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REVIEW ARTICLE

Bone morphogenetic protein use in spine surgery—complications and outcomes: a systematic review

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Abstract
Purpose Because of significant complications related to the use of autologous bone grafts in spinal fusion surgery, bone substitutes and growth factors such as bone morphogenetic protein (BMP) have been developed. One of them, recombinant human (rh) BMP-2, has been approved by the Food and Drug Administration (FDA) for use under precise conditions. However, rhBMP-2-related side effects have been reported, used in FDA-approved procedures, but also in off-label use.A systematic review of clinical data was conducted to analyse the rhBMP-2-related adverse events (AEs), in order to assess their prevalence and the associated surgery practices.
Methods Medline search with keywords "bone morphogenetic protein 2", "lumbar spine", "anterolateral interbody fusion" (ALIF) and the filter "clinical trial". FDA published reports were also included. Study assessment was made by authors (experienced spine surgeons), based on quality of study designs and level of evidence.
Results Extensive review of randomised controlled trials (RCTs) and controlled series published up to the present point, reveal no evidence of a significant increase of AEs related to rhBMP-2 use during ALIF surgeries, provided that it is used following FDA guidelines. Two additional RCTs performed with rhBMP-2 in combination with allogenic bone dowels reported increased bone remodelling in BMP-treated patients. This AE was transient and had no consequence on the clinical outcome of the patients. No other BMP-related AEs were reported in these studies.
Conclusions This literature review confirms that the use of rhBMP-2 following FDA-approved recommendations (i.e. one-level ALIF surgery with an LT-cage) is safe. The rate of complications is low and the AEs had been identified by the FDA during the pre-marketing clinical trials. The clinical efficiency of rhBMP-2 is equal or superior to that of allogenic or autologous bone graft in respect to fusion rate, low back pain disability, patient satisfaction and rate of re-operations. For all other off-label use, the safety and effectiveness of rhBMP-2 have not been established, and further RCTs with high level of evidence are required.

Keywords Bone morphogenetic protein · Spinal fusion · Osteoinduction · Adverse effects

Introduction

Bone morphogenetic proteins (BMPs) include an extensive group of growth factors, of which over 20 types have been identified to date and have been proved to be indispensible in fractured bone healing [1–4]. The first reports on the use of BMP in bone surgery came from Urist and co-workers [5, 6], who purified the protein and used it in clinical applications, with encouraging results. As the extraction from cadaver bone and purification of human BMP provided small amounts, the production was limited. Therefore, human recombinant gene technology was used to develop BMPs (rhBMP) and focused on those with the greatest bone induction properties. In the following years, BMP products were developed to increase the rate of solid bone fusion in lumbar surgeries, and therefore to reduce the need for subsequent revision surgery and avoid potential side effects of iliac crest bone harvesting. Eventually,

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recombinant human BMP-2 (rhBMP-2) was approved by the FDA in 2002 for anterior lumbar interbody fusion (ALIF) surgeries in indications including one-level degenerative disc disease and grade I spondylolisthesis, between L4 and S1 [7]. During surgery, BMP soaked collagen sponge (InFUSE®; Medtronic Sofamor Danek, Memphis, TN) is inserted into an LT-cage (Lumbar Tapered Fusion Device; Medtronic Sofamor Danek, Memphis, TN). All data were published on the FDA website [7] and in level I publications, including randomised controlled trials (RCTs) [8–10].

Soon after its approval in the United States, the use of BMP dramatically increased, up to nearly 25 % of all spine fusion procedures in 2006 [11]. A high proportion of surgeries performed with BMP deviated from the original FDA approved indications (e.g. use with a different fusion device, surgery methods or medical indications, or at a different concentration than recommended). Thus, while BMP was used for ALIF in only 16.6 % of the reported cases in the United States, it was mainly used off-label in first-time posterior lumbar interbody fusion (PLIF) or transforaminal interbody fusion (TLIF) (30.0 % for both), first-time posterolateral spine fusion (20.4 %), cervical fusions (13.6 %) and first-time thoracolumbar fusions (3.9 %) [12]. Since, for most of these indications (except posterolateral lumbar fusion), very few RCTs on safety and efficacy have been published, the risks and benefits of these off-label use of BMP remain under-evaluated. Off-label use of BMP has also been reported in general orthopaedic surgery and trauma, and recommendations have been issued in a recent literature review [13].

