Rivaroxaban, an Oral, Direct Factor Xa Inhibitor: A New Option for Thromboprophylaxis

To the Editor:

Thank you for your comments on the important issues raised in your commentary on the article “Rivaroxaban, an Oral, Direct Factor Xa Inhibitor: A New Option for Thromboprophylaxis.” I would like to clarify several points. First, rivaroxaban is approved for the prevention of venous thromboembolism after elective hip or knee arthroplasty in adults. The body of data from the RECORD program (which consisted of approximately 13,000 patients undergoing elective total hip or knee arthroplasty) objectively establishes the safety and efficacy of rivaroxaban for venous thromboembolism prophylaxis in postoperative orthopedic patients with no significant difference in the rate of major bleeding compared with enoxaparin. Recently, these data have been confirmed by XAMOS, a phase IV noninterventional study.2

On the issue of treatment reversal, no agent-specific antidotes exist for newer antithrombotic agents. Protamine sulfate can reverse the anticoagulant effects of unfractionated heparin but is rarely used, and reversing the effect of low-molecular-weight heparins using protamine sulfate is less effective and associated with some side effects. Although warfarin can be reversed with vitamin K, reversal with this agent is not effective for several hours, and the alternative option, fresh frozen plasma, may not be immediately available. Rivaroxaban has a short half-life (ie, 5 to 9 hours in healthy young individuals and 11 to 13 hours in elderly individuals); therefore, treatment reversal is not likely to be necessary. In the unlikely event that emergency reversal of a fully anticoagulated patient arises, several reversal strategies may used, although these approaches have not been studied in prospective randomized trials: prothrombin complex concentrate has recently shown promising results in healthy volunteers, as have Factor VIII inhibitor bypassing activity and recombinant activated Factor VII. In addition, activated prothrombin complex concentrate and rAntidote have demonstrated potential value in preclinical studies. Furthermore, anticoagulation reversal protocols have been established in many institutions.

The Editor has also cautioned on the use of rivaroxaban in the trauma setting, owing to reversibility concerns. Rivaroxaban is not indicated for use in the trauma setting, nor is any other antithrombotic agent used for the prevention of venous thromboembolism. Therefore, use in this scenario would be driven by physicians making decisions based on the risks and benefits to the individual patients. Nearly 2 million patients worldwide have been treated with rivaroxaban.

These points, taken together with other supporting evidence for rivaroxaban detailed in the article, indicate that rivaroxaban has clear advantages over traditional anticoagulants. Thank you for your courtesy and consideration.

REFERENCES

Louis M. Kwong, MD, FACS
Torrance, California

EDITOR’S COMMENT

Again, as stated during initial publication of Dr Kwong’s article in the June 2012 issue of Orthopedics, the Editor would like to issue a word of caution on rivaroxaban use, especially in surgical settings where bleeding issues exist and in situations that may require the need for sudden reversal. Bleeding issues were experienced with dextran in the 1960s. Reversal techniques currently exist with heparin and coumadin, and not having the ability to reverse treatment, especially in the trauma and surgical settings, is a limitation of rivaroxaban. I have not changed my prophylaxis regimen since the approval of rivaroxaban.

Robert D. D’Ambrosia, MD
Editor-in-Chief, ORTHOPEDICS
Bone Morphogenic Protein 3 Signaling in the Regulation of Osteogenesis

To the Editor:

Bone morphogenic protein (BMP) 3 is the most abundant BMP in bone, accounting for >65% of the total BMP stored in the bone matrix. Bone morphogenic protein 3 plays a role in fracture healing, mechanical loading of the skeleton, development, and osteoporosis. Bone morphogenic protein 3 inhibits osteoblast differentiation and is thus a negative regulator of bone density. Understanding how BMP-3 diminishes bone mass has significant clinical implications.

Bone morphogenic protein 3 inhibits responsiveness to BMP-2 by antagonizing BMP-2 signaling. It activates a signaling pathway that interferes with the osteogenic BMP pathway. Bone morphogenic protein 3 interferes with osteogenic BMPs by binding to a shared receptor while having no inherent signaling function. Bone morphogenic protein 3 has also recently been shown to promote the proliferation of mesenchymal stem cells and may play a role in adipogenesis.

Bone morphogenic protein 3 blocks the BMP-2–mediated differentiation of osteoprogenitor cells into osteoblasts. Bone morphogenic protein 3 null mice have twice as much trabecular bone as their wild-type littermates. Bone morphogenic protein 3 expression is higher in the patent rat sagittal suture. Bone morphogenic protein 3 is expressed in rat cranial sutures in a temporal pattern, suggesting involvement in cranial suture patency and fusion. Transgenic mice, which overexpress BMP-3, display spontaneous rib fractures.

Bone morphogenic protein 3 has a unique localization pattern with strong expression in the developing perichondrium. Expression of BMP-3 in the perichondrium regulates cartilage cell proliferation by modulating the levels of osteogenic BMP signaling, ensuring proper enchondral ossification. Bone morphogenic protein 3 may modulate the level and timing of BMP signaling, ensuring the proper formation of individual skeletal elements during bone formation. During early limb development, little overlap exists in the expression of BMP-3 and other BMPS.

Mice that overexpress BMP-3 have defects in differentiation of the periosteum and late hypertrophic chondrocytes, resulting in thinner cortical bone. Bone morphogenic protein 3 is thought to expand the hypertrophic zone.

Bone morphogenic protein 3 plays an essential role as a modulator of osteogenic BMPS. Although therapies to accelerate bone healing have used BMP-2 and BMP-7, inhibition of BMP-3 would have the same effect, perhaps at a lower cost. Bone morphogenic protein 3 provides a novel therapeutic intervention point for the treatment of diseases from osteopenia to fracture nonunion.

References


Mark S. McMahon, MD
Boston, Massachusetts

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