

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Current Insights on the Risk of Thrombogenicity With Off-label Use of rFVIIa

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H&O What are the current developments regarding the risk of thrombosis associated with the off-label use of recombinant activated factor VII?

NK The risk of thrombosis associated with recombinant activated factor VII (rFVIIa) in the off-label setting has been an issue of ongoing debate for several years. However, the recent developments stem from the completion of a randomized placebo-controlled study in patients with intracranial hemorrhage showing that rFVIIa was associated with an increased risk of thrombosis. Patients with hemorrhagic stroke were randomized to receive rFVIIa or placebo. rFVIIa proved to be efficacious, but was associated with a risk of serious thrombotic events, mainly myocardial or cerebral infarction. These events occurred in 7% of patients treated with rFVIIa, versus 2% of patients given the placebo.

These findings prompted the US Food and Drug Administration (FDA) to issue a warning regarding the off-label use of rFVIIa, based on its potential to cause thrombotic events. The study, which was published in the *New England Journal of Medicine*, provided the best data yet on this long-debated issue.

H&O Could you describe the history of rFVIIa use, both its approved indication and off-label use?

NK This agent is approved by the FDA for the treatment of a subset of patients with hemophilia. These individu-

als are deficient in clotting factor VIII or IX. A subset of patients develops antibodies against the clotting factor after transfusion. These so-called inhibitors will neutralize any subsequent factor VIII that is administered. When it is not possible to eliminate these antibodies, bleeding in these patients can be difficult to treat. rFVIIa was developed for the treatment of these patients.

It was suggested some years ago that rFVIIa may be beneficial in other clinical situations characterized by major bleeding, and it has been used off-label in such settings as heavy bleeding after pregnancy delivery, trauma, certain types of surgery, such as back surgery, and liver resection associated with heavy blood loss. There is a great deal of anecdotal evidence regarding the use of rFVIIa in settings other than hemophilia, and there are situations in which it is clearly beneficial. The challenge with these reports is that they have not been evaluated in a clinical trial setting. Better designed studies are now beginning to be reported, such as the one in intracranial hemorrhage described above.

H&O Did the findings of this study change the general perception about the thrombogenic risk of rFVIIa?

NK The 5–7% risk reported in this study was significantly higher than the commonly held belief that the risk was about 1%. Many patients who experience an intracranial hemorrhage are elderly and often immobile, which might be an important message with respect to patient selection. Better data on thrombotic risk in specific populations will help clinicians make a more informed judgment of the risk/benefit profile of off-label usage of rFVIIa.

It is important to note that the median age of the patients in the study was over 65 years old. Administering a drug intended to boost coagulation may be associated with a higher risk in an elderly individual than in a younger individual. Thrombotic events occurring in the arterial circulation can be closely related to atherosclerotic blood vessels and older age. Therefore, the thrombotic risk of administering a hemostatic agent may be higher in the older age group. While all of the risk factors for thrombogenic events in association with rFVIIa have not

been determined, it seems fair to conclude for now that advanced age is associated with greater risk.

It is also important to remember that these findings were in an off-label setting, and do not relate to any risk associated with rFVIIa administration in the setting of hemophilia, for which its use is approved.

H&O How do these findings change the clinical perception of rFVIIa, if at all?

NK If these findings change the clinical perception of rFVIIa, it will most likely be in terms of its spectrum of application. When rFVIIa was initially developed, it was suggested that it might have the potential to be used as a “universal hemostatic agent” that could control bleeding in a wide range of clinical settings. However, pushing the coagulation system with any hemostatic agent is likely to increase the risk of unwanted clotting. The debate about the potential hemorrhagic settings in which rFVIIa should or should not be used had been proceeding in the literature based on insufficient data. Now, data are becoming available that are confirming what many clinicians intuitively thought to be the case.

H&O How might these findings change the off-label use of rFVIIa?

NK These findings add to the rationale that off-label use of rFVIIa should be based on an assessment of individual patient risk. The age of the patient, the patient’s history of atherosclerotic disease, other concurrent medications—these should all weigh into the treatment decision. There has been a tendency to use rFVIIa as a last attempt in patients for whom there are no other therapeutic options.

However, there are limited data showing a benefit in these types of settings.

H&O What other issues do these findings raise?

NK In general, the off-label use of rFVIIa has drawn attention to the fact that there are relatively few pharmacologic approaches available for the treatment of intracranial hemorrhage and many other serious bleeding disorders.

Also, further research is needed to advance our understanding of what differentiates one type of bleeding from another. Why does rFVIIa work in one setting but not another? We do not yet have an answer to this question. The off-label use of rFVIIa to treat severe bleeding conditions is encouraging in that it gives us the sense that the development of effective agents for life-threatening bleeding disorders is within reach. At the same time, the study findings underscore the value of randomized prospective clinical trials, and any further research of candidate agents in these diverse settings must also be done in the context of carefully conducted clinical trials.

Suggested Reading

Mayer SA, Brun NC, Begtrup K, et al; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med.* 2005;352:777-785.

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