In a systematic literature review, Mroz et al. [14] concluded that the overall strength of evidence regarding BMP-related safety was "low" for cervical spine surgery and "very low" for thoracic spine surgery. This conclusion is in line with the FDA notification of 2008: "Since the safety and effectiveness of rhBMP for treatment of cervical spine conditions has not been demonstrated, and in light of the serious adverse events described, FDA recommends that practitioners either use approved alternative treatments, or consider enrolling as investigators in approved clinical studies" [15]. Therefore, the objective of this review is to analyse articles published since 2002, listing the different uses of rhBMP-2 in lumbar spine surgery, in approved and off-label indications, excluding cervical and thoracic surgery, and give precise up-to-date recommendations.

Methods

We searched the PubMed database with the following keywords: bone morphogenetic protein 2, lumbar spine, anterolateral lumbar fusion. The search was limited to the period from 1 January 2002 to 15 December 2012 and identified a total of 231 articles. We applied the Oxford level of evidence scale to select final articles for the review. As a final choice, we included two original RCTs [8, 9], the FDA approval document [7], four subsequent RCTs [10, 16–18], seven controlled series [19–25], all of which were of level of evidence 1 to 3 (Table 1). Seven additional reports on clinical use of BMP in ALIF surgery [20, 26–31] are also discussed because of their detailed clinical complications reports. Other relevant publications were also included to argument discussion [14, 32].

Results

The results are summarised in Tables 2 and 3.

Bone remodelling and subsidence (see Table 2)

Subsidence (i.e. reduction in disk space between two adjacent vertebral bodies) is commonly observed in stand-alone ALIF surgeries [33] and results from osteolysis and remodelling of the allogenic bone graft and/or the endplate of the adjacent vertebrae. The pilot RCTs mentioned no case of subsidence greater than 1 mm [7–9]. Overall, the subsidence rates reported by the FDA were 2.4 % in the BMP group (276 patients) and 1.4 % in the control group (136 patients), respectively [7]. No subsidence was observed in two other studies with follow-ups ranging from six months to six years [10, 20].

In another RCT performed by Burkus et al. [16], rhBMP-2 was used in conjunction with allograft bone dowels in 24 ALIF patients, compared to 22 control patients who received bone dowels and autograft. Of note, this technique using allograft is not currently approved by the FDA, but is quite close to the approved indication. No subsidence was reported at 24 months of follow-up. However, in a subsequent comparable multi-centre RCT that included 79 patients in the investigational group and 52 in the control group, the same authors found "localised areas of bone remodelling in the vertebral body adjacent to an allograft dowel" in 18 % of BMP patients, which appeared as lucent areas on patient's radiographs. However, this bone remodelling was transient and had resolved by 24 months after surgery [17, 18]. This could explain why, examining figures of the first study [16], Smoljanovic and Pecina [34] found clues of bone remodelling and resorption of vertebral bodies occurring six months after surgery.

An early premarketing prospective study was conducted by Kleeman et al. [26], who performed laparoscopic ALIF using NOVUS LT tapered cages (Sofamor Danek, Memphis, TN) and rhBMP-2 soaked sponges on 22 consecutive patients. No AEs were reported and the clinical outcomes were very satisfactory, with all patients showing solid fusion at six months according to computed tomography scan read by a radiologist. Post-marketing data were reported later on. In a controlled cohort study published by Vaidya et al. [23], BMP was applied together with allogenic spacers (plus posterior fixation) in ALIF surgery. Data analysis found significantly increased

