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Bone Morphogenetic Proteins & Spinal Surgery for Degenarative Disc Disease

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

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).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practicing medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

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Executive Summary

Objective

This review is intended to summarize the evidence of safety and effectiveness of a recently licensed spinal fusion surgery device that includes a recombinant human bone morphogenetic protein (BMP).

Bone Morphogenetic Proteins

BMP are proteins that occur naturally in the matrix of human bone and stimulate bone growth. For spinal surgery, BMP must be delivered to the vertebral level where bone growth is desired. The BMP device currently available in Canada comprises a specific cage device and a bovine collagen sponge that delivers BMP. This sponge must be implanted in combination with this specific cage device from the same manufacturer. The device is marketed under the trade name INFUSE™ and provides an alternative to autologous bone graft in spinal fusion.

Review Strategy

Published literature identified through searches of MEDLINE and EMBASE was supplemented with material submitted by the device manufacturer as part of regulatory approval in the United States and available through the public access area of the website of the Food and Drug Administration.

Summary of Findings

Evidence submitted to regulatory bodies in the USA and Canada indicates that the INFUSE™ device appears safe.

The largest number of spinal fusion cases using BMP devices has been for anterior lumbar interbody fusion. Although radiologic fusion occurs at a consistently faster rate among recipients of the BMP device than among recipients of autologous bone grafts, clinical outcomes (pain and disability) appear no different. Regardless of technique, improvements in pain and disability are reported by similar proportions of participants in all the arms of all the trials.

BMP devices for cervical fusion have yet to be approved in Canada but one small scale trial has reported radiologic fusion in all participants in both BMP and autologous bone graft arms and improvement in neck pain scores for all participants.

BMP devices for lumbar fusion are licensed, safe and appear equivalent to autologous bone graft procedures for spinal fusion in terms of patient outcomes with the notable exception that patients undergoing autologous bone graft report pain at the donor site. Laparoscopic approaches yield reductions in postoperative length of stay compared to conventional open approaches.

Objective

This review is intended to summarize the evidence of safety and effectiveness of a recently licensed spinal fusion surgery device that includes a recombinant human bone morphogenetic protein (BMP).

Background

Clinical Need

Degenerative disc disease (DDD) is defined in terms of anatomic, biomechanical, radiological and clinical changes, most frequently noted in the lumbar or cervical spine. DDD is somewhat of a misnomer as it is not a disease *per se*, but rather a degenerative process which, in some people, may cause clinically-evident symptoms. The symptom most commonly reported by patients is pain, exacerbated by activities such as sitting that increase loads on the intervertebral discs. With the growth of magnetic resonance imaging, radiologic evidence of DDD has been described in rough proportion to age i.e. 40% of people at age 40 rising to over 80% among people over age 80. While imaging techniques are a potentially valuable tool, their use has added to diagnostic uncertainty due to false positive findings, since not all persons with radiologic DDD will report pain or other symptoms.

The literature on management of DDD encompasses a wide range of surgical and non-surgical techniques. In the United States, the numbers of person undergoing surgical treatment has expanded rapidly over the last decade.[1]

Surgical management of DDD encompasses a range of procedures intended to provide additional support at the level of the degenerated disc. These can be categorized as spinal fusion, which uses various instrumentation coupled with bone tissue from the patient or a cadaveric donor to link the vertebrae at the level of the degenerated disc to adjacent vertebrae, or spinal arthroplasty. The second of these is addressed in a separate review.

Based on population-based physician claims data, approximately 2000 spinal fusion procedures are performed in Ontario annually. Most are lumbar fusions. This number is expected to grow in the coming decades as the population of older Ontarians grows and thus, the number of surviving people with clinically significant DDD increases. In Ontario, spinal fusion surgery is overwhelmingly performed by physicians trained in either orthopaedics or neurosurgery.

