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REVIEW ARTICLE

Clinical application of bone morphogenetic proteins for bone healing: a systematic review

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Abstract
Purpose This paper documents the existing evidence on bone morphogenetic proteins (BMPs) use for the treatment of bone fractures, non-union, and osteonecrosis, through a review of the clinical literature, underlying potential and limitations in terms of cost effectiveness and risk of complications.
Methods A systematic review was performed on the PubMed database using the following string: (bone morphogenetic proteins OR BMPs) and (bone repair OR bone regeneration) including papers from 2000 to 2016. The search focused on clinical trials dealing with BMPs application to favor bone regeneration in bone fractures, non-union, and osteonecrosis, in English language, with level of evidence I, II, III, and IV. Relevant data (type of study, number of patients, BMPs delivery material, dose, site, follow-up, outcome, and adverse events) were extracted and analyzed.
Results Forty-four articles met the inclusion criteria: 10 randomized controlled trials (RCTs), 7 comparative studies, 18 case series, and 9 case reports. rhBMP-2 was documented mainly for the treatment of fractures, and rhBMP-7 mainly for non-unions and osteonecrosis. Mixed results were found among RCTs and comparative papers: 11 reported positive results for BMPs augmentation, 3 obtained no significant effects, and 2 showed negative results. The only study comparing the two BMPs showed a better outcome with rhBMP-2 for non-union treatment.
Conclusion Clinical evidence on BMPs use for the treatment of fractures, non-union, and osteonecrosis is still controversial, with the few available reports being mainly of low quality. While positive findings have been described in many studies, mixed results are still present in the literature in terms of efficacy and adverse events. The difficulties in drawing clear conclusions are also due to the studies heterogeneity, mainly in terms of different BMPs applied, with different concomitant treatments for each bone pathology. Therefore, further research with well-designed studies is needed in order to understand the real potential of this biological approach to favour bone healing.

Keywords BMPs · Bone · Fractures · Non-union · Osteonecrosis

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Introduction

Bone healing is a complex process that requires the synergistic action of cells, cytokines, and growth factors (GFs) [1, 2]. Over the past few decades, the therapeutic application of GFs for bone regeneration gained increasing attention in the scientific community, for their ability to trigger cells to facilitate intracellular signal transduction for endochondral and intramembranous bone formation [3]. Among several GFs involved in skeletal remodeling and repair, the discovery by Urist of bone morphogenetic proteins (BMPs) at the end of the nineteenth century [4] was of great importance in understanding the complex biological cascade of osteogenesis.

BMPs are extensively studied and widely recognized as key factors in a variety of chondrogenic and skeletogenic

functions during normal embryonic development [5]. BMPs belong to the transforming growth factor β (TGF-β) super family and are considered to be a diverse group of phylogenetically conserved GFs, 20 members of which have been identified so far [6]. Multiple BMPs are considered to have a crucial signalling role in chemotactic proliferation and differentiation of osteoprogenitor cells, thereby inducing bone formation. It has been reported that BMPs play a central role in the regulation of the three major stages of fracture healing (inflammation response, chondrogenic phase, and osteogenic phase); however, the molecular mechanisms of action are still being investigated [7, 8]. Currently, there are two commercially available BMPs, recombinant human rh BMP-2 and rhBMP-7. They have been tested in several preclinical studies showing the ability to induce bone regeneration [9–11], and evaluated in clinical trials to treat various bone disorders such as non-unions, open fractures, and osteonecrosis [12–17]. The successful application of BMPs led, in July 2002, to the approval by the European Medicines Agency (EMA) of rhBMP-2 (InductOs®) for the treatment of single-level lumbar spine fusion and for acute tibial fractures in adults [18]. In November 2002, the American Food and Drug Administration (FDA) approved the use of rhBMP-2 (INFUSE® Bone Graft Device) for the treatment of open tibial fractures after stabilization with intramedullary nail (IM) fixation [18]. rhBMP-7 received official approval by EMA in 2004 as Osteogenic Protein-1 (OP-1® or Osigraft®) implant for the treatment of recalcitrant long bone non-unions [19]. Nevertheless, despite early promising results, some severe complications have been reported in clinical setting, such as ectopic bone formation, haematomas in soft tissues, and bone resorption around implants [20–22]. Thus, while BMPs seemed promising for bone regeneration, potential and limitations remains debated.

