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Review

Regeneration of the Skeleton by Recombinant Human Bone Morphogenetic Proteins

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A B S T R A C T

Recombinant human bone morphogenetic proteins (rhBMPs) have past a long journey in human orthopaedic surgery during the last 15 years. From the first reports of the use of rhBMPs in hostile environments such as critically-sized bone defects, avascular femoral head necrosis, unstable thoracolumbar vertebral fractures, instability between the atlas and axis due to rheumatoid arthritis; over the use for nonunions of long bones and the scaphoid, reconstructive and revision surgeries of the hip, acute fractures, allograft nonunions, congenital pseudarthrosis, and various approaches of lumbar and cervical spine fusions, rhBMPs overgrow to a safe and reliable device in the treatment of open tibial shaft fractures, nonunions of long bone fractures, anterior lumbar interbody fusion and revision posterolateral lumbar fusions. Systematic review of the published literature of rhBMPs is presented.

Key words: *recombinant human bone morphogenetic proteins (rhBMPs), orthopaedic applications*

Introduction

In 1965, Marshall R. Urist made the seminal discovery that the extracellular matrix of bone contains the capacity to induce new bone formation by implanting a substance into extraskeletal sites in a host[1] which he later named bone morphogenetic protein (BMP).

By 1988, the molecular clones had been characterized, as well as the activities associated with this protein, and the amino acid sequence from a highly purified preparation from bone was derived. This led to the isolation and expression of complementary DNAs, which were recognized as members of the transforming growth factor-β supergene family. In humans, two of 15 isolated BMP molecules have been particularly well described, BMP-2 and BMP-7 (also named osteogenic protein-1, OP-1). Both of them have been isolated, sequenced, and manufactured using the recombinant DNA techniques what allowed a reproducible production of a single BMP, at a known concentration and purity.

After many animal studies which have illustrated the potential of BMPs to repair critical-size defects, accelerate a union, enhance spinal fusions, enhances the bone graft incorporation and the implant fixation, increases the remodeling and bone ingrowth of bone grafts and bone substitutes, and heal articular cartilage lesions, the clinical application of BMPs started[2].

The composite device consisting of rhBMP-2 carried by an absorbable collagen sponge was trademarked as INFUSE (Medtronic Sofamor Danek, Memphis, TN, USA) and the one consisting of rhBMP-7 (OP-1) pre-mixed by bovine collagen was trademarked as OP-1 Implant (Stryker Biotech, Hopkinton, MA, USA). The addition of 230 mg carboxymethylcellulose (CMC) to the OP-1 Implant forms OP-1 Putty (Stryker Biotech, Hopkinton, MA, USA).

The purpose of this work is to give a systematic review of the use of rhBMPs in regeneration of the skeleton.

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Nonunions and Bone Defects of Long Bones

Despite the intrinsic regenerative and reparative capacity of bone and the ongoing advances in the treatment of fractures, impaired healing continues to be one of the severe complications of fractures.

Cancellous autogenous bone grafting (AUBG) remains the gold standard procedure used to promote union by stimulating the local biology at the nonunion site. However, its limited available quantity, as well as the donor site morbidity and complications, dictated the need for the development of alternatives in the management of nonunions and often present bone defects.

The corner stone of rhBMP efficacy in humans was set by Geesink et al.[3] (Table 1). In a previously validated critically-sized human fibular defect created during high tibial osteotomy for osteoarthritis of the knee, 6 patients were treated with rhBMP-7 combined with a collagen type-I carrier and the other 6 patients were treated with collagen type-I alone. Five of 6 patients showed formation of new bone 6 weeks after rhBMP-7 implantation. None of the fibular defects treated with only the collagen carrier went on to heal.

At 9 months following the insertion of an intramedullary rod accompanied by rhBMP-7 or AUBG, 81% of the rhBMP-7 treated tibial nonunions (n=63) and 85% of those receiving AUBG (n=61) were judged by clinical criteria to have been treated successfully[4]. There was no statistically significant difference in outcome between the two groups of patients at the same time point.

A successful use of rhBMP-7 in the treatment of more than 20 long bone nonunions was reported[5]. Later, Pecina et al. additionally reported on a preamputation nonunion of the distal tibia in a patient with 11 previously failed surgical treatments who healed after implantation of rhBMP-7 and external fixation by Ilizarov[6].

Two clavicular nonunions healed at three months after the treatment with rhBMP-7, iliac AUBG, internal fixation and electrical stimulation[7].

In addition to rhBMP-7 all the patients with atrophic humeral diaphyseal nonunions[8] went on to an eventual union including the nonunions in 11 patients treated with rhBMP-7 without iliac AUBG.

Both, clinical and radiological union occurred after the treatment with rhBMP-7 and different fixation procedures in 24 upper and lower limb atrophic nonunions (92.3%) and in two of them after second rhBMP-7 application, within a mean time of 4.2 months and 5.6 months, respectively[9].

