

Preliminary experience with the combined use of recombinant bone morphogenetic protein and bisphosphonates in the treatment of congenital pseudarthrosis of the tibia

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Abstract

Purpose Congenital pseudarthrosis of the tibia (CPT) is a rare but serious disorder in children. No single approach has clearly emerged as superior in terms of operative procedure, fixation, optimal time for surgery or adjunctive pharmaceutical intervention. CPT is frequently associated with neurofibromatosis type 1 (NF1), a condition featuring deficient bone anabolism and excessive catabolism. We have therefore combined the use of bone morphogenetic proteins (BMP) with bisphosphonates (BP) as an adjunct to surgical intervention.

Methods Between 2002 and 2008 we administered BMP-7 (OP-1) at the time of surgery followed by BP (pamidronate or zoledronic acid) in eight Crawford type IV CPT cases in seven patients (six with a confirmed diagnosis of NF1) with a median age of 7 years (range 2 years 11 months to 12 years) at surgery.

Results In six of eight cases, this approach led to primary healing after a mean of 5.5 months (range 4–7 months). One of these cases represented 17 months after primary healing of a proximal CPT with a new further distal fracture that required multiple operations to finally unite at 19 months. The two remaining cases ultimately reached union after multiple operations at 14 and 30 months, respectively, but required recent treatment for refractures.

Conclusion Based on these clinical data (primary healing in 6/8 cases) and prior pre-clinical findings, we propose that BP therapy may be helpful in preserving the BMP-induced bone formation by inhibiting the osteoclastic bone loss. Key factors to achieve union in CPT include sufficient fixation, meticulous resection of the dysplastic tissue and the establishment of a net anabolic environment for bone healing. Whether our biological concept of balancing the anabolic and catabolic responses with BMP and BP improves healing rates in the complex treatment of NF1 CPT remains uncertain and warrants larger prospective multicentre trials.

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Introduction

Congenital tibial pseudarthrosis (CPT) associated with neurofibromatosis type 1 (NF1) is a challenging condition to manage [1]. While CPT is an uncommon manifestation of NF1 (2–4%), patients with NF1 make up the majority of children that develop CPT [2]. CPT presents as a congenital tibial dysplasia associated with characteristic anterolateral bowing. This can be associated with tapering of the tibial diaphysis or with cystic or dysplastic lesions,

although the precise aetiology remains unclear. There is some evidence to suggest that bone lesions or pseudarthrosis may be associated with a localized loss of the second NF1 allele [3], although this has not been definitively examined in a large study. The natural history of CPT is progression to fracture at walking age with subsequent non-union. Further management is complicated by reduced bone healing potential in NF1 (decreased anabolism) as well as susceptibility to bone resorption (increased catabolism) [4]. Once fractured, current strategies for the management of CPT focus on re-establishing stability and augmenting bone healing using a range of different surgical approaches and bone anabolic agents.

Timing of surgery is still controversial, and no specific method for fixation has evolved as clearly superior. The published series show union rates of 60–100% and attribute their success to various variables, such as fixation of the fibula, a specific fixation method or cortical bonegraft. However, the results of small and heterogeneous patient series are difficult to compare, and all treatment strategies have some failures or refractures. In addition, there are still a significant number of amputations in the long-term studies. Consequently, there is still room for improvement! [5–19]. There is, however, consensus that all pseudarthrotic tissue should be resected and bone graft applied to promote healing.

Both cancellous bone graft and, more recently, cortical bone graft have been used as anabolic stimuli to promote repair [8]. Recombinant human bone morphogenetic proteins-2 and -7 (BMP-2 and BMP-7/OP-1) are also employed as anabolics for the treatment of adult fractures in specific circumstances, such as large diaphyseal defects [20, 21]. BMP use in children is off-label, but thus far none of the published CTP series using BMP in children have reported any side effects, adverse events or induction or stimulation of tumour growth [22, 23]. A paper looking at complications of BMP in children and adolescents reviewed 81 patients under 18 years of age [24]. However, careful monitoring of patients following the use of potent growth factors in the presence of a defective tumour suppressor gene, such as NF1, is obligatory.

In the context of NF1/CPT treatment, a variety of results from small case series utilizing BMP have been reported. These range from unsuccessful, when the use of BMP-7 resulted in primary healing in only one of five cases, to some success when primary healing occurred in five of the seven cases involving BMP-2 and intramedullary rodding. In the latter series, four of the seven patients had NF1, and both non-unions were observed in these four NF1 patients, one of whom progressed to amputation for persistent non-union [22, 23, 25].