The aim of this review was to document and summarize the existing evidence on BMPs use for the treatment of bone fractures, non union, and osteonecrosis, through a systematic revision of the clinical literature, underlying potential and limitations in terms of cost effectiveness and risk of complications of this promising approach to favour bone healing.

Materials and methods

A systematic review was performed by two independent reviewers (GSK and DR) on the PubMed database using the following string: (bone morphogenetic proteins OR BMPs) and (bone repair OR bone regeneration), including papers from 2000 to 2016. An initial screening was performed on all abstracts. The search focused on clinical trials dealing with BMPs application to favor bone regeneration in the treatment of bone fractures, non union, and osteonecrosis, in English language, with level of evidence I, II, III, and IV. In the second step, full texts of the selected articles were screened, with further exclusions according to the previously described criteria. Reference lists from the selected papers were also screened. Relevant data (type of study, number of patients, BMPs delivery material, dose, commercial name, anatomical site, follow-up, outcome, and adverse events) were then extracted and collected in a database with consensus of the two reviewers, to be analyzed for the purposes of the present systematic review. A flowchart of the literature analysis is reported in Fig. 1.

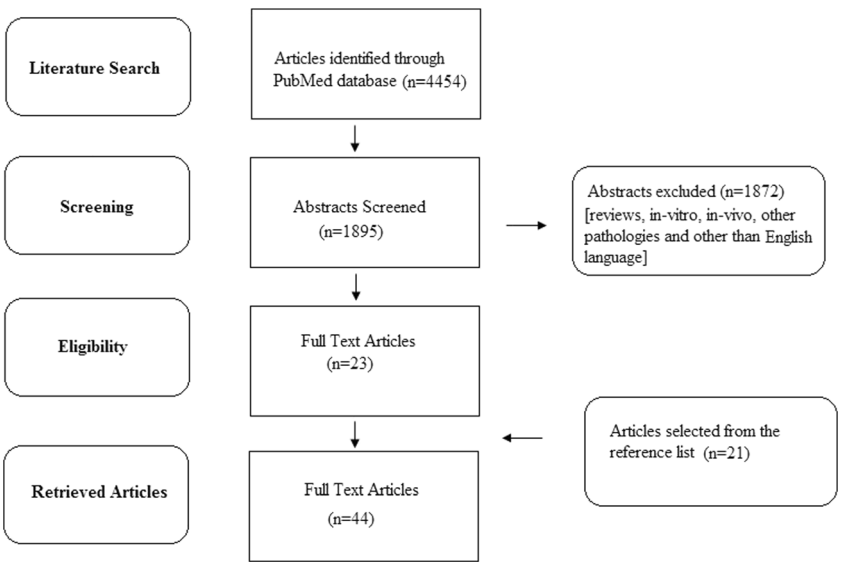

Fig. 1 Flow chart of the systematic literature review

Table 1 Synopsis of clinical trials dealing with rhBMPs application in fractures

rhBMP	Authors	Study	No of patients	Delivery	Dose	Commercial name	Site	F-up	Result	Adverse events
rhBMP-2	Govender 2002 [12]	RCT	150 pts. IM 151 pts. IM + low dose rhBMP-2 149 pts. IM + high dose rhBMP-2	ACS	0.75 mg/ml Vs 1.5 mg/ml	Inductos®	Tibia	12 m	+ For high dose	None
	Jones 2006 [23]	RCT	15 pts. ABG 15 pts. allograft + rhBMP-2	ACS	1.5 mg/ml	Infuse®	Tibia	12 m	+	None
	Swiontkowski 2006 [16]	RCT	131 pts. Gustilo-Anderson III (66 + rhBMP-2) 113 pts. IM (65 + rhBMP-2)	ACS	1.5 mg/ml	Infuse®	Tibia	12 m	+	None
	Schwartz 2008 [24]	Case report	1 pt. rhBMP-2 + Mastergraft®	ACS	1.5 mg/ml	Infuse®	Ulna	22 m	+	None
	Boraiah 2009 [25]	Comparative study	23 pts. allograft 17 pts. allograft + rhBMP-2	ACS	1.5 mg/ml	Infuse®	Tibia	18 m	−	Heterotopic bone formation in rhBMP-2 group (10/17)
