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Application of BMP-7 to tibial non-unions: A 3-year multicenter experience

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Summary The effective treatment of the often debilitating, longlasting and large-asset-consuming complication of fracture non-unions has been in the centre of scientific interest the last decades. The use of alternative bone substitutes to the gold standard of autologous graft includes the osteoinductive molecules named bone morphogenetic proteins (BMPs). A multicenter registry and database (bmpusergroup.co.uk) focused on the application of BMP-7/OP-1 was created in December 2005. We present the preliminary results, using the prospective case-series of aseptic tibial non-unions as an example. Sixty-eight patients fulfilled the inclusion criteria for this observational study, with a minimum follow-up of 12 months. The median duration of tibial non-union prior to BMP-7 application was 23 months (range 9–317 mo). Patients had undergone a median of 2 (range 0–11) revision procedures prior to the administration of BMP-7 . In 41% the application of BMP-7 was combined with revision of the fixation at the non-union site. Non-union healing was verified in 61 (89.7%) in a median period of 6.5 months (range 3–15 mo). No adverse events or complications were associated with BMP-7 application. The safety and efficacy of BMP-7 was verified in our case series, and was comparable to the existing evidence. The establishment of multicenter networks and the systematic and long-term follow-up of these patients are expected to provide further information and significantly improve our understanding of this promising osteoinductive bone substitute.

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Abbreviations

ABG: autologous bone grafting
BMPs: bone morphogenetic proteins
MVCs: motor vehicle collisions
NSAIDs: non-steroidal-antiinflammatory-drugs
OP-1: osteogenic protein-1
RhBMP: recombinant human BMP
FDA: food and drug administration

Introduction

The management of fracture non-unions has significantly evolved over the last few decades.[1-7] The effective treatment of this often debilitating, long-lasting and costly[8] complication of trauma has always intrigued the clinicians and basic scientists. Among the different sites that develope non-union, the tibia is the most extensively studied. Due to the fact that it is the most common long-bone to sustain a fracture, it represents the most frequent non-union in routine practice, with an overall non-union rate of 5–10%,[9,10] despite the recent advances of therapeutic modalities. The variation in the management of the different non-union types[11] (septic vs. aseptic, atrophic vs. hypertophic) trails the improvement of our understanding on the biomechanical[10,12,13] and biological[14-16] prerequisites for optimal bone healing. The biological substrate of fracture healing traditionally has been augmented with autologous bone graft.[17,18] The associated donor site morbidity,[19] the uncertain quantity and quality of the gold standard of autograft,[20] dictated the utilisation of different grafting agents.

Among the contemporary grafting alternatives, the use of bone morphogenetic proteins (BMPs), as powerful osteoinductive agents that enhance the biological environment of fracture non-unions,[21,22] has gradually gained the respect of the scientific community and expanded its indications.[23-25] The evidence of their effectiveness and safety is geometrically increased since their initial discovery.[26,27] Currently, two of the 16 different BMP-homologous human molecules[28] have been utilised on several clinical trials and are commercially available.[29-33] In October 2001 rhBMP-7 or OP-1 (Stryker, Kalamazoo, Michigan) received FDA approval for use in patients with recalcitrant long bone non-unions where autograft is unfeasible and alternative treatments have failed, while rhBMP-2 (Infuse; Medtronic Sofamor Danek, Memphis, Tennessee) has been approved for the acute treatment of open tibial fractures together with an intramedullary nail.[34]

The aim of this study is to present a comprehensive analysis of a multicenter prospective effort to systematically record and evaluate the results of BMP-7 in the treatment of aseptic tibial non-unions.