Preclinical studies of BMP-2 have indicated a reduced efficacy in promoting new bone formation in the

NF1-deficient (*Nf1*^{+/-}) mouse line [26]. This study also showed a significant increase in total BMP-induced bone upon co-treatment with a bisphosphonate (BP), suggesting that anti-catabolic treatments could be beneficial in this context. In a rat critical defect model, combining local BMP administration with systemic anti-resorptive agents significantly increased the callus volume, strength and bone mineral content (BMC) [27]. To date, BP represents one of the most cost-effective and widely used bone anti-resorptive approaches; they are able to potently inhibit osteoclast-mediated bone catabolism. BP treatment has been safely used in children with systemic osteopenic conditions, such as osteogenesis imperfecta (OI) for many years. In this report, we describe a series of eight CPT cases in seven patients (six with a confirmed diagnosis of NF1). All patients were treated with a combination therapy with BMP-7 given as an anabolic at the time of surgery and the BP pamidronate or zoledronic acid administered post-operatively with the aim of retaining the BMP-induced bone.

Materials and methods

Patients

We reviewed the patient records of all NF1/CPT cases treated between 2002 and 2008 at The Children's Hospital at Westmead (Sydney, Australia). The retrospective review was approved by the local Children's Hospital at Westmead Human Ethics Committee. All patients were treated with a combination of BMP-7 and BP (pamidronate and/or zoledronic acid).

Eight CPT cases in seven patients were identified. Six of the seven patients had a diagnosis of NF1. The patient age at surgery ranged from 2 years 11 months to 12 years (median 7 years). Pseudarthroses were graded using the Crawford system: Crawford type I is described as an anterolateral bowing of the tibia; type II as "sclerotic" with an anterolateral bowing, increased cortical thickness and a narrow intramedullary canal; type III as a "cystic" lesion; type IV as a fracture or frank pseudarthrosis [28, 29]. All cases reported here were Crawford type IV. Within the patient cohort, one to three prior surgical procedures had been carried out at the same pseudarthrosis site in 63% (5/8) of the cases, and four to seven doses of BP had been administered in 84% (7/8) of the cases, mostly in conjunction with prior surgery.

Surgical treatment

During the surgical procedure, the dysplastic and fibrotic pseudarthrosis tissue was meticulously removed down to

healthy appearing muscle and bone. The tibia was aligned and stabilized with an intramedullary rod and/or Ilizarov frame. Thereafter, the pseudarthrosis site was grafted with a mixture of iliac crest corticocancellous bone graft and 3.5 mg rhBMP-7/OP-1 in 1 g of bovine collagen carrier (Stryker Biotech, Hopkinton, MA). Our off-label use of BMP-7 was approved by our local Institutional Pharmacy Committee.

Details about the choice of intramedullary rods and/or Ilizarov frame as well as required additional surgical procedures are outlined in Tables 1 and 2.

Medical treatment

Prior to the start of BP treatment, all children were assessed by a paediatric endocrinologist who instituted and monitored the BP treatment. All patients had serum 25-hydroxyvitamin D, urea and creatinine concentrations within quoted reference ranges and normal renal ultrasound scans and were assessed by a dentist. After reports of osteonecrosis of the jaw (ONJ) our protocol included dental examination, and any dental work was carried out prior to BP treatment [33]. The children were prescribed a multivitamin containing 400 IU vitamin D per day and calcium supplementation if their dietary calcium intake was suboptimal. Bone mineral density (BMD) values were determined every 6–12 months by dual energy X-ray absorptiometry (DXA) using a Lunar Prodigy apparatus (GE Lunar Radiation Corp, Madison, WI) and evaluated by the paediatric endocrinologist.

BP treatment commenced 2–3 weeks postoperatively (initial dose of pamidronate 0.5–1.0 mg/kg/dose or zoledronic acid 0.0125 mg/kg/dose). A lower initial dose was given to those children who had not previously received BP so as to limit the side effects associated with the first dose. This was followed by two doses at 6–8 weeks and further doses 3–6 months thereafter (pamidronate 1.0–1.5 mg/kg/dose or zoledronic acid 0.025–0.05 mg/kg/dose). Depending on their preoperative BP treatment, their BMD values and projected surgical procedures, the patients received a median of two BP doses (range 1–6 doses) postoperatively.