Table 1 RCTs and cohort-controlled studies on rhBMP-2 in ALIF

Publication				Method					Patients			Follow-up (years)
Ref.	Type	1st author	Year	Surgical approach	No. of levels fused	Fusion device	BMP concentration (mg)	Control graft	Diagnoses	No. BMP	No. control	
[6]	RCT + single-arm	FDA doc P000058	2002	ALIF (open + lap)	1	Interbody cage	2.1-8-4	Morcellised AIBG	DDD, grade I spondylolisthesis	288[a]	139[a]	2
[7]	Pilot RCT	Boden	2000	ALIF (open)	1	Interbody cage	6.5-13	Morcellised AIBG	DDD	11	3	2
[8]	RCT	Burkus	2002	ALIF (open)	1	Interbody cage	4.2-8.4	Morcellised AIBG	DDD	143	136	2
[9]	RCT	Burkus	2003	ALIF	1	Interbody cage	4.2-8.4	Morcellised AIBG	Degenerative lumbar spondylosis	22	20	2
[14]	RCT	Burkus	2002	ALIF (open)	1	Bone dowel	12-18	Morcellised AIBG	DDD	24	20	2
[15]	RCT	Burkus	2005	ALIF (open)	1	Bone dowel	8.4-12	Morcellised AIBG	DDD, grade I spondylolisthesis	79[b]	52[b]	2
[16]	RCT	Burkus	2006	ALIF (open)	1	Bone dowel	8.4-12	Morcellised AIBG	DDD, grade I spondylolisthesis	79[d]	52[d]	2
[17]	Integrated analysis of RCTs	Burkus	2003	ALIF (open + lap)	1	Interbody cage	2.1-8.4	Morcellised AIBG + interbody cage	DDD, grade I spondylo-listhesis	277[c]	402[c]	2
[21]	Prospective. cohort controlled	Vaidya	2007	ALIF (open)	1 to 2	Allograft spacer + post. fixation	2 (+AIBG)	De-mineralised bone	Scoliosis, revision surgery, spondylo-listhesis,	13	11	2
[22]	Prospective cohort controlled	Slosar	2007	ALIF (retroperitoneal)	1 to 3	Allograft + pedicle screw	3-9	Allograft + pedicle screw	DDD, grade I-II spondylolisthesis, degenerative scoliosis	45	30	≥2
[23]	Prospective cohort controlled	Pradhan	2006	ALIF (retroperitoneal)	1	Allograft	ND	Allograft + morcellised AIBG	DDD	9	27	≥2
[19]	Retrospective. cohort controlled	Carragee	2011	ALIF (open)	1 or 2	Femoral ring allograft	4.2 or 8.4 (2 levels)	Femoral ring allograft + de-mineralised bone	DDD, disc herniation, spondylo-listhesis	69	174	>1
[20]	Retrospective cohort controlled	Comer	2012	ALIF (open)	1 or 2	Fermoral ring allograft, or autograft + buttress screw or post. transpedicular fixation	4.2 or 8.4 (2 levels)	ND	Spondylosis or spondylolisthesis	239[e]	233[e]	>1
[29]	Combined analysis of RCTs	Burkus	2012	ALIF	1	Dual paired constructs	ND	Fusion cage + AIBG or metal-on-metal disc arthroplasty device	DDD, up to grade I spondylolisthesis	207[f]	301[f]	2

RCT randomised controlled trial, *ALIF* anterior lumbar interbody fusion, *BMP* bone morphogenetic protein, *DDD* degenerative disc disease, *AIBG* autologous iliac crest bone graft, *lap* laparoscopic, *ND* not determined/not reported

[a] Patient cohort from refs. [7] and [8] plus additional laparoscopic patients (total 134) in BMP group

[b] Patient cohort from ref. [14] plus additional patients

[c] Patient cohort from ref. [8] plus additional laparoscopic and open patients

[d] Same patient cohort as in ref. [15]

e Patient cohorts from ref. [19] plus additional patients

Table 2 Adverse events reported in RCTs and cohort-controlled studies on rhBMP-2 in ALIF

Adverse event	% of patients (cumulative)		Ref.
	BMP	Control	
Subsidence	2.4	1.4	[6]
	0	0	[7]
	ND	ND	[8]
	ND	ND	[9]
	ND	ND	[14]
	ND	ND	[15]
	ND	ND	[16]
	ND	ND	[17]
	70[a]*	6[a]*	[21]
	ND	ND	[22]
	ND	ND	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]
Graft malposition/ graft loosening	3.5	0.7	[6]
	0	0	[7]
	1.4	0	[8]
	ND	ND	[9]
	0	0	[14]
	ND	ND	[15]
	ND	ND	[16]
	ND	ND	[17]
	ND	ND	[21]
	ND	ND	[22]
	ND	ND	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]
Infection	12.2	11.5	[6]
	ND	ND	[7]
	ND	ND	[8]
	ND	ND	[9]
	ND	ND	[14]
	ND	ND	[15]
	ND	ND	[16]
	ND	ND	[17]
	ND	ND	[21]
	2.2	3.3	[22]
	ND	ND	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]
Urogenital AEs	11.5	7.3	[6]
	0	30	[7]
	ND	ND	[8]
	ND	ND	[9]
	ND	ND	[14]
	ND	ND	[15]
	ND	ND	[16]
	ND	ND	[17]
	ND	ND	[21]
	ND	ND	[22]
	ND	ND	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]
Retrograde ejaculation	7.9	1.4	[6]
	ND	ND	[7]
	4.1[a]		[8]
	ND	ND	[9]
	ND	ND	[14]
	ND	ND	[15]
	ND	ND	[16]
	ND	ND	[17]
	ND	ND	[21]
	ND	ND	[22]
	ND	ND	[23]
	7.3*	0.6*	[19]
	6.3*	0.9*	[20]
	3.4	1.7	[29]
	7.2	2.6	[40]
Iliac crest pain	ND	ND	[6]
	ND	ND	[7]
	0[b]*	1.8*	[8]
	ND	ND	[9]
	0[b]	2.2	[14]
	0[c]	46.5[c]	[15]
	ND	ND	[16]
	0	32[c]	[17]
	ND	ND	[21]
	ND	ND	[22]
	ND	ND	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]
Cancer	ND	ND	[6]
	ND	ND	[28]
	3.37	0.5	[43]
	5.9	6.5	[44]

ND not determined

* Reported as statistically significant

[a] Not discriminated between BMP and control groups

[b] Composite pain score (max. 20 points) considering intensity and duration of pain

[c] At 24 months (non-cumulative)

[d] Percentage of fused levels

rates of subsidence in the BMP than in the control group. As previously observed, radiolucency and subsidence mainly developed in the early postoperative period [17]. An off-label use and concentration differences can explain this observation (*see* "Discussion") [35].

