multi-center prospective, randomized trial of 279 patients with spinal DJD. All patients underwent the ALIF procedure through an open approach. The experimental group (N= 143) was treated with the LT-Cage with INFUSE (rhBMP-2) for a single level anterior lumbar interbody fusion. The control group was treated with the same cage filled with iliac-crest autograft. All patients had symptomatic single level DJD and disabling low back and/or leg pain of at least six-month duration. There were no differences in Oswestry outcome scores between the experimental and control groups at any point in the follow up over 24 months, with all groups showing significant improvement. Similarly, ratings of back pain improved in both the experimental and control groups and were not significantly different, and the number of patients who

returned to work was also comparable. Patient satisfaction results were also similar; at 24 months 81.2% of the 122 experimental patients and 80.4% of the 108 controls said they were satisfied with their surgical outcomes. At 24 months, the fusion rate was 94.5% in the experimental group as compared with 88.7% in the control. This large study demonstrated that for patients with single-level DJD undergoing anterior inter-body spinal fusion, clinical and radiographic outcomes are similar with rhBMP-2 or autogenous bone graft with interbody cages. They report a small number of adverse events related to the autograft harvest and one-third of patients report pain at the graft site after two years; however, overall patient satisfaction was comparable with the two procedures.

In addition, two small randomized trials (Boden *et al.*, 2000; and Boden *et al.*, 2002) report on outcomes of patients treated with rhBMP-2 in spinal fusion. Although both of these trials used rhBMP-2 to promote spinal fusion, the carriers for the BMP-2 differed in the two trials as did the treatment for the control groups. In the earlier study (Boden *et al.*, 2000) patients were randomized to receive a lumbar inter-body arthrodesis with a tapered cylindrical threaded fusion cage filled with rhBMP-2/collagen sponge (N=11) or the fusion cage and autogenous iliac crest bone (N=3). Whereas in the latter study (Boden *et al.*, 2002) 27 patients undergoing single level posterolateral lumbar arthrodesis for single level DJD with disc degeneration were randomized to one of three treatments: autogenous iliac crest bone graft with Texas Scottish Rite Hospital (TSRH) pedicle screw instrumentation; rhBMP-2 with the internal fixation provided by the TSRH; and rhBMP-2 with no instrumentation. In this trial, the carrier for the rhBMP-2 was biphasic calcium phosphate granules (BCP). Both studies found that rhBMP-2 can induce interbody spinal fusion in humans similar to controls treated with autogenous bone graft without significant adverse consequences.

In the only published trial that examined the use of rhBMP-2 in cervical spine fusion, Baskin *et al.* (2003) report on a randomized clinical trial of rhBMP-2 (INFUSE) as compared with an autogenous iliac crest bone graft placed inside the CORNERSTONE-SR fibular allograft in anterior cervical discectomy and interbody fusion. Eighteen patients were enrolled in the INFUSE arm; of these 10 underwent a single-level fusion and eight a two-level fusion. In the control arm, eight patients underwent a single-level fusion and seven a two-level fusion. Fusion rates in both groups were 100%. They report no device related adverse events. In this study, rhBMP-2 achieved similar clinical and radiographic outcomes compared with autogenous bone graft when combined with a fibular allograft in anterior cervical discectomy and interbody fusion.

There is only one randomized trial to date that compared rhBMP-2 with standard of care in treatment of open tibial fractures (Govender *et al.*, 2002). In this trial, rhBMP-2 appears to be safe and was effective in reducing secondary interventions and promoting fusion. However, the authors do not address the fact

that a significant percentage of patients in both the experimental and control groups were considered treatment failures (35% of patients in the high dose rhBMP-2 group were considered treatment failures compared with 46% in the low dose BMP-2 group and 53% of the control group). Although this study is promising, more research is needed before we can conclude if rhBMP-2 is an alternative to usual care for the treatment of open tibial fractures.