In evaluation of the type of indications and the efficacy of clinical applications of rhBMP-7 in the United Kingdom, the overall success rate was 82% (535 cases)[10]. In 74% of cases, the application was combined with AUBG, whilst in 23% cases rhBMP-7 was used alone.

Radiographic successful outcome was recorded in 88 patients (83.8%) with nonunion in various sites with the average healing time of 7.9 months[11].

The rhBMP-7 implant (n=16) was more efficacious that platelet rich plasma (PRP) preparations (n=13) in the treatment of long bone nonunions or/and critical size bone defects, as there was a significant failure rate of 38.5% versus 6.2% between the PRP and rhBMP-7 treated patients, respectively[12].

Scaphoid Nonunion

The patients with scaphoid avascular and necrotic proximal pole nonunions were randomly assigned to three treatment groups: (1) iliac AUBG (n=6), (2) iliac AUBG + rhBMP-7 (n=6), and (3) iliac allogeneic bone graft (ALBG) + rhBMP-7 (n=5)[13]. The rhBMP-7 improved the performance of both AUBG and ALBG and reduced the radiographic healing time to 4 weeks as compared to 9 weeks in group 1. Helical CT scans and scintigraphy showed that in rhBMP-7-treated patients sclerotic bone was replaced by a well-vascularized bone.

Congenital Pseudarthrosis of the Tibia

Treatment of congenital pseudarthrosis is challenging and often disappointing and unsatisfactory outcomes may lead to amputation[14].

The use of rhBMP-7 in conjunction with intramedullary stabilization (two rods and three 2-mm K-wires) and AUBG in a boy with atrophic tibial pseudarthrosis associated with neurofibromatosis with 9 unsuccessful previous operations resulted with the bone union after 5 weeks[15].

Another successful healing was reported 5 months after radical resection of sclerotic tibial segments, Ilizarov fixation and administration of rhBMP-7 in a patient with congenital pseudarthrosis of the tibia after 12 unsuccessful surgeries[16].

Allograft Nonunions

The results of 6 femoral allograft nonunions in patients who underwent resection of malignant bone tumors and allograft bone transplantation were analyzed one to 5 years following application of either rhBMP-2 (n=3) or rhBMP-7 combined with corticocancellous allograft (n=3) at the nonunion site[17]. There was neither healing of allograft fractures, nor union of allograft-host junction at a minimal follow-up of 12 months. There was an elongation or enlargement of the callus from the host. There was no tumor recurrence with the use of rhBMPs after a mean follow-up of 39±25 months.

Fractures

The treatment of open tibial shaft fractures continues to be associated with high rates of delayed union and nonunion[18]. Thus, the goal of the initial fracture treatment should be to increase the likelihood of union and reduce the risk and cost of secondary procedures.

TABLE 1
LIST OF PUBLICATIONS RELATED TO TREATMENT OF LONG BONE NONUNIONS, BONE DEFECTS, SCAPHOID NONUNIONS, CONGENITAL PSEUDARTHROSIS OF THE TIBIA, ALLOGRAFT NONUNIONS, FRACTURES, OSTEONECROSIS OF THE FEMORAL HEAD, RECONSTRUCTIVE AND REVISION SURGERY OF THE HIP WITH RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEINS (rhBMPs) INCLUDED

1st Author and Year	Type of the Study	Localization and kind of defect	Sample Size	rhBMP/Carrier	Dose of rhBMP
Geesink[3] (1999)	PRDBS	critically-sized fibular defect	24	rhBMP-7/CT-1	2.5 mg
Schedel[23] (2000)	MRCT	avascular femoral head necrosis	6	rhBMP-2/blood mixture	?
Friedlaender[4] (2001)	CPRPBMCCT FDA/IDA	124 established tibial nonunions	122	rhBMP-7/CT-1	3.5 mg
Cook[24] (2001)	CCS	reconstructive surgery of the hip	4	rhBMP-7/CT-1	3.5 mg
Pecina[5] (2001)	R	resistant nonunions of femur, tibia, radius	20	rhBMP-7/CT-1	OP-1 device (3.5 mg)
Govender[19] (2002)	PRCSBS	open tibial shaft fractures	450	rhBMP-2/CT-1	6–12 mg
Pecina[6] (2003)	CR	pre-amputation non-union of the distal tibia	1	rhBMP-7/CT-1	OP-1 device (3.5 mg)
Evans[7] (2004)	CR	clavicular midshaft nonunion	2	rhBMP-7/CT-1	OP-1 device (3.5 mg)
Delloye[17] (2004)	CT	2 allograft fracture nonunions and 4 nonunions at the allograft-host junction	5	rhBMP-2 or rhBMP-7	12 mg of rhBMP-2, 7 mg of rhBMP-7
Bong[8] (2005)	ISMPCS FDA/IDA	atrophic humeral diaphyseal nonunions	23	rhBMP-7/CT-1	3.5 mg
Dimitriou[9] (2005)	CT	10 tibial, 8 femoral, 3 humeral, 3 ulnar, 1 patellar, and 1 clavicular nonunion	25	rhBMP-7/CT-1	3.5 mg
Giannoudis[10] (2005)	MCS	nonunions of tibia (42%), femur (29%), humerus (11%), clavicle (6%), radius (5%), scaphoid (4%), ankle (4%), olecranon (4%), ulna (3%), tibial plateau (2%), fibular graft (1%) and patella (0.1%)	653	rhBMP-7/?	3.5 mg
Fabeck[15] (2006)	CR	congenital pseudarthrosis of the tibia	1	rhBMP-7/CT-1	3.5 mg
Bilic[13] (2006)	PRDBCPS	proximal pole scaphoid nonunion	18	rhBMP-7/CT-1	3.5 mg
Karrholm[25] (2006)	CCOS	20 acetabular revisions and 41 femoral revisions	61	rhBMP-7/ CT-1 (?) (MAB)	OP-1 device (3.5 mg)
Anticevic[16] (2006)	CR	congenital pseudarthrosis of the tibia	1	rhBMP-7/CT-1	OP-1 device (3.5 mg)
Swiontkowski[20] (2006)	SADCF2PRS	open tibial shaft fractures	510	rhBMP-2/CT-1	6–12 mg
Jones[21] (2006)	PRCT FDA/IDA	tibial diaphyseal fracture and a residual cortical defect	30	rhBMP-2/CT-1	12 mg
Calori[12] (2006)	PRCS	long bone nonunions, critical size bone defects, 10 tibia, 7 femur, 5 humerus, 4 ulna, 3 radius	29	rhBMP-7/CT-1	3.5–7 mg
Ronga[11] (2006)	ORNRS	46 tibial, 23 femoral, 20 humeral, 6 radial, 5 ulnar, 3 forearm, and 2 clavicular nonunions	105	rhBMP-7/?	?

