Injury, Int. J. Care Injured 40 (2009) S3, S54–S61

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

Application of bone morphogenetic proteins to femoral non-unions: A 4-year multicentre experience

N.K. Kanakaris[a], N. Lasanianos[a], G.M. Calori[b], R. Verdonk[c], T.J. Blokhuis[d], P. Cherubino[e], P. De Biase[f], P.V. Giannoudis[a,*]

[a]Department of Trauma and Orthopaedics, Leeds Teaching Hospitals NHS Trust, Leeds General Infirmary, Leeds LS1 3EX, UK
[b]Department of Trauma and Orthopaedic Surgery, Instituto Ortopedico Gaetano Pini, Milan University, Italy
[c]Department of Orthopaedic Surgery, Ghent University, Belgium
[d]Department of Surgery and Traumatology, University Nijmegen Medical Centre, The Netherlands
[e]Department of Orthopaedics and Trauma Sciences, Ospedale di Circolo, Varese, Italy
[f]Department of Trauma and Orthopaedic Surgery, Azienda Ospedaliero Universitaria Careggi, Florence, Italy

ARTICLE INFO

Keywords:
Bone morphogenetic proteins
Non-union
Femur
bmpusergroup.co.uk

ABSTRACT

Fracture non-unions often complicate orthopaedic trauma. BMPs (bone morphogenetic proteins) are currently considered the most appealing osteoinductive agents. Applications of BMP-7 since January 2004 were prospectively recorded in a multicentre registry of aseptic femoral non-unions. The study included 30 patients who had undergone a median of 1 revision operation before BMP-7 application and who were followed up for a median 24 months. In 23/30 cases the application of BMP-7 was combined with revision of the fixation, and in 12 it was combined also with autograft. Non-union healing was verified in 26/30 cases in a median period of 6 months. No adverse events were associated with BMP-7 application.

Our case series supports the safety and efficacy of BMP-7 in femoral non-unions. Multicentre networks and systematic, long-term follow-up of patients may improve understanding of this promising osteoinductive bone substitute.

Introduction

Long-bone fracture non-unions are clinical problems that affect hundreds of thousands of people worldwide.[56] In cases where the biological substrate is compromised several therapeutic approaches have been investigated, including autologous bone transplantation,[20,52] implantation of different biomaterials[39] and application of cytokines, hormones or growth factors.[3,9,34,51]

Non-unions of femoral fractures, in particular, are both rare and very challenging since their successful treatment may be prolonged and may exploit numerous resources.[14,32,63] Management of femoral diaphyseal fractures with intramedullary nailing typically results in union rates ranging between 90% and 100%.[61,62] Nevertheless, femoral non-unions do occur[38] and it should be stated that statistics of previous reports may not now be accurate, in view of the continuously increasing rates of survival of victims of polytrauma and the improving limb salvage techniques of contemporary orthopaedic trauma surgery.[12,29,48]

The variation in the management of the different non-union types[8,40] (septic versus aseptic, atrophic versus hypertrophic) trails the improvement of our understanding of the biomechanical[6,38,45] and biological[42,49,55] prerequisites for optimal bone healing. The standard treatment of the majority of aseptic non-unions is mechanical stabilisation, including various forms of internal or external fixation and with or without biological stimulation, depending on the accurate assessment and classification of the non-union. Autogenous cancellous bone grafting remains the gold-standard biological method for promoting union by stimulating the local biology at the non-union site. However, the limited availability of suitable bone, as well as potential donor site morbidity and complications,[2,19,64] have dictated the development of alternative methods of biological stimulation. Among contemporary alternatives to grafting, the use of bone morphogenetic proteins (BMPs), as powerful osteoinductive agents that enhance the biological environment of fracture non-unions,[33,39,51] has gradually gained the attention of the scientific community and its indications have expanded.[26,28,59] Evidence of the effectiveness and safety of BMPs has continuously increased since their initial discovery,[57] resulting in the approval of two (rhBMP-7 and rhBMP-2) by the US Food and Drug Administration for clinical application.[15,21,27]

The application of BMPs to long-bone non-unions has been examined in a number of reports[7,13,17,30,31,34,50] but, to the best of our knowledge, BMP-treated femoral non-unions have not hitherto been studied specifically. The aim of this investigation is to present a comprehensive analysis of a multicentre prospective effort to systematically record and evaluate the results of BMP-7 application in the treatment of aseptic femoral non-unions.

Patients and methods

A focused electronic databank (bmpusergroup.co.uk) has been created and updated constantly since January 2004. It has

*Corresponding author.
Tel.: +44 (0) 113 39 22750; fax: +44 (0) 113 39 23290.
E-mail address: pgiannoudi@aol.com (P. Giannoudis).

0020-1383/ $ – see front matter

accumulated clinically relevant prospective and retrospective data regarding the use of BMP-7 ever since, and follows the clinical course of all registered patients from six international specialised orthopaedic centres (three Italian university hospitals, one Belgian, one Dutch and one from the UK). The databank was designed to incorporate demographic details, in-hospital peri-operative and follow-up information until final discharge and all radiographic investigations. A site of non-union is defined as healed in the absence of pain on loading or abnormal movement at the non-union site, and in the presence of bridging callus on three of the four cortices as viewed in two different planes in the radiological assessments. The clinical and functional outcomes are recorded and assessed using parameters such as union, complication, rates of return to previous occupation and the European Quality of Life scale (EuroQol 5D).[1] Informed consent was obtained from all the patients regarding the use of BMP-7, and local ethical committee boards approved the present study and the creation of the databank.

