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Recombinant Activated Factor VII for Bleeding in Patients without Inherited Bleeding Disorders

Summary

- ✓ **Recombinant activated factor VII (rFVIIa) is licensed in Canada for the prevention and treatment of bleeding in hemophiliacs, but it is increasingly used to control bleeding in non-hemophilic patients during surgery, or during treatment for severe trauma or intracerebral hemorrhage (ICH).**
- ✓ **In one clinical trial, there was a significant reduction in mortality among patients with ICH treated with rFVIIa. In another trial, administration of rFVIIa significantly reduced the number of trauma patients needing massive blood transfusions although there was no significant difference in mortality.**
- ✓ **Adequately powered randomized controlled trials are needed to clarify the efficacy and safety of rFVIIa for non-bleeding disorder indications. Phase III trials in ICH and trauma are underway.**
- ✓ **There is potential for non-hemophilic use, particularly if clinical efficacy and cost-effectiveness are established.**

The Technology

Also known as eptacog alfa (activated), rFVIIa is a genetically engineered hemostatic agent used for the prevention and treatment of bleeding episodes in patients with hemophilia. It is manufactured by Novo Nordisk in Denmark, and sold as NiaStase® in Canada. Outside Canada, the product is marketed as NovoSeven®. The drug helps to stop bleeding by enhancing the creation of thrombin, an enzyme essential for blood clotting. It works at the site of injury by forming complexes with the exposed protein known as tissue factor; and on the surface of activated platelets.[1,2]

Regulatory Status

In February 1999, Health Canada licensed NiaStase® for the treatment of bleeding episodes in patients who have hemophilia A or B, with inhibitors to clotting factors VIII or IX.[3] NovoSeven® was licensed for the same indication in the US in March 1999,[4] and in the European Union in February 1996.[5] In October 2003 the European Union extended its approval to include patients with factor VII deficiency and Glanzmann's thrombasthenia.[6] In 2005, the US extended its licensed indications to include congenital factor VII deficiency.[7]

Patient Group

rFVIIa has been studied in surgical patients, because they may require transfusion;[8,9] in trauma patients, because 40% of trauma-related deaths are a result of uncontrolled bleeding;[10,11] and in patients with intracerebral hemorrhage (ICH), because of the greater morbidity and mortality that result compared with other forms of stroke (>30% of ICH patients die as a result of the initial event).[12]

Current Practice

Canadian guidelines exist for the use of rFVIIa in hemophilia,[13] but there are no widely recognized guidelines for non-hemophilic indications. Some hospitals[14-16] recommend the administration of rFVIIa for massive bleeding that fails to respond to surgical measures and blood component therapy, but only when a

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good clinical outcome is possible. There are no data available on the use of rFVIIa for non-hemophilic conditions in Canada, but it is believed to have surpassed hemophilic use in some provinces (Catherine Moltzan, St Boniface General Hospital, Winnipeg, MB: personal communication, 2005 Sep), with estimates as high as 90% of total utilization (Wanda Thomas, Nova Scotia Provincial Blood Coordinating Program, Halifax, NS: personal communication, 2005 Sep). A review of rFVIIa use at 21 US hospitals found that 92% of cases were for non-licensed indications.[17] Prescribing practice is believed to vary, as few institutions have written procedures or guidelines.

The Evidence

Eleven double-blind, randomized controlled trials reported in 10 publications used rFVIIa for non-hemophilic conditions.[18-27] All trials compared rFVIIa with placebo. Doses of 10 mcg/kg to 200 mcg/kg were used. Most trials excluded patients who were at risk of thromboembolic or vasocclusive adverse events.[13-16,18-22] All trials reported on one or more health outcomes: total mortality; serious adverse events (SAEs); thromboembolic SAEs; hypovolemic shock rates; massive transfusion or clinically significant bleeding rates; number of patients who needed a transfusion; and number of patients who required a transfusion of ≥3 units of red blood cells.

Two trials[18,19] (n=83 and n=209) in patients with Child-Pugh class B or C hepatic dysfunction scheduled to undergo orthotopic liver transplantation, found increased rates of mortality and SAEs in the rFVIIa-treated patients, but the results were not statistically significant. For thromboembolic SAEs, one trial[18] found a lower rate of mortality in the rFVIIa-treated patients, while another trial[19] found a higher rate in rFVIIa-treated patients. Neither result was statistically significant. In one trial,[19] significantly more rFVIIa-treated patients avoided red blood cell transfusions in the perioperative period compared with placebo (8.3% versus 0%, p=0.0331).

In a trial involving 200 non-cirrhotic patients scheduled for liver resection,[20] there was a statistically non-significant trend toward reduced mortality in the rFVIIa-treated patients. There were no significant differences in the rates of SAEs and thromboembolic SAEs between rFVIIa- and placebo-treated patients. Fewer rFVIIa-treated patients needed transfusions, but this was not significantly different from the placebo group.