PRDBS – prospective, randomized, double-blind study, MRCT – multi-center randomized clinical trial, CPRPBMCCT – controlled, prospective, randomized, partially blinded, multi-center clinical trial, FDA/IDA – Food and Drug Administration approved Investigational Device Exemption, CCS – clinical cases study, R – review, PRCSBS – prospective, randomized, controlled, single-blind study, CR – case report, CT – clinical trial, ISMPCS – industry sponsored multi-center prospective clinical study, MCS – multicenter clinical study, PRDBCPS – prospective, randomized, double blind, clinical pilot study, CCOS – case-control study, SADCF2PRS – subgroup analysis of data combined from two prospective randomized studies, PRCT – prospective, randomized, controlled trial, PRCS – prospective, randomized, clinical study, ORNRS – observational, retrospective, non-randomized study, rhBMP-7 – recombinant human Bone Morphologic Protein-7, CT-1 – collagen type 1, rhBMP-2 – recombinant human Bone Morphologic Protein-2, OP-1 device – commercial composite device consisting of rhBMP-7/CT1 (Stryker Biotech, Hopkinton, MA, USA), MAB – morselized allograft bone

Govender et al. demonstrated in multicenter study that the use of the rhBMP-2 implant was safe and, when 1.50 mg/mL was used, significantly superior to the standard of care in patients with an open fracture of the tibia who were randomized to receive either the standard of care (intramedullary nail fixation and routine soft-tissue management, the control group) (n=150), the standard of care and an implant containing 0.75 mg/mL of rhBMP-2 (n=151), or the standard of care and an implant containing 1.50 mg/mL of rhBMP-2 (n=149)[19]. From the 94% of all patients who were available at 12 months follow up, the 1.50-mg/mL rhBMP-2 treated patients had a 44% reduction in the risk of failure (i.e. secondary intervention because of delayed union), significantly fewer invasive interventions (e.g., bone-grafting and nail exchange), and significantly faster fracture-healing than did the control patients. Significantly more patients treated with 1.50 mg/mL of rhBMP-2 had the fracture healing at the postoperative visits from ten weeks through twelve months. Compared with the control patients, those treated with 1.50 mg/mL of rhBMP-2 also had significantly fewer hardware failures, fewer infections (in association with Gustilo-Anderson type-III injuries), and faster wound--healing (83% compared with 65% had wound-healing at six weeks). A subgroup analysis of the data from previous study and from another one with the same study design was conducted to investigate more clearly mentioned significant reduction in the rate of infection in the type-III open fractures treated with rhBMP-2 and the reduction of the rate of secondary intervention with the addition of rhBMP-2 in patients treated with reamed as well as unreamed intramedullary nailing[20].

The patients with a tibial diaphyseal fracture and a mean length of residual cortical defect 4 cm who were randomly assigned to receive either allograft with 1.50 mg/mL rhBMP-2/sponge or traditional AUBG for staged reconstruction of the tibial defect indicated that the two treatments were equally effective as 13 patients treated with rhBMP-2/allograft and 10 with autograft had healing without further intervention[21].

Osteonecrosis of the Femoral Head

Surgical treatment for lower stages of the disease includes core decompression, bone grafting, and osteotomy[22].