- 2) For which patients is rhBMP-2 a viable alternative? Based on inclusion and exclusion criteria from the trials, patients should have symptomatic single-level degenerative disc disease and symptoms of disabling back and/or leg pain of at least six months duration that has not responded to conservative treatment. Exclusion criteria include patients with known hypersensitivity to rhBMP-2 or Type-1 collagen, patients who are skeletally immature, pregnant, with an active infection at the operative site, or with an allergy to titanium (www.back.com).
- 3) Is it safe? There have been no adverse events attributable to rhBMP-2 reported in the clinical trials to date. In fact, there appear to be more adverse events associated with autogenous bone grafting than with rhBMP-2. In light of the available data, rhBMP-2 appears to be safe provided that it is placed accurately and not allowed to come into contact with decompressed areas, is contained in the region of fusion, and is used with caution in the presence of dural defects (Poynton and Lane, 2002).

In conclusion, primarily on the basis of one large randomized trial, rhBMP-2 when used with an interbody cage appears to lead to fusion rates and clinical outcomes that are comparable to those achieved by the control group consisting of autogenous bone graft patients. Results from three other randomized trials support this conclusion.

RECOMMENDATION

It is recommended that rhBMP-2 carried on a type 1 collagen sponge used in conjunction with an FDA approved device for the treatment of patients undergoing single level anterior lumbar interbody spinal fusion for symptomatic single level degenerative disc disease at L4-S1 of at least six months duration that has not responded to non-operative treatment meets CTAF criteria.

All other uses of rhBMP-2 including its use in cervical spinal fusions and for treatment of open tibial fracture do not meet CTAF criteria.

February 16, 2005

The CTAF panel voted to accept the recommendation as written.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center Medical Advisory Panel has not conducted a review of this topic.

Centers for Medicare and Medicaid Services (CMS)

CMS does not have a national or local decision specific to the use of rhBMP-2.

California Orthopedic Association (COA)

The COA representatives attended the meeting and provided testimony in support of the use of this technology.

California Association of Neurological Surgeons (CANS)

The California Association of Neurological Surgeons has provided the following statement:

The Board of Directors of the California Association of Neurological Surgeons (CANS) supports the use of Recombinant Human Bone Morphogenetic Protein-2 for spinal surgery for selective use in lumbar fusion surgeries.

A CANS representative was not be able to attend the meeting.

Abbreviations used in this assessment:

