The East of England
Priorities Advisory Committee
Hosted by PrescQIPP

GUIDANCE STATEMENT

Dibotermin alfa for the management of acute tibial fractures in adults

PAC recommendations

These recommendations apply to the use of bone morphogenetic proteins (BMPs) in the conditions detailed below which are commissioned by Integrated Care Boards (ICBs). The use of BMPs in conditions not specifically included in this policy which may be commissioned by ICBs, is not supported.

The recommendations do not include the use of BMP for specialist services/conditions commissioned by NHS England, e.g. revision of previous spinal surgery. See NHS England policies at: http://www.england.nhs.uk/

ICB commissioning of BMP is recommended:

1. For acute tibial fractures with Grade IIIB fractures (i.e. more severe cases):

Dibotermin alfa is recommended as an adjunct to standard care using open fracture reduction and intramedullary nail fixation in patients in whom there is a substantial risk of non-union. It is restricted to patients treated with unreamed intramedullary nails.

ICB commissioning is not recommended:

1. In skeletally immature individuals defined as those who can reasonably be expected to not have fusion of the long bone epiphyses, in other words they are still growing (normally in girls below 16 years and in boys below 19 years).

2. For repeat doses or sequential use of BMPs due to the possible development of antibody production.

Background

Bone morphogenetic proteins (BMPs) are growth factors or osteo-inductive proteins, that promote ectopic bone formation and can be extracted from demineralised bone matrix.[1]

Most fractures heal within 20 weeks, although the exact time to fracture union depends on a number of factors, including: severity of injury, presence of an open wound, number of fracture fragments, associated vascular injury, part of the bone fractured and method of fracture treatment. If a fracture does not heal in the time expected, as established by the clinician, it is considered to be a delayed union. A fracture that demonstrates motion at the bony ends and is not completely healed within six months is considered a non-union. Non-unions can lead to significant pain, inhibition of function and decreased personal and professional productivity with the potential for associated reductions in patients' health-related quality of life.[2]

The rate of delayed unions varies by fracture severity but has been reported to range from 16-60% for less severe fractures, to 43-100% for more severe fractures. The rate of non-unions has been reported

to range from 4-10%.[2] Tibial fractures have the highest incidence of non-union (0–15%), followed by femur fractures (1–11%) and humerus fractures (0–13%).[3] A study specifically in relation to Scotland has estimated the relative incidence of fracture non-union as 18.94 per 100,000 population per annum for Scotland.[4]

There is currently one BMP product available in the UK, dibotermin alfa (rhBMP-2) (InductOs®), which is produced by recombinant technology.[1]

Eptotermin alfa (rhBMP-7) (Osigraft®) was withdrawn from the EU market in December 2015 at the request of the marketing authorization holder.[1,5]

Dibotermin alfa (rhBMP-2) is licensed for:

- Single-level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition.
- The treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.[6]

Evidence

There is currently no NICE guidance specifically regarding the use of BMP for the treatment of fractures. BMP is also not considered or included as a treatment option in relevant NICE clinical guidance regarding the management of complex and non-complex fractures.[7,8]

In 2007, the Scottish Medicine Consortium approved the use of dibotermin alfa, across NHS Scotland, for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation in patients in whom there is a substantial risk of non-union. Dibotermin alfa is restricted to patients treated with unreamed intramedullary nails.[9]

Several studies were included in the portfolio of evidence submitted to the SMC.

In one study, a single blinded phase III study (BESTT study), 450 patients; age range of 17 to 87 years with a sustained open tibial fracture, of which the major fracture was diaphyseal component, were randomised into one of three groups: standard of care only (control) involving intramedullary nail fixation and routine soft tissue management; standard of care plus 0.75mg/ml dibotermin alfa implant or standard of care plus 1.50mg/ml dibotermin alfa implant. Patients were stratified on the basis of Gustilo-Anderson classification of open fractures (types IA, IIA, IIIA and IIIB) . Definitive fracture fixation with intramedullary nailing (reamed or unreamed) was performed no later than 14 days (median 1 day) after the injury. The primary efficacy end point was the proportion of patients who received secondary interventions to promote fracture union within 12 months post definitive wound closure. 421 patients were followed up for the full 12 months. The proportion of patients requiring secondary interventions was 26% and 37% for 0.75mg/ml and 1.50mg/ml implants respectively vs. 46% for standard of care (p=0.0004). The patients who received the dibotermin alfa 1.5 mg/ml implant had a 44% reduction of risk (0.56 relative risk, 95% confidence interval [CI] 0.40 to 0.78) for a secondary intervention compared to standard of care alone. There were no significant differences between treatment groups for the median time to secondary interventions. Both the number and invasiveness of the interventions were significantly lower in the 1.50mg/ml implant than in the control group. The rate of secondary interventions was also reported to be significantly lower in dibotermin alfa group after adjustment for reaming and for fracture severity on the Gustilo-Anderson classification.[10]