In patients with avascular femoral head necrosis who received rhBMP-2 (n=3) after decompression of the core, regression was observed in one patient (from ARCO IIc to I) and in the other two deceleration of progress of illness[23]. Two of three patients who did not receive rhBMP-2 after decompression had a progression of the disease (from ARCO III to IV–V and from ARCO IIa to IIIb).

Reconstructive and Revision Surgery of the Hip

The challenges of complex THA and even more of revision surgery of the hip include bone loss in the proximal femur and acetabulum and deformity, cortex perforation, and periprosthetic fracture.

The initial cases of the use of rhBMP-7 in conjunctions with morcellized ALBG or cortical strut ALBG for revision of the previously failed proximal femoral allografts, deficient proximal femurs, an absent femoral cortex and acetabular reconstruction were successful due to the greater and earlier new bone formation in the more challenging biologic environment compared to allograft bone alone[24].

Recently, rhBMP-7 mixed with morselized allograft in hip revisions did not reveal any significant difference in the acetabular cup migration between the study and standard care of treatment patients[25]. The four sockets of 10 in the rhBMP-7 treated patients were classified as radiographically loose after 5 years and 2 of them were revised after 5 years. One stem of 11 in the rhBMP-7 group loosened and was revised during the third year of observation.

Spinal Surgery

The two primary drawbacks in performing a spinal fusion are the morbidity of harvesting iliac AUBG which is needed in almost all instances and the relatively high frequency of pseudarthrosis.

In an effort to eliminate the need to harvest bone graft from the iliac crest and to reduce the incidence of the nonunion, a search for bone graft substitutes has intensified as shown in Table 2.

Vertebral Fractures

The first published use of BMPs in 5 patients with unstable thoracolumbar burst fractures has been disappointing, as the rhBMP-7/sponge was not capable of inducing a sufficient early structural bone support[26]. There were even indications to suggest that application of rhBMP-7 sponge at a fracture site in humans in some cases may result in an inappropriate enhancement of bone resorption as the primary event.

Anterior Spinal Interbody Fusion (ASIF) – Lumbar Spine

Solid fusion was achieved in 11 patients 6 months after the treatment with rhBMP-2/collagen sponge inside two tapered titanium interbody fusion cages during the lumbar ASIF[27].

Solid radiologic fusion was achieved in all 21 patients who were available for follow-up at 6 months after the laparoscopic lumbar ASIF with tapered titanium fusion cages filled with rhBMP-2[28].

The higher fusion rate (94.5 vs. 88.7%) remained after two years of a follow up in 143 patients who had lumbar ASIF using rhBMP-2 within tapered titanium interbody cages versus 136 patients who received iliac AUBG[29].

The data from previous two studies[28,29] and an unpublished study of a similar large-scale clinical trial with a total of 679 patients were integrated to check the statistical

TABLE 2
LIST OF PUBLICATIONS RELATED TO TREATMENT OF SPINAL DISORDERS WITH RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEINS (rhBMPs) INCLUDED