Other studies on rhBMP-2 used in ALIF surgeries, reported a high rate of bone resorption and subsidence, but again, these were off-label use [25, 27].

Infection (see Table 2)

The first investigational device exemption RCTs for the use of rhBMP-2 in ALIF with tapered interbody cages did not report any infection in the investigational group, including the six year follow-up [8, 9, 20]. However, the FDA approval document that gathered data from all known patients implanted with InFUSE™ Bone Graft/LT-CAGE™ (including the above-mentioned published cases) mentioned rather high infection rates [7]. This discrepancy has been recently underlined by Carragee et al. [36], who criticised the lack of documentation of infection rates in the original publication of these studies. However, as the incidence of infection was similar in the investigational than in the control groups, the FDA considered this as not related to rhBMP-2 [7].

None of the subsequent RCTs conducted by Burkus and co-workers did report infections during the follow-up period [10, 16, 17, 37]. Also, no specific concerns were reported in prospective or retrospective series where rhBMP-2 was used in ALIF procedures [23–27].

A recent retrospective review by Williams et al. [32] examined the role of BMP in peri-operative complications of spine fusion cases from the US Scoliosis Research Society (SRS) database. Despite this report gathering a wide range of indications and surgical techniques, it remains valuable as it compiles data from 5374 thoracolumbar interbody fusions, including 2,049 with adjunction of BMP. The analysis revealed a higher rate of deep wound infections in patients undergoing anterior/posterior thoracolumbar surgery with BMP, compared with patients in which BMP was not used (1.1 % versus 0.2 %; $p < 0.001$). However, regarding anterior-only thoracolumbar fusion, the authors found no significant differences in the rates of superficial or deep wound infection whether BMP was used or not (1.1 % versus 0.9 %, $p = 0.5$). Accordingly, univariate analysis of 328,468 American patients who underwent spinal fusion procedures (regardless of indication and surgical approach) revealed that lumbar fusions were not associated with a higher rate of wound-related complications, whereas cervical fusions were [11].

Thus, there is no strong evidence that BMP increases the rate of early or delayed infections in ALIF surgery.

Table 3 Clinical outcome in RCTs and cohort-controlled studies on rhBMP-2 in ALIF

Parameter	BMP	Control	Ref.
Fusion rate (% at 2 years)	98.3	97.1	[6]
	100	66.7	[7]
	94.5	88.7	[8]
	94.4*	89.4*	[9]
	100	68.4	[14]
	98.5*	76.1*	[15]
	ND	ND	[16]
	94.4	89.4	[17]
	100	100	[21]
	98	82	[22]
	44	63	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]
Oswestry score (1 year)	ND	ND	[6]
	13.5	20.0	[7]
	25.5	25.6	[8]
	23.1*	25.7*	[9]
	18.9	30.0	[14]
	20.9*	29.3*	[15]
	ND	ND	[16]
	23.1	25.7	[17]
	"no sign difference"		[21]
	30.0	32.8	[22]
	ND	ND	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]
Patients satisfied (% at 2 years)	ND	ND	[6]
	100[a]	66.7[a]	[7]
	81.2	80.4	[8]
	ND	ND	[9]
	83.4	55	[14]
	ND	ND	[15]
	ND	ND	[16]
	ND	ND	[17]
	ND	ND	[21]
	86	79	[22]
	ND	ND	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]
Re-operations (% at 2 years)	10.4	13.7	[6]
	0	33.3	[7]
	7.0	10.3	[8]
	10.8	18.7	[9]
	4.2	15	[14]
	3	15	[15]

Table 3 (continued)

Parameter	BMP	Control	Ref.
	0	9.6	[16]
	2.89	7.96	[17]
	ND	ND	[21]
	0	13	[22]
	33	26	[23]
	ND	ND	[19]
	ND	ND	[20]
	ND	ND	[29]

* Reported as statistically significant

[a] Defined as rating the outcome of surgery as excellent or good

ND not determined

Retrograde ejaculation (see Table 2)

Retrograde ejaculation (RE) is a rare but serious AE of ALIF surgery. Rates reported in the literature vary widely (0.42-5.9 %) [38].