PLIF - posterior lumbar interbody fusion

TLIF – transforaminal lumbar interbody fusion

ALIF – anterior lumbar interbody fusion

DJD – degenerative joint disease

DDD – degenerative disc disease

IM – intermedullary

L – lumbar spine

S – sacral spine

REFERENCES

1. Barnes B, Rodts GE Jr, Haid RW Jr, Subach BR, McLaughlin MR. Allograft implants for posterior lumbar interbody fusion: results comparing cylindrical dowels and impacted wedges. *Neurosurgery* 2002 Nov; 51(5):1191-8; discussion 1198.
2. Baskin DS, Ryan P, Sonntag V, *et al.* A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate. *Spine* 2003;28(12):1219-1225.
3. Boden SD, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans; a prospective, randomized clinical pilot trial. *Spine*. 2002;27(23):2662-2673.
4. Boden SD, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine*. 2000 Feb 1;25(3):376-81.
5. Bose B, Balzarini MA. Bone graft gel: autologous growth factors used with autograft bone for lumbar spine fusions. *Adv Ther* 2002 Jul-Aug;19(4):170-5.
6. Brislin B, Vaccaro AR. Advances in posterior lumbar interbody fusion. *Orthop Clin North Am* 2002 Apr;33(2):367-74.
7. Burkus JK, Dorchak JD, Sanders DL. Radiographic assessment of interbody fusion using recombinant human bone morphogenetic protein type 2. *Spine*. 2003 Feb 15;28(4):372-7.
8. Burkus JK, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech*. 2002 Oct;15(5):337-49.
9. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. Is INFUSE Bone Graft Superior to Autograft Bone? An integrated analysis of clinical trials using the LT-CAGE lumbar tapered fusion device. *J Spinal Disord Tech*. 2003 16(2):113-122
10. Burkus JK, Heim SE, Gornet MF, Zdeblick TA. The effectiveness of rhBMP-2 in replacing autograft: an integrated analysis of three human spine studies. *Orthopedics*. 2004 Jul;27(7):723-8.
11. Burkus JK, Intervertebral fixation: clinical results with anterior cages. *Orthop Clin North Am* 2002 Apr;33(2):349-57.
12. Burkus JK, Transfeldt EE, Kitchel SH, Watkins RG, Balderston RA. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. *Spine* 2002 Nov 1;27(21):2396-408.
13. Christensen FB, Karlslose B, Hansen ES, Bungler CE. Radiological and functional outcome after anterior lumbar interbody spinal fusion. *Eur Spine J*. 1996;5(5):293-8.
14. Colterjohn NR, Bednar DA. Procurement of bone graft from the iliac crest. An operative approach with decreased morbidity. *J Bone Joint Surg Am* 1997 May;79(5):756-9.
15. Damien CJ, Parsons JR. Bone graft and bone graft substitutes: a review of current technology and applications. *J Appl Biomater* 1991 Fall;2(3):187-208.
16. Devereaux, MW. Neck and low back pain. *Med Clin North Am*, 2003 May; 87(3): 643-662.

17. Einhorn TA. Clinical applications of recombinant human BMPs: early experience and future development. *J Bone Joint Surg Am*. 2003;85-A Suppl 3:82-8.
18. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. *Physiotherapy* 1980 Aug;66(8):271-3.
19. Fowler BL, Dall BE, Rowe DE. Complications associated with harvesting autogenous iliac bone graft. *Am J Orthop* 1995 Dec;24(12):895-903.
20. Femyhough JC, Schimendle JJ, Weigel MC, Edwards CC, Levine AM. Chronic donor site pain complicating bone graft harvesting from the posterior iliac crest for spinal fusion. *Spine* 1992 Dec;17(12):1474-80.
21. Friedlaender GE, Perry CR, Cole JD, Cook SD, Ciemy GF, Zych GA, Calhoun JH, LaForte AJ, Yin S. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions: a prospective, randomized clinical trial comparing rhOP-1 with fresh bone autograft. *J Bone Joint Surg Am* 2001;83(Suppl 1 II):S1151-8.
22. Fritzell P, Hagg O, Wessberg P. Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish lumbar spine study group. *Spine*, 2001, 26(3): 2521-2534.
23. Geesink RG, Hoefnagels NH, Bulstra SK. Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. *J Bone Joint Surg Br*. 1999 Jul;81(4):710-8.
24. Govender S, Csimma C, Genant HK, Valentin-Opran A, Amit Y, Arbel R, Aro H, Atar D, Bishay M, Borner MG, Chiron P, Choong P, Cinats J, Courtenay B, Feibel R, Geulette B, Gravel C, Haas N, Raschke M, Hammacher E, van der Velde D, Hardy P, Holt M, Josten C, Ketterl RL, Lindeque B, Lob G, Mathevon H, McCoy G, Marsh D, Miller R, Munting E, Oevre S, Nordsletten L, Patel A, Pohl A, Rennie W, Reynders P, Rommens PM, Rondia J, Rossouw WC, Daneel PJ, Ruff S, Ruter A, Santavirta S, Schildhauer TA, Gekle C, Schnettler R, Segal D, Seiler H, Snowdowne RB, Stapert J, Taglang G, Verdonk R, Vogels L, Weckbach A, Wentzensen A, Wisniewski T; BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) Study Group. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. *J Bone Joint Surg Am*. 2002 Dec;84-A(12):2123-34.
25. Grauer JN, Beiner JM, Kwon BK, Vaccaro AR. Bone graft alternatives for spinal fusion. *BioDrugs*. 2003;17(6):391-4.
26. Haid RW, Branch CL, Alexander JT, Burkus JK. Posterior lumbar interbody fusion using recombinant human bone morphogenetic protein type 2 with cylindrical interbody cages. *Spine J*, 2004, 4:527-539.
27. Heim SE, Altimari A, Laproscopic approaches to fusion of the lumbosacral spine: latest techniques. *Orthop Clin North Am* 2002 Apr;33(2):413-20.
28. Janssen ME, Lam C, Beckham R. Outcomes of allogenic cages in anterior and posterior lumbar interbody fusion. *Eur Spine J* 2001 Oct;10(Suppl 2):S158-68.
29. Johnson EE, Urist MR. Distal metaphyseal tibial nonunions associated with significant bowing deformity and cortical bone loss: treatment with human bone morphogenetic protein (h-BMP) and internal fixation. *Nippon Seikeigeka Gakkai Zasshi* 1989 May;63(5):613-20.
30. Johnson EE, Urist MR, Finerman GA. Bone morphogenetic protein augmentation grafting of resistant femoral nonunions. A preliminary report. *Clin Orthop Relat Res* 1988 May;(230):257-65.

