The use of recombinant human bone morphogenetic protein-2 for the treatment of a delayed union following femoral neck open-wedge osteotomy

Axel W.A. Baltzer,[1] Martin S. Ostapczuk,[2] Daniel Stosch,[1] Markus Granrath[1]

[1]Königsallee, Centre for Molecular Orthopaedics Düsseldorf, [2]Heinrich-Heine-University Düsseldorf, Germany

Abstract

Although the clinical potential of bone morphogenetic proteins (BMPs) has been known for decades, their use in humans has only been approved for a limited number of orthopaedic conditions. Promising results in animals demonstrate the utility of BMP-2 in regional bone repair *without* using osteoconductors. To our knowledge, no comparable human case has been described. We report the case of a 50-year-old who suffered a femoral neck fracture. After 9 months of extensive treatment, he was still not pain-free. The following open-wedge osteotomy resulted in a therapy-resistant delayed union. We therefore conducted 4 computer tomography-guided injections of recombinant human (rh) BMP-2 into the bone gap. No osteoconductor was employed. Six weeks later, there was a 55-60% defect filling. Follow-up examination showed a complete union of the bone defect. Our case report shows that in a complicated delayed union rhBMP-2 can be successfully used to induce bone formation *without* any osteoconductor.

Introduction

Femoral neck fractures (FNF) belong to the most frequent fractures in patients of all ages. In younger patients (<55 years), internal fixation, *e.g.*, by hip-screws, is preferred, while arthroplasty is commonly used in older patients (>70 years).[1] Although the vast majority of human fractures show normal bone healing, approximately 5% per year do not heal and are to be classified as delayed or non-unions.[2,3]

Delayed and non-unions constitute an obstacle in the treatment of bone defects, since they usually cause pain and possibly result in limb length differences, potentially leading to avascular necrosis and a severe loss of function.[4] Intervention is therefore inevitable: although surgery using internal or external fixation combined with (autologous) bone-grafts is still considered the gold standard in the treatment of non-unions, extracorporeal shock-wave therapy (ESWT) and osteotomy are also said to result in useful outcomes.[2-5] Trochanteric open-wedge osteotomy is invasive in nature and therefore associated with the common operative risks. In addition, the procedure itself can foster trochanteric non-union.[6] The advantages of ESWT are its non-invasiveness and low rate of complications.[7] Results on its efficacy, however, are still controversial.[3-5] In autologous bone-grafting, there is only a limited quantity of bone available to harvest and the procedure is also associated with significant complications, such as persistent donor-site pain, local infection and paresthesia.[2]

Recently, bone morphogenetic proteins (BMP) have become available to enhance bone repair. BMP-2 and BMP-7 are supposed to have the greatest osteoinductive capacity both in animal and in human trials. However, little is known about long-term effects, and to date, the use of BMPs in humans has only been approved for the treatment of a limited number of orthopaedic conditions;[2,8,9] the benefits of BMPs in the treatment of delayed and non-unions remain unclear.[10,11] One of the clinical challenges in the use of BMPs is to transport the growth factors to the bone repair-site and to maintain a sustained, therapeutic concentration at repair-site, high enough to evoke an adequate osteoinductive reaction.[1,2] In animal trials, there have been first successful attempts to enhance fracture repair by regional use of BMP-2 *without* the use of traditional osteoconductors: Baltzer *et al.*[12] injected adenoviral vectors encoding for BMP-2 into the segmental defect-site in femora of rabbits. Schmidmaier *et al.*[13] stabilized closed tibial fractures with BMP-2-coated titanium Kirschner wires. Tang *et al.*[1] used cannulated screws with holes delivering recombinant human BMP-2 (rhBMP-2) to the site of FNFs in dogs. To our knowledge, there is no comparable case in humans like ours in current literature, though.

The purpose of this case report was to show that in a complicated delayed union following a trochanteric open-wedge osteotomy after FNF and treatment with ESWT, rhBMP-2 can be successfully used to induce bone formation via computed tomography-guided injections *without* any osteoconductor instead of autologous bone-grafting. The patient was informed that data from the case would be submitted for publication, and gave his consent.

Case Report

In a skiing-accident, a 50-year-old man sustained a medial FNF (Pauwels III°), initially treated by 2 hip-screws. At presentation in our practice after 4 months, the patient was limping in pain and had leg shortening following incomplete fracture healing (Figure 1).