Bone Morphogenetic Proteins

Bone morphogenetic proteins (BMP) are a family of naturally-occurring substances involved in tissue growth and development. Despite their name, BMP are also active in tissues other than bone. In bone, BMP stimulate new bone formation. BMP were first described in 1965,[2] isolated in 1988,[3] and are now available for therapeutic uses via recombinant production. Seven BMP have been identified and described.[4] Commercial clinical use of BMP has advanced most in the area of spinal fusion surgery products for both lumbar and cervical spine indications.

Prior to the introduction of BMPs and various artificial disc technologies (see accompanying review), the surgical approach to clinically-significant DDD focused on fusion of adjacent spinal segments using bone graft with or without instrumentation, typically pedicle screws inserted posteriorly. Rates of fusion varied widely in reported case series, from 45% to 100% in one review.[5] The remaining patients would have no fusion, creating a pseudarthrosis, and these patients were also likely to incur a later complication of 'transitional syndrome' or 'adjacent segment disease' due to increased workload of segments adjacent to the fusion, even if successful.

Over the last two decades, interbody cage devices have come to market that are intended both to support new bone growth and provide mechanical support. These devices are surgically inserted into the spine, using an anterior or posterior approach, and provide a scaffold for autologous bone, typically taken from the patient's iliac crest or allograft bone.[6] Some procedures have combined interbody devices with pedicle screws. For some patients, autologous bone graft procedures appear to confer improved post-operative function when compared to non-surgical alternatives, but also yield pain at the site of bone harvest and incision-related risks, albeit low, at the harvest site.

In the context of spinal surgery, BMP must be delivered to the spine at the vertebral level where repair is desired. In the product currently available, BMP is delivered to the spine via a bovine collagen sponge and this vehicle must be implanted in combination with a specific cage device from the same manufacturer. Research into alternative delivery vehicles, particularly gene therapy, has yet to yield commercially-available products.

Regulatory Status

Two BMP-associated products have been approved for clinical use in Canada. Following Health Canada approval on February 13, 2002, Stryker Biotech markets a product containing BMP-7 (also named OP-1) for use following non-union of long bone fractures. Pilot studies of BMP-7/OP-1 for use in spinal fusion have been reported in the literature.[7,8] However, regulatory approval has yet to occur for this product for spinal fusion use.

Following Health Canada approval on November 1, 2002, Medtronic markets a product containing BMP-2 (INFUSE™). This product was approved for the indication of 'spinal fusion in skeletally mature patients with degenerative disc disease at one level from L4-S1. The patients may have up to Grade 1 spondylolithesis (slippage of one vertebrae in relation to another; grade 1 is least severe) at the involved level. Patients should have had at least six months of nonoperative treatment prior to treatment with the device. The device may be implanted via an anterior open or an anterior laparoscopic approach.' The Canadian approval was based on the same information submitted for Food and Drug Administration (FDA) approval in the United States.[9]

INFUSE™ must be used with the LT-CAGE™ device. The LT-CAGE™ product used with autologous bone graft is approved for use in the United States and was used as the comparison intervention in the randomized trial of equivalence of INFUSE™ that was the basis for marketing approval in both countries.

Literature Review

Objective

This literature review addresses two objectives: to summarize information on the safety of the INFUSE™ product, and to summarize information on the efficacy of this product in comparison to alternatives for spinal fusion.

Questions to Be Answered

1) Given that INFUSE™ is a recombinant biological potentially active at tissue sites other than bone, is there evidence of clinically significant antibody formation or tissue reactions to either the BMP component or the collagen sponge delivery vehicle?
2) How do outcomes with INFUSE™ compare to those with alternative approaches, particularly autologous bone grafts?