From the existing data on the databank we extracted those referring to people treated with BMP-7 for an established femoral aseptic non-union (duration >9 months) with a minimum follow-up of 12 months. Each unit used of BMP-7 (Osigraft®; Stryker Biotech, Hopkinton, Massachusetts, MA) contained 3.5 mg rhBMP-7 mixed with 1 g type I bovine-derived collagen. The total volume per unit was approximately 4 ml. One unit per non-union site was applied in all cases. According to the agreed protocol, it was up to the surgeon's discretion whether to augment the BMP-7 implantation with an autograft for non-union sites with a defect greater than 1 cm, according to a 'graft expanding' rationale.

Descriptive statistics were used for a more comprehensive presentation of the results of our prospective case series.

Results

The series comprised 30 consecutive cases of femoral aseptic atrophic non-union treated with BMP-7, with a minimum follow-up of 12 months (Table 1). Of these participants, 8 were women and 22 were men, with an average age of 42 years (range 20 to 78, median 43.2 years); 9 were smokers,[10] 2 had been receiving non-steroidal anti-inflammatory drugs[25,41] as painkillers for >1 month and 1 had diabetes mellitus.[4]

All the original injuries were femoral fractures, due in 20 cases to motor vehicle collisions, in 4 to motorcycle accidents and in 6 to falls; 17 of the fractures affected the femoral shaft (Fig. 1), 4 the sub-trochanteric area (Fig. 2) and 9 the supracondylar area (Fig. 3).

The fractures comprised 22 closed and 8 open injuries – 4 grade II and 4 grade IIIb. The initial treatment method varied; for 15 fractures intramedullary nailing (IMN) was selected and for 10 plate open reduction internal fixation (ORIF). External fixation was applied to five fractures as a damage control procedure. The external fixators were converted to IMN in one case and to circular frames in four (one Hybrid, three Ilizarov). The median time from initial injury to BMP-7 operation was 24 months (range 9 to 65, mean 27.5 months), with a median of one operation before the BMP-7 grafting (range 1 to 5, mean 1.6 operations). In all cases this was the first time BMP-7 had been applied, and in 9 cases autologous bone graft (ABG) had already been used unsuccessfully.

At the time of application of the BMP-7, all non-unions were aseptic according to intraoperative microbiology samples and the overall clinical profile of each case. For 7 participants, when BMP-7 was applied no other surgical intervention or revision of the existing fixation was performed. For the remaining participants, BMP-7 grafting supplemented 14 IMNs (11 exchange nailings and 3 revisions from ORIF), 6 ORIFs (1 from IMN, 5 ORIF exchange) and 2 circular frames (1 from IMN and 1 exchange). In 12 cases, the BMP-7 accompanied the use of ABG according to the graft expansion rationale.[23]

The median follow-up in these cases lasted 30 months (range 12 to 68, mean 31.2 months). The union rate for that period of time was 86.7% (26 healed non-unions), and the median time to union was recorded as 6 months (range 4 to 10, mean 6.2 months). Four people did not progress to successful healing of their non-union. Of these, three underwent further revision of their ORIF fixation with graft substitute, new BMP-7 application, and autograft implementation, respectively, and one underwent two further operations with removal of plate due to infection and renewed BMP-7 application. One of the above fractures (case 15) united 4 months following re-implantation of BMP-7, and the remaining three are still under clinical review.

On the last follow-up appointment, 19 of the 27 participants in work had returned to their previous occupation, 7 had changed occupation and 1 had retired. As to the different parameters of the EuroQol 5D health questionnaire, nine participants reported some problems with their mobility, nine some discomfort with their usual activities and two some discomfort with self-care. Two people reported moderate anxiety and/or depression, and six moderate pain in the extremity. The visual analogue scale for their overall health status reached a median score of 82.5 (range 45 to 95, mean 77.3).

No systemic allergic reactions or adverse effects were encountered following the application of BMP-7, and no complications related to the bone substitute were observed. Only mild to moderate local postoperative complications were noted (two superficial wound infections treated with antibiotics, one haematoma, one deep vein thrombosis).

Discussion

The healing rate of femoral fractures is usually >90%.[18,43,53,61,62] However, when femoral non-union does occur, its treatment may be laborious and long lasting. Different treatment methods or combinations of methods are required according to the classification of the fracture.[13,36] Whereas hypertrophic non-unions usually heal by the provision of stable skeletal fixation alone, atrophic non-unions are considered more difficult because they indicate a poor biological environment at the non-union site.[25] Among the several agents that may contribute to the biological enhancement of an atrophic non-union site, BMPs seem to be the most promising and have been most rapidly adopted.[15,33]

Following on the initial periods of experimental[37] and clinical[60] investigation of BMPs, and the recent internationally wide spread of their use to accelerate bone healing, the establishment of focused multicentre registries appears to be the next step. These could systematically evaluate the efficacy and safety of BMP therapy and further advance our understanding of these molecules in the clinical setting.[31]

However, most of the studies in the literature are not specific to femoral non-union but refer to long bones in general, although some do include femoral cases.[7,17,50] The present report describes the preliminary results of the management of specifically femoral non-unions using BMP-7, in six different European university centres over a period of almost 5 years. The fact that this is an observational, uncontrolled study limits the level of evidence that the results represent, and also the extent of their statistical analysis. The results may also be influenced by the differing strategies of fixation followed in the contributing centres, the numbers and skills of the surgeons involved,[10] and the differences between patient populations. However, this research does present the actual clinical reality and reflects the current clinical practice of these six university centres.