In the original ALIF with BMP/LT-cage RCT, RE was observed in six of the 146 male patients (4.1 %) [9]. Instead of reporting RE rates in BMP and control groups separately as has been done for other AEs, the rate of RE was reported for the total patient population. In a later response to a commentary by Smoljanovic et al. [39], Burkus et al. stated that the RE rate in the original RCT was 6.4 % in the BMP group and 1.5 % in the control group, a statistically non-significant difference ($p=0.216$). Why RE rates were not separately reported for BMP and control groups in the corresponding publication remains unclear. Burkus et al. [9] chose to compare RE AEs whether patients underwent a transperitoneal or a retroperitoneal approach (13.3 % and 1.8 %, respectively, $p=0.017$). The subsequent FDA approval document contained additional data on BMP patients where the fusion device was implanted through a laparoscopic approach. Here, the RE rate in the BMP group was higher than in the control group (7.9 % versus 1.4 %) [7]. The laparoscopic surgical technique in itself has been shown to increase the risk for RE, so that it cannot be directly blamed on BMP [38, 40, 41].

No other cases of RE have been reported in subsequent RCTs and follow-up publications from Burkus et al. [10, 16–18, 20]. A retrospective analysis of RE complications extracted from five RCTs (i.e. 508 patients: 207 with rhBMP-2, 301 without) concluded that the incidence of RE was increased in the rhBMP-2 group, but the difference was not statistically significant (3.4 % versus 1.7 % in the control group, $p=0.242$) [31]. The other prospective and retrospective series of ALIF did not mention rhBMP-2 as a risk factor for RE [23–27] except that of Carregee et al. In this publication, the authors performed a retrospective cohort-controlled study on rhBMP-2 versus demineralised bone matrix, in conjunction with allogenic femoral rings and posterior instrumentation in ALIF surgery (1-2 levels). They observed RE in 7.2 % of the 69 rhBMP-2 patients as opposed to 0.6 % of the 174 control patients ($p=0.0025$). All patients underwent a transrectus or anterior-lateral retroperitoneal approach with a similar incidence between groups, so that the approach could not be incriminated. This significant difference in RE rates seems, therefore, attributable to rhBMP-2 [21]. Similar results have been published by the same authors more recently [22]. However, it is noticeable that in both of these non-randomised studies, the use of rhBMP-2 did not follow FDA-approved guidelines. The subjects of these studies underwent surgery at separated periods (2002-2003, then 2010-2011 without rhBMP-2; 2003-2010 with rhBMP-2). As noticed by the authors, "there was a trend to a decrease in RE rate in the 4th quartile of patients" (i.e. those having surgery later than mid-2008) [22], suggesting that a careful handling of rhBMP-2 may improve its safety. One more recent review article reported higher RE rates in ALIF with BMP, but it was not statistically significant (7.3 % versus 2.3 %; $p=0.03$) [42].

Other urogenital events (see Table 2)

The pilot RCT published by Boden et al. [8] reported one event of urinary retention, which occurred in a control patient. In the original publication of the pivotal RCT, Burkus et al. [9] did not mention urogenital events as BMP-related AEs. However, in the extended FDA approval document, urogenital events were reported and were more frequent in the rhBMP-2 group (11.5 %) compared with the control group (7.2 %) [7]. This difference was not statistically tested and did not lead to specific concern in the safety report. No other case of urogenital event has been reported in the subsequent RCTs and follow-up publications from Burkus et al. [10, 16–18, 20], nor in the prospective and retrospective series of rhBMP-2 associated-ALIF [23–27]. The review article of Carragee et al. [36] reported higher rates (7.9 % in the BMP group versus 3.6 % in the control group, $p=0.04$), but it only referred to the zero to nine weeks period after surgery. Between ten weeks and 30 months, the rate of urogenital events was similar in BMP and control patients (4.9 % and 4.3 %, respectively). Urogenital AEs appear very variable, and the correlation to BMP cannot be established.

Clinical outcome (see Table 3)