We treated the patient with 4 ESWT-sessions using a PIEZO-Wave 6A-A 236+TQF10G4 therapeutic device (Richard Wolf Enterprises, Knittlingen, Germany; 2000 impulses, 0.403mJ/mm^2, 8Hz, each). Treatment resulted in adequate healing of the initial fracture-site and in pain reduction, but with major leg shortening inducing major problems in sports activities, and activities of daily living (ADL). Ten months after the accident/initial surgery, the patient underwent femoral derotational open-wedge osteotomy at an external hospital. Surgery reduced the length difference to 2.5 cm and improved limping; 2.5-month-postoperative radiographs, however, revealed no sign of ossification or calcification in the 1×4×6 cm osteotomy-gap (Figure 2). We repeated 4 ESWT-sessions over 3 weeks which did not at all enhance union. Four months after osteotomy, the open-wedge gap still showed no sign of ossification (Figure 3).

Unwilling to undergo another surgery, *e.g.*, autologous bone-grafting, the patient agreed on a minimally-invasive *off-label* alternative: 4 computed tomography-guided injections of 2 mg of rhBMP-2 (Inductos®) each were

Correspondence: Axel W.A. Baltzer, Associate Practice at Königsallee, Centre for Molecular Orthopaedics, Königsallee 53-55, 40212 Düsseldorf, Germany.
Tel. +49.211.828.937-10 - Fax: +49.211.828.937-11.
E-mail: axel@baltzer.at

Key words: rhBMP-2, delayed union, femoral neck fracture, open-wedge osteotomy, extracorporeal shock-wave therapy.

Contributions: AWAB, designed the study, treated the patient, wrote the initial draft and ensured the accuracy of the data; MSO, co-designed the study, gathered and analyzed the data and wrote parts of the initial draft; DS, gathered the data, ensured their accuracy and wrote parts of the initial draft; MG, co-designed the study, analyzed the data and ensured their accuracy.

Conflict of interest: the authors report no conflict of interests.

Received for publication: 4 February 2012.
Accepted for publication: 4 March 2012.

Orthopedic Reviews 2012; 4:e4
doi:10.4081/or.2012.e4

administered into the repair-site. The first 3 injections were given at an interval of 1 week followed by a computed tomography (CT) control. A final injection was given 3 weeks later. No osteoconductor was employed. On follow-up, 6-week-post-treatment CT images showed an approximately 55-60% union (Figure 4), while later radiographs documented a complete union of the osteotomy-gap (Figure 5). During follow-up examination, ADL and sports activities were fully restored, the patient was pain-free and did not report any side-effects.

Discussion

We present the case history of a healthy 50-year-old man who suffered a traumatic medial FNF. Following surgical intervention, he developed a major leg length difference. The correction of this difference by open-wedge osteotomy resulted in a therapy-resistant delayed union at repair-site. We followed an *off-label* use of a procedure based on a regional and minimally-invasive protocol to treat the bone defect: The administration of 4 CT-guided rhBMP-2 injections into the defect-site *without* the use of any osteoconductor or viral vectors successfully induced bone repair in the open-wedge osteotomy-defect. Six weeks after the last administration, rhBMP-2 had already triggered the initial spark by initiating a 55-60% union of the repair-site. On follow-up examination, the patient had normal radiographs showing bone healing *ad integrum* and normal ADL including sports activities.

Although the clinical potential of growth factors to enhance fracture repair has been known for decades,[13] little is known about their long-term effects and they have only been approved for the treatment of a very limited range of orthopaedic conditions.[2,8,9] The benefits of BMPs in the treatment of delayed and non-unions are still being discussed controversially.[10,11] This case report emphasizes that rhBMP-2 can be successfully used for the treatment of complicated delayed unions and possibly non-unions as well as an equivalent alternative to the gold standard of autologous bone-grafting. In specific, we have shown that rhBMP-2 can induce and enhance bone repair even *without* using osteoconductors which contradicts the conventional notion of bone repair. Traditionally, bone healing is supposed to require 3 components: an *osteoconductor*, *i.e.*, a scaffold over which new bone can form, an *osteoinductor*, *i.e.*, a growth factor directing cellular differentiation, and *pluripotent mesenchymal stem cells*, *i.e.*, the target cell for the growth factors.[8,11] In animal trials, however, Baltzer *et al.*[12] and Schmidmaier *et al.*[14] as well as Tang *et al.*[1] have already demonstrated the capacity of rhBMP-2 to enhance bone repair *without* osteoconductors - either by using viral vectors encoding for BMP-2 in rabbits,[12] BMP-2-coated Kirschner wires in rats[13] or specific

