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Mini review

BMPs in bone regeneration: Less is more effective, a paradigm-shift☆

Katharina Schmidt-Bleek[d,1,2], Bettina M. Willie[a,b,1], Philipp Schwabe[c,3], Petra Seemann[d,4], Georg N. Duda[d,*]

[a] Julius Wolff Institute, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
[b] Research Center, Shriners Hospitals for Children-Canada, Department of Pediatric Surgery, McGill University, 1003 Decarie Blvd., Montreal, Quebec H4A 0A9, Canada
[c] Centre for Musculoskeletal Surgery, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany
[d] Berlin-Brandenburger Center for Regenerative Therapies, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany

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ABSTRACT

Worldwide, the clinical application of BMP2 (bone morphogenetic protein 2) has helped an increasing number of patients achieve bone regeneration in a clinical area lacking simple solutions for difficult bone healing situations. In this review, the historical aspects and current critical clinical issues are summarized and positioned against new research findings on efficacy and function of BMP2. Knowledge concerning how the dose of this growth factor as well as its interaction with mechanical loading influences the efficacy of bone regeneration, might open possible future strategies in cases where bony bridging is unachievable so far. In conclusion, it is apparent that there is a substantial need for continued basic research to unravel the details of its function and the underlying signaling pathways involved, to make BMP2 even more relevant and safe in daily clinical use, even though this growth factor has been known for more than 125 years.

1. Historical reflection of BMP2

1.1. Discovery of bone morphogenetic protein

In 1889, Senn reported that decalcified bone induced healing in bone defects with osteomyelitis [1]. Levander demonstrated in a series of studies starting in 1934 that bone extract injected into muscles caused ectopic bone formation [2–4]. In 1945, Lacroix reported a substance he called “osteogenin”, which he had extracted from the cartilaginous epiphysis of the long bones of newly born rabbits. He subsequently injected the osteogenin into the thigh muscles of other rabbits and induced the formation of an osteoma, revealing the presence of all the structures of a growing long bone [5]. The name, bone morphogenetic proteins was only termed in 1971 by Urist [6], although six years earlier Urist described the bone morphogenic properties of demineralized, lyophilized segments of bone and demonstrated that they could initiate ectopic bone formation in adult animals [7]. In 1972, Reddi and Huggins described the fibroblast-chondroblast-osteoblast transformation (Fig. 1) and thus endochondral ossification, which they induced with a powder of acid insoluble bone matrix (thus BMPs), demonstrating the potential of these proteins for future clinical use [8] (Fig. 2).

1.2. FDA approval and clinical trials

BMPs are growth factors (also known as cytokines or metabologens) that are part of the transforming growth factor-β super family. There are approximately 25 different known BMPs, although BMP2, -4, -6, -7 and -9 specifically play major roles in bone morphogenesis. Recombinant human bone morphogenetic protein-2 (rhBMP2; INFUSE® Bone Graft, Medtronic Spinal and Biologics, Memphis, TN) received FDA approval in 2002, 2004, and 2007 for the treatment of interbody spinal fusion, open tibial fractures, and sinus augmentation and alveolar ridge

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* Corresponding author. Fax: +49 30 450 559969.
E-mail addresses: Katharina.Schmidt-Bleek@charite.de (K. Schmidt-Bleek), bwillie@shriners.mcgill.ca (B.M. Willie), Philipp.schwabe@charite.de (P. Schwabe), Petra.Seemann@charite.de (P. Seemann), georg.duda@charite.de (G.N. Duda).
[1] These authors contributed equally to the manuscript.
[2] Fax: +49 30 450 559969.
[3] Fax: +49 30 450 552958.
[4] Fax: +49 30 450 539436.

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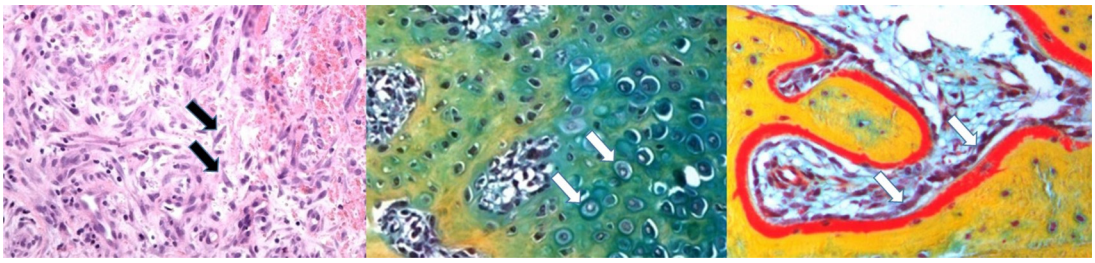

Fig 1. Histological images of consecutive bone healing phases highlighting fibroblasts (left), chondroblasts (middle) and osteoblasts (right). Haematoxylin Eosin and Movat Pentachrome staining respectively with the cell type indicated by arrows.