1st Author and Year	Type of the Study	Kind of spinal damage	Sample Size	rhBMP/Carrier	Dose of rhBMP/Level
Laursen[26] (1999)	PS	SL unstable burst FR	5	rhBMP-7/CT-1	2.5 mg
Boden[27] (2000)	PRCCTP FDA/IDA	SL lumbar DDD	14	rhBMP-2/CT-1	from 3.9 to 7.8 mg 1.50 mg/mL
Kleeman[28] (2001)	PCNRS FDA/IDA	SL DDD or LG SLI	22	rhBMP-2/CT-1	from 4.2 to 8.4 mg 1.50 mg/mL
Burkus[29] (2002)	MPRNBS	SL lumbar DDD	279	rhBMP-2/CT-1	from 4.2 to 8.4 mg 1.50 mg/mL
Johnsson[48] (2002)	PRS	L5 SLO, GR 1 or 2	20	rhBMP-7/CT-1	7 mg
Boden[49] (2002)	PRCPT	SL DDD or SLI GR 1	25	rhBMP-2/BCP	40 mg
Baskin[38] (2003)	PRCCTP FDA/IDA	SL or 2L cervical DDD	33	rhBMP-2/CT-1	0.6 mg 1.50 mg/mL
Burkus[30] (2004)	MPRNBS FDA/IDA	SL lumbar DDD	46	rhBMP-2/CT-1	from 8.4 to 12 mg 1.50 mg/mL
Burkus[30] (2004)	IAMCS	SL DDD or LG SLI	679	rhBMP-2/CT-1	from 4.2 to 8.4 mg 1.50 mg/mL
Burkus[30] (2004)	MPRNBS FDA/IDA	SL lumbar DDD	44	rhBMP-2/CT-1	from 8.4 to 12 mg 1.50 mg/mL
Lanman[39] (2004)	PPS	SL, 2L or 3L cervical DDD	20	rhBMP-2/CT-1	? 1.50 mg/mL (IBG)
Lanman[42] (2004)	PCT	discogenic pain, SLI GR 1, nonunion from previous surgery	43	rhBMP-2/CT-1	? 1.50 mg/mL (IBG)
Kuklo[34] (2004)	CCS	lumbar DDD, isthmic SLI, revision surgeries, failed-back syndrome	35	rhBMP-2/CT-1	4.2 mg 1.50 mg/mL (IBG)
Mummaneni[43] (2004)	RCR	DDD or LG SLI	44	rhBMP-2/CT-1	8.4 mg 1.50 mg/mL (IBG)
Haid[47] (2004)	PRNBS FDA/IDA	SL DDD or LG SLI	67	rhBMP-2/CT-1	from 4 to 8 mg 1.50 mg/mL
Vaccaro[50] (2005)	MCPS	SL LG SLI	12	rhBMP-7/CT-1 + CMC	7 mg
Schwender[44] (2005)	CS	DDD with DH or SLI or Chance-type seat belt FR	49	rhBMP-2/CT-1	?
Boakye[40] (2005)	RECT	acute DH, cervical SLO, ossification of the PLL, PA after a prior ACDF, SCC and DH, fall-related C7-T1 subluxation	24	rhBMP-2/CT-1	≈ 1 or 2.1 mg 1.50 mg/mL (IBG)
Glassman[52] (2005)	PRNBS FDA/IDA	SL DDD or LG SLI	74	rhBMP-2/ CT-1 and CRM	40 mg 2 mg/mL
Luhmann[37] (2005)	PSNCS FDA/IDA	adult spinal deformity	70	rhBMP-2/CT-1 or CRM and BCP	from 4 to 40 mg group 1 mean 10.8 mg group 2 mean 13.7 mg group 3 mean 28.6 mg
Vaccaro[51] (2005)	PRCMCS FDA/IDA	SL LG SLI	36	rhBMP-7/CT-1 + CMC	7 mg
Villavicencio[45] (2005)	RCS	lumbar DDD, spinal instability, spinal stenosis, FJA, degenerative SLI	74	rhBMP-2/CT-1	from 4.2 to 12 mg 1.50 mg/mL (IBG)
Burkus[31] (2006)	MPRNBS FDA/IDA	SL lumbar DDD	131	rhBMP-2/CT-1	from 8.4 to 12 mg 1.50 mg/mL
Wang[36] (2006)	RCR	SL lumbar DDD	32	rhBMP-2/CT-1	? 1.50 mg/mL (IBG)
Hansen[33] (2006)	CR	lumbar DDD	1	rhBMP-2/CT-1	4.8 mg

(continued on next page)

TABLE 2
LIST OF PUBLICATIONS RELATED TO TREATMENT OF SPINAL DISORDERS WITH RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEINS (rhBMPs) INCLUDED
(continued from the previous page)

1st Author and Year	Type of the Study	Kind of spinal damage	Sample Size	rhBMP/Carrier	Dose of rhBMP/Level
Pradhan[35] (2006)	PCS	SL lumbar DDD	36	rhBMP-2/CT-1	? 1.50 mg/mL (IBG)
Singh[53] (2006)	PSICCMCS	SL-3L level LG SLI	52	rhBMP-2/CT-1	12 mg 1.50 mg/mL (IBG)
Anand[46] (2006)	PCS	SL-2L DDD with or without SLI	100	rhBMP-2/CT-1	8.4 mg (4.2 mg) 1.50 mg/mL (IBG)
McClellan[32] (2006)	RRE	SL-2L DDD with or without radiculopathy	26	rhBMP-2/CT-1	from 4.2 to 12 mg 1.50 mg/mL (IBG)
Dimar[54] (2006)	PRNBS FDA/IDA	SL lumbar DDD or LG SLI	98	rhBMP-2/CRM	40 mg 2.0 mg/mL

PS – pilot study, PRCCTP – prospective, randomized, controlled, clinical pilot trial, FDA/IDA – Food and Drug Administration approved Investigational Device Exemption, PCNRS – prospective, controlled, nonrandomized study, MPRNBS – multicenter, prospective, randomized, nonblinded study, PRS – prospective, randomized study, PRCPT – prospective, randomized, clinical, pilot trial, IAMCS – an integrated analysis of multiple clinical studies, PPS – prospective study, PCT – prospective, clinical trial, CCS – consecutive case series, RCR – retrospective chart review, PRNBS – prospective, randomized, nonblinded study, MCPS – multicenter, clinical, pilot study, CS – clinical study, CR – case report, RECT – retrospectively evaluated clinical trial, PSNCS – prospective, single-center, nonblinded, clinical study, PRCMCS – prospective, randomized, controlled, multicenter clinical study, RCS – retrospective clinical study, PCS – prospective, cohort study, PSICCMCS – prospective, single institution, clinical case-matched cohort study, RRE – retrospective, radiographic evaluation, SL – single-level, FR – fracture, rhBMP-7 – recombinant human Bone Morphologic Protein-7, CT-1 – collagen type 1, DDD – degenerative disc disease, rhBMP-2 – recombinant human Bone Morphologic Protein-2, LG – low grade, GR – grade, SLI – spondylolisthesis, SLO – spondylosis, 2L – two level, 3L – three level, IBG – Infuse bone graft (Medtronic Sofamor Danek) (»kit» of rhBMP-2/InFUSE may contain anywhere from 4 to 12 mg), CMC – carboxymethylcellulose, DH – disc herniations, PLL – posterior longitudinal ligament, PA – pseudarthrosis, ACDF – anterior cervical discectomy and fusion, SCC – spinal cord contusion, CRM – compression resistant matrix carrier (a carrier consisting of bovine collagen and tricalcium/hydroxyapatite), BCP – biphasic calcium phosphate granules, FJA – facet joint arthropathy