	Aro 2011 [26]	RCT	136 pts. IM 139 pts. IM + rhBMP-2	ACS	1.5 mg/ml	Infuse®	Tibia	5 m	=	More infections (19%) in rhBMP-2 Other complications peripheral oedema (26%), heterotopic ossification (26%), pain (63%)
	Capo 2011 [27]	Case report	1 pt ABG + rhBMP-2	ACS	1.5 mg/ml	Infuse®	Radius and Ulna	9 m	+	None
	Baltzer 2012 [28]	Case report	1 pt. rhBMP-2 injection	None	2 mg/ml	Inductos®	Femoral neck	2 m	+	None
	Julka 2012 [29]	Case report	1 pt. rhBMP-2	ACS	1.5 mg/ml	Infuse®	Humerus	4–5 m	+	Heterotopic bone formation, secondary vein compression, massive inflammatory reaction
	Lyon 2013 [30]	RCT	62 pts. IM 122 pts. IM + low dose rhBMP-2 125 pts. IM + high dose rhBMP-2 60 pts. IM + buffer	CPM	1 mg/ml Vs 2 mg/ml	N/A	Tibia	13 m	−	Severe-treatment adverse events more frequently in rhBMP group (25%)
rhBMP-7	Maniscalco 2002 [31]	RCT	7 pts. EF 7 pts. EF + rhBMP-7	ACS	3.3 mg/ml	OP-1 Stryker	Tibia	6 m	=	None
	Mc Kee 2005 [32]	RCT	62 pts. IM 62 pts. IM + rhBMP-7	ACS	N/A	N/A	Tibia	6 m	+	None
	Risitiniemi 2007 [33]		20 pts. EF		3.3 mg/ml	Osigraft®	Tibia	20 m	+	

Table 1 (continued)

rhBMP	Authors	Study	No of patients	Delivery	Dose	Commercial name	Site	F-up	Result	Adverse events
		Comparative study	20 pts. EF + rhBMP-7	Coll I powder						Heterotopic ossification in rhBMP group, no symptoms
2 and 7	Axelrad 2008 [34]	Case series	3 pts. rhBMP-7 + thrombin pouch 1 pt. rhBMP-2	Coll I Powder and ACS	3.3 mg/ml rhBMP-7 1.5 mg/ml rhBMP-2	Infuse® OP-1 Stryker	Humerus	6–12 m	–	4/4 pts. developed heterotopic bone formation

Abbreviations: RCT: randomized control trail, BMP-2: bone morphogenetic protein 2, BMP-7: bone morphogenetic protein 7, ABG: autologous bone grafting, IM: intramedullary reaming, EF: external fixator, ACS: absorable collagen sponge, CPM: calcium phosphate matrix, Coll I: collagen type I; N/A: information not available, +: positive response for BMPs, –: negative response for BMPs

Results

According to the PubMed search analysis, a total of 4454 abstracts were screened and, among these, 44 articles met the inclusion criteria: 10 randomized controlled trials (RCTs), 7 comparative studies, 18 case series, and 9 case reports. This systematic review highlighted that the clinical use of BMPs as biological augmentation for bone regeneration presents a steady interest among physicians with new studies published in recent years. All papers are reported in three different tables according to the pathology considered (Tables 1, 2, 3), but only randomized trials have been further analyzed and described in the following paragraphs, according to the BMP used and the pathological target.