Patients and Methods

A focused electronic databank (bmpusergroup.co .uk) was created and updated constantly since December 2005. It accumulates clinical relevant prospective and retrospective data regarding the use of BMP-7 ever since, and follows the clinical course of all the registered patients from 6 international specialised orthopaedic centres (3 Italian University hospitals, 1 Belgian, 1 Finnish, and 1 from the United Kingdom). The databank was designed to incorporate demographic details, inhospital, peri-operative and follow-up information of all enrolled patients till their final discharge from the outpatient clinics, together with the radiographic investigations available in the entire course of their treatment. A non-union site was declared 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 assessment. The clinical and functional outcome was recorded and assessed using parameters like union, complication, return-to-previous-occupation rates, and the EuroQol 5D.[35] Informed consent was obtained from all the patients regarding the use of the BMP-7, and local ethical committee boards have approved the protocol of the present study and the creation of the databank. From the existing data on this databank (bmpusergroup.co.uk) we have extracted those referring to patients treated with BMP-7 due to an established tibial aseptic non-union (duration of over a period of 9 months) with a minimum follow-up of 12 months. Each unit of BMP-7 (Osigraft, by Stryker Biotech Hopkinton, Massachusetts, MA, USA) contained 3.5 milligrams of the rhBMP-7 mixed with 1 gram of type I bovine-derived collagen. The total volume per unit was approximately 4 millilitres. One unit per non-union site was applied in all cases. According to the agreed protocol, it was up to the surgeon's discretion to augment the BMP-7 implantation with autograft in a "graft expanding" rationale for non-union sites with a defect greater than 1 cm. Descriptive statistics were used for a more comprehensive presentation of the results of our prospective case-series.

Results (Table 1)

Sixty-eight consecutive cases with tibial aseptic atrophic non-unions treated with BMP-7, with a minimum follow-up of 12 months comprised the presented case series. Eighteen patients were females (26.5%) and 50 males (73.5%), with a median age of 41.5 years (range 19–78 yrs, mean 42.6 yrs). Twenty-three were smokers[36] (33.8%) and eleven patients were also taking NSAIDs[37,38] as painkillers for over a month (16.2%).All original injuries were tibial fractures due to car accidents (25, 36.8%), falls (13, 19.1%), motorcycle (7, 10.3%), work-related/industrial (7, 10.3%), pedestrian (7, 10.3%), or sports-related accidents (2, 2.9%). Three of the non-unions (4.4%) occurred after tibial osteotomies, 2 after missile penetrating trauma (2, 2.9%), and 2 after assaults (2, 2.9%). There were 36 closed (52.9%), 29 open injuries (42.7%) – 4 type I, 5 type II, 5 type IIIa, 13 type IIIb, 2 type IIIc.[39] Initially they were treated with plate fixation (ORIF), intramedullary nailing (IMN), external fixators, or nonoperatively in 33–48.5%, 26–38.2%, 8–11.8% and 1–1.5% of the cases respectively.

The median time between initial injury and the BMP-7 procedure was 23 months (range 9–317, mean 42.7 mo). Patients had a median of 2 previous operations before the procedure of BMP-7 grafting (range 0–11, mean 2.5). In all cases this was the first application of BMP-7, and in 24 of the cases (35.3%) autologous bone graft has been used before unsuccessfully. At the time of BMP-7 application, all non-unions were aseptic according to the intraoperative microbiology samples and the overall clinical profile of each patient. In 28 of the cases (41%) at the time of the

Table 1
Comparative data in-between the present case series and the classic RCT of Friedlaender et al.[30]

Parameters	Present prospective case series	Friedlaender GE et al.[30] 2001, JBJS (Am)
Indication	Aseptic tibial non-unions	Aseptic tibial non-unions
No. of patients	68	63
Gender ratio (females/males)	18/50	21/42
Mean age	42.6	38
Smoking	23, 33.8%	47, 74%
NSAIDs	11, 16.2%	n/a
Diabetes mellitus	1, 1.5%	n/a
% of Open #	29, 42.7%	36, 58%
Initial management	ORIF 45.6%; IMN 39.7%; ExFix 13.2%; Plaster 1.5%	IMN 54%*
Prior autograft	22, 32.3%	27, 43%
Median time from initial injury	23 months (range 9–317)	27 months (SD ±16)
Median no. of previous operations	2 (range 0–11)	n/a
% Revision of fixation	26, 38.2% ORIF; 7, 10.3% IMN; 1, 1.5% fibulectomy; 6, 8.8% ExFix	57, 90.5% IMN; 40, 63.5% fibulectomy
Graft expansion with autograft	25, 36.8%	0, 0%
Clinical union rates	89.7%	81%
Median time to union	6.5 months (3–15)	9 months
No. of re-operations	4, 6%	3, 5%
No. of complications**	22	46

