An Osteoblast Differentiation Promoting Compound, TAK-778, combined with $\beta$-Tricalcium Phosphate used for Packing Interbody Fusion Cages

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ABSTRACT

A synthetic 3-benzothiepin derivative, TAK-778, promotes osteoblast differentiation. If a mixture of TAK-778 and $\beta$-tricalcium phosphate ($\beta$-TCP) can be a substitute for autografts used for packing interbody fusion cages, donor-site related complications should be avoided.

The lumbar vertebrae from L1 to L5 were exposed in 8 dogs using a posterolateral approach, and discectomy and interbody cage fusion were performed in three disc spaces. In group A, the cage was filled with autograft bone, in group B with $\beta$-TCP, and in group C with $\beta$-TCP and TAK-778. The lumbar spine was excised at 16 weeks post-surgery, and mechanical, microradiographical and histological evaluations were made.

The microradiographical and histological examinations revealed four fusions in eight operations in group A (50.0%), three in group B (37.5%), and five in group C (62.5%). The mean percentage of trabecular bone area in the cages was 53.4% in group A, 45.6% in group B and 64.4% in group C.

Although the effect was not significant, addition of TAK-778 to $\beta$-TCP had some beneficial influence and there was a trend toward an improved fusion status in cages filled with $\beta$-TCP and TAK-778. $\beta$-TCP combined with TAK-778 could be used as a substitute for autografts in clinical spine surgery, especially for those patients who are anticipated to have a poor graft bone status.

Key word: TAK-778, Tricalcium Phosphate, Cervical Interbody Fusion Cage, Autograft, Osteoinduction

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INTRODUCTION

Since Cloward [5], and Smith and Robinson [28] introduced the anterior approaches to the cervical spine, various methods have been introduced to stabilize the cervical spine and preserve the physiologically natural alignment. With most of these methods, an autograft is used to achieve cervical anterior interbody fusion. However, good results are not obtained for multi-level fusions, and graft collapse and graft expulsion have been noted [2]. In addition, the use of autogenous iliac crest grafts

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induces donor-site related complications [2,37] such as wound infection, pelvic fracture, ureteral injury, and donor site pain. The morbidity rate has been reported to be as high as 30% [2,37].

Bagby [6] introduced the idea of an interbody fusion cage made of metal. A cage is designed to autostabilize, so additional fixation by an anterior cervical plate is not necessary [21]. Autogenous bone is packed in its inner space to increase the rate of union between adjacent vertebral bodies. The cage demonstrates good clinical outcomes [10,12,21] and its usage in anterior cervical interbody fusion has been established. However, donor-site related complications still remain to be solved, even though the harvested amount of autogenous bone is reduced.

Several materials have been examined as a substitute for autogenous bone grafts in anterior cervical interbody fusion surgery, such as allografts [20], ceramics [17,32], and a variety of osteoinductive agents [3]. Some of them have been used clinically and have given acceptable surgical results. However, all have their problems, such as allograft-related infection or immunologic rejection, variability among ceramics in mechanical strength, bioresorability, and osteoconductivity, uncertain safety of bone morphogenetic protein (BMP), and so on. In our previous study [27], synthetic beta-tricalcium phosphate (Ca3(PO4)2) (\(\beta\)-TCP) was examined. When \(\beta\)-TCP without any additives was used, no significant differences were observed between interbody fusion cages filled with autogenous bone and \(\beta\)-TCP in the examinations of microradiographs and histological sections [27]. Thus, the results suggest that \(\beta\)-TCP is a good candidate as a substitute for autogenous bone for the interbody fusion cages. However, satisfactory results were not obtained in the rate of contiguous trabeculation spanning the fusion site from the adjacent vertebral bodies in either experimental group.

Notoya et al [25] have evaluated the pharmacological profile of TAK-778 ([2R,4S]-(-)-N-(4-diethoxyphosphorylmethyl)-1,2,4,5-tetrahydro-4-methyl-7,8-methylene-dioxy-5-oxo-3-benzothiepin-2-carboxyamide] (mw 505.53) in osteogenesis and showed that it markedly promoted osteogenesis in vitro and enhanced new bone formation during skeletal regeneration and bone repair in vivo. Oda et al [26] also reported that it was a potential agent to stimulate osteogenesis. TAK-778-containing sustained-release microcapsules (MC), TAK-778 / poly (d,l-lactic / glycolic) acid (PLGA)-MC, have been shown to increase the area of newly formed bone in a rat skull defect model, and a rabbit tibial fracture model [25].