BMPs and fractures

The literature search for BMPs use in open fractures found: 7 RCTs, 2 comparative studies, 1 case series, and 5 case reports. With regard to the defect site, 9 papers dealt with tibial fractures, 3 with humeral fractures, 2 with forearm fractures, and 1 with femoral fractures (Table 1).

rhBMP-2 and fractures

In 2002, the BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) RCT [12] investigated safety and efficacy of rhBMP-2 for the treatment of tibial fractures in 450 patients randomized into three groups: 151 patients received 0.75 mg/ml of rhBMP-2 enclosed in a bovine derived Absorbable Collagen Sponge (ACS, Helistat; Integra LifeScience, Plainsboro, New Jersey), 149 patients received 1.50 mg/ml of rhBMP-2 enclosed in ACS, and 150 patients received only IM fixation. After 12 months, rhBMP-2 demonstrated to be safe and effective in accelerating tibial fractures healing at the dosage of 1.5 mg/ml. Overall, the frequency of secondary interventions, the rate of infections, and the invasiveness of the procedures were relatively lower. A subsequent analysis in 2006 [16] on the BESTT study patients plus a United States study group, was conducted taking into account the type of fractures and 1.5 mg/ml dosage. Subgroup I: 131 patients with Gustilo-Anderson type IIIA or IIIB tibial fractures — 65 patients as IM control group and 66 patients as experimental rhBMP-2 group; and Subgroup II: 113 patients with Gustilo-Anderson type I through type IIIB tibial fractures — 48 patients as IM control group and 65 patients as experimental rhBMP-2 group. The subgroup analysis revealed that the addition of rhBMP-2 was able to significantly reduce the frequency of bone grafting procedures and other secondary interventions at 12 months for the treatment of type III tibial fractures. In 2006 Jones et al. [23] investigated the treatment of tibial diaphyseal fractures associated with substantial bone loss in 30 patients: 15 patients with autolo-

Table 2 Synopsis of clinical trials dealing with rhBMPs application non-union

rhBMP	Authors	Study	No of patients	Delivery	Dose	Commercial name	Site	F-up	Result	Adverse events
rhBMP-2	Crawford 2009 [35]	Case series	9 pts. rhBMP-2	N/A	N/A	N/A	Humerus	N/A	+	None
	Tressler 2011 [36]	Comparative study	74 pts. ABG 19 pts. allograft + rhBMP-2	ACS	12 mg/cm^2	Infuse®	Multiple locations	20 m	+	None
	Desai 2010 [37]	Case series	9 pts. ABG + rhBMP-2	ACS	1.5 mg/ml	Infuse®	Tibia	5 m	+	None
rhBMP-7	Friedlaender 2001 [14]	RCT	61 pts. ABG 61 pts. rhBMP −7	Coll I powder	3.3 mg/ml	OP-1 Stryker	Tibia	24 m	+	Higher rate of osteomielytis in ABG group (13/61)
	Pecina 2003 [38]	Case report	1 pt. rhBMP-7 + BMAC	Coll I powder	3.3 mg/ml	OP-1 Stryker	Tibia	18 m	+	None
	Kujala 2004 [39]	Case series	5 pts. coral frame + rhBMP-2 (autografts if required)	Collagen carrier	2–5 mg/cm^3	None	Ulna	14 m	+	None
	Giannoudis 2005 [15]	Case series	395 pts. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	OP-1 Stryker	Multiple locations	15.3 m	+	None
	Bong 2005 [40]	Case series	23 pts. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	Osigraft®	Humerus	9 m	+	1/23 pts. heterotopic ossification and nerve complications
	Dimitriou 2005 [41]	Case series	25 pts. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	OP-1 Stryker	Multiple locations	15.3 m	+	None
	Calori 2006 [42]	RCT	16 pts. rhBMP-7 13 pts. PRP	Coll I powder	3.5 mg/ml	Osigraft®	Multiple locations	18.8 m	+	None
	Ronga 2006 [43]	Case series	105 pts. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	Osigraft®	Multiple locations	29.2 m	+	None
	Wysocki 2007 [44]	Case report	1 pt. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	OP-1 Stryker	Humerus	2 m	–	Heterotopic ossification of the triceps muscles
	Kanakaris 2008 [45]	Case series	68 pts. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	Osigraft®	Tibia	18 m	+	None
	Desmyter 2008 [46]	Case series	62 pts. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	OP-1 Stryker	Tibia	12 m	+	None
	Calori 2008 [13]	RCT	60 pts. rhBMP-7 60 pts. PRP	Coll I powder	3.5 mg/ml	Osigraft®	Multiple locations	12 m	+	None
	Giannoudis 2009 [47]	Case series	45 pts. ABG + rhBMP-7	Coll I powder	3.5 mg/ml	Osigraft®	Multiple locations	24 m	+	None
	Zimmermann 2009 [48]	Comparative study	82 pts. ABG 26 pts. rhBMP-7	Coll I powder	3.5 mg/ml	Osigraft®	Tibia	12 m	+	None
	Kanakaris 2009 [49]	Case series	30 pts. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	Osigraft®	Femur	24 m	+	None
	Moghaddam 2010 [50]	Case series	54 pts. rhBMP-7 (autografts if required)	ACS	3.5 mg/ml	Osigraft®	Multiple locations	6 m	+	None
	O'hEireamhoin 2011 [51]	Case series	13 pts. rhBMP-7	Coll I powder	3.5 mg/ml	Osigraft®	Multiple locations	9 m	+	None
	Papanna 2012 [52]	Case series	52 pts. rhBMP-7 (autografts if required)	Coll I powder	3.5 mg/ml	Osigraft®	Multiple locations	12 m	+	1/52 pts. developed distal tibiofibular synostosis