31. Johnson EE, Urist MR, Finerman GA. Distal metaphyseal tibial nonunion. Deformity and bone loss treated by open reduction, internal fixation, and human bone morphogenetic protein (hBMP). *Clin Orthop Relat Res* 1990 Jan;(250):234-40.
32. Johnson R, Stromqvist B, Aspenberg P. Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumented posterolateral lumbar fusion. *Spine* 2002;27(23):2654-2661.
33. Jung RE, Glauser R, Scharer P, Hammerle CH, Sailer HF, Weber FE. Effect of rhBMP-2 on guided bone regeneration in humans. *Clin Oral Implants Res*. 2003 Oct;14(5):556-68.
34. Kleeman TJ, Ahn UM, Talbot-Kleeman A., Laparoscopic anterior lumbar interbody fusion with rhBMP-2: a prospective study of clinical and radiographic outcomes. *Spine*. 2001;26(24):2751-2756.
35. Kowalski RJ, Ferrara LA, Benzel EC. Biomechanics of bone fusion. *Neurosurg Focus* 2001 Apr;10:1-7.
36. Kurz LT, Garfin SR, Booth RE Jr. Harvesting autogenous iliac bone grafts. A review of complications and techniques. *Spine* 1989 Dec;14(12):1324-31.
37. Lanman TH, Hopkins TJ. Lumbar interbody fusion after treatment with recombinant human bone morphogenetic protein-2 added to 70:30 poly(L-lactide-co-D,L-lactide) bioresorbable implants. *Neurosurg Focus*, 2004, 16(3).
38. Ludwig SC, Kowalski JM, Boden SD. Osteoinductive bone graft substitutes. *Eur Spine J* 2000 Feb;9(Suppl 1):S119-25.
39. MacKenzie EJ, Cushing BM, Jurkovich GJ, Morris JA Jr, Burgess AR, deLateur BJ, McAndrew MP, Swiontkowski MF. Physical impairment and functional outcomes six months after severe lower extremity fractures. *J Trauma* 1993 Apr;34(4):528-38; discussion 538-9.
40. Maniscalco P, Gambera D, Bertone C., *et al.* Healing of fresh tibial fractures with OP-1: a preliminary report. *Acta Biomed Ateneo Parmense*. 2002;73(1-2):27-33.
41. McAfee PC. Interbody fusion cages in reconstructive operations on the spine. *J Bone Joint Surg Am* 1999 Jun;81(6):859-80.
42. Murakami H, Boden SD, Hutton WC. Anterior lumbar interbody fusion using a barbell-shaped cage: a biomechanical comparison. *J Spinal Disord* 2001 Oct;14(5):385-92.
43. Polly DW Jr, Ackerman SJ, Shaffrey CI, *et al.* A cost analysis of bone morphogenetic protein versus autogenous iliac crest bone graft in single-level anterior lumbar fusion. *Orthopedics* 2003;26(10):1027-1037.
44. Poynton AR, Lame JM. Safety profile for the clinical use of bone morphogenetic proteins in the spine. *Spine*. 2002;27(16 suppl):S40-S48.
45. Rengachary SS. Bone morphogenetic proteins: Basic concepts. *Neurosurg Focus*. 2002;13(6):1-6.
46. Riedel GE, Valentin-Opran A. Clinical evaluation of rhBMP-2/ACS in orthopedic trauma: a progress report. *Orthopedics*. 1999 Jul;22(7):663-5.
47. Sandhu HS. Bone morphogenetic proteins and spinal surgery. *Spine*. 2003 Aug 1;28(15 Suppl):S64-73.