Outcome analysis

We evaluated the pre-operative and follow-up anteroposterior (AP) and lateral radiographs with regards to healing of the pseudarthrosis site, callus formation and incorporation or resorption of the bone graft and BMP-7 composite. The primary outcomes were the best Johnston grade and RUST (Radiographic Union Score for Tibial fractures) score within 12 months of surgery. Johnston grade 1 indicates unequivocal union; grade 2, an equivocal union

with a residual transverse or longitudinal cortical deficiency and/or $>15^\circ$ deformity; grade 3, a persistent non-union/pseudarthrosis or refracture [15]. The RUST system scores each of the four cortices on AP and lateral radiographs: a fracture line with no callus scores 1 point; callus present but still a visible fracture line scores 2 points; and bridging callus without evidence of a fracture line scores 3 points. The added individual scores give a total score between 4 (definitely not healed) and 12 (definitely healed). In the context of CPT and prior BP treatment, a fracture line or CPT lesion may be visible even though solid union has already been achieved. Therefore, we considered a total score of 10 points to indicate total healing [30]. Time from the index procedure to union as well as complications, additional procedures and radiographic as well as functional outcome at the last review (final outcome) were recorded.

Results

Case reports

Examples of successful and recalcitrant cases are shown in Fig. 1 (Case 7A, primary union) and Fig. 2 (Case 6, insufficient fixation). Case data are summarized in Tables 1, 2 and 3. Key features of the individual cases are described below.

Case 1

A 12-year-old boy with a distal CPT healed by 6 months after resection of the pseudarthrosis, bone graft, BMP-7, Sofield rodding and Ilizarov frame, with two doses of BP. A pin track infection was successfully treated with oral antibiotics.

Case 2

A 2-year 11-month-old boy presented with a distal CPT after bracing and five previous BP doses. He healed at 7 months post excision, bone graft, BMP-7 and Sofield rod transfixing the ankle to the calcaneus, with one further BP dose. At age 5 years, the rod was pushed proximally to free the ankle. Two undisplaced fractures after falls with the rod in situ healed at age 6 and 8 years.

Case 3

An 11-year-old boy, the only patient without NF1, showed no signs of healing in 1 year 10 months after four operations, including repeat excision of a distal CPT, two bone

Table 1 Surgical and medical treatment of eight cases of congenital tibial pseudarthrosis in seven patients

Case	Previous surgery (age)	NFI	Sex, age at surgery	Surgical procedure at CPT	Fibula	Previous BP treatment [total no. doses/total dose (mg)/total dose (mg/kg)]	Postoperative BP treatment until union [total no. doses/total dose (mg)/total dose (mg/kg)]
1	None	Yes	Male, 12 years	Excision of pseudarthrosis, Ilizarov bone transport and Sofield rod, BMP-7 and bone graft	Intact Prox. osteotomy No fixation	0	2/ 1.6 mg ZA/ 0.036 mg/kg ZA
2	None	Yes	Male, 2 years 11 months	Excision of pseudarthrosis, Sofield rod with ankle transfixation, BMP-7 and bone graft	Intact No osteotomy No fixation	5/ 2.3 mg ZA/ 0.170 mg/kg ZA	1/ 0.8 mg ZA/ 0.05 mg/kg ZA
3	Bonegraft, Sofield rod (9 years)	No	Male, 11 years	Removal of previous rod, excision of pseudarthrosis, insertion of Sofield rod, Ilizarov, BMP-7 and bone graft	Pseudarthrosis No fixation	4/ 4.0 mg ZA/ 0.154 mg/kg ZA	6/ 4.7 mg ZA/ 0.147 mg/kg ZA
4	Bone graft, Ilizarov, Sofield rod (4 years 6 months, 6 years)	Yes	Female, 7 years	Excision of pseudarthrosis, Ilizarov for compression, BMP-7 and bone graft, Sofield rod left in situ	Pseudarthrosis No fixation	7/ 192 mg Pam/ 7.0 mg/kg Pam	2/ 60 mg Pam/ 2 mg/kg Pam
5	Bonegraft, K-wire to fibula (5 years 8 months) + 2 revisions	Yes	Male, 10 years	Excision of proximal pseudarthrosis, Ilizarov, BMP-7 and bone graft	Pseudarthrosis No fixation	4/ 124 mg Pam/ 4.1 mg/kg Pam	3/ 2.9 mg ZA/ 0.060 mg/kg ZA
6	Bonegraft, BMP-7, plaster (2 years 4 months, Crawford Type III lesion at that stage)	Yes	Female, 5 years	Excision of pseudarthrosis, FD telescoping rod, BMP-7 and bone graft	Intact No osteotomy No fixation	7/ 2.4 mg ZA/ 0.12 mg/kg ZA	3/ 1.0 mg ZA/ 0.05 mg/kg ZA
7A left	Bone graft, Ilizarov (2 years 6 months) + revision	Yes	Male, 3 years 8 months	Excision of pseudarthrosis, Sofield rod, BMP-7 and bone graft	Pseudarthrosis K-wire	4/ 120 mg Pam/ 6.0 mg/kg Pam	3/ 2.6 mg ZA/ 0.10 mg/kg ZA
7B right	None	Yes	Male, 7 years	Excision pseudarthrosis with stress fracture, BMP-7 and bone graft	Intact Osteotomy No fixation	7/ 120 mg Pam 6.0 mg/kg Pam/ 2.6 mg ZA 0.10 mg/kg ZA	1/ 1.5 mg ZA/ 0.05 mg/kg ZA