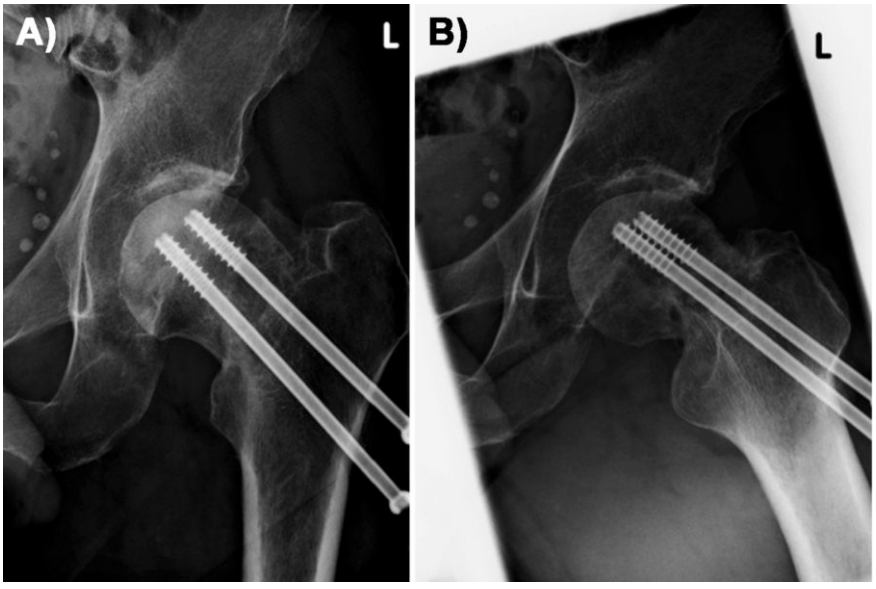

Figure 1. Anteroposterior (A) and lateral (B) radiographs of the left femur 4 months after initial surgery (2 hip-screws) show an impaction of the femoral head into the femoral neck.

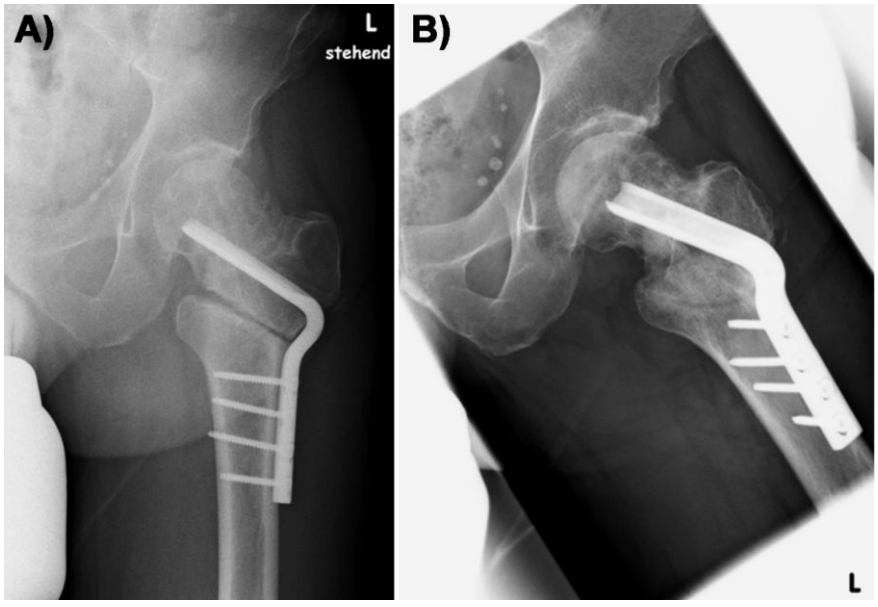

Figure 2. Anteroposterior (A) and lateral (B) radiographs of the left femur 2.5 months after derotational open-wedge osteotomy and before extracorporeal shock-wave therapy show no sign of ossification or calcification in the osteotomy-gap.