Clinical outcome—measured by fusion rate, low back pain disability (Oswestry questionnaire), patient satisfaction and rate of reinterventions—has been reported in several clinical studies comparing ALIF surgeries [8, 9, 17–19]. In all studies, fusion with BMP was equally or more efficient than allogenic or autologous bone graft alone. Low back pain disability was equal or lower in BMP treated patients, and patient satisfaction was equal or higher. In addition, the reintervention rate

was lower in the BMP group in all studies [8, 9, 17–19]. Conversely to the assertion of deliberate omission [36] in the pivotal RCT report, 11 (7.0 %) and 14 (10.3 %) patients were reported to have undergone a second surgery before the 24-month follow-up in the investigational and control groups, respectively [9]. Reintervention rates were also listed in the FDA safety and effectiveness data summary (10.4 % and 13.7 % in the investigational and control groups, respectively) [7]. The six year follow-up report also mentioned 18 second surgeries for failures before 24 months [20]. In a prospective cohort where rhBMP-2-treated patients were compared with historical retrospective controls without rhBMP-2, Pradhan et al. [25], however, found a trend "toward a higher nonunion rate with rhBMP-2, although this was not significant with the numbers available". This is the only study that reported lower fusion rates with rhBMP-2 than without. Note that the overall rate of treatment failure was rather high in this short series, regardless of the grafting material. Several other non-RCT studies showed results in favour of a benefit for the patient, with an improvement of the fusion rate and a higher degree of patient satisfaction [23, 24, 27].

Recently, Lykissas et al. [43] analysed nerve injury and recovery after lateral lumbar interbody fusion through a retroperitoneal approach with and without BMP2 in a cohort-controlled study. At the last follow-up, there was a significantly higher number of patients in the BMP group who complained of persistent anterior thigh or groin pain than the control group (8 versus 0 patients) (OR 16.470; 90 % CI, 1.477-183.700; $p = 0.006$). The author suggested a potential direct deleterious effect of rhBMP-2 on the lumbosacral plexus. In this study the confidence intervals and the statistical evidence were very weak, making it very difficult to draw conclusions.

Carcinogenicity (see Table 2)

Carcinogenicity of rhBMP-2 has been suspected, but not argued by preclinical or clinical data. In the FDA approval document, one pancreatic cancer was reported at the 12-month visit [7]. This case seems to be random, however, as the large retrospective cohort study performed in elderly patients failed to show any increased risk of pancreatic cancer linked to rhBMP-2 exposure [29]. Carragee et al. [44] reported the results extracted from an RCT for spine fusion including 239 BMP patients and 224 patients in the control group. At 24 months, the cancer risk was increased with rhBMP-2 (risk ratio, 3.45; 95 % CI, 1.98–6.00), but event rates were low and cancer was heterogeneous and 37 % of patients were lost at five years of follow-up, which decreased significantly the power of statistical analysis. More recently, Kelly et al. [45] reported a retrospective series analysing the incidence of cancer in 467,916 Medicare patients undergoing spinal arthrodesis from 2005 to 2010. The relative risk of developing cancer after BMP exposure was 0.938 (95 % CI, 0.913–0.964), which was significantly low. Cancer rates were similar in BMP and control groups (5.9 % versus 6.5 %). The conclusion was that use of BMP was not associated with an increased risk of developing cancer within a mean 2.9-year time window [45].

Other complications (see Table 2)

Based on the FDA's safety and effectiveness data summary, some AEs, such as back and leg pain, neurological, gastrointestinal and cardiovascular events, were frequently reported during patient follow-up. However, their frequency was similar in the rhBMP-2 group and control group [7].

Ectopic bone formation has been described as a side effect of inappropriate BMP usage, particularly in PLIF, TLIF and anterior cervical discectomy and fusion (ACDF) [46], but not ALIF. Burkus et al. [9, 10, 16, 17 did not observe any case of ectopic bone formation in their published RCTs]. Neither did other prospective and retrospective series [23–27]. Similarly, painful seroma or epidural haematoma was never mentioned as a side effect of ALIF, although some cases were reported in TLIF surgeries, posterolateral lumbar fusions and anterior cervical fusions [46, 47]. Latzman et al. [30] raised a potential concern about transient renal impairment associated with rhBMP-2 in a small retrospective cohort of 24 patients, controlled with 105 patients who underwent lumbar or lumbosacral fusion [48]. A case report was also published on similar effects. This AE could be related to a high dose of rhBMP-2 or to an allergic reaction. However, the lack of surgical approach specification in those cases prevents the drawing of any definitive conclusion.

Discussion

Whereas the FDA-approved indication of rhBMP-2 (i.e. surgical treatment of degenerative disc disease by ALIF) is the only one to be well supported by a wide body of data [14], off-label use in other pathologies and surgical approaches has dramatically increased since 2002 [11, 12]. RCTs have been conducted to compare rhBMP-2-soaked collagen sponges to iliac crest autograft posterolateral lumbar arthrodesis [8, 37, 49–52]. But to our knowledge, only one RCT reporting the use of BMP has been published for PLIF [53], one for ACDF [54], and none for TLIF. In the posterolateral approach, Papakostidis et al. [55] conducted a meta-analysis of RCTs to evaluate the effectiveness of BMPs (rhBMP-2 or rhBMP-7) and concluded to highly significant superiority of rhBMP-2 compared with iliac crest bone graft in promoting fusion, particularly when additional instrumentation reinforced the construct. Based on a wide multisurgeon database, Williams et al. [32] realised univariate and multivariate analyses of the incidence of complications in spine fusion procedures, stratified according to the addition or not of rhBMP-2, the spine area and the surgical approach. Overall, rhBMP-2 use did not

emerge as a risk factor for complications in anterior-only thoracolumbar fusion procedures, although patients who received the product were older and had more frequently undergone revision surgery. Conversely, considering anterior cervical fusion procedures, rhBMP-2 was a predictor of higher complication rates, particularly for wound infection. Similar results were reported by Cahill et al. [11].

