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SURVEY

Adverse Events After Recombinant Human BMP2 in Nonspinal Orthopaedic Procedures

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Abstract

Background The FDA has approved recombinant human bone morphogenetic protein 2 (rhBMP-2) for treating acute, open tibial shaft fractures. However, the nature and frequency of complications after the use of rhBMP-2 in nonspinal orthopaedic surgery have not been well characterized.

Questions/purposes To determine what types of adverse events have been reported after the use of rhBMP-2, whether they were severe enough to require additional surgery, and after what types of operations these adverse events occurred.

Methods Adverse events reported to the FDA's Manufacturer and User Facility Device Experience database were reviewed and summarized.

Results Through December 31, 2011, the FDA has received 62 reports of adverse events involving rhBMP-2 in nonspinal orthopaedic procedures. Surgical site infections and other wound complications, heterotopic bone, pseudarthrosis, and local inflammation were among the most commonly reported adverse events. Almost half of the reports (30 reports; 48%) stated that the patients required secondary interventions to address the reported adverse events. The majority (49 reports; 79%) described adverse events occurring after unapproved uses, such as management of tibial plateau fractures, treatment of congenital pseudarthrosis of the tibia, and humeral reconstruction.

Conclusions Serious adverse events can occur after the use of rhBMP-2 in nonspinal orthopaedic procedures and may necessitate additional surgery. Most events in this analysis occurred after off-label uses. Postmarketing review of adverse event reports remains an important approach for identifying potential safety concerns.

Introduction

The FDA evaluated recombinant human bone morphogenetic protein 2 (rhBMP-2) (INFUSE® Bone Graft, Medtronic Sofamor Danek USA, Inc, Memphis, TN, USA) under a premarket approval, and found reasonable assurance of safety and effectiveness for the treatment of acute, open tibial shaft fractures that have been stabilized with intramedullary nail fixation after appropriate wound management, and within 14 days after the initial fracture [6]. In a prospective, controlled, single-blind study [1] of open tibial shaft fractures, 450 individuals were randomized to receive standard care alone (intramedullary nail fixation and soft tissue management), with rhBMP-2 (0.75 mg/mL), or with rhBMP-2 (1.50 mg/mL; the concentration that is approved for this indication in the US). The investigators reported that the rates of hardware failure and overall pain were lower in the rhBMP-2 groups than among the control subjects [1]; among individuals with the most severe injuries, the rate of infection

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was lower after rhBMP-2 [1]. The rate of secondary interventions was considerably lower after 1.50 mg/mL of rhBMP-2 than the standard care [1, 2, 7]. No ectopic ossification was reported in the clinical study [1, 2, 7].

INFUSE® Bone Graft is contraindicated in patients with known hypersensitivities to rhBMP-2, bovine type I collagen, or other components of the formulation; patients with any active malignancies, and those undergoing treatments for malignancies; skeletally immature patients; patients with inadequate neurovascular status, compartment syndromes of the affected limbs, or active infections at the operative sites; and INFUSE® Bone Graft should not be used in pregnant women [2]. Finally, it should not be used in the vicinity of a resected or extant tumor [2]. The manufacturer's package insert also includes: warnings about potential adverse effects during pregnancy and lactation; warnings about bone resorption, fluid formation, and edema; precautions regarding the potential for ectopic, heterotopic, or exuberant bone formation; an itemized list of 21 potential adverse events that can occur after the use of rhBMP-2 in the treatment of acute, open tibial shaft fractures; and a statement that additional surgery may be necessary to address these complications [2]. In addition, the product label states, "The safety and effectiveness of INFUSE Bone Graft for nonacute fractures, with forms of internal fracture fixation other than intramedullary nails, implanted at locations other than the tibial shaft, or used in surgical techniques other than open reduction and internal fixation after appropriate wound management have not been established" [2]. A PubMed search performed on July 23, 2012 for the terms "orthopaedic", "tibia", "femur", "humerus", "BMP", "Infuse", "complications", and "adverse events" yielded no citations pertaining to adverse events after the use of rhBMP-2 in nonspinal orthopaedic surgery.

Therefore, several important questions remain unanswered: What kinds of adverse events have been reported after the use of rhBMP-2? Were they severe enough to require additional surgery? After what types of operations did these adverse events occur?

Methods and Materials

The FDA's Manufacturer and User Facility Device Experience (MAUDE) database contains reports of adverse events involving medical devices [10]. A report does not necessarily reflect a conclusion by the party submitting the report or the FDA that the device caused or contributed to the adverse event [10]. Surveillance systems such as MAUDE are subject to many limitations, including underreporting, incomplete information in many reports, inability to verify reported diagnoses easily, inconsistent data quality, and lack of a direct and unbiased comparison group. Serious adverse events, such as those resulting in hospitalization, surgery, or death, are more likely to be reported than those with no such sequelae [3, 5, 11]. Because of these and other limitations, it usually is not possible to determine causal associations between devices and adverse events from MAUDE reports.