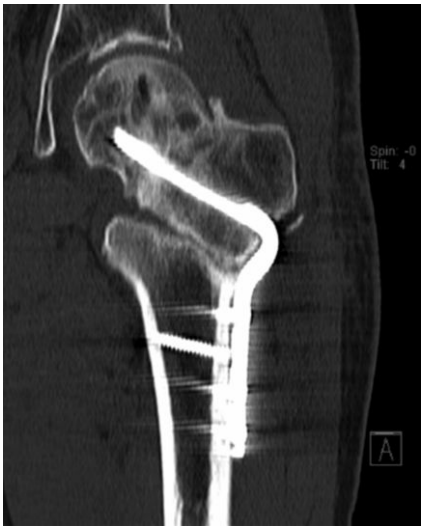

Figure 3. Computed tomography image of the left femur 4 months after osteotomy and 2 weeks after the last extracorporeal shock-wave therapy-session shows an unchanged delayed union in the open-wedge osteotomy-gap.

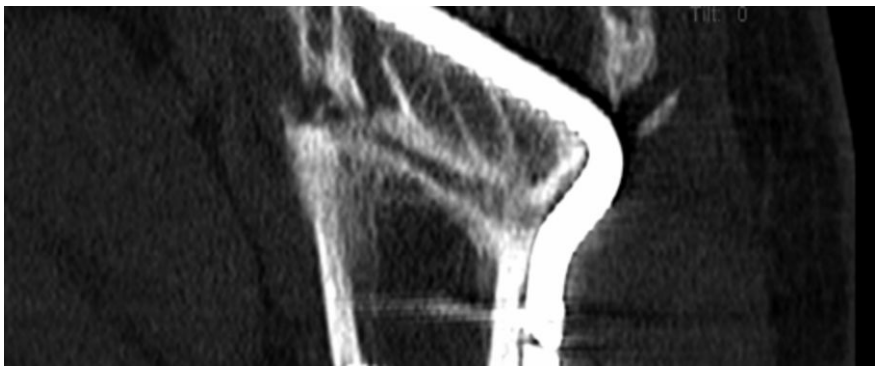

Figure 4. Computed tomography image 6 weeks after the last recombinant human bone morphogenetic protein-2 injection shows an approximately 55-60% union of the bone defect.

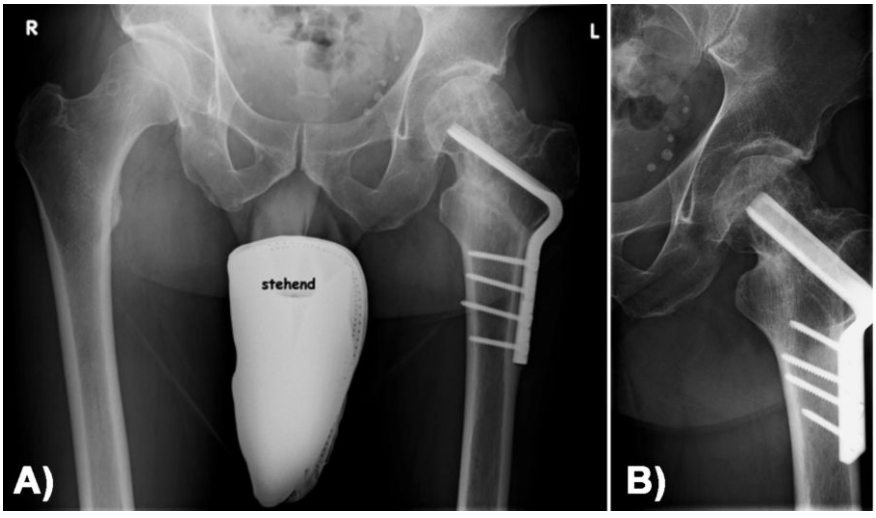

Figure 5. Nine-month-follow-up anteroposterior (A) and lateral (B) radiographs of the left femur show a complete union of the bone defect.

delivering devices in dogs[1] ensuring a high therapeutic concentration of BMP-2 at repair-site. In contrast to these efforts in the animal model, we did neither adopt the gene therapeutical approach by Baltzer *et al.*[12] - which is currently not approved of in Germany - nor the invasive techniques by Schmidmaier *et al.*[14] or Tang *et al.*[1] Instead, we used CT-guided injections to transport rhBMP-2 directly to the repair-site and administered the injections repeatedly to maintain a sustainable regional concentration of the growth factor. This approach seems technically safe and risk-free. Importantly, it is additionally much less invasive and painful than autologous bone-grafting[2] which was important to our patient, as he did not want to undergo a third surgery within 13 months.