Among Child-Pugh class B or C cirrhotic patients, 242 with active upper gastrointestinal bleeds (of presumed variceal origin) were randomized to receive rFVIIa or placebo within six hours of admission to hospital.[21] Increased mortality and decreased SAE rates were seen among rFVIIa-treated patients. These results were not statistically significant. The incidence of thromboembolic SAEs was also not statistically different between groups.

Two studies (reported in one publication) involved a total of 277 patients with blunt or penetrating trauma, who were followed for 30 days.[22] Lower mortality and SAE rates were seen in rFVIIa treated-patients. These results were not statistically significant. The incidence of thromboembolic SAEs was also not significantly different between groups. Significantly fewer blunt trauma patients (p=0.03) in the rFVIIa-treated group needed massive transfusions, with a similar though statistically non-significant trend seen among penetrating trauma patients in the rFVIIa-treated group.

Two trials[23,24] (n=472 and n=399) investigated patients with ICH; both trials required ICH to be confirmed by computed tomography (CT) imaging ≤3 hours after symptom onset. Patients received rFVIIa or placebo ≤1 hour after the CT scan. Both trials reported reductions in mortality among the rFVIIa-treated patients (8.3% versus 18.2%, not statistically significant;[23] 18.5% versus 29.2%, p=0.02).[24] The dose-finding trial[23] reported reduced SAEs in rFVIIa-treated patients (not statistically significant), and both trials[23,24] reported increased rates of thromboembolic SAEs in the rFVIIa-treated patients (not statistically significant).

In a trial of 100 hematopoietic stem cell transplantation patients with bleeding for three consecutive days (41% had a bleeding score of 2, defined as minor bleeding not requiring transfusions beyond routine requirements), there were increased rates of mortality, SAEs, and thromboembolic SAEs at 96 hours in the rFVIIa-treated patients. These results were not statistically significant.[25]

Thirty-six patients who were scheduled for retropubic prostatectomy were randomized to receive one bolus intravenous dose of rFVIIa or placebo.[26] No adverse events or serious thromboembolic adverse events occurred in either group. There was also a reduced need for transfusions among the rFVIIa-treated patients compared with those receiving placebo. The difference was not statistically significant.

Forty-eight patients who were scheduled to undergo pelvic-acetabular reconstructive orthopedic surgery were randomized to receive one intravenous bolus dose of rFVIIa or placebo.[27] A statistically non-significant trend toward a reduced need for transfusions in the rFVIIa treated patients was reported.

Adverse Effects

SAEs associated with rFVIIa include thrombotic events, such as myocardial infarction, cerebrovascular thrombosis, other arterial thromboses, pulmonary embolism, and other venous thromboses.[28,29] There is a 1% to 2% incidence of thrombotic complications associated with rFVIIa administration.[1] In general, trials excluded patients at high risk of thromboembolic SAEs before randomization.

Administration and Cost

rFVIIa is available in 1.2 mg, 2.4 mg, and 4.8 mg vials as a powder that must be reconstituted with sterile water for intravenous injection. The recommended dose in patients with hemophilia is 70 mcg/kg to 90 mcg/kg, administered every two hours, and repeated three to four times as necessary.[13] There are no standard doses for non-bleeding disorder indications. The dose may be repeated, with the recommended interval between first and second doses ranging from 20 minutes to two hours.[14-16] A third dose may be considered.[16]

The cost of rFVIIa is C$940 per milligram.[25] Based on the doses used in clinical trials, the cost per dose for a 70 kg adult can range from C$658 to C$13,160. A review of 86 patients receiving rFVIIa for non-hemophilic indications at a US hospital found a mean drug cost of US$6,805 per patient.[14]

Concurrent Developments

Several topical hemostatic agents for massive bleeding are emerging in the US market. Concerns about efficacy and safety have been expressed, because experience has been limited to animal data and case reports.[26,27,30] These products need to be applied to a wound, which limits their potential range of application, compared with that of rFVIIa.

Rate of Technology Diffusion

There is a growing interest among clinicians about rFVIIa for non-hemophilic indications. Blood bank specialists are considering rFVIIa as a replacement for blood components, particularly in remote communities. The constraints on widespread non-hemophilic use are the limited clinical evidence and high cost. Cost is less of a direct constraint than it is for prescription drugs, because rFVIIa is funded through provincial and territorial blood budgets, rather than provincial drug plans. The manufacturer has applied for European marketing approval for the use of rFVIIa in ICH, and has phase III trials underway in ICH and trauma.[31]

Implementation Issues

rFVIIa may conserve blood components and reduce intensive care stays.[32] More evidence is needed to assess rFVIIa's benefit and harm, optimum dose, time of administration, and cost-effectiveness. Additional issues include which type(s) of hospital(s) should stock rFVIIa, for which indication(s), and which processes should govern its use.

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CCOHTA appreciates comments from its reviewers.

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Dr. Bormanis has given talks sponsored by NovoNordisk. Dr. Makris has attended meetings organized by NovoNordisk, has entered patients into a NovoNordisk trial of NovoSeven for hemophilia and has received a fee for one lecture.

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