Table 2 (continued)

rhBMP	Authors	Study	No of patients	Delivery	Dose	Commercial name	Site	F-up	Result	Adverse events
	Murena 2014 [53]	Case report	2 pts. allograft +BMAC + rhBMP-7	Coll I powder	3.5 mg/ml	Osigraft®	Humerus	12 m	+	None
	Calori 2015 [54]	Comparative study	44 pts. ABG 44 pts. rhBMP-7	Coll I powder	3.5 mg/ml	Osigraft®	Multiple locations	9 m	+	None
	Ollivier 2015 [55]	Case series	20 pts. rCPBS + rhBMP-7	Coll I powder	3.5 mg/ml	Osigraft®	Tibia	14 m	+	1/24 infection
2 vs 7	Conway 2014 [56]	Comparative study	112 pts. ABG + rhBMP-2 63 pts. ABG + rhBMP-7	Coll I powder and ACS	1.5 mg/ml 3.3 mg/ml	Infuse® Osigraft®	Multiple locations	32 m	BMP-2 > 7	None

Abbreviations: RCT: randomized control trail, rhBMP-2: recombinant human bone morphogenetic protein 2, rhBMP-7: recombinant human bone morphogenetic protein 7, ABG: autologous bone grafting, PRP: platelet-rich plasma, IBG: impacted bone graft, ACS: absorable collagen sponge, CPM: calcium phosphate matrix, rCPBS: resorbable calcium phosphate bone substiute, BMAC: bone marrow aspirate cells, N/A: Information not available, +: positive response for BMPs, −: negative response for BMPs

Table 3 Synopsis of clinical trials dealing with rhBMPs application osteonecrosis

rhBMP	Authors	Study	No of patients	Delivery	Dose	Commercial name	Site	F-up	Result	Adverse events
rhBMP-2	Sun 2014 [17]	Comparative study	26 pts. IBG 20 pts. IBG + rhBMP-2	N/A	1.50 mg/ml	N/A	Femoral head	6.1 y	=	None
rhBMP-7	Lieberman 2004 [57]	Case series	15 pts. allograft + NCP + rhBMP-7	Gelatin capsule	50 mg	None	Femoral head	53 m	+	None
	Marsell 2014 [58]	Case report	1 pt. ABG + rhBMP-7	Coll I powder	3.5 mg/ml	Osigraft®	Humeral capitulum	4 m	+	None
	Papanagiotu 2014 [59]	Case series	7 pts. AFG + rhBMP-7	Coll I powder	3.5 mg/ml	Osigraft®	Femoral head	48 m	+	4/7 developed heterotopic ossification