superiority of rhBMP-2/sponge to autograft used inside the threaded intervertebral fusion cagd[30]. The fusion success rate in the combined rhBMP-2 treated patients was 94.4% (201 of 213) at two years after surgery compared to 89.4% (252 of 282) in the autograft treated patients. At the same time, in the autograft open patients, nearly a third (32%) continued to have some pain at their harvest site.

The rhBMP-2 within threaded cylindrical titanium cages had also superior results compared with the same cage filled with autograft[30] during lumbar ASIF.

After the successful use of rhBMP-2 inside the titanium threaded intervertebral fusion cage in patients who have undergone lumbar ASIF, the use of structural threaded cortical allograft bone dowels filled with rhBMP-2/sponge was investigated. At the final two-year radiographic follow-up examination, 99% of the patients in the study group (n=79) had evidence of a fusion compared to 76% of control patients (n=52). At the same time the pain at the donor site of the iliac bone graft was observed to persist in a 46.5% of control patients. Thorough radiographic assessment of the incorporation of the allograft and new bone formation using serial thin-slice CT scans of these patients at 12 months revealed that 14 of the investigational patients (18%) developed a transient, localized area of bone remodeling within the vertebral body adjacent to the allograft dowel[31]. These radiolucent areas had resolved by 24 months after surgery without of any effect on the clinical outcomes.

Similar bone resorption within the vertebral body but after transforaminal lumbar interbody fusion (TLIF) with placement of rhBMP-2 within the disc space with a variety of interbody fusion cages, allografts and additional instrumentation posteriorly was noticed in 22 of the 32 levels reviewed (69%) by CT scans three months after surgery[32].

The connection between the last two studies and others where different degrees of resorption of the vertebrae were observed, was an additional rhBMP-2 sponge which was placed adjacent to the interbody implant in direct contact with the vertebral endplates and more importantly in all this studies an early (under one year) CT follow up had been performed[26,31–35].

As mentioned, a resorptive response resembling infection was noticed in a patient within the interbody space and adjacent disc spaces in the early months following the lumbar ASIF with a femoral ring allograft (FRA) filled with an rhBMP-2/sponge[33].

Further on, it was found that the use of rhBMP-2 did not enhance the fusion rate in the stand-alone lumbar ASIF with FRAs compared with FRAs filled with iliac AUBG[35]. Although, without statistical significance due

to early termination of the recruitment of rhBMP-2 treated patients after suboptimal results were noted, a trend was toward a higher nonunion rate with rhBMP-2.

The rhBMP-2 was used within titanium cages during lumbar ASIF as the first part of lumbar stabilization followed by a rigid spinous process plate in 21 patients which was compared to the bilateral pedicle screw (BPS) fixation in 11 patients[36].

The rhBMP-2 was also used in adult patients with spinal deformities in multilevel anterior and posterior fusions with a minimum 1-year follow-up[37]. For the anterior fusion group (n=46) with titanium mesh cages and protected with posterior instrumentation, operative levels were deemed fused in 89 of the 93 (96%) levels. For the posterior, i.e. posterolateral fusion group (n=41), a solid fusion was assessed in 110 of 118 (93%) operative levels. For the »compassionate-use« patients, i.e. patients who had prior surgeries, prior iliac harvesting, and substantial comorbidities the overall fusion rate was 100% (52 of 52 operative levels).

Anterior Spinal Interbody Fusion (ASIF) – Cervical Spine

After the application of rhBMP-2 had demonstrated consistent and clear osteoinduction in lumbar ASIF the use in cervical ASIF started.

All patients treated with allograft fibular graft filled either with rhBMP-2 sponge (n=18) or with iliac AUBG (n=15) during cervical ASIF with anterior cervical plate had solid fusions 6, 12, and 24 months after surgery[38].

The bridging bone was demonstrated in all patients three months after the cervical ASIF with rhBMP-2 contained within a poly(L-lactide-co-D,L-lactide) bioabsorbable implants with anterior cervical plate[39].

Solid fusion was present in all patients who had undergone cervical ASIF involving the placement of polyetheretherketone (PEEK) spacers filled with rhBMP-2 and anterior cervical plating and who were available for 12 to 16 months follow-up[40].

After these promising results without major adverse effects except for new heterotopic bone formation[38,40], dysphagia in three patients[39,40], transient recurrent laryngeal nerve injury, transient C-5 paresis, and cerebrospinal fluid leakage[40], investigators paid more attention and reported several complications after the use of rhBMP-2 in cervical ASIF. Bennett et al. consider that the large BMP dose in the cervical spine was not needed as they successfully used in hundreds of their patients a dose of 1.05 mg of rhBMP-2 placed in the center of an interbody graft for the cervical ASIF without deleterious side effects[41].