%; percentage, ExFix; external fixation, IMN; intramedullary nail, n/a; not available, NSAIDs; non steroidal antiinflammatory drugs, ORIF; open reduction internal fixation, SD; standard deviation, *Besides the fractures treated with an IMN no other mention on the Friedlander et al. paper on other methods of initial management. **None related directly to the use of BMP-7, or considered as a related adverse event of its application. The presented data include the absolute number of Infections, Hematomas, Compartment syndrome, Implant failures – (not the number of patients).

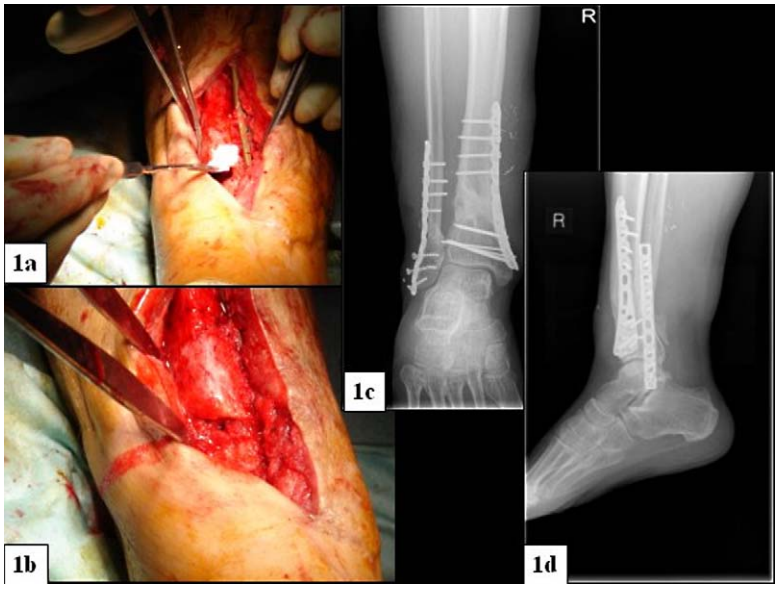

Fig. 1. (a,b) Intraoperative application of BMP-7 at the non-union site (male patient, age 43, non-smoker, distal tibial closed fracture, initially ORIF, 18 months post-injury, 1 previous attempt with autograft). (c,d) Five and a half months post BMP-7 application clinical and radiological healing at the non-union site.