With regard to negative long-term effects, our conclusions are restricted to the (positive) results of the 9-month-post-treatment follow-up. Future studies should use longer follow-up intervals, for patient safety must be our number one priority, as such a new technique is taken from the bench to the bedside.[2] Besides, it is hard to tell whether our positive outcome would have been the same in an older patient, as bone healing is known to be more complicated in the elderly.[15,16] In spite of these limitations, we believe it appropriate to consider the regional use of rhBMP-2 as an alternative to the last resort of autologous bone-grafting. In view of the positive outcome of the present case, further prospective, controlled, randomized studies in a larger patient population seem warranted. In specific, an examination of the appropriate dosage and administration intervals of rhBMP-2 would be desirable.

Delayed or non-unions are a key obstacle in all types of fractures or open-wedge osteotomies.[1,4] Current treatment recommendations for delayed and non-union include both invasive procedures, such as autologous bone-graft or osteotomy, and non-invasive techniques, such as ESWT.[2-5] The present case report shows that growth factors, for instance, rhBMP-2, can also be successfully used to treat complicated delayed union following open-wedge osteotomy in a minimally-invasive procedure *without* the use of traditional osteoconductors.

References

1. Tang P, Yao Q, Zhang W, et al. A study of femoral neck fracture repair using a recombinant human bone morphogenetic protein-2 directional release system. Tissue Eng Part A 2009;15:3971-8.
2. Baltzer AWA, Lieberman JR. Regional gene therapy to enhance bone repair. Gene Ther 2004;11:344-50.
3. Birnbaum K, Wirtz DC, Siebert CH, Heller KD. Use of extracorporeal shock-wave therapy (ESWT) in the treatment of non-unions. A review of the literature. Arch Orthop Traum Surg 2002;122:324-30.
4. Dhar SA, Gani NU, Butt MF, et al. Delayed union of an operated fracture of the femoral neck. J Orthopaed Traumatol 2008;9:97-9.
5. Zelle B, Gollwitzer H, Zlowodzki M, Buhren V. Extracorporeal shock wave therapy: current evidence. J Orthop Trauma 2010; 24Suppl1:S66-70.
6. Capello WN, Feinberg JR. Trochanteric excision following persistent nonunion of the greater trochanter. Orthopedics 2008; 31:711.
7. Ottomann C, Stojadinovic A, Lavin PT, et al. Prospective randomized phase II trial of accelerated reepithelialization of superficial second-degree burn wounds using extracorporeal shock wave therapy. Ann Surg 2012;255:23-9.
8. Hawkins BJ. Biologics in foot and ankle surgery. Foot Ankle Clin N Am 2010;15:577-96.
9. Valdes MA, Thakur NA, Namdari S, et al. Recombinant bone morphogenic protein-2 in orthopaedic surgery: a review. Arch Orthop Trauma Surg 2009;129:1651-7.
10. Garrison KR, Shemilt I, Donell S, et al. Bone morphogenetic protein (BMP) for fracture healing in adults. Cochrane Database Syst Rev 2010;6:1-155.
11. Nauth A, Giannoudis PV, Einhorn TA, et al. Growth Factors: beyond Bone Morphogenetic Proteins. J Orthop Trauma 2010;24:5 43-6.
12. Baltzer AWA, Latterman C, Whalen JD, et al. Genetic enhancement of fracture repair: healing of an experimental segmental defect by adenoviral transfer of the BMP-2 gene. Gene Ther 2000;7:734-9.
13. Urist MR. Bone: formation by autoinduction. Science 1965;150:893-9.
14. Schmidmaier G, Wildemann B, Cromme F, et al. Bone morphogenetic protein-2 coating of titanium implants increases biomechanical strength and accelerates bone remodelling in fracture treatment: a biomechanical and histological study in rats. Bone 2002;30:816-22.
15. Figl M, Weninger P, Jurkowitsch J, et al. Unstable distal radius fractures in the elderly patient - volar fixed-angle plate osteo-synthesis prevents secondary loss of reduction. J Trauma 2010;68:992-8.
16. Marsh DR, Li G. The biology of fracture healing: optimising outcome. Br Med Bull 1999; 55:856-69.