Although several factors (comorbidities, fracture patterns, therapies and postoperative parameters) may influence the clinical and functional outcome of femoral fractures, these final results appear encouraging in all the reviewed clinical trials (Table 2),

Table 1
Overall values for the patients examined

Case	Gender	Age (y)	Fracture	Anatomical site	Sequence of operative interventions	Revisions before using BMP-7	Previous ABG	Follow-up since BMP-7 (months)	Union	Time to union following BMP-7 (months)	Reoperations after BMP-7
1	F	45	cl	Shaft	1. IMN 2. Dynamisation 3. BMP-7	1	no	27	yes	6	0
2	M	44	Grade I	Supracondylar	1. ORIF 2. ORIF revision 3. BMP-7	1	no	30	yes	6	0
3	M	20	Grade III	Supracondylar	1. ORIF 2. ORIF revision and autograft 3. BMP-7	2	yes	53	yes	8	0
4	M	38	cl	Shaft	1. IMN 2. Dynamisation 3. Exchange IMN and BMP-7	1	no	21	yes	5	0
5	M	25	cl	Shaft	1. IMN 2. Exchange IMN 3. Exchange IMN and BMP-7	1	no	12	yes	4	0
6	M	40	cl	Subtrochanteric	1. IMN 2. Dynamisation 3. Exchange IMN and BMP-7	1	no	39	yes	6	0
7	M	24	cl	Shaft	1. IMN 2. Dynamisation 3. Exchange IMN, BMP-7 and autograft	1	no	12	yes	5	0
8	F	31	Grade I	Supracondylar	1. Ex-Fix 2. Ex-Fix hybrid 3. Ilizarov and BMP-7	1	no	68	no	N/A	1
9	F	51	cl	Shaft	1. ORIF 2. IMN 3. Exchange IMN and BMP-7	1	no	15	yes	5	0
10	M	22	cl	Supracondylar	1. ORIF 2. IMN 3. Exchange IMN, BMP-7 and autograft	1	no	23	yes	6	0
11	M	49	cl	Shaft	1. IMN 2. Dynamisation 3. Exchange IMN 4. ORIF, BMP-7 and autograft	2	no	58	yes	9	0
12*	M	24	cl	Supracondylar	1. ORIF 2. ORIF revision and autograft 3. ORIF revision, BMP-7 and autograft	1	yes	12	yes	8	0
13	F	42	cl	Shaft	1. ORIF 2. ORIF revision 3. ORIF revision and BMP-7	1	no	12	yes	5	0
14	M	40	Grade III	Shaft	1. Ex-Fix 2. IMN 3. Exchange IMN and BMP-7	1	no	13	yes	5	0
15	M	28	Grade II	Shaft	1. Ex-Fix 2. Ilizarov 3. Ilizarov revision 4. ORIF and autograft 5. ORIF revision and autograft 6. ORIF revision, BMP-7 and autograft	4	yes	42	no	N/A	2
16	M	70	Grade I	Shaft	1. Ex-Fix 2. Ilizarov 3. IMN 4. Ilizarov and BMP-7	2	no	55	no	N/A	1
17	F	77	cl	Subtrochanteric	1. IMN 2. Exchange IMN 3. Exchange nail, BMP-7 and autograft	1	no	48	yes	7	0
18	F	78	cl	Supracondylar	1. ORIF 2. Removal and Ex-Fix 3. ORIF and autograft 4. Blade plate and autograft 5. Autograft 6. BMP-7 and autograft	4	yes	20	yes	10	0

continued on next page

Table 1
(*continued*)