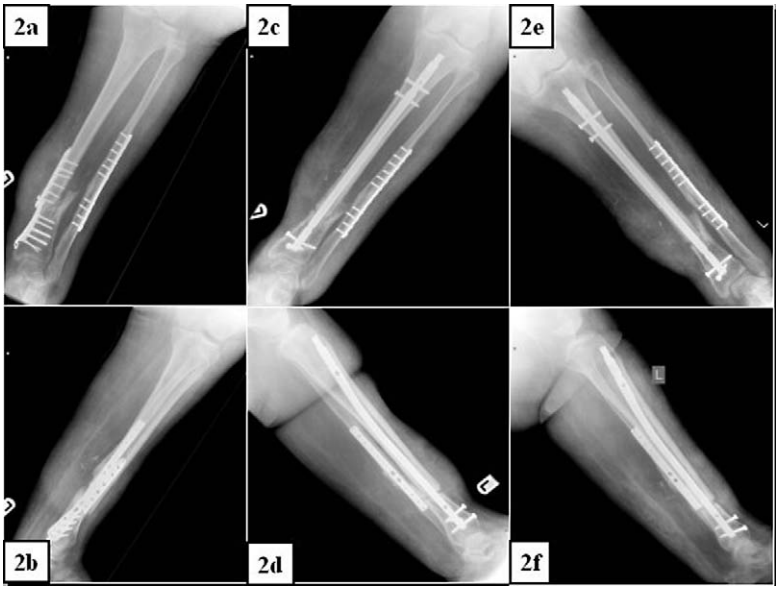

Fig. 2. (a,b) Tibial non-union with failure of original ORIF (female patient, age 34, smoker, open IIIa tibial fracture, initially locking plate fixation, 8 months post injury). (c,d) New failure of IMN that followed the revision of the initial fixation (14 months post-injury). (e,f) Final clinical and radiological healing after BMP-7 application and exchange nailing (23 months post injury and 6 months post-BMP-7 application).

BMP-7 application no other surgical intervention or revision of the existing fixation was performed. For the rest of the cases BMP-7 grafting supplemented 25 revisions of ORIF, 7 exchange nailings, 6 circular frames, 1 revision of IMN to plate fixation, and 1 nail dynamisation together with a fibular osteotomy. In 25 cases (36.8%) the BMP-7 was combined with the use of autologous bone graft (ABG), out of which 14 (56%) had been previously treated unsuccessfully with ABG.

The median follow-up of these patients was 18 months (range 12–30, mean 20.8 mo). The union rate during that period was 89.7% (61 healed unions), and the median time to union was recorded to be 6.5 months (range 3–15 mo) (Figures 1&2). Seven patients (10.3%) did not progress to successful healing of their non-union, four of them underwent further revision of their fixation and bone grafting, and are all still followed up at the outpatient clinics. By

the last follow-up appointment, forty (58.8%) of the patients had returned to their previous occupation, nine (13.2%) had changed occupation, and the rest had retired (27.9%). As to the different parameters of the EuroQol 5D health questionnaire, 8 patients reported problems with mobility, 1 with self-care, and 11 with usual activities. Four patients reported moderate anxiety/depression, and 9 moderate amount of pain. The visual analogue scale for their overall health state reached a median score of 82.5 (range 35–100, mean 79.3). 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 noticed (12 superficial wound infections treated with antibiotics, 3 hematomas, 2 deep vein thrombosis, and 1 compartment syndrome treated with fasciotomies).

Discussion

After the initial period of experimental[40,41] and clinical investigations[29,42] focused on bone morphogenetic proteins, and the recent international widespread use of these osteoinductive agents in order to accelerate bone healing, the need for establishing a focused multicenter registry was the next step, in order to systematically evaluate efficacy and safety and further advance our understanding of these molecules in the clinical setting. The present study describes the preliminary results of such an effort, using as an example the management of tibial non-unions using BMP-7 in 6 different University centers of Europe over a period of almost 3 years. The fact that this is an observational non-controlled study limits the level of evidence that the presented results represent, and the extent of their statistical analysis. They may also be influenced by the different strategies of fixation of the contributing centers, the number (10) and skills of the involved surgeons , and the possible differences of the patient populations.

However, it represents the actual clinical reality and reflects the current clinical practice at least of these 6 University centers. The overall number of the reported tibial non-unions (68) is comparable with that of the largest existing series in the English and German literature, as well as the period of follow-up (Table 2). A comparison of the basic demographic, clinical and final outcome parameters of our study population with those of the landmark randomised trial of Friedlaender et al.[30] show equivalent efficacy and safety of the BMP-7 use (Table 1).