Transforaminal Lumbar Interbody Fusion (TLIF)

After the successful start of use of the rhBMP-2 in ASIF it started to be used also in TLIF procedures.

Successful interbody fusion was observed in 98% of 41 patients 6 months after TLIF with rhBMP-2/sponge contained within a poly(L-lactide-co-D,L-lactide) bioabsorbable implants and various posterior spinal fixation systems[42].

In an another study, where the same absorbable interbody spacers were used with an additional rhBMP-2 containing sponge sometimes placed in front of the interbody spacer the radiographic fusion rate for the 22 patients reported (mean duration 12.4 months) was 87.2%[34].

TLIF involving rhBMP-2 within and in front of interbody spacers promoted a more rapid fusion[43].

The rhBMP-2 was used for augmentation of local AUBG or allograft bone in few patients who underwent the minimally invasive TLIF with bilateral percutaneous pedicle screw–rod placement and the structural support was achieved with the allograft bone or interbody cages[44]. At a minimum of 18 months' follow-up, all cases appeared to have solid radiographic fusions.

The efficacy of rhBMP-2 was not dependent on which approach was used, minimally invasive (n=43) or open approach (n=31), or the number of spinal levels (one, two or three-level) that were treated with TLIF as the radiographic fusion rate in all patients was 100% at 12 and 24 months after the surgery[45].

The fusion rate was 100% using rhBMP-2 and the structural allograft with a local AUBG during cantilever TLIF technique with pedicle screw fixation and the PLSF at two years follows up[46].

Posterior Lumbar Interbody Fusion (PLIF)

Although the fusion rate of PLIF with stand-alone cylindrical threaded titanium fusion cages was not statistically different at 2 years follow up, the rhBMP-2 treated patients (n=34) the fusion rate of 92.3% was higher than in iliac AUBG patients (n=33) at 77.8%[47].

Posterolateral Spinal Fusion (PLSF)

There was no significant difference between the results of noninstrumented PLSF augmented with the rhBMP-7 implant (n=10) contrary to fusion with AUBG (n=10)[48]. Although rhBMP-7 demonstrated a bone-forming response in 9 of 10 patients, the rhBMP-7 implant did not yield better formation of stabilizing bridging bone than the autograft bone in human noninstrumented PLSF.

Boden et al. considered that the mentioned clinical failure with BMPs during PLSF likely resulted from suboptimal carrier matrices used to deliver the BMP and a failure to recognize the requirement for the substantially increased doses of BMP needed to induce bone formation in humans, as compared with other tested animals in who BMPs demonstrated consistent success[49]. Accordingly, the authors used for PDSF 20 mg of rhBIP-2 on each side which was delivered on a carrier consisting of 60% hydroxyapatite and 40% tricalcium phosphate granules. The fusion rate was 40% (2/5) in the autograft/pedicle screw fixation treated patients and 100% (20/20) in patients treated with rhBMP-2 with or without the pedicle screw fixation.

In the study of uninstrumented PLSF augmented with rhBMP-7 as an adjunct to the iliac AUBG and mixed with the carboxymethylcellulose (CMC) at two year follow up 50% of 10 available patients with radiographic follow-up achieved a solid fusion. The bridging bone on the anteroposterior film was observed in 70% of patients[50].

Vaccaro et al. reported on the randomized study of PLSF without instrumentation augmented with rhBMP-7 (n=24) or AUBG (n=12)[51]. At two year time point radiographic fusion was observed in 55% patients treated with rhBMP-7 and 40% patients treated with AUBG and this difference still was not statistically significant.

The instrumented PLSF augmented by rhBMP-2 in conjunction with HA-TCP compression resistant matrix (CRM) (n=36) or iliac AUBG (n=36) was compared by CT scans[52]. CT scans at 6 and 12 months were graded from grade 1–5. Mean fusion grade at 6 months after surgery was 4.35 in the rhBMP-2/CRM treated patients versus 3.09 in the iliac AUBG treated patients. At one year after surgery mean fusion grade was 4.62 in the rhBMP-2/CRM treated patients versus 3.77 in the iliac AUBG treated patients.

Two years after instrumented PLSF with either rhBMP-2 wrapped around a bulking agent (local and iliac AUBG) (n=52) or iliac AUBG 97% of rhBMP-2 treated patients had a fusion compared to 77% in iliac AUBG treated patients[53].

In the similar study, but with rhBMP-2/CRM instead of rhBMP-2 wrapped around a bulking agent, in the rhBMP-2/CRM treated patients the fusion rate (88%; n=53) was significantly higher than in the iliac AUBG treated patients (73%; n=45) at a two year follow up[54].