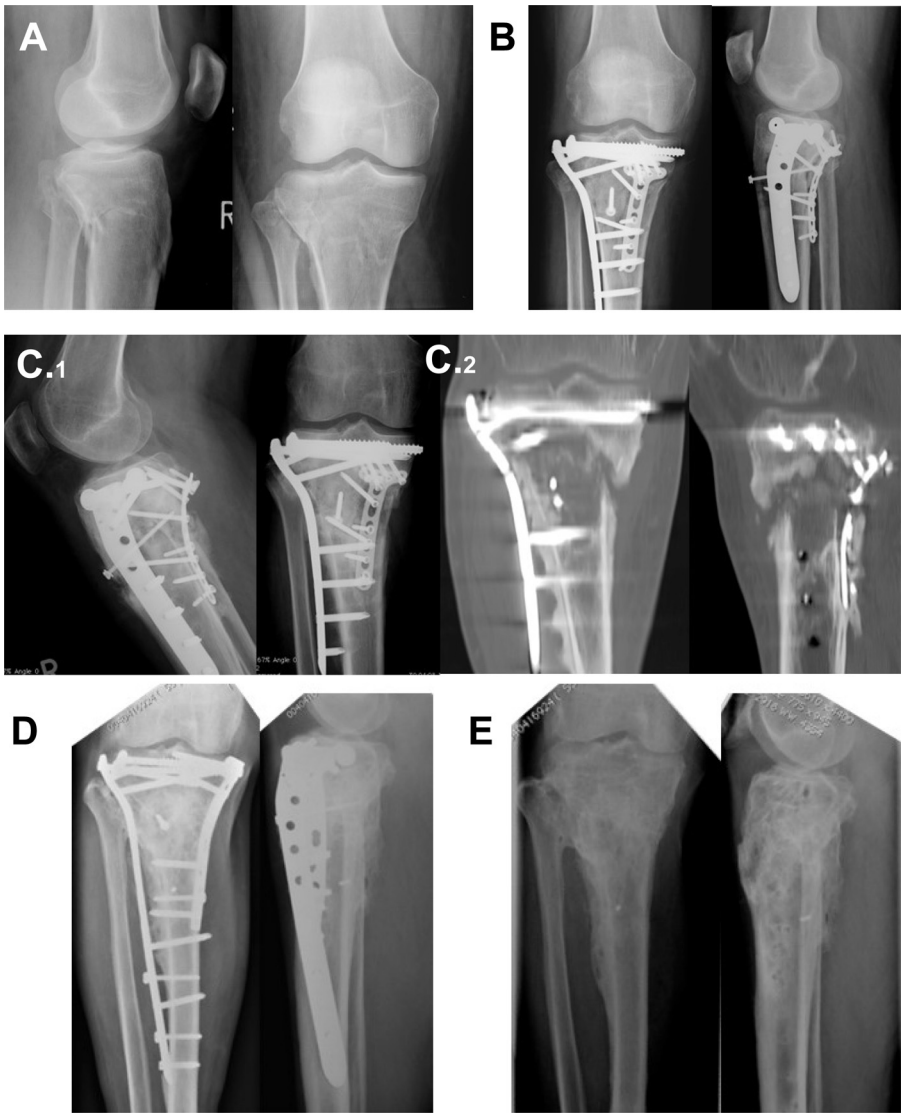

Fig. 2. Successful treatment of a non-union with BMP2: A radiograph after fracture; B primary fracture treatment; C resulting non-union (C.1) with CT image in C.2; D healing after revision with re-osteosynthesis and BMP2; E implant removal.

augmentation for defects associated with extraction sockets, respectively. Approval in Europe through the European Agency for the Evaluation of Medicinal Products (EMA) came already in 2002 for rhBMP2 in open tibial fractures stabilized with an intramedullary nail. Both the EMA and FDA approvals were granted following the pivotal study performed by the BMP2 Evaluation in Surgery for Tibial Trauma (BESTT) study group, who conducted a prospective, randomized, controlled trial in 450 patients [9]. They compared patients receiving standard of care (intramedullary nail fixation and standard soft tissue management) with patients receiving standard of care plus rhBMP2 (0.75 mg/mL or 1.5 mg/mL rhBMP2 with absorbable collagen sponges) [9]. The primary endpoint of the study was to determine the number of patients requiring a secondary intervention within 12 months. The study reported a 44% dose-dependent reduction in secondary interventions in patients receiving rhBMP2, with 74% of rhBMP2 treated