Abbreviations: BMP-2: bone morphogenetic protein 2, BMP-7: bone morphogenetic protein 7, ABG: autologous bone grafting, ALG: allograft, PRP: platelet-rich plasma, IBG: impacted bone graft, AFG: autologous fibular grafting, NCP: non collagenous protein, N/A: information not available, +: positive response for BMPs, −: negative response for BMPs)

gous bone graft (ABG) and 15 with rhBMP-2 in combination with allograft. At 12 months, there was no significant difference in healing rate, bone-graft integration, and improvement in quality of life scores, underlying that the combination of rhBMP-2/allograft is a clinically beneficial and a safe alternative to ABG for tibial fractures with extensive traumatic diaphyseal bone loss. A large RCT was performed in 2011 by Aro et al. [26] evaluating rhBMP-2 addition for tibial fractures treatment. Three hundred patients were enrolled: 136 underwent IM fixation and 139 received IM fixation with rhBMP-2 in combination with ACS. The healing of tibial fractures was not significantly accelerated by the addition of rhBMP-2, although the chance of secondary intervention and invasive post surgery procedures was higher in the control group. However, the authors also described that the incidence of infection was higher in the rhBMP-2 group. Similarly, in 2013 Lyon et al. [30] showed no significant difference with or without rhBMP-2 for the treatment of tibial fractures: 62 patients received IM treatment, 122 patients received IM fixation with 1 mg/ml (low dose) of rhBMP-2 injection in a calcium phosphate matrix (CPM), 125 patients received IM fixation with 2 mg/ml (high dose) of rhBMP-2/CPM injection, and 60 patients IM fixation with buffer/CPM injection. After a mean follow-up of 13 months, the time to radiographic fracture union of the experimental groups was not improved. Likewise, pain free full-weight bearing was not significantly improved by both dosages of rhBMP-2/CPM and the rhBMPs group experienced more adverse events (as heterotopic ossification, oedema) compared with the IM or IM/buffer groups.

rhBMP-7 and fractures

In 2002, Maniscalco et al. [31] investigated the effect of external fixation (EF) with or without rhBMP-7 for the treatment of tibial fractures in 14 patients (seven patients EF and seven patients EF+ rhBMP-7). After 6 months, all patients had bony consolidation and no intra- or post-operative complications, with analogous healing time. In 2005, the Canadian Orthopaedic Trauma Society [32] evaluated the safety and efficacy of rhBMP-7 for tibial shaft fractures healing. The study consisted of 124 patients divided into two groups with 62 patients in the standard care IM treatment and 62 patients in the rhBMP-7 group. After 6 months, the incidence of delayed union, non-union, and secondary intervention was significantly lower in the rhBMP-7 group, which also presented a radiographically increased union rate with no adverse reactions.

BMPs and non-unions

The literature search for BMPs use in non-unions identified: 3 RCTs, 4 comparative studies, 15 case series, and 3 case reports. The anatomical location included a multitude of sites in 12 studies, such as femur, tibia, humerus, ulna etc., 7 papers treated tibial non-unions, 4 humeral non-unions, 1 ulna non-unions, and 1 femoral non-unions (Table 2).

rhBMP-7 and non-unions

In 2001, Friedlaender et al. [14] investigated safety and efficacy of rhBMP-7 in treating tibial non-unions: 122 patients (124 limbs) were divided into 61 patients receiving a combination of rhBMP-7 and type I collagen powder and 61 patients receiving ABG; all patients underwent IM fixation. At 9 and 24 months, all treated non-unions healed without differences between groups. In 2006, Calori et al. [42] compared safety and efficacy of rhBMP-7 and platelet-rich plasma (PRP) as biological augmentation for the treatment of non-unions in different anatomical sites. The study design included 29 patients treated with homologous or heterologous grafts divided into 16 patients receiving rhBMP-7 and 13 PRP placed directly within the graft. Preliminary results showed that rhBMP-7 seemed to be more effective, with higher healing rate and lower failure rate. These results were later confirmed in 2008 during the final analysis of this study [13] on a large cohort of 120 patients: 60 patients in each group. Clinical and radiological unions were superior in the rhBMP-7 group, also showing a lower radiographic healing time.