NFI Neurofibromatosis type 1, CPT congenital tibial pseudarthrosis, BP bisphosphonate, BMP Bone morphogenetic protein, FD Fassier-Duval, Pam pamidronate, ZA zoledronic acid

Table 2 Radiographic outcome and complications of eight cases of Crawford Type IV CPT in seven patients

Case	Primary outcome within 12 months		Time to union (months)	Complications	Additional procedures	Final radiological follow-up	Final outcome	
	Johnston	RUST					Johnston	RUST
1	1	10	6	Pin track infection treated with oral antibiotics	None	3 years 7 months	1	12
2	1	10	7	At 3 years and 5 years undisplaced fractures after major falls, healing without intervention with rod in situ	None	6 years 4 months	1	12
3	3	6	30	Refracture 2 years 4 months after union at 4 years 10 months post-index procedure	At 6 weeks: adjustment Sofield rod At 6 months: repositioning of Sofield rod and compression with Ilizarov At 10 months: re-excision pseudarthrosis, bone graft and BMP-7 At 22 months: removal of rod, excision pseudarthrosis, application of Ilizarov for chondrodiastasis bone transport At 24 months: revision osteotomy and bone-marrow graft to the non-union site At 4 years 10 months: distal third tibial refracture: retrograde insertion of female FD-rod component transfixing ankle and Ilizarov frame for proximal lengthening	5 years 5 months	2 ^a	7 ^a
4	1	10	4	Ankle valgus	At 3 years 3 months: distal medial tibial hemi-epiphyseodesis	7 years 0 months	1	11
5	1	12	5	At 2 years presentation with distal CPT, while the original proximal CPT site stayed solidly united	At 2 years: excision of distal pseudarthrosis, Fassier-Duval telescoping rod, BMP-7 and bone graft At 2 years 6 months: posterolateral bone graft and BMP-7	3 years 10 months	1	12
6	3	5	14	Non-union of the distal CPT Hematoma Refracture	At 3 years 3 months: FD-rod removed, locked humeral nail inserted, re-bone graft and BMP-7 At 2 days: fasciotomy for suspected compartment-syndrome and hematoma (muscle healthy) At 4 months: re-bone graft and BMP-7 via posterolateral approach, FD-rod in situ At 9 months: FD-revision, cortico-cancellous bone graft At 12 months: application of Ilizarov frame to further stabilize distal segment At 2 years 0 months: refracture: retrograde insertion of female FD-rod component transfixing ankle and Ilizarov frame	2 years 1 month	3 ^b	4 ^b

Table 2 continued

Case	Primary outcome within 12 months		Time to union (months)	Complications	Additional procedures	Final radiological follow-up	Final outcome	
	Johnston	RUST					Johnston	RUST
7A left	1	10	7	Post-op subalar rod irritation Persistent fibula pseudarthrosis Valgus ankle	At 1 week: repositioning of Sofield rod At 2 months: repositioning Sofield rod—pushed further into tibial epiphysis At 21 months fibula 1.6 mm K-wire and bonegraft + lateral tibial onlay bonegraft At 3 years: medial malleolar screw epiphysiodesis for valgus ankle and debridement and bone grafting fibular non-union	7 years 10 months	1	12
7B right	1	12	4	Valgus ankle	At 2 years: medial malleolus screw epiphysiodesis	3 years 4 months	1	12

Johnston Johnston grade, RUST Radiographic Union Score for Tibial fractures

^a 7 months post refracture

^b Refracture and surgery at time of submission

graft and BMP-7 applications, Sofield rodding, Ilizarov frame and six BP doses. He finally healed with 5 cm shortening and a stiff ankle after a total of 2 years 6 months (8 months after repeat excision and Ilizarov bone transport with distal tibial chondrodiastasis). After a further 2 years 4 months he re-presented with a refracture after a fall, required surgery with rodding through the ankle and was healing at the time that this report was being written.