The publicly available version of the MAUDE database was searched for reports for the brand name, "infuse bone graft." All reports were read and reviewed by the author. If one condition appeared likely to have caused the others, then it was deemed the principal event. For example, if osteolysis led to pain and pseudarthrosis, then the adverse event was classified as "osteolysis." Interventions, such as revision surgery, were noted. Institutional review board approval was not required. The analysis took place after surgery and exposure to rhBMP-2. Furthermore, the public data set does not contain any patient identifiers, so there was no risk to confidentiality. No potential conflict of interest exists, nor any funding source.

Results

Through December 31, 2011, MAUDE received 62 reports of adverse events following the use rhBMP-2 in nonspinal orthopaedic operations; events included surgical site infections and other wound complications, heterotopic bone formation, pseudarthrosis, local inflammation, osteolysis, compartment syndrome, peripheral nerve injuries, and other complications (Table 1). No deaths were reported to MAUDE after the use of rhBMP-2 in nonspinal orthopaedic procedures. Eight reports stated that rhBMP-2 had been used in operations on skeletally immature patients (seven received the product under compassionate use exemptions). Among these, a child with preexisting intracranial gliomas received rhBMP-2 to treat congenital pseudarthrosis of the tibia; the gliomas progressed, and the patient required multimodal chemotherapy. There were no reports stating that rhBMP-2 had been used in operations in pregnant or lactating women or in people with known hypersensitivities to any of the device components.

Almost half of the reports (30 reports; 48%) stated that the patients required secondary operations to address the reported adverse event (Table 1). Of the 12 reports describing heterotopic ossification, five stated that the patients required surgery to remove extra bone (Table 1). For example, a patient sustained an open supracondylar fracture of the humerus, and fixation was performed 22 days later. Radiographs taken 7 weeks postoperatively revealed callus formation, fracture reduction, and heterotopic bone posteriorly. Five months after surgery, the patient presented with an acute decrease in ROM and the

Table 1. Adverse events reported after the use of rhBMP-2

Principal adverse event	Reports (n = 62)	Cases requiring secondary operation (n = 30)
Surgical site infection/wound complication	15	6
Heterotopic/ectopic bone	12	5
Pseudarthrosis	10	7
Local edema/erythema	9	1
Osteolysis/resorption	5	4
Compartment syndrome	2	2
Peripheral nerve injury*	2	0
Other†	7	5

* Brachial plexopathy (one report) or radial nerve palsy (one report); †other reported events included dysesthesia (one report), hardware failure (one report), progression of preexisting intracranial gliomas (one report), radioulnar synostosis (one report), rash (one report), and unspecified adverse reaction (two reports); rhBMP-2 = recombinant human bone morphogenetic protein-2.

elbow was fixed at 90°. Radiographs revealed bridging heterotopic ossification from the olecranon to the distal humerus, extending into the posterior fascial planes. Surgical intervention included excision of the heterotopic bone, capsular release, and manipulation under anesthesia. In the other four cases that required excision of heterotopic bone, the interval from the index operation was not reported. For pseudarthrosis, the time to revision surgery ranged from 3 weeks to 2.8 years (median, 11 months; in two cases, the interval was not specified). The type of reoperation varied depending on the original indication for surgery and the circumstances surrounding nonunion. For instance, a smoker who had several unsuccessful operations for a pertrochanteric femoral fracture underwent surgery with local autograft and rhBMP-2; the proximal femoral locking plate failed within 3 weeks. The patient had a revision procedure with autogenous iliac crest bone graft, an implantable bone stimulator, and rhBMP-2. One year later, plain films revealed complete consolidation, and the patient was pain-free with good motor function and ROM. In a separate example, a patient underwent an operation with rhBMP-2 to treat congenital pseudarthrosis of the tibia. Persistent nonunion was noted 2.8 years after surgery. A below knee amputation was performed, and the patient was reportedly doing well with a prosthesis.

The types of operations after which these adverse events occurred included the approved indication (eight reports; 13%) and unapproved uses, such as the management of tibial plateau fractures, treatment of congenital pseudarthrosis of the tibia, and humeral reconstruction (Table 2). Twenty-six reports (42%) described the use of rhBMP-2 during salvage and revision procedures.

Table 2. Operative sites at which rhBMP-2 was reportedly used

Operative site	Approved use (n = 8)	Unapproved use (n = 49)	Use could not be determined‡ (n = 5)	Total (n = 62)
Tibia				
Diaphysis	8	6*		14
Plateau		10		10
Humerus		13		13
Femur		7†		7
Foot/ankle		7		7
Ulna		4		4
Clavicle		1		1
Metacarpal		1		1
Unspecified			5	5

* Pediatric cases conducted under compassionate use exemptions; †includes one Van Nes rotationplasty in a child, performed under a compassionate use exemption; ‡reported as "tibia, femur, or humerus" (four reports) or "femur or tibia" (one report); the use could not be determined as either approved or off-label; rhBMP-2 = recombinant human bone morphogenetic protein-2.