Subsidence may result from osteoclast stimulation and bone resorption, a phenomenon that has been described in case of high rhBMP-2 concentration [35], progressively followed and replaced by a reactivation of osteoblasts and new bone formation. Hinsenkamp and Collard [56] recently reported the importance of concentration of rhBMP that may introduce some interactions with the effectiveness. The difference in concentration between DBM (demineralised bone matrix) and BMPs can vary to a magnitude order of 10^6, and this may explain the variability in efficiency and the adverse effects.

The unsatisfactory radiological outcomes reported in several series are likely to be attributable to the substitution of titanium cages with femoral ring [25] or bone dowel allografts [17, 18, 27]. The resorptive effect of rhBMP-2 on femoral ring allografts has also been mentioned in a case report [28]. Strengthening the construct with posterior pedicle screws during the time of bone remodelling may be a favourable option, as shown by Slosar et al. [24] in a prospective series of 75 patients (165 surgical levels). However, the majority of studies found no correlation between subsidence rates and lower clinical outcome in ALIFs [33, 57, 58]. Smoljanovic and Pecina [34] also commented on the transient period of bone remodelling observed by Burkus et al. [17] that "a clinical significance in this case seems to be negligible". Other studies concluded the same [23, 27].

AEs associated with BMP include: ectopic bone formation, bone resorption or remodelling, haematoma, neck swelling and painful seroma [14, 46, 59]. Extradiscal, ectopic or heterotopic bone formation have been mainly reported for posterolateral fusions, TLIF or PLIF procedures [14]. A pilot RCT on the use of BMP in PLIF was stopped by the FDA due to several cases of intracanal bone formation [60]. The risk of foraminal bone formation and subsequent spinal cord compression may be increased when placing rhBMP-2-soaked sponges close to the dura mater; thus it may be decreased by inserting anterior fusion cages [61]. However, in most cases, those observations of unintended bone formation were not related to any lower clinical outcome neither did they require additional surgery or treatment [14, 62].

As might have been expected, dysphagia, neck swelling or respiratory difficulties occur more frequently after cervical surgery with rhBMP-2. These AEs remain scarce in lumbar fusion and with similar incidence whether rhBMP-2 is applied or not, no matter the surgical approach [11]. As a consequence, the United States' authorities issued a public health notification in order to warn surgeons from inconsiderate usage of rhBMP-2 in cervical spine fusion, before any safe technique had been characterised and validated [15]. Based on animal studies, noxious effects of the exogenous growth factor on the nervous system have been assumed [63]. Neurological troubles, such as radiculitis, have not been reported for ALIF, and they remain a minor issue for patients after TLIF or PLIF [14, 47], even in case of intra-operative dural tear repair [47]. It should be emphasised that in the first RCTs, the surgeons preserved the posterior annulus and the posterior longitudinal ligament. This procedure decreased the risk for posterior rhBMP-2 leakage.

The application of rhBMP-2 in FDA-approved ALIF surgeries has received criticism for its potentially high rate of related AEs, which have been under-reported in the original publications on RCTs [36]. Thus, Carragee et al. claimed that some specific complications, notably subsidence, infections, RE and other urogenital events, arose more frequently in patients who received rhBMP-2 during ALIF surgery compared with those receiving autologous iliac crest bone graft without BMP. The controversy raised by Carragee et al. is questionable, as data from industry-sponsored pre-marketing studies were transmitted to the health authorities [7]. Carragee et al. [36] also present infection rates with bias. For instance, the authors pointed out high infection rates in BMP patients, but did not mention that the rates were similar in control patients. The authors also noted that early infection complications (<6 weeks after surgery) were similar in BMP and control patients according to FDA documents, while delayed infections (within 6-12 months after surgery) were more common in the BMP group (4.2 %) than in the control group (1.4 %). Again, the information is biased, as the authors did not mention that, if not only the six to 12 months but also the 12-24 months observation period is included in the calculation, the infection rate rises to 2.9 % in the control group. If only the 12-24 months period is considered, infection rates are 0 % and 1.4 % in the BMP and control groups, respectively [7]. Thus, depending on the observation period, fluctuations in the infection rates occur within both patient groups, whereas the overall rate of infections is similar in BMP and control patients (12.2 % versus 11.5 %).