Complications

The use of BMPs raised some concerns on safety issues due to several negative effects that have been reported. The most severe complications were described in spine surgery, where the use of rhBMP-2 was associated with an increasing rate of vertebral osteolysis, graft subsidence, graft migration, formation of neutralizing antibodies against BMPs, radiculitis, haematoma or seroma, ectopic bone formation, pulmonary and neurological complications [60–62]. Due to these problems and to the high proportion of surgery performed with BMPs deviating for the original approved indications [63], the FDA issued a warning regarding the off label use of rhBMP-2 (INFUSE®) in cervical spine [64].

Considering the potential adverse events of BMPs, this systematic review on the treatment of bone fractures, non union, and osteonecrosis, also focused on the literature evidence of complications related to these orthopaedic conditions. The analysis of the comparative studies underlining a higher percentage of complications, showed that the majority of complications after BMPs treatment were related to heterotopic ossification, which were reported in 3 papers on fracture repair [25, 29, 34], in 2 papers on non union treatment [40, 44], and in 1 paper on osteonecrosis [59] involving both rhBMP-2 and 7. Moreover, other described complications were infections [26, 55], peripheral oedema, heterotopic ossification/soft-tissues calcification, new or increased pain

[26], and the development of distal tibiofibular synostosis (1/52) described with rhBMP-7 for non-union treatment [52].

Finally, regarding systemic reactions related to the use of BMPs, only 1 paper by Aro et al. [26] described elevated titres of rhBMP-2 antibody levels in 2% of patients. Interestingly, no clear association between immune response and reported adverse events or lack of efficacy was observed. All other papers did not report any systemic or allergic reactions following BMPs administration.

Economical aspects

Although there is currently good evidence supporting the efficacy and safety of BMPs in the treatment of fractures and non-unions, concerns are still raised about cost implications associated with its use. Considering the application in fractures repair, Alt el al. [65] showed that the use of rhBMP-2 reduced secondary interventions in patients with grade III tibial fractures treated with an unreamed nail, leading to net financial savings in Germany, France, and the UK. With regard to non-unions, a prospective non-randomized study conducted by Dahabreh et al. [66] demonstrated that the cost implications associated with the use of rhBMP-7 for the treatment of tibial non-unions were being offset by a reduction in other costs incurred with iliac crest bone grafting. Moreover, the same research group also suggested that the financial burden on the hospital could be reduced by early rhBMP-7 administration whenever a non-union fracture was present or anticipated. Finally, Calori et al. [67] performed a regional cost analysis on the Italian healthcare system for the use of rhBMP-7. The study demonstrated that, without appropriate reimbursement, the hospital underwent significantly higher surgical expenses when using rhBMP-7 instead of a gold standard technique (ABG). However, in contrast to these losses, the costs incurred during the follow-up were on average higher in patients treated with ABG compared to those receiving rhBMP-7.

Discussion

This systematic review highlighted that the clinical use of BMPs is a promising tool in supporting bone regeneration.

These positive findings explain the interest on this topic, which is also confirmed by the numerous (more than 50) ongoing clinical trials on BMPs in bone regeneration found at clinical trials.gov. On the other hand, this literature research also revealed that most of the clinical findings are based on case reports or case series with small patient populations, characterized by different delivery approaches, anatomical locations, bone pathologies and dosages, which makes it difficult to draw any final conclusion about the real potential of BMPs therapy and the best protocol they can be applied to [43–59]. Therefore, further research in this direction is needed.

Bone pathologies such as fractures, non-union or osteonecrosis represent a significant challenge for orthopaedic surgeons. Among the 6.2 million fractures occurring annually in the United States, 5 to 10% on average develop into delayed unions or non-unions with great expenditure for the national health system in terms of costs and work force loss [47]. In this scenario, BMPs have been suggested as a promising treatment approach for bone repair, since they are considered the most potent osteoinductive agents [68]. However, this systematic review found mixed results among the available RCTs and comparative papers: 11 reported positive results for BMPs augmentation, 3 obtained no significant effects, and 2 showed negative results.

Besides mixed results, the difficulties in drawing clear conclusions on BMPs are also due to the heterogeneity of the published studies, mostly in terms of different BMPs applied, with different concomitant treatments for each bone pathology.