48. Sandhu HS, Anderson DG, Andersson GB, *et al.* Summary statement: Safety of bone morphogenetic proteins for spine fusion. *Spine*. 2002;27(16 suppl 1):S86.
49. Sandhu HS, Khan SN. Recombinant human bone morphogenetic protein-2: use in spinal fusion applications. *J Bone Joint Surg Am*. 2003;85-A Suppl 3:89-95.
50. Starr AJ. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures. *J Bone Joint Surg Am*. 2003 Oct;85-A(10):2049; author replies 2049-50.
51. Steffen T, Tsantrizos A, Fruth I, Aebi M. Cages: designs and concepts. *Eur Spine J* 2000 Feb;9(Suppl 1):S89-94.
52. Summers BN, Eisenstein SM. Donor site pain from the ilium. A complication of lumbar spine fusion. *J Bone Joint Surg Br* 1989 Aug;71(4):677-80.
53. Vaccaro AR, Anderson DG, Toth CA. Recombinant human osteogenic protein-1 (bone morphogenetic protein-7) as an osteoinductive agent in spinal fusion. *Spine*. 2002 Aug 15;27(16 Suppl 1):S59-65.
54. Vaccaro AR, Chiba K, Heller JG, Patel TCh, Thalgott JS, Truumees E, Fischgrund JS, Craig MR, Berta SC, Wang JC; North American Spine Society for Contemporary Concepts in Spine Care. Bone grafting alternatives in spinal surgery. *Spine J*. 2002 May-Jun;2(3):206-15.
55. Vaccaro AR, Cirello J. The use of allograft bone and cages in fractures of the cervical, thoracic, and lumbar spine. *Clin Orthop Relat Res* 2002 Jan;(394):19-26.
56. Vaccaro AR, Patel T, Fischgrund J, *et al.* A pilot safety and efficacy study of OP-1 putty (rhBMP-7) as an adjunct to iliac crest autograft in posterolateral lumbar fusions. *Eur Spine J*. 2003;12(5):495-500.
57. Valentin-Opran A, Wozney J, Csimma C, Lilly L, Riedel GE. Clinical evaluation of recombinant human bone morphogenetic protein-2. *Clin Ortho Rel Res*, 2002, 395:110-120.
58. Weinstein JN, Boden SD, An H. Emerging technology in spine: Should we rethink the past or move forward in spite of the past? *Spine*. 2003;28(15 suppl):S1.
59. Wigfield CC, Nelson RJ. Nonautologous interbody fusion materials in cervical spine surgery: how strong is the evidence to justify their use? *Spine* 2001 Mar 15;26(6):687-94.
60. Wolfe MW, Salkeld SL, Cook SD. Bone morphogenetic proteins in the treatment of non-unions and bone defects: historical perspectives and current knowledge. *Univ PA Orthop J* 1999 Spring;12:1-6.
61. Yoon ST, Boden SD. Spine fusion by gene therapy. *Gene Ther*. 2004;11(4):360-367.
62. Zdeblick TA, David SM. A prospective comparison of surgical approach for anterior L4-L5 fusion: laparoscopic versus mini anterior lumbar interbody fusion. *Spine* 2000 Oct 15;25(20):2682-7.