Nevertheless, Carragee et al. also highlighted relevant safety concerns. When examining follow-up studies reported by Burkus et al. together with data published by the FDA, it becomes evident that rates of subsidence, RE and other urogenital events were higher in the BMP group [7, 21]. Additional reports on RE rates in ALIF surgeries performed with and without BMP have been published. A low incidence of RE (0.4 % and 1.3 %) was reported in two studies with over 600 patients receiving open ALIF surgeries, but no BMP [64, 65]. In another study, the RE rate in over 200 patients treated with ALIF surgery was 6.4 %. However, the authors did not report the type of graft applied in those patients, nor the presence of rhBMP-2 [66], so that the conclusion of Carragee et al. [36], that this relatively high RE rate was due to the application of BMP seems unfounded. The more recent review by

Singh et al. [42] is nevertheless in favour of a higher rate of RE, particularly if high doses of BMP are used which can be considered as off-label usage.

The laparoscopic approach has been assumed to be a risk factor for some AEs (RE, subsidence, device loosening/displacement) in the FDA report [7], although a later publication did not confirm a higher frequency of subsidence and device-related events in the laparoscopic group [20]. The potential role of the laparoscopic surgical approach with the use of BMP in the occurrence of AEs was not evaluated, as the approach was left at the surgeon's discretion, to avoid the need for learning a new technique. However, the original RCTs did not include any laparoscopic patient, whereas RE and subsidence rates were higher in the BMP group. Thus, although these increased rates of AEs may not have been statistically significant, the omission of a more detailed report on potentially BMP-related AEs gave rise to questions and mistrust amongst spinal surgeons [36]. The multivariate analysis of combined RCT data confirmed that RE incidence was significantly different whether ALIF was performed through a retroperitoneal or a transperitoneal approach ($p = 0.029$) [31]. As shown by Sasso et al. [38], the transperitoneal approach is a known cause of RE. The retroperitoneal approach appears much safer, with a limited rate of AEs, especially of RE (10 times less). Further studies are needed to clearly assess these safety concerns in the FDA-approved rhBMP-2 usage, *i.e.* ALIF procedure with tapered fusion cages. Supposed carcinogenicity of rhBMP-2 that was suspected in 2011 [36] is definitively not supported by the largest retrospective study reported by Kelly et al. [45] on half a million patients treated for lumbar fusion with and without BMP. As shown by Albilia et al. [67], the serum level of BMP is highly correlated with degenerative joint diseases and therefore it is impossible to associate the use of one dose of BMP-2 that disappeared completely of the body after 1 week to be responsible of cancer. This is confirmed by Kelly et al.'s study [45].

Conclusions and recommendations

The purpose of this review was to examine the safety profile of rhBMP-2 when used in ALIF surgery according to FDA approval [7]. After extensive review of RCTs and controlled series published up to the present point, we found no strong evidence of a significant increase of AEs related to rhBMP-2 during ALIF surgeries if its application follows FDA guidelines (level 1 evidence, two RCTs, one single-arm study, a total of 288 patients treated with BMP) [9, 10, 20]. Two additional RCTs performed with rhBMP-2 in combination with allogenic bone dowels reported increased bone remodelling in BMP patients. This AE was transient, and it had no consequence on the clinical outcome in those patients [16, 17]. No other BMP-related AEs were reported in these studies (level 1 evidence, two RCTs, a total of 79 patients treated with BMP).

Significantly increased rates of subsidence [23] and RE [21] were reported in case of an ALIF with rhBMP-2 (two cohort-controlled studies, level 2-3 evidence). Although these studies suggest that BMP was associated with an increased risk for those AEs, neither of them applied rhBMP-2 as approved by the FDA (indication, surgical method and implant, BMP dose). Notably, the following paragraph can be found in the respective FDA approval documents: "The safety and effectiveness of the BMP Bone Graft component with other spinal implants, implanted at locations other than the lower lumbar spine, or used in surgical techniques other than anterior open or anterior laparoscopic approaches have not been established" [7]. The clinical efficiency of rhBMP-2 is equal or superior to that of allogenic or autologous bone graft with respect to fusion rate, low back pain disability, patient satisfaction and rate of re-operations, provided that the treatment protocol closely adheres to FDA guidelines for the use of BMP/LT-cages in ALIF surgeries. In contrast, off-label application of rhBMP-2 in lumbar fusion surgery may lead to increased subsidence and RE, and possibly other unanticipated AEs.

Compliance with ethical standards

Declaration of competing interests Nothing to disclose for the authors.

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