Case	Gender	Age (y)	Fracture	Anatomical site	Sequence of operative interventions	Revisions before using BMP-7	Previous ABG	Follow-up since BMP-7 (months)	Union	Time to union following BMP-7 (months)	Reoperations after BMP-7
19	M	59	cl	Shaft	1. IMN 2. Dynamisation 3. Exchange nail and BMP-7	1	no	30	yes	6	1
20	M	53	cl	Shaft	1. IMN 2. Exchange IMN 3. Exchange nail, BMP-7 and autograft	1	no	29	no	6	0
21*	F	73	cl	Shaft	1. ORIF 2. IMN 3. Exchange IMN and BMP-7	1	no	16	yes	5	0
22*	M	62	cl	Subtrochanteric	1. IMN 2. Exchange IMN 3. Exchange IMN, BMP-7 and autograft	1	no	18	yes	6	0
23	M	33	cl	Shaft	1. IMN 2. Exchange IMN 3. BMP-7 and autograft	1	no	6	yes	5	0
24	M	36	Grade III	Supracondylar	1. ORIF 2. MSC injection 3. ORIF revision 4. ORIF revision and autograft 5. ORIF revision, BMP-7 and autograft	3	yes	47	yes	8	0
25	M	53	cl	Subtrochanteric	1. IMN 2. Dynamisation 3. Exchange IMN and BMP-7	1	no	49	yes	7	0
26	F	28	cl	Shaft	1. IMN 2. Dynamisation 3. Exchange IMN and BMP-7	1	no	49	yes	7	0
27	M	44	cl	Supracondylar	1. Ex-fix 2. Ilizarov 3. lizarov revision 4. ORIF and BMP-7	2	yes	32	yes	5	0
28	M	30	Grade III	Supracondylar	1. ORIF 2. ORIF revision and bone marrow aspirate injection 3. BMP-7 and autograft	1	yes	39	yes	5	0
29	M	38	cl	Shaft	1. IMN 2. Dynamisation 3. Exchange IMN 4. Autograft 5. Autograft 6. Exchange IMN and autograft 7. BMP-7	5	yes	31	yes	5	0
30	M	38	cl	Shaft	1. IMN 2. Dynamisation 3. Exchange IMN 4. Autograft 5. Exchange IMN and BMP-7	3	yes	30	yes	6	0

BMP-7, bone morphogenetic protein-7; ABG, autologous bone grafting; F, woman; M, man; cl, closed fracture; Ex-Fix, external fixation; IMN, intramedullary nailing; N/A, not applicable; ORIF, open reduction internal fixation; MSC, mesenchymal stem cells.
*Cases also presented in Figs 1–3.

as well as in all of the six different centres included in the present study. Healing rates range between 75% and 100% with a mean of 83.6% (in our study group this was 86.7%).[7,17,30,50] The conventional gold-standard treatment with autograft or exchange nailing reaches similar levels of non-union healing (87–100%).[13,46,52] However, considerable morbidity is associated with these established procedures, including blood loss, nerve and muscle injury, chronic pain at the donor site and local infection.[11,19,54] The limited availability of autograft and the poorer results among older people should also be taken into account.[5] Furthermore, a large number of the cases where BMP-7 has been used have been those where autologous bone graft or exchange nailing have already failed (30% and 26.7%, respectively, in our sample), and these represent a resistant and difficult-to-treat group of non-unions.

An even larger consensus appears to exist among authors as to the safety of local application of BMP-7. No adverse events directly associated with this procedure were recorded in our series. Despite the fact that there are sporadic clinical reports of osteoclastic bone resorption,[24,35,47] there were no indications of such

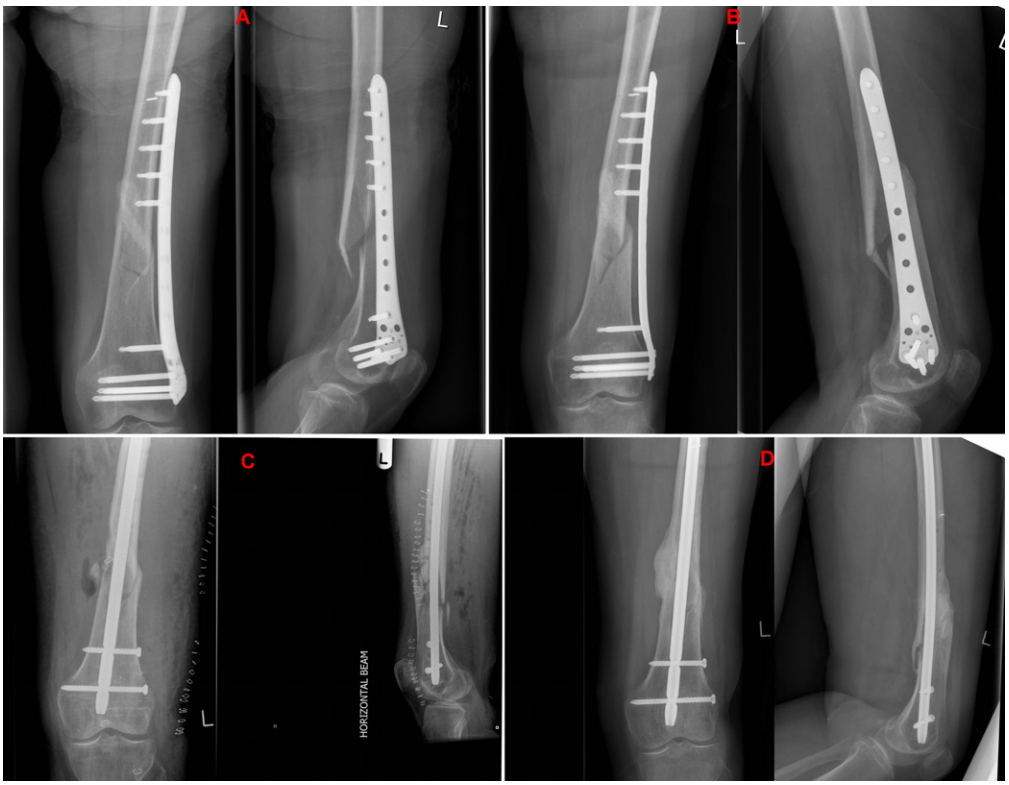

Fig. 1. Case 21, 73-year-old woman after road traffic accident. Left spiral femoral shaft fracture treated with locking less invasive stabilisation system and minimally invasive percutaneous plate osteosythesis (LISS MIPPO) at another centre; no healing 9 months later. (A) Intramedullary nail fixation and BMP-7 application at 9 months after injury. (B) Pain-free function of the extremity and radiological healing 5 months after (A).