Overview

The rhBMP-7 was successfully used in a human fibular defect and nonunions of the tibia and the tibial plateau, clavicle, humerus, femur, ulna and olecranon, radius and the scaphoid. Incidentally, the use of rhBMP-7 in nonunions of ankle, patella and fibular graft and in the other surgical procedures as periprosthetic fracture treatment and osteotomies, enhancement of fracture healing following acetabular reconstruction, distraction osteogenesis, free fibular graft and arthrodesis of joints were reported.

Congenital pseudarthrosis of the tibia was successfully healed by rhBMP-7 in two published case reports, but in a third report of 5 cases, the use of rhBMP-7 was not enough to overcome the poor healing environment that is associated with congenital the disease.

The rhBMP's (rhBMP-2 and rhBMP-7) alone were not sufficient to achieve healing in allograft nonunions and fractures following wide resection including periosteum and soft tissues, and adjuvant therapies.

The use of rhBMP-2 was significantly superior to the standard of care in reducing the frequency of secondary interventions and the overall invasiveness of procedures, accelerating fracture and wound-healing, and reducing the infection rate in patients with an open fracture of the tibia. The rhBMP-2 was also effective for reconstruction of diaphyseal tibial fractures with cortical defects, too.

Regression and deceleration of progress of osteonecrosis of the femoral head was observed in patients treated with core decompression and rhBMP-2.

The results of use of rhBMP-7 in reconstructive surgery of the hip were currently doubtful.

The first use of rhBMPs in spinal surgery resulted in formation of insufficient structural bone support in patients with unstable thoracolumbar burst fractures causing vertebral resorption.

However, rhBMP-2 was successfully used for ALIF when rhBMP-2/sponge was placed either inside threaded intervertebral fusion cages or cylindrical threaded cortical allograft dowels with or without other instrumentation. The use of FRA filled with rhBMP-2 for ALIF was connected with an early dislodgment of the interbody graft, with a resorptive response of rhBMP2 simulating infection and finally with a higher nonunion rate compared with FRA filled with AUBG. Recently, the resorption of vertebral bodies was observed by CT during the first months of the follow up after the use of an additional rhBMP-2 sponge in a direct contact with the vertebral endplates. The patients with cervical spine pathology were successfully treated with cervical ASIF with rhBMP-2.sponge žlaced either inside the allograft fibular grafts or poly(L-lactide-co-D,L-lactide) bioabsorbable implants or PEEK spacers. Lately, it was observed in two retrospective studies that rhBMP-2 used for cervical ASIF had caused complications in patients mostly as dramatic swelling.

The use of rhBMP-7 for atlanto-axial posterior fusion after wire fixation in patients on chronic steroid treatment was not successful. The success with rhBMP-7 was achieved in patients with medical risk factors that would inhibit osseous fusion during cervical and lumbar posterolateral fusions with or without instrumentation, CEC or CRM. The rhBMP-2 was also successfully used to achieve PHLF.

The rhBMP-2 alone or contained within a poly(L-lactide-co-D,L-lactide) bioabsorbable implants or other interbody cages together with various spinal fixation system was successfully used for TLIF. The use of rhBMP-2 for PLIF was successful, but it was connected to the new bone formation extending outside the disc space and into the spinal canal or neuroforamina.

Finally, rhBMP-2, i.e. InFUSE is approved by the FDA for anterior lumbar interbody fusion (ALIF) when used with an lumbar tapered titanium interbody fusion device (LT-Cage; Medtronic Sofamor Danek, Memphis, TN)[55] and for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation[56]. The rhBMP-7, i.e. OP-1 Implant is currently approved by the FDA for treatment of nonunions of long bone fractures[57] and OP-1 Putty is approved as a substitute for autogenous bone when attempting revision posterolateral lumbar fusions[58].

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REGENERACIJA KOSTURA REKOMBINIRANIM LJUDSKIM KOŠTANIM MORFOGENETSKIM PROTEINIMA

S A Ž E T A K

Rekombinirani ljudski koštani morfogenetski proteini (recombinant human Bone Morphogenetic Proteins, rhBMP) su prešli dug put tijekom posljednjih 15 godina primjene u ljudskoj ortopediji. Od prvih izvješća o primjeni rhBMP-a u »neprijateljskim« uvjetima kao što su kritični koštani defekti, avaskularne nekroze glave bedrene kosti, nestabilni torakolumbarni prijelomi kralješaka, nestabilnosti između atlasa i aksisa kao posljedica reumatskog artritisa; preko korištenja kod pseudartroza dugih kostiju i skafoida, rekonstruktivnih i revizijskih operacija kuka, akutnih prijeloma, pseudartoza koštanih alogeničnih presadaka, kongenitalnih pseudartroza, te svih poznatih pristupa fuziji vratne i lumbalne kralježnice, rhBMP-ovi su se razvili do sigurnog i pouzdanog sredstva u liječenju otvorenih prijeloma tibije, pseudartroza dugih kostiju, prednje interkorporalne fuzije lumbalnih kralježaka i revizijskih posterolateralnih fuzija lumalne kralježnice. Prikazujemo sistematičan pregled objavljene literature o rhBMP-u.