Discussion

Encompassing more than 7 years of postmarketing experience since rhBMP-2 was approved for treating tibial shaft fractures, this summary presents the range of adverse events that have been reported, the necessity of additional surgery in some cases, and the types of procedures after which the adverse events occurred.

There are several important limitations and unresolved issues. First, the current findings do not necessarily reflect the true range or proportions of adverse events that can occur after nonspinal orthopaedic operations involving rhBMP-2. The risks of surgical site infections, heterotopic ossification, and other adverse events after treatment with rhBMP-2 might vary depending on the type and location of the fracture and the surgical approach. Second, underreporting or overreporting can occur and the number of people who are at risk for adverse events is not known. Therefore the numbers of reports in MAUDE should not be used in conjunction with utilization data to estimate incidence rates of adverse events. Furthermore, it is inappropriate to compare these numbers with frequencies reported in the literature after similar operations without rhBMP-2. Third, because of differential reporting for serious and nonserious reports [3, 5, 11], these results might present a skewed view of the need for secondary operations after the use of rhBMP-2 in nonspinal orthopaedic surgery. Notwithstanding, these limitations do not invalidate the results. Surveillance data are valuable for detecting potential safety signals and describing adverse

events that might not have been observed before product approval. For instance, the US package insert was updated to include warnings about resorption and fluid-filled cysts [2]; the changes were prompted by a labeling modification required by the European Union as a result of an analysis of reported adverse events [8]. Furthermore, the data can be used to describe patterns of adverse events and to guide further investigation using epidemiologic methods.

Adverse events in this summary included many complications that are typical after operations for the conditions being treated (eg, persistent pseudarthrosis) or after surgery in general (eg, wound infections), and unexpected ones (eg, ectopic bone formation). Some may simply be coincidental and might reflect risks associated with the operation or with the original fracture. Two categories warrant more detailed discussion: heterotopic ossification and pseudarthrosis. The incidence of heterotopic, ectopic, or exuberant bone formation after the use of rhBMP-2 in the treatment of fractures in locations other than the tibial shaft is not known. In this analysis, all reported instances of heterotopic ossification followed off-label uses of rhBMP-2. Because of insufficient information about the time course, the MAUDE reports do not shed any light on the risk window during which this complication might be the most likely to occur. Nevertheless, these findings are important reminders to clinicians that the formation of undesirable exuberant bone is potentially serious and may require additional surgery. Pseudarthrosis was reported after tibial and other orthopaedic operations involving rhBMP-2. In the clinical study [1, 2, 7], the rate of nonunions of tibial shaft fractures was lower among subjects who had received rhBMP-2 (1.5 mg/mL) than those who had received the standard care; however, among individuals requiring secondary interventions, subjects who had received rhBMP-2 were more likely than controls to have nonunions 12 months after the index operations [2]. Most cases of pseudarthrosis reported to MAUDE occurred after off-label uses. It is possible that the overall rate of nonunion after treatment with rhBMP-2 varies for different types of fractures. Delayed unions or persistent nonunions in cases requiring revision surgeries might simply reflect the refractory nature of certain fractures (ie, confounding by indication [4]). Because the information in many reports was incomplete, risk factors for pseudarthrosis and other adverse events could not be evaluated. In many cases, the characteristics (eg, multiple medical problems, diabetes mellitus, tobacco use) that predisposed a patient to nonunion or delayed union might have influenced the surgeon's decision to use rhBMP-2 in the first place. Thus, the causal relationship with rhBMP-2 is not clear. Moreover, the reported outcomes could not be confirmed. Some patients with short-term complications of the procedures involving rhBMP-2 may have achieved long-term success.

Almost half of the reports stated that the patient required revision surgery or another invasive procedure because of the adverse event. The need for additional surgery might reflect the complex nature of the operations and the patients' original indications for surgery. For example, some reports described persistent nonunion after three or four prior operations; the observation of persistent pseudarthrosis after the use of rhBMP-2 might indicate that the bone's capacity to heal was severely limited, regardless whether an autograft, allograft, or a recombinant product was used.

This analysis indicates that rhBMP-2 is being used to treat fractures in locations other than the tibial shaft and for conditions other than acute fracture, although the product's safety and effectiveness have not been established for such uses [2]. In addition, the occurrence of serious adverse events after the use of rhBMP-2 in patients in whom the product was contraindicated is described. Off-label uses are not illegal, but practitioners should remember that approval is given for a specific indication. Alternative uses may be explored under humanitarian device exemptions if there is sufficient information for the FDA to determine that the probable benefit to health outweighs the risk of injury or illness, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment [9].

This summary of MAUDE data indicates that serious adverse events can occur after the use of rhBMP-2 in nonspinal orthopaedic procedures. Whether they are coincidental or are related to the product remains unknown. In the absence of a randomized, controlled trial to assess adverse events after the use of rhBMP-2 to treat fractures in locations other than the tibial shaft or nonacute fractures, adverse event reporting and review remain important approaches for identifying potential safety concerns.

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