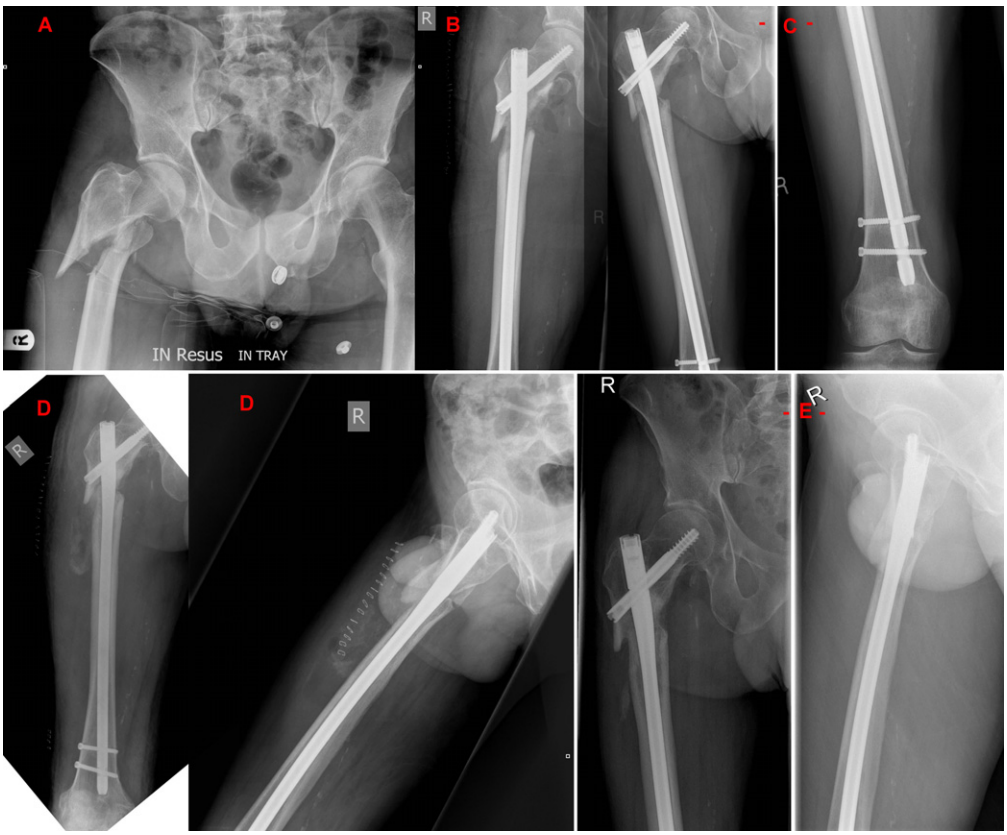

Fig. 2. Case 22, 62-year-old man after a fall. (A) Subtrochanteric right femoral fracture. (B) Initial intramedullary nail fixation following malreduction in varus angulation and distraction. (C) Eighteen months after initial fixation and failed exchange nailing. (D) Revision of the nail and application of BMP-7 and autograft. (E) Radiologically and clinically evident healing 6 months after (D).

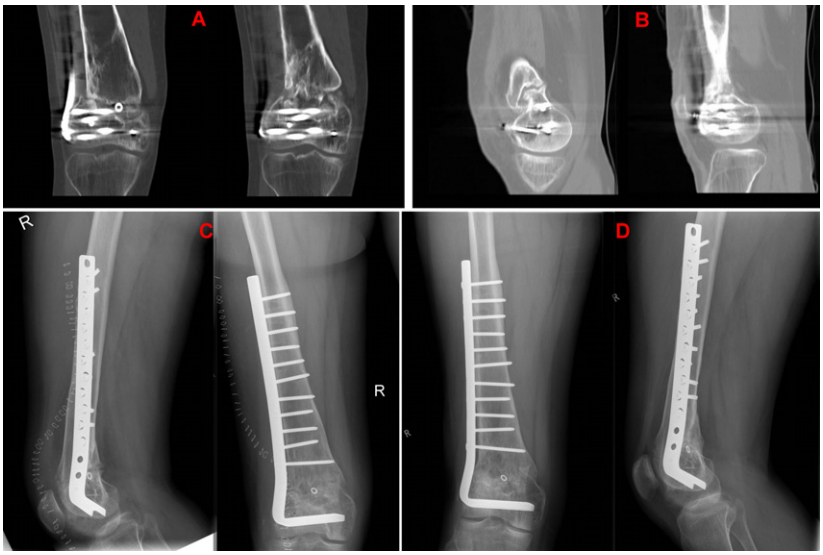

Fig. 3. Case 12, 24-year-old man after road traffic accident; 2-D computed tomography (CT) coronal reconstruction of supracondylar right femoral fracture 12 months after injury, using open reduction with internal fixation (ORIF), followed by revision with locking less invasive stabilisation system (LISS); first two operations performed at another centre, 2-D CT sagittal reconstruction. (A) Postoperative films (anteroposterior and lateral) after revision ORIF with a blade plate and BMP-7 application. (B) Radiologically evident healing and free full weight bearing 8 months after BMP-7 application.