Case 4

A 7-year-old girl presented with a distal CPT after three previous operations and seven previous BP doses. She went on to union 4 months post-excision, bone graft, BMP-7, Sofield rodding and Ilizarov compression, with two further BP doses. Within 1 month following union of the pseudarthrosis, a 5-cm Ilizarov lengthening was done over the rod, which healed without complications.

Case 5

A 10-year-old boy presented with a CPT of the proximal tibial shaft after three previous surgeries with bone grafting and four previous BP doses. He healed by 5 months post-resection of the pseudarthrosis, bone graft, BMP-7, Ilizarov and three BP doses.

At age 12 years he re-presented with a new distal fracture in the same tibia. The previously treated proximal pseudarthrosis site still showed solid union. The new fracture was treated with a telescoping Fassier-Duval (FD) rod, bone graft, BMP-7 and one dose of BP. The bone graft was only partially resorbed but failed to unite at 5 months and thus was re-grafted with BMP-7. No further BP was given due to the high number of previous BP doses and a lumbar spine BMD Z-score of +2.9.

Over the following 9 months the rod gradually collapsed (“negative telescoping”) and then protruded into the ankle. The telescoping rod was exchanged for a locked humeral nail and bone graft with BMP-7 applied for a third time. Healing was achieved at 2 months after this third operation with retention of the bone graft and bridging callus.

Case 6

A 5-year-old girl with a distal CPT after one previous operation and four previous BP doses was treated with excision, bone graft, BMP-7, a telescoping FD rod and two further BP doses. Persistent non-union warranted two additional bone grafting procedures (the first with BMP-7) at 4 and 9 months. The bone graft was mainly retained, but only after adding stability with an Ilizarov frame at 12 months, union was achieved 6 weeks thereafter (Fig. 2).