In this study, the potential of TAK-778 combined with \(\beta\)-TCP was examined as a substitute for autografts, used for packing interbody fusion cages, through biomechanical, radiographical and histological evaluations.

MATERIALS AND METHODS

<Study Design>
Posterolateral lumbar interbody fusion of three consecutive levels was performed, using titanium cages in 8 adult male colony-reared hounds. The first cage was filled with autograft bone (group A), the second with \(\beta\)-TCP (group B) and the third with \(\beta\)-TCP combined with TAK-778 (group C). Mechanical, microradiographical and histological examinations of surgical sites were performed at 16 weeks post-surgery. This protocol was approved by the Animal Care and Use Committee of the Institute for Frontier Medical Sciences of Kyoto University.

<Lumbar Interbody Fusion>
A total of 8 adult male hounds (7-9 months old, 17-18 kg in body weight) from Nosan:NRB (Yokohama, Japan) were used in the current investigation. They were housed in an established animal facility for a minimum of 1 week before surgery to determine their condition and allow acclimatization. Each animal was placed under sedation with an intramuscular injection of ketamine (15 mg/kg body weight) and xylazine (2.5 mg/kg body weight). A venous route was then obtained and kept with a drip infusion of normal saline. Through the venous route, 3 mg/kg body weight of sodium pentobarbital was given. The dogs were then intubated, and intravenous sodium pentobarbital was intermittently administered to maintain a general anesthesia. Prophylactic antibiotics (1g of
intravenous cefalotin) were administered perioperatively. The dogs were shaved, placed in a left decubitus position and prepared in a standard surgical fashion. A dorsal paramidline incision was made on the right side. The ipsilateral lumbar mastoid articular process was identified and exposed. This bony process is about 1cm long, contains cancellous bone and is located at the base of the spinous process. Intraoperative fluoroscopy was performed to determine the adequate operating lumbar level. Four consecutive disc spaces (L1/2, 2/3, 3/4, 4/5) were then revealed more thoroughly. Titanium cages of 6-mm-diameter (CCM®) and a new type of instrumentation set were kindly donated by A-spine (Oakland, CA). The CCM cage is a threaded, hollow, porous, titanium-alloy cylinder, which has an open anterior and posterior end. At first, the disc spaces and vertebral endplates were reamed. The reamed channel was tapped, and an interbody fusion cage was inserted into three consecutive disc spaces. At the end of the insertion, the handle must be perpendicular to the spinal axis and parallel to the disc space, to have a well positioned hole in the cage.

It divided into three experimental groups. Cages packed with autogenous bone graft were used in group A, cages packed with \( \beta \)-TCP in group B, and cages packed with a mixture of \( \beta \)-TCP and TAK-778 in group C. A disc space without any treatment, that is, a natural disc space, was also examined as a control. All four models were prepared in each animal and the order of the consecutive disc spaces used for each model was systematically rotated in the series experiment. Autogenous bone graft was collected from adjacent mastoid articular processes, which contained cancellous bone. Then, 0.3 g of \( \beta \)-TCP granules (OSFERION®), purchased from Olympus (Tokyo, Japan) was used to pack the cage for groups B and C. Microcapsules containing TAK-778 were kindly donated by Takeda Chemical Industries Co., Ltd. (Osaka, Japan). Each microcapsule consists of a biodegradable polymer, PLGA, with a copolymer ratio of 85:15 (mol / mol) and an average molecular weight of 14,000 (Wako Pure Chemical Industries, Ltd., Osaka, Japan) [13,14]. The release of TAK-778 in vivo from the microcapsules was observed for over 4 weeks after local injection [13,14]. Microcapsules (5 mg TAK-778 / 60 mg MC) were mixed with 0.3 g of \( \beta \)-TCP granules and then packed into the cage. The amount of TAK-778 in this experiment was determined in consideration of previous studies using rats [13,25] and rabbits [15,16]. Fascia and muscle layers were approximated with a 3-0 silk suture and the skin was closed with a 3-0 nylon suture.