Table 2
Original clinical studies on the application of bone morphogenetic proteins to femoral fractures with an indication of non-union

Reference	Type of study, LOE	Non-unions treated with BMPs*	Indication	Union rates (femur)	Mean time to union (range)	Reoperation rate	Functional outcome
Johnson EE et al.[30]	Prospective observational (hBMP and allograft), IV	12 (25)	Tibial, femoral or humeral non-union	75%	6 months (3–14)	20%	14 excellent, 5 good, 5 fair
Dimitriou R et al.[17]	Prospective observational (BMP-7), IV	8 (25)	Tibial, femoral, humeral, forearm or clavicular non-union	100%	5.6 months (2.5–11)	12%	N/A
Ronga M et al.[50]	Retrospective observational (BMP-7), IV	23 (105)	Tibial, femoral, humeral, forearm or clavicular non-union	78.3%	7.9 months (2–21)	16.2%‘	N/A
Calori GM et al.[9]	Prospective randomised controlled (BMP-7 vs PRP), II–III	5 (16)	Tibial, femoral, humeral or forearm non-union	100%	8 months (+/− 0.43)	6.2%	N/A
Present study	Prospective observational (BMP-7), IV	30	Femoral non-union	86.7%	6 months (4–10)	13.3%	21 excellent, 5 good, 4 poor (reoperation)

LOE, level of evidence; BMP, bone morphogenetic proteins; PRP, platelet rich plasma; N/A, not applicable.
*Values without parenthesis indicate number of femoral non-unions, with parenthesis indicate total non-unions.

an event at any of the existing sites of BMP-7 application in this database. We appreciate, however, that the possible development of a BMP-7 or collagen-I specific immunological response was not evaluated in our study; mostly clinically apparent adverse events and complications were recorded. The existing evidence on immunological interaction with the currently used composite implant (3.5 mg rhBMP-7 mixed with 1 g type I bovine-derived collagen) describes an incidence of anti-BMP-7 and anti-collagen antibodies of 5–10%.[16,21,44,58] The extent of this sensitisation and any translation at the clinical level remain unclear and are presently under investigation.

Another important parameter in the contemporary evaluation of any therapeutic strategy, besides its safety and efficacy, is its financial implication. There are currently a few available studies[14,22,32] which have assessed the crucial aspect of health economics in the clinical setting of BMP-7 treatment of non-unions. Dahabreh et al.[14] estimated that the overall cost of treatment of persistent fracture non-unions with rhBMP-7 was 47.0% less than that of the numerous previous unsuccessful treatments. The authors concluded that treating fracture non-unions is costly, but this could be reduced by early rhBMP-7 administration when a complex or persistent fracture non-union is present or anticipated. Thus the existing evidence appears to be encouraging as to the financial aspect of BMP-7 therapy.[14,22,32] The establishment of prospective data registries regarding the use of the BMPs is anticipated to provide the information needed for a thorough evaluation of these apparently expensive agents as to their cost effectiveness, particularly if direct and indirect costs are impregnated to the analysis.

In the contemporary age of informatics, systematic collaborative work based on modernised methods of registering data between multiple centres and countries appears to emerge in almost all fields of medicine. In clinical practice this translates mostly to multicentre clinical trials with a time deadline and often limited follow-up. The establishment of a BMP-user registry over the past few years appears to provide more consistent methods in the continuous quest for evidence-based clinical practice.

Competing interests: All the authors declare that no funding was provided for this manuscript. PVG has received consulting fees, last 3 years, from Stryker, Synthes, Depuy.