Methods

A search of the literature from Medline and Embase covering the period 1966 through November, 2003 yielded 244 citations. Most of these were basic science papers or pre-clinical animal studies. In addition, the public access area of the Food and Drug Administration (FDA) website includes the premarketing approval submission made for INFUSE™, which provided an overview of safety and efficacy data.[10]

For question 1, the safety data submitted by the manufacturer to the FDA provide the largest case series, for they include patients in both published and unpublished series. These safety data are summarized in the results section

For question 2, randomized controlled trials (RCT) and case series comparing the INFUSE™ product to autologous bone graft were identified. A total of 8 studies were reviewed and are summarized in section 2) below.

Results of the Literature Review

Safety

The summary of effectiveness data submitted to the FDA included results on 349 persons who received the INFUSE™ device and 183 controls.

Table 1: Summary of effectiveness data submitted to FDA regarding the INFUSE™ device

	INFUSE™ Recipients	Control Device Recipients
Anti-rhBMP-2 antibodies	2/349 (0.6%)	1/183 (0.5%)
Anti-bovine Type 1 collagen antibodies	18.1%	14.2%
Anti-human Type 1 collagen antibodies	None	None

Although the submission does not comment on this, the difference between the proportions of the two groups with antibodies to bovine collagen does not reach statistical significance ($p>0.25$). In light of the relatively high rate of bovine collagen antibodies among control participants, (who did not receive the bovine collagen used in the INFUSE™ device), it may well be that the antibody assay also detects cross-reacting antibodies. The incremental occurrence of antibodies to bovine type 1 collagen is 3.9%, which translates into 1 per 25 INFUSE™ recipients. The clinical significance of these antibodies is not known. In addition, no cases of 'ectopic, heterotopic or undesirable exuberant bone formation' were reported.

In summary, within the limitations of relatively short follow-up and a few hundred cases, the INFUSE™ product appears to be safe. Both Health Canada and the FDA have directed the manufacturer to complete longer-term follow-up safety studies among patients in whom this device is implanted.

Clinical Outcomes

At this time in Canada, BMP-related devices are approved for lumbar surgery only and thus the review focused on studies of lumbar spinal surgery. One trial reporting use of a BMP device in cervical spinal surgery is also briefly summarized. Regulatory approval for this indication may occur within the next 12-24 months.

Overall, surgery for DDD remains a technique about which there is little consensus. A Cochrane review of studies published through December 31, 1999 identified 16 randomized or quasi-randomized trials and concluded 'there is no scientific evidence about the effectiveness of any form of surgical decompression or fusion for degenerative lumbar spondylosis compared with natural history, placebo, or conservative treatment.'[11]

Since that review, investigators leading a reasonably well-designed Swedish study concluded that lumbar fusion by any of three techniques (posterolateral fusion, posterolateral fusion with internal screw fixation, and posterolateral fusion with internal screw fixation and interbody fusion) yielded statistically significant reductions in patient-reported back pain and disability compared to conservative treatment consisting of physiotherapy. Results among the various surgical groups did not differ significantly, suggesting that no particular approach was superior.[12] In addition, social insurance records were used to assess work disability and the 'net back to work rate' was 36% among surgical patients compared to 13% among the non-surgical patients.[13] Even in this study, however, the authors stress the importance of careful selection of patients for surgery, a view that is widespread in the literature on surgical management of DDD.

In addition, the literature is marked by a lack of consensus on the selection of outcome instruments. Performance analysis of the most widely used instrument, the Oswestry Disability Index, (ODI) has been reported, but estimates of the minimum clinically significant change (MCSC) range almost threefold from 5.2 to 16.3.[14] The ODI asks patients to rate their performance for each of ten items (e.g. sitting, travelling) on a six point ordinal scale, yielding a maximum possible total score of 100.[15]

The authors of the Swedish randomized trial compared ODI results with those of a global assessment by patients and concluded that the MCSC was 10 points. However, this was noted to be within the 95% 'tolerance interval' of 10 points which the authors calculate as a measure of the standard error of the ODI.[14] As a practical matter then, a change of at least 20 points would appear to represent a clinically significant change and encompass all published estimates of MCSC.