<Postoperative Care>

After surgery, the animals were observed until fully recovered from the general anesthesia. Activity was allowed in an indoor pen. Eating habits, ambulatory activities, and the wound condition were checked daily. At 16 weeks post-surgery, the animals were put down using an intravenous injection of an excess amount of sodium pentobarbital. The lumbar spine then was excised and the specimen was radiographed.

<Radiographic Analysis>

Lateral and anteroposterior radiographs of the lumbar spine were obtained immediately after surgery and thereafter the location of the cages was examined radiographically at 2, 4, 8, 12 and 16 weeks. Radiographs of the lumbar spines excised at 16 post-operative weeks were analyzed for the absence or presence of lucent lines surrounding each cage. If a lucent line was seen on either the anteroposterior or lateral radiograph, it was judged that there is no calcification bridging the cage and adjacent vertebral bodies. This interpretation is used commonly in the clinical settings [19]. All final interpretations were reported by the attending radiologist.

<Biomechanical Testing>

In preparation for nondestructive biomechanical testing, the removed lumbar spine was cleaned of soft tissues and disarticulated into two operative motion segments and one adjacent intact motion segment for a control. Care was taken to preserve all ligamentous attachments and not to disrupt the integrity of the fusion site. Both ends of the operative motion segments were fixed to a custom-made biomechanical testing device that was designed to measure the
The percent area of bone formed between upper and lower vertebral body through the cage (area A)

![Graph showing the percent area of bone formed between upper and lower vertebral body through the cage (area A) in three experimental groups.]

Fig.1: The percent area of bone formed between upper and lower vertebral body through the cage (area A) in three experimental groups.

![Anteroposterior View and Lateral View radiographs of a lumbar spine excised at 16 post-operative weeks. The radiograph showed lucency (arrow) and no lucency (arrow-head) around the cages.]

Fig.2: Anteroposterior (left) and lateral (right) radiographs of a lumbar spine excised at 16 post-operative weeks. The radiograph showed lucency (arrow) and no lucency (arrow-head) around the cages.

stiffness of axial rotation, flexion-extension, and lateral bending. Functional spinal unit stiffness was calculated as the peak value of the load (newton or newton-meter), which was sensed by a load cell unit (Kyowa Dengyo, Tokyo, Japan), divided by the corresponding segmental displacement (millimeter or degree). In total, 24 disc spaces for the experimental groups (8 in each group) and 8 disc spaces for the control group were biomechanically analyzed. The peak stiffness is used for quantifying the overall rigidity of the functional spinal unit. Although it must be recognized that the nonlinear elastic behavior of the functional spinal unit can be further divided into neutral zones and a range of motion, these features were not included for discussion in this study.

<Histologic and Microradiographic Analysis>

After nondestructive biomechanical testing, specimens were removed from the testing device. They were fixed with 20% formaldehyde, embedded into polyester resin (Showa Koubunshi, Tokyo, Japan), and cut into sagittal sections of about 400 μm
thickness at the level of the fusion site using a diamond saw (Maruto, Tokyo, Japan). These slices were then ground to a thickness of 90 \( \mu \)m using a microgrinding device (Maruto, Tokyo, Japan). A sagittal microradiograph of the specimen was obtained in a HITEC type HX-100 unit (HITEC CO., LTD., Tokyo, Japan). The specimens were placed 30 cm from the beam source and exposed for 120 seconds, at a peak of 25 kV and 3 mA. The area of bone formed between upper and lower vertebral body through the cage (Fig. 1) was evaluated from the resultant high resolution microradiographs using a computerized histomorphometric system (NIH Image Analysis). It was also used for evaluation of the fusion status. A successful fusion was implied by the existence of contiguous trabeculation stretching through the cage from the adjacent vertebral bodies. Next, the specimens were stained with toluidine blue for histological examination.

**<Statistical Analysis>**

All stiffness data is shown as a mean with a standard deviation. Statistical analysis included a one-way analysis of variance using Fisher's probability of least significant difference (PLSD) for multiple post hoc group comparisons. Statistical results at \( P<0.05 \) were considered significant.