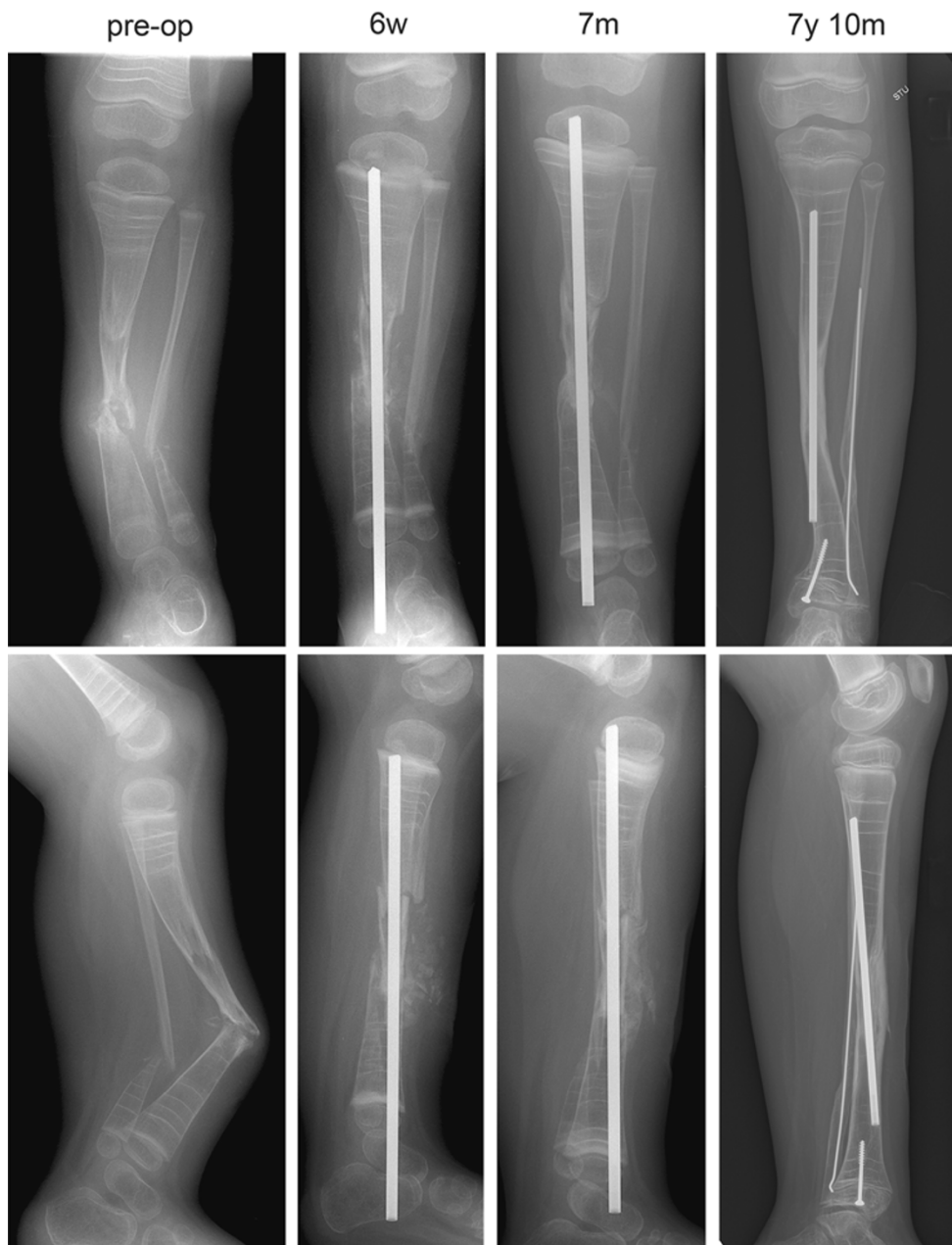


Fig. 1 Case 7A: Crawford IV tibia pseudarthrosis in a 3-year 8-month-old boy healed at 7-months post-excision, bone graft, bone morphogenetic protein-7 (BMP-7), Sofield rodding and five doses of

bisphosphonates (BP). Radiographs are shown pre-operatively, healed at 7 months (*m*) and remodelled at 7 years (*y*), 10 months. *w* weeks

A refracture at 2 years (time of submission) required a re-operation with rodding through the ankle.

Case 7A

A boy of 3 years 8 months showed no healing of his left CPT after two previous operations and four BP doses. He healed at 7 months post-excision, bone graft, BMP-7,

Sofield rodding and two minor rod-repositioning operations with two further BP doses (Fig. 1).

Case 7B

At age seven years, the boy described in Case 7A presented with a proximal CPT of his opposite right side, which healed 4 months post-iliac crest and Vitoss (Orthovita,