References

1. EuroQol – a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199–208.
2. Arrington ED, Smith WJ, Chambers HG, et al. Complications of iliac crest bone graft harvesting. Clin Orthop 1996;329:300–9.
3. Atkins RM. Principles of management of septic non-union of fracture. Injury 2007;38(Suppl 2):S23–32.
4. Beam HA, Parsons JR, Lin SS. The effects of blood glucose control upon fracture healing in the BB Wistar rat with diabetes mellitus. J Orthop Res 2002;20:1210–6.
5. Boskey AL, DiCarlo E, Paschalis E, et al. Comparison of mineral quality and quantity in iliac crest biopsies from high- and low-turnover osteoporosis: an FT-IR microspectroscopic investigation. Osteoporos Int 2005;16:2031–8.
6. Brinker MR, O'Connor DP. Exchange nailing of ununited fractures. J Bone Joint Surg Am 2007;89:177–88.
7. Calori GM, D'Avino M, Tagliabue L, et al. An ongoing research for evaluation of treatment with BMPs or AGFs in long bone non-union: protocol description and preliminary results. Injury 2006;37(Suppl 3):S43–50.
8. Calori GM, Phillips M, Jeetle S, et al. Classification of non-union: need for a new scoring system? Injury 2008;39(Suppl 2):S59–63.
9. Calori GM, Tagliabue L, Gala L, et al. Application of rhBMP-7 and platelet-rich plasma in the treatment of long bone non-unions: a prospective randomised clinical study on 120 patients. Injury 2008;39:1391–402.
10. Castillo RC, Bosse MJ, MacKenzie EJ, Patterson BM. Impact of smoking on fracture healing and risk of complications in limb-threatening open tibia fractures. J Orthop Trauma 2005;19:151–7.
11. Chapman MW, Bucholz R, Cornell C. Treatment of acute fractures with a collagen-calcium phosphate graft material. A randomized clinical trial. J Bone Joint Surg Am 1997;79:495–502.
12. Civil ID. Improved outcomes after polytrauma: do we know the reasons? Injury 2007;38:991–2.
13. Crowley DJ, Kanakaris NK, Giannoudis PV. Femoral diaphyseal aseptic non-unions: is there an ideal method of treatment? Injury 2007;38(Suppl 2): S55–63.
14. Dahabreh Z, Dimitriou R, Giannoudis PV. Health economics: a cost analysis of treatment of persistent fracture non-unions using bone morphogenetic protein-7. Injury 2007;38:371–7.
15. De Biase P, Capanna R. Clinical applications of BMPs. Injury 2005;36(Suppl 3): S43–6.
16. DeLustro F, Dasch J, Keefe J, Ellingsworth L. Immune responses to allogeneic and xenogeneic implants of collagen and collagen derivatives. Clin Orthop 1990;260: 263–79.
17. Dimitriou R, Dahabreh Z, Katsoulis E, et al. Application of recombinant BMP-7 on persistent upper and lower limb non-unions. Injury 2005;36(Suppl 4)S51–9.
18. el Moumni M, Leenhouts PA, ten Duis HJ, Wendt KW. The incidence of non-union following unreamed intramedullary nailing of femoral shaft fractures. Injury 2009;40:205–8.
19. Fernyhough JC, Schimandle JJ, Weigel MC, et al. Chronic donor site pain complicating bone graft harvesting from the posterior iliac crest for spinal fusion. Spine 1992;17:1474–80.
20. Finkemeier CG. Bone-grafting and bone-graft substitutes. J Bone Joint Surg Am 2002;84:454–64.
21. Friedlaender GE, Perry CR, Cole JD, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. J Bone Joint Surg Am 2001;83(Suppl 1)S151–8.
22. Garrison KR, Donell S, Ryder J, et al. Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review. Health Technol Assess 2007;11:1–150.
23. Giannoudis PV, Kanakaris NK, Dimitriou R, et al. The synergistic effect of autograft and BMP-7 in the treatment of atrophic nonunions. Clin Orthop 2009, 24 April [Epub ahead of print].
24. Giannoudis PV, Kanakaris NK, Einhorn TA. Interaction of bone morphogenetic proteins with cells of the osteoclast lineage: review of the existing evidence. Osteoporos Int 2007;18:1565–81.
25. Giannoudis PV, MacDonald DA, Matthews SJ, et al. Nonunion of the femoral diaphysis. The influence of reaming and non-steroidal anti-inflammatory drugs. J Bone Joint Surg Br 2000;82:655–8.
26. Giannoudis PV, Psarakis S, Kanakaris NK, Pape HC. Biological enhancement of bone healing with bone morphogenetic protein-7 at the clinical setting of pelvic girdle non-unions. Injury 2007;38(Suppl 4):S43–8.
27. Govender S, Csimma C, Genant HK, et al. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg Am 2002;84:2123–34.
28. Harwood PJ, Giannoudis PV. Application of bone morphogenetic proteins in orthopaedic practice: their efficacy and side effects. Expert Opin Drug Saf 2005;4:75–89.
29. Hildebrand F, Giannoudis P, Kretteck C, Pape HC. Damage control: extremities. Injury 2004;35:678–89.
30. Johnson EE, Urist MR, Finerman GA. Resistant nonunions and partial or complete segmental defects of long bones. Treatment with implants of a composite of human bone morphogenetic protein (BMP) and autolyzed, antigen-extracted, allogeneic (AAA) bone. Clin Orthop 1992;277:229–37.
31. Kanakaris NK, Calori GM, Verdonk R, et al. Application of BMP-7 to tibial non-unions: a 3-year multicenter experience. Injury 2008;39(Suppl 2):S83–90.