Although the final clinical and functional outcome is apparently influenced by multiple patient-, fracture-, therapy-, postoperative-related factors, it appears to be encouraging in all the reviewed clinical trials (Table 2), as well as in all of the 6 different centers as documented in the present study. Healing rates range between 81% and 100% with an average of 84.8% (in our study group it was 89.7%).[30,43-48] The gold standard of autograft reaches similar levels of non-union healing (87–100%).[49] Nevertheless, one should take under consideration the complication rate reported and associated with autologous bone harvesting (3–9% are major complications and 20% minor ones),[19,50] as well as other considerations regarding its quality in the elder patients and its limited available quantity.[20] Furthermore, a large number of the cases where BMP-7 is applied consists of cases where autologous bone grafts have failed (32.3% in our sample), and thus represents a resistant and difficult to treat group of non-unions.

An even larger consensus appears to exist between the authors as far as the safety of the local application of BMP-7. No adverse events directly associated with the application of the molecule were recorded in our patients. Despite the fact that there are sporadic clinical reports on osteoclastic bone resorption,[51-54] there were no indications of such an event at any of the existing sites of BMP-7 application of this database. We appreciate that the development of a BMP-7 or collagen-I specific immunological response has not been evaluated in our study group. Mostly clinical apparent adverse events and complications have been recorded. The existing evidence on the immunological interaction with the currently used composite implant (3.5 mg of rhBMP-7 mixed with 1 gram of type I bovine-derived collagen) describes an incidence of anti-BMP-7 and anti-collagen antibodies of 5–10%.[30,55-57] However, still the extent of this sensitization, and its translation, if any, at the clinical level is unclear and under investigation.

Another important parameter in the contemporary evaluation of any therapeutic strategy, besides its safety and efficacy, is its financial implications. There are currently a few available studies[58-60] which have assessed the crucial aspect of health economics in the clinical setting of BMP-7 treatment of non-unions. The existing evidence appears to be encouraging as to the financial aspect, as well.[58-60] The establishment of prospective data registries regarding the use of

Table 2
Original clinical studies on the application of BMPs at the anatomical site of the Tibia with an indication of non-union

Authors, Journal	Type of Study	Level of evidence	No. of cases of BMPs	Indication	Union rates	Time to union	Re-Operations	Functional Outcome
Zimmermann G et al. 2007,[43] Unfallchirurg	Prospective comparative (BMP-7 vs. ABG)	III	26	Tibial non-unions	92.3%	n/a	7.7%	n/a
Ronga M et al. 2006,[44] Injury	Retrospective observational (BMP-7)	IV	46	Tibial non-unions	84.8%	n/a	15.2%	n/a
Calori GM et al. 2006,[45] Injury	Prospective randomised controlled (BMP-7 vs. PRP)	II-III	16	Tibial-Femoral-Humeral-Forearm non-unions	94%	mean 8 months (±0.43)	6.2%	n/a
Dimitriou R et al. 2005,[46] Injury	Prospective Observational (BMP-7)	IV	25	Tibial-Femoral-Humeral-Forearm-Clavicle non-unions	92.3%	mean 5.6 months (2.5–11)	12%	n/a
Friedlaender GE et al. 2001,[30] JBJS (Am)	Prospective randomised controlled (BMP-7 vs. ABG)	II	63	Tibial non-unions	75–81%	9 months	5%	n/a
Johnson EE et al. 1992,[47] CORR	Prospective observational (hBMP & allograft)	IV	25	Tibial-Femoral-humeral non-unions	96%	mean 6 months (3-14)	20%	14 excellent 5 good 5 fair
Johnson EE et al. 1990,[48] CORR	Prospective observational (hBMP)	IV	4	Distal Tibial non-unions	100%	mean 4.4 months (4-5.2)	0%	2 very good 1 good 1 fair

ABG; autologous bone graft, DBM; demineralised bone matrix, BMP; bone morphogenetic proteins, LOE; level of evidence, PRP; platelet rich plasma, SMFA; short musculoskeletal function assessment.

the BMPs is anticipated to provide the available information needed for a thorough evaluation of these apparently expensive agents as to their cost effectiveness, especially if direct and indirect costs are impregnated to the analysis.

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

Conflict of Interest statement

All authors declare that no benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. No funds were received in support of this study. They also declare that they have full control of all primary data and agree to allow the journal to review them if requested.

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