In a second study, sub group analyses were conducted by combining the data from the BESTT study with a previously unpublished United States study.[11] Both studies utilised the same design and study protocol. A total of 510 patients were included: 450 patients from the first trial and 60 from the US study. Only the control and the commercially available 1.50mg/ml implant were compared in the per protocol (PP) population, with 169 patients in each PP analysis group. This was further divided into two sub-groups: patients with Gustilo-Anderson type IIIA or IIIB open tibial fractures (n=131; 65 in the

control group and 66 patients in the 1.5mg/ml dibotermin implant group) and patients with fractures treated with reamed intramedullary nailing (n=113; 48 patients in the control group and 65 patients in the implant group). Patients could be included in more than one subgroup.

In the type III subgroup, 13 patients (20%) in the control group and one patient (2%) in the implant group received a secondary autologous bone-grafting procedure to treat delayed union or non-union of fractures with a relative risk reduction (RRR) for the implant of 90% (95% CI 41% to 98%; p=0.0005). Eighteen patients (28%) in the control group and six patients (9%) in the implant group required an invasive secondary intervention, with a RRR of 68% (95% CI 24% to 86%; p=0.0065). Fracture healing, as measured by time to full weight bearing was 95.1 days in the implant group compared to 126.6 days for the control group. No difference was observed between the two treatment groups with respect to the need for nail dynamization.[11]

In the reamed intramedullary nailing subgroup, no significant difference between the control and the implant groups was observed. Three patients (6%) in the control group and one patient (2%) in the implant group required bone grafting [RRR=67%; 95% CI -201% to 96%, p=0.31] and seven patients (15%) in the control group and five patients (8%) in the implant group required an invasive secondary intervention [RRR=47%, 95% CI – 64% to 83%, p=0.3549]. Time to achievement of full weight bearing was 84 days for the control group versus 80 days for the implant group.[11]

A Cochrane review, published in 2010, assessed the incremental effectiveness and costs of BMP on fracture healing in acute fractures and non-unions compared with standards of care.[2] Eleven randomised controlled trials (RCTs), all at high risk of bias, and four economic evaluations were identified and included. Eight studies used eptotermin alfa, two studies, including the previously mentioned BESTT study, used dibotermin alfa and one study used BMP and natural non-organic bone (NNB). Apart from one study, the times to fracture healing were comparable between the BMP and control groups. There was some evidence for increased healing rates, without requiring a secondary procedure for BMP compared with usual care control in acute, mainly open, tibial fractures (risk ratio (RR) 1.19, 95% CI 0.99 to 1.43). The pooled RR for achieving union for non-united fractures was 1.02 (95% CI 0.90 to 1.15). One study found no difference in union for patients who had corrective osteotomy for radial malunions. Data from 3 RCTs indicated that fewer secondary procedures were required for acute fracture patients treated with BMP versus controls (RR 0.65, 95% CI 0.50 to 0.83). The review authors concluded that there is a paucity of data on the use of BMP in fracture healing as well as considerable industry involvement in currently available evidence. The limited evidence available suggests that BMP may be more effective than controls for acute tibial fracture healing, however, the use of BMP for treating non-union remains unclear. BMP treatment for acute open tibial fractures may be more favourable economically when used in patients with the most severe fractures.[2]

In a multicenter single-blinded study, 277 patients with acute open tibial fractures treated with reamed intramedullary nail fixation, were randomised (1:1) to receive either standard of care (SOC), consisting of intramedullary nail fixation and routine soft-tissue management or SOC plus an absorbable collagen sponge implant containing 1.5 mg/mL of dibotermin alfa (dibotermin/ACS group). Randomization was also stratified by fracture severity. The primary endpoint was the proportion of subjects with a healed fracture as demonstrated by radiographic and clinical assessment at 13 and 20 weeks post definitive wound closure. Thirteen percent of the fractures were Gustilo-Anderson Type IIIB. The proportions of patients with fracture-healing were 60% and 48% at week 13 (p=0.0541) and 68% and 67% at week 20, in the dibotermin/ACS and SOC only groups respectively. Twelve percent of the subjects underwent secondary procedures in each group with more invasive procedures (e.g. exchange nailing) accounting for 30% of the procedures in the dibotermin alfa/ACS group and 57% in the SOC group (p=0.1271). Infection was seen in 27 (19%) patients in the dibotermin/ACS group and 15 (11%) patients in the SOC group (p=0.0645; difference in infection risk = 0.09 [95% CI 0.0 to 0.17]). The adverse event incidence was otherwise similar between the treatment groups.[12]