In this context, the relevant question becomes one of demonstrating, at a minimum, the equivalence of surgery with the BMP product to prevailing surgical methods. For policy purposes, any relative outcome improvement for the BMP product over prevailing practice is important as an input to comparing cost-effectiveness of the various approaches to surgical management of DDD.

Summary of Medical Advisory Secretariat Review

Following the format of the Medical Advisory Secretariat, the table below summarizes the provenance of the literature describing studies of effectiveness of human BMP-associated devices for spinal fusion surgery.

Table 2: Level of evidence of effectiveness on bone morphogenetic proteins, to November 2003

Level of Evidence	Study Design	Number of Eligible Studies
1	Large randomized controlled trial, systematic reviews of RCTs	1
1(g)	Large randomized controlled trial unpublished but reported to an international scientific meeting	
2	Small randomized controlled trial	4
2(g)	Small randomized controlled trial unpublished but reported to an international scientific meeting	2
3a	Nonrandomized study with contemporaneous controls	
3b	Nonrandomized study with historical controls	
3(g)	Nonrandomized study presented at international conference	
4a	Surveillance (database or register)	
4b	Case series (multi-site)	1
4c	Case series (single site)	
4d	Retrospective review, modelling	
4(g)	Case series presented at international conference	

The tables below summarize the results of these 8 studies. Outcomes have been classified as radiologic (typically assessed by the presence of fusion on computerized tomography (CT) images), patient (pain, disability), and health system & societal (length of stay, rehabilitation costs, return to work).

Table 3: Summary of randomized controlled trial (RCT) literature on bone morphogenetic proteins (anterior lumbar interbody fusion) for degenerative disc disease, to November 2003

Study	Burkus 2003 (16)	Burkus 2002 (17;18)	Boden 2000 (19)	Burkus 2002 (20)
BMP Device	INFUSE™ - LT Cage	INFUSE™ - LT Cage (laparoscopic approach)	INFUSE™ - LT Cage	INFUSE™ machined allograf bone dowel
Number of subjects for device	143	134	11	24
Control device	LT Cage and autologous bone		LT cage and autologous bone	Allograft bone dowel and autologous bone
Number of subjects for control device	136		3	23
Radiologic outcomes	BMP: 120/127 (95%) vs autologous 102/115/(89%) with radiologic fusion at 24 months	-81/86 patients had radiologic fusion at 24 months	11/11 BMP patients and 2/3 LT cage and autologous bone patients had radiologic fusion at 6 months	24/24 BMP patients and 17/19 allograft bone dowel patients had radiologic fusion at 12 months
Patient Outcomes	-BMP: mean pre-operative ODI score=53.7; at 24 months=23.9 -Autologous: mean pre-operative ODI=55.1; at 24 months=23.8			ODI improved for BMP (52.4-18.9) at 24 months vs 55.3-32.8 for allograft bone dowel patients
Health system and societal outcomes	Median time to return to work: -BMP=116 days vs 171 days -Open BMP: 165 days laparoscopic BMP:89 days	-Mean hospital stay=1.3 days vs 3 days for laparoscopic autograft (18)		At 24 months, 66.7% of BMP patients were working vs 35% in control group

Table 4: Summary of studies on bone morphogenetic proteins (posterior lumbar and posterolateral lumbar fusion) for degenerative disc disease, to November 2003