**RESULTS**

**<Surgical Procedure>**

All 8 dogs successfully underwent an operation and survived without any difficulties during 16 postoperative weeks. Neither vascular nor neurologic complications were observed. No complication related with surgical site infection was detected.

**<Radiographic Results>**

None of the cages were displaced during the postoperative observation period. Radiographs of lumbar spines excised at 16 post-operative weeks were analyzed for the absence or presence of lucent lines surrounding each cage to determine the fusion rate. Figure 2 shows a radiograph in which a lucent line is observed as indicated by an arrow. Lucency around the cage was seen in three cases (37.5%) in group A, four cases (50.0%) in group B, and only one case (12.5%) in group C. So, from the radiographic studies, the fusion rate (per disc space) was 62.5% for group A, 50.0% for group B and 87.5% for group C.
<Microradiographic and Histologic Results>

No TCP remnant was recognized in any cages after 16 post-operative weeks. The combined indications obtained from examinations of microradiographs and histologic sections (Fig.3, Fig.4) demonstrated four fusions in eight operations (50.0%) in group A, three in eight (37.5%) in group B and five in eight (62.5%) in group C. These values are lower than the fusion rates estimated from macroscopic radiographs of the lumbar spines in all of the experimental groups. Although this discrepancy was not explained clearly, it revealed that the absence of lucent lines surrounding a cage does not always mean good bone formation between the cage and adjacent vertebral bodies. However, the radiographic and microradiographic results were well correlated. This result is very important because we can use radiography only to judge bone fusion in the clinical settings. In most cases, a cage that had lucency on the radiogram was recognized to be a failed fusion from the microradiogram. The mean percent area of trabecular bone formed between upper and lower vertebral body through the cage that was estimated from the resultant high resolution microradiographs using NIH Image Analysis was 53.4 ± 26.3% in group A, 45.6 ± 31.8% in group B and 64.4 ± 25.4% in group C on histomorphometry (Fig.1). From figure 1, it is suggested that more than 55% area of bone formed between upper and lower vertebral body through the cage would be fusion case.

<Biomechanical Analysis>

Figure 5 shows representative data of nondestructive biomechanical testing of the operated lumbar functional spinal units. With these nondestructive methods, fusion site disruption was not observed in any of the specimens tested. The test revealed that the three experimental groups (group A, B and C) demonstrated significantly higher values of functional unit stiffness than those observed in natural intact spine with all three testing methods. The lumbar spines with a cage with a successful arthrodesis tended to be stiffer than those with a cage with less trabecular bone formation in all experimental groups as seen in Figure 6. Statistically, there was a significant difference in stiffness between fusion cases and nonunion cases with all three testing methods: axial rotation, p<0.001; flexion-extension, p<0.001; and lateral bending, p<0.001.

DISCUSSION

The need for fusion after anterior cervical discectomy and osteophyctomy remains controversial [29]. The expected clinical advantages of fusion [31,37] are the immediate stabilization of the cervical spine and preservation of an adequate interbody space and physiological lordosis. On the other hand, in patients who undergo anterior cervical interbody graft fusion, the specific complication is bone graft resorption which causes disc space narrowing and collapse [2], and thus the preoperative cervical symptoms recur. Other complications are caused by graft expulsion, pseudarthrosis, even in the hands of experienced surgeons [30].

To avoid these complications and to achieve immediate and better stability, the anterior cervical fusion cage has been developed [6,10,11,20]. The CCM cage successfully maintained the stability of the disc space, although the animals began to run and jump within a few hours after surgery. Autogenous iliac bone is used for cage packing to further increase interlocking strength between the cage and vertebral.
bone. However, autologous iliac bone is not always of good quality, especially in the elderly or those who have undergone hemodialysis for a long time or been smokers. The use of autogenous iliac crest bone may also be associated with graft-site related morbidity [2,37]. So in our previous study, we examined \( \beta \)-TCP as a substitute for autografts used for packing interbody fusion cages in the canine lumbar spine [27].