Safety

In a pooled safety data analysis included in the SMC submission, the type III fracture patients receiving 1.50mg/ml had significantly lower screw breakage; 11% vs. 25%, and significantly lower infection rates; 21% vs. 40% than in the control group respectively. In the reamed intramedullary nailing subgroup the infection rate was lower than the control group, however the between group difference was not significant. Overall, pain was significantly lower in the dibotermin alfa implant groups; 67%, 68% and 79% in the 0.75mg/ml, 1.50mg/ml and control groups respectively. Antibodies to BMP-2 and type-I bovine collagen have been reported to occur in 6-10% and 5-20% respectively. Patients with hardware failure (mostly screw breakage or bending) were significantly lower in patients treated with the 1.50mg/ml dibotermin alfa implant compared to the control group; 11% and 22% respectively. One patient died in each of the three groups but none of the deaths were considered to be due to the implant. Local adverse events for dibotermin alfa include leg pain, oedema, infection, knee and ankle pain and hardware failure.[9]

Financial and commissioning considerations

Integrated Care Boards (ICBs, formerly CCGs) are responsible for commissioning routine non-complex surgeries such as treatment of acute tibial fractures.[13]

NHS England is currently responsible for commissioning complex spinal surgery and has approved the use of dibotermin alfa for anterior lumbar interbody fusion surgery, posterior interbody fusion more than two levels, posterior lumbar instrumented fusion more than two levels, and posterior cervical and thoracic instrumented fusion with no spinal cord decompression only for patients who have failed fusion from previous iliac crest bone graft (ICBG) or where ICBG cannot be harvested.[13,14] In the roadmap for the specialist services transition, adult orthopaedic surgery, adult orthopaedic revision and complex spinal surgery services, have been identified as suitable and ready for greater ICS leadership from April 2023.[15]

A cost-utility evaluation based on the data from the primary phase III trial for dibotermin alfa (the BESTT study) was submitted to the SMC review. Although adding dibotermin alfa increases the costs of treatment, partial cost offsets were obtained from a reduction in need for secondary interventions, lower rate of infections and reduced number of outpatient visits due to faster healing time for the dibotermin alfa patients. Overall, utility gains were obtained from faster healing time for patients receiving dibotermin alfa, resulting in a net incremental cost per QALY gained of £14,007. The overall QALY gain was influenced by the overall severity of the fracture: the estimate of incremental cost per QALY grade IIIA fractures treated with dibotermin alfa was over £30,000 and for grade II fractures was over £54,000, whereas for grade IIIB fractures incremental cost-effectiveness was estimated at £1,600 per QALY gained. The SMC review concluded that the economic case for dibotermin alfa for all patients with open tibial fractures has not been demonstrated, although there is a case for cost-effectiveness for a sub-group with grade IIIB fractures.[9]

A NHS health technology assessment published in 2007, assessed the clinical effectiveness and cost-effectiveness of BMP for the treatment of spinal fusions and the healing of fractures compared with the current standards of care. At the time of publication, the incremental cost of BMP for open tibial fractures was estimated to be about £3.5 million per year in the UK with an estimated incremental cost per quality-adjusted life-year (QALY) gained of £32,603. The probability that the cost per QALY gained is less than £30,000 for open tibial fracture was determined as 35.5%.[16]

Comments sought from: East of England clinicians via PAC members

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Document history

PAC approval date	16th January 2023
Version	Version 3
Document history	v2 December 2014 v1 Revised after withdrawal of Osigraft from market in August 2014 v1 September 2013
Consultation process	East of England clinicians via PAC members
QA process	Katie Smith, Director of Clinical Quality, PrescQIPP 6th March 2023

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Assessment against ethical and commissioning principles