	Posterior lumber interbody fusion	Posterolateral lumber fusion		Cervical Fusion
Study	Alexander 2003 (21)	Luque 2003 (22)	Boden 2002 (5)	Baskin 2003 (23)
Device	INFUSE™ plus Interfix cage	BMP-2 in $CaPo_4$ granules, bilateral implant	BMP-2 in $CaPo_4$ granules ± instrumentation	INFUSE™ plus machined fibular ring graft
Number of subjects for device	34	8	11 patients with instrumentation; 9 without	10 single level, 8 2 level
Control device	Interfix cage and autologous bone graft	BMP-2 in $CaPo_4$ granules, unilateral implant, contralateral autologous bone graft	Autologous bone graft and instrumentation	Machined fibular ring graft plus autologous bone graft
Number of subjects for control device	33	7	5	15
Radiologic outcomes	92.3% fusion in BMP group vs. 77.8% in control group	At 12 months, 8/8 unilateral and 6/7 contralateral BMP treated sides vs 4/7 autografts had fusion	11/11, 9/9 of BMP and 2/5 of control group had fusion at 17 months	100% had fusion at 6 months
Patient Outcomes	ODI scores 'similar' in both groups	8/8 and 6/7 patients with BMP had 'successful' outcomes assessed by ODI	ODI improved in all groups but more rapidly in BMP group	'Less' improvement for neck pain score in 2-level group
Health system and societal outcomes	Mean hospital stay=3.4 days for BMP patients vs. 5.1 days for autograft patients			Operative blood loss less in treatment group vs control group (91.4 vs 123.3 ml)

Summary of Evidence

- Evidence submitted to regulatory bodies in the USA and Canada indicates that the INFUSE™ device appears safe. Long-term safety can only be assessed after additional follow-up as has been mandated by regulatory bodies in both countries.

- The greatest experience with BMP devices for spinal surgery is for anterior lumbar interbody fusion. For this procedure, radiologic fusion occurs at a consistently faster rate among recipients of the BMP device than among recipients of autologous bone grafts. However, clinical outcomes (pain and disability) appear no different. Regardless of the particular technique, improvements in pain and disability are reported by similar proportions of participants in all the arms of all the trials. Reports of health system and societal outcomes are sparse.

- Posterolateral fusion results from animal studies with BMP have been disappointing. New bone formation appears to be impeded by muscular compression of the collagen sponge carrier. These poor results in animal studies for posterolateral fusion have fuelled an ongoing search for a compression-resistant carrier for the BMP.[24] Small scale trials of BMP devices for posterior and posterolateral lumbar fusion report results consistent with anterior fusion trials, namely high rates of radiologic fusion and improvement in patient reports of pain and disability for all techniques.

- BMP devices for cervical fusion have yet to be approved in Canada but one small scale trial has reported radiologic fusion in all participants in both BMP and autologous bone graft arms and improvement in neck pain scores for all participants.

- Taken together, BMP devices for lumbar fusion are licensed, safe and appear equivalent to autologous bone graft procedures for spinal fusion in terms of patient outcomes with the notable exception that patients undergoing autologous bone graft report pain at the donor site. Laparoscopic approaches yield reductions in postoperative length of stay compared to open approaches.

- Excepting the absence of donor site pain, evidence that the INFUSE™ device is superior to autologous bone graft has yet to emerge. Thus, relative costs of BMP devices compared to alternatives may be an important consideration in decisions about the role of BMP devices for lumbar fusion at this time.

Economic Analysis

Given the apparent equivalence of spinal fusion with the INFUSE™ device and spinal fusion with autologous bone graft, one of the challenges in economic analysis is trading off patient preferences for avoiding the pain of the iliac crest bone harvest against the higher cost of the device.

At this time, the availability of this device does not appear to expand the spectrum of indications, nor does it appear to free up substantial resources for increasing surgical case volumes. Contrary to the United States where surplus hospital bed and operating room capacity, coupled with relatively generous Medicare reimbursement for persons over 65 and a higher ratio of neurosurgeons to population appear to be driving rates of surgery, the Canadian context does not have appreciable amounts of hospital or operating room capacity available.

One published cost-effectiveness analysis of the INFUSE™ was identified which stated that the cost of the BMP device was US$3380. These authors, who state they have received grants and other forms of remuneration from the manufacturer of the device, conclude that this is likely to be offset to a significant extent by savings related to other medical resources. The evidence supporting this conclusion does not appear particularly robust.[25]

At this time, given the device's relatively low sales in Canada, price data are likely to overstate costs, since volume purchasing would be expected to lower per-device costs. In addition, laparoscopic approaches, while reportedly shortening hospital stay, may have other instrumentation costs that need to be assessed.