32. Kanakaris NK, Giannoudis PV. The health economics of the treatment of long-bone non-unions. Injury 2007;38(Suppl 2):S77–84.
33. Kanakaris NK, Giannoudis PV. Clinical applications of bone morphogenetic proteins: current evidence. J Surg Orthop Adv 2008;17:133–46.
34. Kanakaris NK, Paliobeis C, Manidakis N, Giannoudis PV. Biological enhancement of tibial diaphyseal aseptic non-unions: the efficacy of autologous bone grafting, BMPs and reaming by-products. Injury 2007;38(Suppl 2):S65–75.
35. Karrholm J, Hourigan P, Timperley J, Razaznejad R. Mixing bone graft with OP-1 does not improve cup or stem fixation in revision surgery of the hip: 5-year follow-up of 10 acetabular and 11 femoral study cases and 40 control cases. Acta Orthop 2006;77:39–48.
36. Lammens J, Van Laer M, Motmans R. Ilizarov treatment for femoral mal-union or non-union associated with fatigue fracture of an intramedullary nail. Injury 2008;39:256–9.
37. Lind M. Growth factor stimulation of bone healing. Effects on osteoblasts, osteotomies, and implants fixation. Acta Orthop Scand Suppl 1998;283:2–37.
38. Lynch JR, Taitsman LA, Barei DP, Nork SE. Femoral nonunion: risk factors and treatment options. J Am Acad Orthop Surg 2008;16:88–97.
39. Mahendra A, Maclean AD. Available biological treatments for complex non-unions. Injury 2007;38(Suppl 4):S7–12.
40. Motsitsi NS. Management of infected nonunion of long bones: the last decade (1996–2006). Injury 2008;39:155–60.
41. Murnaghan M, Li G, Marsh DR. Nonsteroidal anti-inflammatory drug-induced fracture nonunion: an inhibition of angiogenesis? J Bone Joint Surg Am 2006; 88(Suppl 3):140–7.
42. Niikura T, Hak DJ, Reddi AH. Global gene profiling reveals a downregulation of BMP gene expression in experimental atrophic nonunions compared to standard healing fractures. J Orthop Res 2006;24:1463–71.
43. Nikolaou VS, Papathanasopoulos A, Giannoudis PV. What's new in the management of proximal femoral fractures? Injury 2008;39:1309–18.
44. Nilsson OS, Urist MR. Immune inhibition of repair of canine skull trephine defects implanted with partially purified bovine morphogenetic protein. Int Orthop 1991;15:257–63.
45. Phieffer LS, Goulet JA. Delayed unions of the tibia. Instr Course Lect 2006;55: 389–401.
46. Pihlajamaki HK, Salminen ST, Bostman OM. The treatment of nonunions following intramedullary nailing of femoral shaft fractures. J Orthop Trauma 2002;16:394–402.
47. Poynton AR, Lane JM. Safety profile for the clinical use of bone morphogenetic proteins in the spine. Spine 2002;27:S40–8.
48. Probst C, Pape HC, Hildebrand F, et al. 30 years of polytrauma care: An analysis of the change in strategies and results of 4849 cases treated at a single institution. Injury 2009;40:77–83.
49. Puleo D. Biotherapeutics in orthopaedic medicine: accelerating the healing process? BioDrugs 2003;17:301–14.
50. Ronga M, Baldo F, Zappala G, Cherubino P. Recombinant human bone morphogenetic protein-7 for treatment of long bone non-union: an observational, retrospective, non-randomized study of 105 patients. Injury 2006;37(Suppl 3):S51–6.
51. Schmidmaier G, Schwabe P, Wildemann B, Haas NP. Use of bone morphogenetic proteins for treatment of non-unions and future perspectives. Injury 2007; 38(Suppl 4):S35–41.
52. Sen MK, Miclau T. Autologous iliac crest bone graft: should it still be the gold standard for treating nonunions? Injury 2007;38(Suppl 1):S75–80.
53. Shukla S, Johnston P, Ahmad MA, et al. Outcome of traumatic subtrochanteric femoral fractures fixed using cephalo-medullary nails. Injury 2007;38: 1286–93.
54. St John TA, Vaccaro AR, Sah AP, et al. Physical and monetary costs associated with autogenous bone graft harvesting. Am J Orthop 2003;32:18–23.
55. Tsiridis E, Giannoudis PV. Transcriptomics and proteomics: advancing the understanding of genetic basis of fracture healing. Injury 2006;37(Suppl 1): S13–9.
56. Tzioupis C, Giannoudis PV. Prevalence of long-bone non-unions. Injury 2007; 38(Suppl 2):S3–9.
57. Urist MR. Bone: formation by autoinduction. Science 1965;150:893–9.
58. Urist MR, Nillsson OS, Hudak R, et al. Immunologic evidence of a bone morphogenetic protein in the milieu interieur. Ann Biol Clin (Paris) 1985;43: 755–66.
59. Vaibhav B, Nilesh P, Vikram S, Anshul C. Bone morphogenetic protein and its application in trauma cases: a current concept update. Injury 2007;38:1227–35.
60. White AP, Vaccaro AR, Hall JA, et al. Clinical applications of BMP-7/OP-1 in fractures, nonunions and spinal fusion. Int Orthop 2007;31:735–41.

61. Winquist RA, Hansen Jr ST, Clawson DK. Closed intramedullary nailing of femoral fractures. A report of five hundred and twenty cases. J Bone Joint Surg Am 1984;66:529–39.
62. Wolinsky PR, McCarty E, Shyr Y, Johnson K. Reamed intramedullary nailing of the femur: 551 cases. J Trauma 1999;46:392–9.
63. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. Bull World Health Organ 2003;81:646–56.
64. Younger EM, Chapman MW. Morbidity at bone graft donor sites. J Orthop Trauma 1989;3:192–5.