Treatment assessed	Dibotermin alfa for the management of acute tibial fractures in adults
East of England Priorities Advisory Committee recommendation	These recommendations apply to the use of bone morphogenetic proteins (BMPs) in the conditions detailed below which are commissioned by Integrated Care Boards (ICBs). The use of BMPs in conditions not specifically included in this policy which may be commissioned by ICBs, is not supported. The recommendations do not include the use of BMP for specialist services/ conditions commissioned by NHS England, e.g. revision of previous spinal surgery. See NHS England policies at http://www.england.nhs.uk/ **ICB commissioning of BMP is recommended:** 1. For acute tibial fractures with Grade IIIB fractures (i.e. more severe cases): Dibotermin alfa is recommended as an adjunct to standard care using open fracture reduction and intramedullary nail fixation in patients in whom there is a substantial risk of non-union. It is restricted to patients treated with unreamed intramedullary nails. **ICB commissioning is not recommended:** 1. In skeletally immature individuals defined as those who can reasonably be expected to not have fusion of the long bone epiphyses, in other words they are still growing (normally in girls below 16 years and in boys below 19 years). 2. For repeat doses or sequential use of BMPs due to the possible development of antibody production.
Clinical effectiveness	A randomized, controlled, single-blind study of 450 patients (14 - 87 years) with a sustained open tibial fracture, received either standard of care involving intramedullary nail fixation and routine soft tissue management (control); standard of care plus 0.75mg/ml dibotermin alfa implant or standard of care plus 1.50mg/ml dibotermin alfa implant. The proportion of patients requiring secondary interventions was 46%, 37% and 26% for standard of care and dibotermin alfa 0.75mg/ml and 1.5mg/ml respectively. The relative risk of secondary intervention for the dibotermin alfa compared to control was 0.56 (95% CI 0.40 to 0.78). There were no significant differences between treatment and control groups for the median time to secondary interventions. Both the number and invasiveness of the interventions were significantly lower in dibotermin alfa than in the control group. The rate of secondary interventions was also reported to be significantly lower in dibotermin alfa group after adjustment for reaming and for fracture severity on the Gustilo-Anderson classification. In a multicenter single-blinded study, 277 patients with acute open tibial fractures treated with reamed intramedullary nail fixation, received either the standard of care (SOC/control), consisting of intramedullary nail fixation and routine soft-tissue management or SOC plus an absorbable collagen sponge implant containing 1.5 mg/mL of dibotermin alfa (dibotemin/ACS group). The proportions of patients with fracture-healing were 60% and 48% at week 13 (p=0.0541) and 68% and 67% at week 20 in the dibotermin and control groups respectively. Twelve percent of the subjects underwent secondary procedures in each group with more invasive procedures (e.g. exchange nailing) accounting for 30% of the procedures in the dibotermin group and 57% in the control group (p=0.1271). Infection was seen in 27 (19%) patients in the dibotermin group and 15 (11%) patients in the control group (p = 0.0645; difference in infection risk = 0.09 [95% CI 0.0 to 0.17]). The adverse event incidence was otherwise similar between the treatment groups. A Cochrane review found limited evidence to suggest that BMPs may be more effective than controls for acute tibial fracture healing, however, the use of BMPs for treating non-unions remained unclear.

Cost effectiveness	There is limited cost effectiveness data. A cost-utility evaluation based on the BESTT study was submitted to the SMC review in 2007. Although adding dibotermin increases the costs of treatment of open tibial fractures, partial cost offsets were obtained from a reduction in need for secondary interventions, lower rate of infections and reduced number of outpatient visits due to faster healing time for the dibotermin patients. Overall, utility gains were obtained from faster healing time for patients receiving dibotermin, resulting in a net incremental cost per QALY gained of £14,007 but was influenced by the overall severity of the fracture. The estimate of incremental cost per QALY gained for the dibotermin patients with grade IIIA fractures treated with dibotermin, was over £30,000 and for grade II fractures was over £54,000, whereas for grade IIIB fractures incremental cost-effectiveness was estimated at £1,600 per QALY gained. The SMC review concluded that the economic case for dibotermin for all patients with open tibial fractures had not been demonstrated, although there is a case for cost-effectiveness for a sub-group with grade IIIB fractures.
Equity	No issues identified.
Needs of the community	Eligible patients could potentially avoid surgery.
Need for healthcare (incorporates patient choice and exceptional need)	Potential advantages include reduction in the duration of NHS care, the number of outpatient visits or the number of X-rays that patients need.
Policy drivers	None
Disinvestment	None