In fracture healing, the most used rhBMPs is the type 2 described in 10 papers, while 4 papers were about rhBMP-7, and 1 paper used both rhBMPs. Among RCT and comparative trials, 5 papers reported positive results, 2 no significant effects, and 2 negative results. rhBMPs were effective in accelerating tibial fractures healing, reducing the frequency of secondary interventions and the rate of infections [12, 16, 23, 32, 33]. Moreover, they showed to be a valid approach in combination with allografts, as an alternative to ABG, leading to the same beneficial effects but avoiding the drawbacks related to invasive autologous bone harvesting procedures [23]. The negative results reported were related to the higher rate of complications in the rhBMPs group, i.e., heterotopic ossification or calcification [25, 30], local oedema, or calcinosis [30].

For non-union treatment, the most used rhBMPs was the type 7 with 21 papers, 3 used rhBMP-2, and 1 compared type 2 and 7. Among RCTs and comparative studies, all 6 papers reported superior results with rhBMPs, in terms of clinical outcome, radiographic consolidation, and healing time acceleration [13, 14, 36, 42, 48, 54]. Moreover, rhBMPs provided comparable results to ABG treatment [14, 48, 54] with shorter operative time, reduced operative blood loss, and avoiding donor site morbidity [14, 36]. Regarding safety, comparative studies did not show a higher complication rate, with some adverse events reported only in 3 non-comparative papers [40, 44, 52] describing cases of heterotopic ossification [40, 44] or tibiofibular synostosis [52].

Finally, little evidence has been reported on osteonecrosis, with four published studies, one of which was comparative [17] and described similar results with or without rhBMPs. No complications or adverse events have been reported in these studies.

In general, while there is a tendency to use rhBMPs for certain indications, there is no consensus about the best BMPs for the regeneration of each specific bone pathology and the only comparison was performed by Conway et al. [56] in a retrospective study, with a higher and faster rate of radiographic bone non-union healing with rhBMP-2 compared to rhBMP-7, and no difference in the complication rate between groups. However, the overall lack of well-designed comparative studies prevents determining if both BMPs are equally effective or if they differ in terms of enhancement potential of bone healing in heterogeneous orthopaedic conditions.

Another critical point is the delivery method, since most of the available commercial products combined BMPs with biomaterials, and structural and biomechanical properties of carriers are considered key aspects for the modulation of BMPs availability at the site of injury [69]. In fact, these molecules are relatively soluble, and if not maintained by an appropriate carrier, they will be cleared from the site and diffuse into adjacent undesirable tissues, promoting adverse reactions (such as ectopic bone formation) [69]. Several materials have been tested in pre-clinical settings, such as collagen, calcium phosphate ceramics, and synthetic polymers but only bovine collagen based BMPs delivery devices (ACS or powder) with official approval for clinical use were documented [70]. Despite the use of delivery devices, large doses of BMPs are required to achieve the desired osteogenic effects, which makes the procedure expensive and increases the risk of clinical complications related to their supra-physiological concentration [71]. Therefore, new solutions for BMPs delivery able to maintain a more sustained and effective release pattern still need to be explored.

Conclusion

This systematic review showed controversial clinical evidence on BMPs use for the treatment of fractures, non union, and osteonecrosis. Knowledge on this topic is still preliminary and the few available reports are mainly of low quality. While positive findings have been described in many studies, overall literature still presents mixed results in terms of efficacy and adverse events. The difficulties in drawing clear conclusions on BMPs are also due to the heterogeneity of the published studies, mostly in terms of different BMPs applied, with different concomitant treatments for each bone pathology. Further well designed comparative studies are needed to confirm the promising findings and optimize BMP use both in terms of best delivery method and most successful indications for the treatment of bone pathologies.

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Compliance with ethical standards

Conflict of interest Elizaveta Kon declares:
Zimmer-Biomet (USA): Paid presenter or speaker.
Cartiheal (Israel): Paid consultant; Stock or stock options.
Fidia (Italy): Paid presenter or speaker.
Finceramica (Italy): Paid presenter or speaker.
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