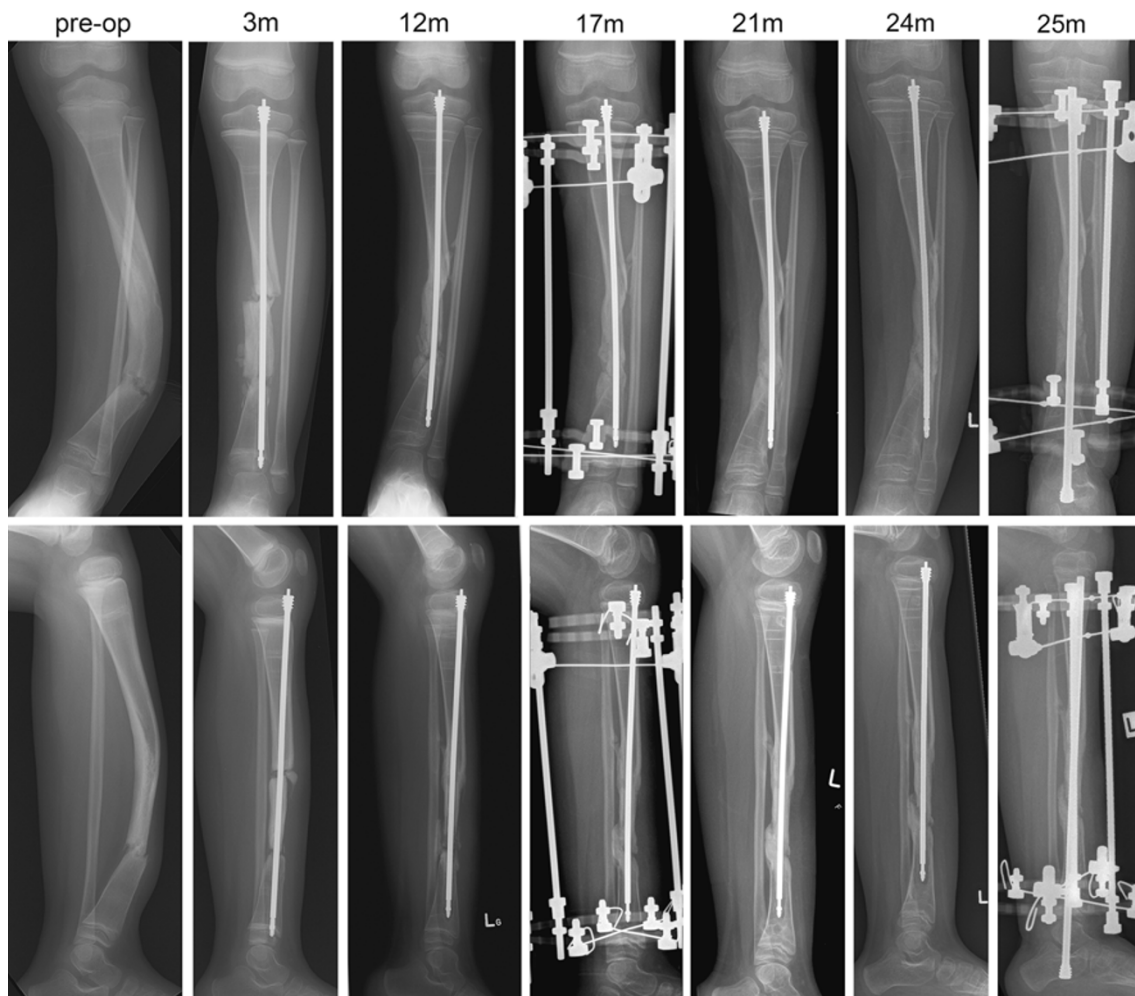


Fig. 2 Case 6: Congenital tibial pseudarthrosis in a 5-year-old girl after one previous operation and four previous BP doses treated with excision, bone graft, BMP-7, a telescoping Fassier-Duval (FD) rod and two further BP doses. Persistent non-union warranted two additional bone grafting procedures (the first with BMP-7) at 4 and 9 months, respectively. Bone graft and callus had been retained after

intervention with BMP/BP, but telescopic rod fixation alone was insufficient to achieve union and later failed to prevent a refracture. After improving stability to the short distal tibial segment with an Ilizarov frame, it went on to unite, but refractured 5 months (*m*) after removal of the frame and required additional surgery with rodding through the ankle at the time of manuscript submission

Table 3 Clinical outcome at latest follow-up of eight cases of Crawford Type IV CPT in seven patients

Case	Follow-up	Pain	Activity	Brace	LLD (cm)	Ankle ROM	Ankle	Foot position
1	3 years 7 months	None	No restrictions	None	2.5	Full	15° valgus	Plantigrade
2	6 years 4 months	None	No contact sports	KAFO	2	Full	12° valgus	Plantigrade
3	5 years 5 months	Minimal	FWB in frame	N/A	4	0	Neutral	Plantigrade
4	7 years 0 months	None	No contact sport	DynAFO	0.5	Full	Neutral	Plantigrade
5	3 years 10 months	None	No restrictions	KAFO	6	Full	Neutral	Plantigrade
6	2 years 1 month	Mild	PWB in frame	N/A	0	0	Neutral	Plantigrade
7A left	7 years 10 months	None	No contact sports	Clamshell AFO	+2.5	Full	10° varus	Plantigrade
7B right	3 years 4 months	None	No contact sports	SMFO	-2.5	Full	10° valgus	Loss of medial arch

ROM Range of motion, LLD limb length discrepancy, DynAFO Dynamic Ankle–Foot–Orthosis, KAFO Knee–Ankle–Foot–Orthosis, FWB full-weight bearing, PWB partial-weight bearing, SMFO Supra-Malleolar–Foot–Orthosis, N/A not applicable (in frame)

Malvern, PA) bone graft, BMP-7 and plaster treatment. Due to his seven previous BP doses in conjunction with his surgeries of the opposite CPT, only one further BP was given.

Discussion

In this paper we report on a series of eight CPT cases in seven patients treated with an anabolic/anti-catabolic approach using adjunctive BMP/BP pharmacotherapy. The choice of BMP-7 over BMP-2 was one of availability at our centre. Patients were treated post-operatively with the BP pamidronate or zoledronic acid for the purpose of maintaining BMP-7-induced bone. With this strategy, we achieved rapid primary union in 75% of cases (6/8) at a mean of 5.5 months (range 4–7 months) (Fig. 1). Furthermore, all cases eventually healed, which compares favourably with the literature, even though both of our cases that failed primary union required recent surgery for refractures. Retrospective examination of the two recalcitrant cases revealed that both cases lacked stable fixation of the short distal tibial segment. Bone graft and callus had been retained after intervention with BMP/BP, but telescopic rod fixation alone was insufficient to achieve union and later failed to prevent a refracture (Fig. 2). After improving stability to the short distal tibial segment with an Ilizarov frame, it went on to unite, but refractured 5 months after removal of the frame.