Synthetic ceramics, such as hydroxyapatite, \( \beta \)-TCP and biphasic calcium phosphate, have been commonly used as a bone substitute not only in dental [22], otological [9], plastic [12] and orthopedic [4] surgery but also in anterior cervical fusion surgery [17]. The various ceramics differ in mechanical strength, biodegradability, osteoconductibility, and so on. We selected \( \beta \)-TCP for the interbody fusion cage [27], because it shows good tissue tolerance with no immunological or toxic reactions, has good biocompatibility, and characteristics of absorption, and is effectively replaced by natural bone in an appropriate period of time [4,7,8,22,23].

A large number of studies reported that BMPs can accelerate bone fracture repair and also engineer dentin regeneration. Although BMPs are expected to be useful and biologically active peptides in

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**Fig. 6:** Results of biomechanical tests.

6A: axial rotation stiffness (mean±standard deviation)
6B: flexion-extension stiffness (mean±standard deviation)
6C: lateral bending stiffness (mean±standard deviation)

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<th>A</th>
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orthopedic [38], plastic and dental surgery [36] they
are still difficult to use routinely in a clinical setting.
BMPs play crucial roles in the various stages of
ontogeny and thus it is difficult to fully deny their
induction of serious side effects even in adults [35].
In addition, BMPs induce ectopic bone formation
when used in high doses [18,33,34].

In this study, we examined a synthetic chemical,
TAK-778. Notoya et al [24] have demonstrated that
ipriflavone (7-isopropoxy-isoflavone; mw 280.32), a
derivative of natural isoflavone isolated from alfalfa
(Medicago setiva L.), stimulates the formation of
bone-like nodules in rat bone marrow stromal cells.
Also, by examining structure-activity relationships,
Oda et al [26] have recently found a novel series of 3-
benzothiepin-2-carboxyamides having a 4-(di-
lalloxy-phosphorylmethylphenyl) moiety, derived from
ipriflavone as the lead compound. These compounds
induce potent cellular alkaline phosphatase activity in
rat bone marrow stromal cell culture. Notoya et al
[25] have further evaluated the pharmacological
profile of one of the most potent compounds, TAK-
778 [(2R,4S)-(+)N-(4-dihaloxyphosphorylmethyl)1,2,4,5-tetrahydro-4-methyl-7,8-methylene-dioxy-5-
oxo-3-benzothiepin-2-carboxamide] (mw 505.53), in
osteogenesis and showed that it promoted
osteogenesis in vitro and enhanced new bone
formation during skeletal regeneration and bone
repair in vivo. TAK-778 stimulated the expression of
the osteoblast phenotype, that is, alkaline phosphatase
activity, soluble collagen release, and osteocalcin
secretion, with a slight increase in cellular
proliferation in the presence of dexamethasone in rat
bone marrow stromal cell culture. The process of
bone-like nodule formation in vitro resembles that of
intramedullary bone formation in repair of bone
marrow tissue after local injury: pluripotential
osteoprogenitor cells in the marrow stroma proliferate
and differentiate to functional osteogenic cells,
resulting in the formation of woven bone in the bone
marrow [1]. TAK-778-containing sustained-release
microcapsules (MC), TAK-778 / poly (d,l-lactic / glycolic)
acid (PLGA)-MC, have been shown to
increase the area of newly formed bone in a rat skull
defect model, and a rabbit tibial fracture model [25].

The superiority of TAK-778 to BMPs is that it
does not induce ectopic bone formation [25,26].
Therefore, if too much TAK-778 is applied in spinal
fusion surgery, there would be little possibility of
nerve root compression by newly generated bone
masses. TAK-778 was supplied to us in a microcapsulated
form. It is available only for experimental use and
commercially unavailable at present. The PLGA
microcapsules were designed to release the compound
over 4 weeks [13,14] for the following reasons [25].
First, callus formation occurs during 4-40 days
postfracture after the immediate inflammatory
reaction-hematoma stage. Second, the in vitro
activities of TAK-778 were dependent on the duration
of exposure to the compound. The new bone
generated in response to TAK-778 was woven and
normally mineralized [15,16,25]. The amount of
TAK-778 at the application site progressively
decreased for 4 weeks after administration, and the
serum level of TAK-778 was sustained over the same
period [13,14].