In summary, definitive evidence of a per-procedure cost increment or savings over current approaches to spinal fusion is not available. Data on negotiated device prices could be a useful input to a cost-effectiveness analysis, ideally to be completed within the context of a broader review of surgical management of DDD.

References

1. Abelson R, Petersen M. An operation to ease back pain bolsters the bottom line, too. New York Times 31 December, 2003.

2. Urist MR. Bone: formation by autoinduction. Science, 1965; 150:893-899.

3. Wang EA, Rosen V, Cordes P, et al. Purification and characterization of other distinct bone-inducing factors. Proc Natl Acad Sci USA, 1988; 85:9484-9488.

4. www.hprd.org/report?function=ligand. Accessed December 10, 2003.

5. Boden SD, Kang J, Sandhu H et al. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans. Spine 2002; 27:2662-2673.

6. Blumenthal SL, Ohnmeiss DD. Intervertebral cages for degenerative spinal diseases. Spine J 2003; 3:301-309.

7. Johnsson R, Stromqvist B, Aspenberg P. Randomized radiostereometric study comparing osteogenic protein-1 (BMP-7) and autograft bone in human noninstrumental posterolateral lumbar fusion. Spine 2002; 27:2654-2661.

8. 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; 12:495-500.

9. Personal Communication. Nancy Shadeed, Health Canada. December 17, 2003.

10. Available at www.fda.gov/cdrh/pdf/p000058b.pdf

11. Gibson JNA, Waddell G, Grant IC. Surgery for degenerative lumbar spondylosis (Cochrane Methodology Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd.

12. Fritzell P, Hagg O, Wessberg P, et al. Chronic low back pain and fusion: a comparison of three surgical techniques: a prospective multicenter randomized study from the Swedish lumbar spine study group. Spine 2002; 27:1131-1141.

13. Fritzell P, Hagg O, Wessberg P, et al. Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish lumbar spine study group. Spine 2001; 26:2521-2532.

14. Hagg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. Eur Spine J 2003; 12:12-20.

15. Fairbank JC, Couper J, Davies JB, et al. The Oswestry low back pain disability questionnaire. Physiotherapy 1980; 66:271-273.

16. Burkus JK, Heim SE, Gornet MF, et al. 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; 16:113-122.

17. Burkus JK, Gornet MF, Dickman CA, et al. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. J Spinal Disord Tech 2002; 15:337-349.

18. Sandhu HS. Bone morphogenetic proteins and spinal surgery. Spine 2003; 28:15S:S64-S73.

19. Boden SD, Zdeblick TA, Sandhu HS, et al. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. Spine 2000; 25:376-381

20. Burkus JK, Transfeldt EE, Kitchel SH, et al. Clinical and radiographic outcomes of anterior lumbar interbody fusion using recombinant human bone morphogenetic protein-2. Spine 2002; 27:2396-2408.

21. Alexander JT, Branch Jr. CL, Haid Jr. RW, et al. An analysis of the use of rhBMP-2 in PLIF constructs: clinical and radiographic outcomes. Cited in Sandhu HS. Bone morphogenetic proteins and spinal surgery. Spine 2003; 28:15S:S64-S73.

22. Luque E. Latest clinical results using demineralized bone materials and rhBMP-2: the Mexican experience. Cited in Sandhu HS, Khan SN. Recombinant human bone morphogenetic protein-2: use in spinal fusion applications. J Bone Joint Surg 2003; 85A(S3): 89-95.

23. 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; 28:1219-1225.

24. Sandhu HS, Khan SN. Recombinant human bone morphogenetic protein-2: use in spinal fusion applications. J Bone Joint Surg 2003; 85A(S3): 89-95.

25. Polly Jr DW, 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; 26:1027-1037.