This study focuses on achieving union and has sufficient follow-up to account for early complications, re-operations and refractures. However, achieving union is only the start of a successful treatment path, which includes controlling leg length inequality and deformity and maintaining robust union to skeletal maturity and, most importantly, sound limb function.

In terms of systematic evaluation of BMP/BP therapy, this study has several limitations. The study is retrospective and shows a wide heterogeneity of ages and fixation technique and no standardization in BP intervention. This is reflective of the evolution of a treatment strategy over 8 years. Nevertheless, these experiences have been extremely informative at our centre and continue to guide practice. CPT is a relatively uncommon, albeit serious condition and, in the context of NF1 CPT, the sample size of eight cases represents a substantial patient cohort. However, the results of diverse and often complex treatment strategies applied to small and heterogeneous patient series are difficult to compare, and thus conclusions regarding long-term benefits of isolated treatment factors must be guarded.

There is a strong theoretical basis for our strategy of balancing anabolism and catabolism by adding an anti-resorptive agent to BMP. However, in our experience, all

successfully united cases required stable fixation of the distal tibial fragment. We therefore postulate that treatment success in CPT is multifactorial. Key factors that appear to be required to achieve union include adequate fixation, meticulous resection of all dysplastic tissue and the establishment of a net anabolic environment with bone graft and possibly adjunctive pharmaceuticals, such as BMP and BP.

Our own preclinical studies of BMP-2-induced heterotopic bone formation in NF1-deficient mice (*Nf1^{+/-}*) have illustrated the advantages of BP therapy. Zoledronic acid co-treatment produced a fivefold increase in BMD and a fourfold increase in bone volume/tissue volume (BV/TV) after BMP/BP co-treatment when compared to BMP-2 alone [26]. These findings indicate that BMP may be functional but less effective in an NF1 setting and strongly suggest that further adjunctive approaches may be advantageous. The clinical case series of Lee et al. supports these findings, with the bone graft mostly resorbed and just one of five cases healed within 1 year after BMP-7 alone [23].

In contrast, a recent study reported primary healing after Williams rodding and BMP-2 alone in five of seven cases of CPT. Only four of the seven patients had a confirmed diagnosis of NF1, and both non-unions were observed in NF1 patients (50% success rate in NF1 only). One of these cases, notably with the highest dose of BMP-2 in the whole series, led to a persistent non-union that required a below-knee amputation [22]. It is possible that CPT is even more difficult to treat when associated with NF1. As previously mentioned, it is extremely difficult to compare a small heterogeneous patient series, and it is even more difficult to prove any causality. At this point, the relative merits of BMP-2 or BMP-7 in this disease remain to be investigated.

In our series, the short-term BP treatment commenced 2–4 weeks after surgery, once the callus was formed. This was based on pre-clinical data from rat closed fracture and critical defect models where the best results in terms of callus size and mechanical strength were achieved when the BP treatment was delayed for 2 weeks [27, 31]. A recent report of children treated with BP over a period of 1 to 1 year 6 months for localized bone disorders, such as avascular necrosis or Perthes disease of the hip, showed no adverse affect on growth and no cases of fractures associated with increased bone density or ONJ [32]. One serious complication of BP is ONJ, which usually occurs after high-dose treatment for malignancy, with the highest rates in myeloma and breast cancer patients [33]. No cases of ONJ have been reported in children to date, but routine dental examination prior to commencing on BP therapy is a common sensible precaution we follow to minimize the need for dental surgery during BP therapy. The concerns about BP-related inhibition of fracture repair only seems to apply to patients on very long-term BP therapy that may

result in reduced bone turnover affecting both anabolic and catabolic responses [34, 35]. All of our CPT cases treated with BMP and BP eventually healed and remodelled (Fig. 1). Furthermore, we did not observe signs or a correlation between high numbers of previous BP doses with delayed or increased time to union. We therefore concluded that the described short-term BP regime is safe to use in CPT.

Conclusion

The combined use of BMP and BP may be helpful in preserving the BMP-induced bone formation by inhibiting osteoclastic bone loss. Care should be taken to ensure mechanically stable fixation, particularly of the small distal tibial segment. Whether or not this biological concept of enhanced anabolism and inhibition of catabolism translates into improved healing rates in the complex treatment puzzle of CPT remains to be investigated with larger prospective multicentre trials.

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