There are significant advantages to using TAK-
778 / PLGA-MC and β-TCP as an auto- or
allograft bone substitute because it allows for an
unlimited supply of material that is free of infectious
agents or immunologic proteins. This composite
material eliminates the need to harvest autogenous
bone and may be convenient to use clinically.

Although a canine model was used in this study,
the fusion rate would most likely be higher in humans
because the animals in our model were not upright.
Although the autogeneous bone used to pack the
cages in our study contained cancellous bone, it is not
equivalent to iliac crest bone. So we must take the
different qualities of these two kinds of bones into
consideration.

In our previous study [27], interbody fusion cages
filled with β-TCP demonstrated comparable
efficacy to cages with autogenous bone in
examinations of microradiographs and histological
sections or in the nondestructive mechanical test. In
the present study, we found that the interbody fusion
cages, which were filled with β-TCP combined with
TAK-778, provide a higher histologic union rate and
induced stiffer lumbar spines than cages filled with
autogenous bone or β-TCP alone as seen in Figure

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6. Actual data of mean radiographical fusion, mean stiffness and mean percentage of trabecular bone formation area rank equal in order, that is, first in the \( \beta \)-TCP and TAK-778 group, second in the autograft bone group and third in the \( \beta \)-TCP group. The addition of TAK-778 to \( \beta \)-TCP had an additional beneficial influence and there was a trend toward improved fusion status in cages filled with \( \beta \)-TCP and TAK-778. This suggests that \( \beta \)-TCP and TAK-778 could be used as a substitute for autografts in clinical spine surgery, especially for those patients who are anticipated to have a poor graft bone status, such as the elderly or those who have undergone hemodialysis for a long time or been smokers.

**CONCLUSIONS**

The radiographic, mechanical, microradiographical and histological grades of experimental groups rank equal in order, that is, best in the \( \beta \)-TCP and TAK-778, followed by the autograft bone, and worst in the \( \beta \)-TCP group. Addition of TAK-778 to \( \beta \)-TCP gives additional beneficial effects and there was a trend toward improved fusion status in cages filled with \( \beta \)-TCP and TAK-778. \( \beta \)-TCP and TAK-778 could therefore be used as a substitute for autografts in clinical spine surgery, especially for those patients who are anticipated to have a poor graft bone status.

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The authors address the efficacy of TAK-778 to enhance spinal interbody fusion with a titanium cage containing $\beta$-tricalcium phosphate in a canine model. TAK-778 is a novel osteoblast differentiation-promoting compound that has an osteogenic potential to accelerate bone regeneration and repairment in bone defect or fracture. This is a new avenue in the field of spine surgery and neurosurgery. The present study reports advanced fusion with interbody cages filled with TAK-778 and $\beta$-tricalcium phosphate compared with that of cages containing autograft or $\beta$-tricalcium phosphate alone. Although the statistical analysis showed no significant difference, this is an important report on the effect and safety of TAK in in vivo. The authors indicate the possibility of using a new alternative substitute for autograft, which avoids donor site complications and facilitates bone fusion even in aged patients. To examine the efficacy of TAK-778, further study is strongly encouraged in other experimental setting.

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Since Bagby GW, et al. introduced a metallic interbody fusion cage for the degenerative discogenic diseases in the cervical spine in 1984, cervical fixation using this technique has increased the popularity in Japan. It is true that bone fusion is essential in any kind of spinal instrumentation, however harvesting bone grafts from the iliac crest has serious clinical complications such as donor site pain, wound hematoma or ilium fracture. In addition, majority of the patients with the degenerative disc diseases is elderly, so harvesting good bone grafts is not always easy. Various substitutes including allografts, ceramics or BMPs have been introduced as graft materials. Unfortunately, allografts and BMPs are not clinically available in Japan. Ceramics have uncertain effect of osteoconductivity. Therefore, the authors proposed the use of beta-TCP and TAK-778 for the better fusion in performing cervical fixation with interbody fusion cages, and showed it's superiority microangiographically and histologically in their canine experimental model. Furthermore, TAK-778 dose not have a potential excessive ectopic bone formation causing re-compression of the spinal cord. I have the same feeling that a substitute for autografts is appreciated in patients with a poor graft bone status or in eliminating donor site complications. I hope that the authors will provide the further detailed data to confirm their experimental results.