

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

## A New Era of Therapy for Congenital Factor XIII Deficiency



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### **H&O** Could you please describe the clinical presentation of factor XIII deficiency?

**MC** Children with this condition usually present within the first 2 weeks of life. Features that are consistent with a diagnosis of factor XIII deficiency include ongoing umbilical bleeding and intracranial hemorrhage. Cases that are not diagnosed in the first few weeks of life are often detected before the age of 1 or 2 years as a result of significant bruising, bleeding with surgery, or an intracranial hemorrhage. In some cases, the diagnosis is made later in childhood.

### **H&O** What causes factor XIII deficiency?

**MC** Factor XIII deficiency is a rare genetic disorder. As an autosomal recessive condition, it affects people who have 2 abnormal genes for factor XIII production: one inherited from each parent. Consequently, factor XIII deficiency is most common when there is parental consanguinity, although cases do occur with nonconsanguineous parents.

### **H&O** What is the role of genetic testing?

**MC** Determining the mutations responsible for the condition traditionally has not been part of routine care or even considered important. The role of genetic testing is now beginning to expand as we learn more about genotype-phenotype associations of the disease; that is, which gene mutations are associated with more severe or less severe disease.

### **H&O** What causes certain patients with factor XIII deficiency to develop alloantibodies to factor XIII concentrate upon exposure?

**MC** The development of an alloantibody to factor XIII is a rare but potentially devastating event that can lead to neutralization or destruction of the activity of factor XIII. We

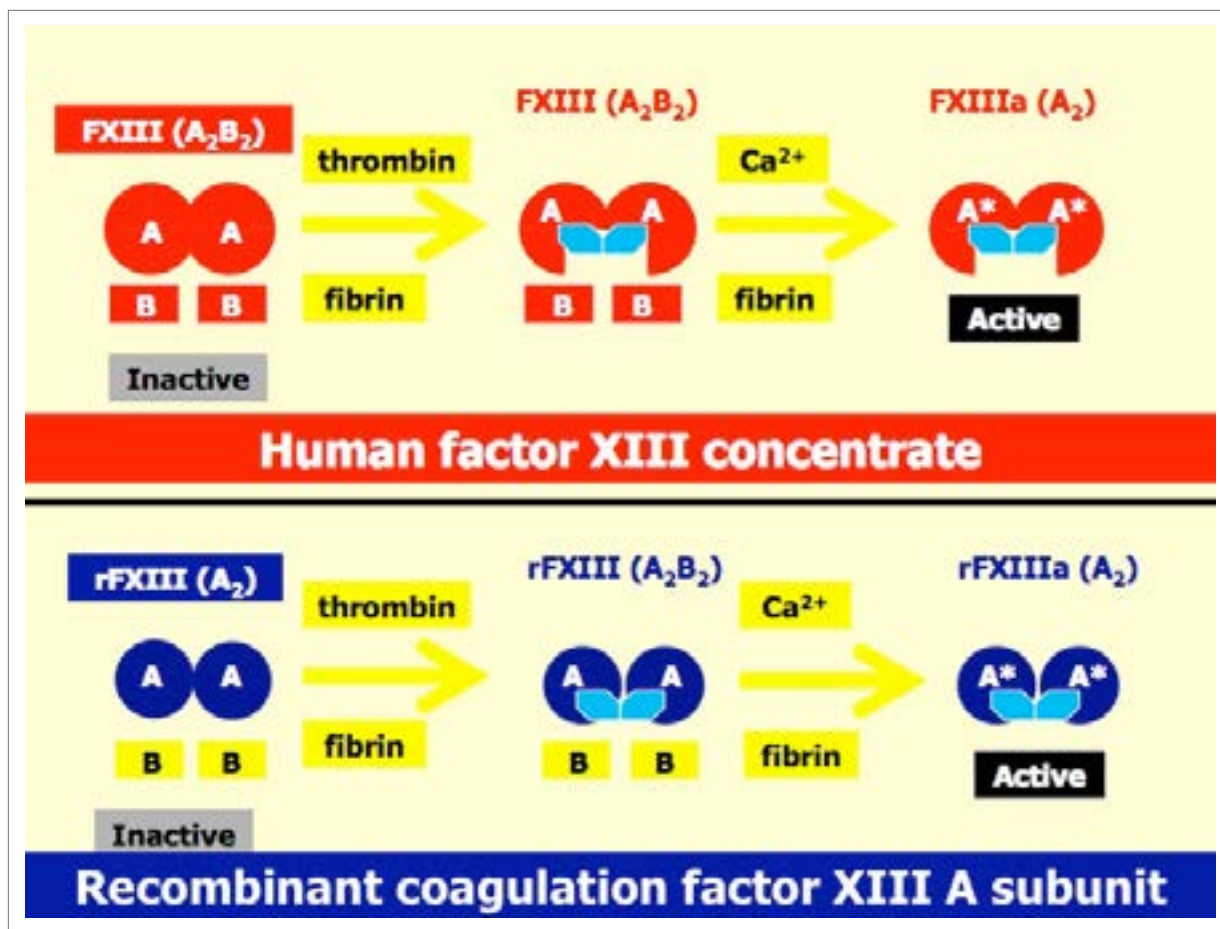
know very little about why some patients develop neutralizing alloantibodies to factor XIII. It may have something to do with genetics, but as it stands right now we do not know enough to be able to say which genetic mutations increase the likelihood of this occurring.

### **H&O** How is factor XIII deficiency diagnosed?

**MC** After an astute clinician picks up on the fact that a particular child manifests the typical findings of factor XIII deficiency, a variety of tests can be used to make the diagnosis. The test that is most commonly available is the clot solubility lysis test. Although this test will generally pick up severe deficiencies of factor XIII, it can miss deficiencies that are less severe and those in patients who have been recently exposed to any blood products. Tests that are more sensitive are starting to become more readily available. One of these is a factor XIII assay, which measures specific factor XIII activity and will not miss the diagnosis in patients who have been exposed to a small amount of factor XIII from a blood product. Another test that is becoming somewhat more available than it had been in the past is subunit analysis to determine whether the patient has a subunit A or subunit B deficiency. Approximately 95% of cases of factor XIII deficiency involve subunit A deficiency.

### **H&O** Are there any challenges associated with using these diagnostic assays?

**MC** One challenge is that the condition is rare, so these tests are not used frequently. As a result, just a few laboratories are able to carry the various reagents that are required to conduct these tests. Our health care system does not always accommodate the sending of blood samples to specialized laboratories as needed; a test that cannot be provided by the standard laboratory for that hospital or practice may not get performed at all. In the future, as we learn more about



**Figure.** A comparison of the activation of human factor XIII concentrate (in red; consisting of both subunit A and B) vs recombinant coagulation factor XIII A subunit (in blue; consisting of only subunit A). Upon infusion, recombinant coagulation factor XIII A subunit binds to the patient's endogenous subunit B, forming the inactive factor XIII (A<sub>2</sub>B<sub>2</sub>) molecule. Human factor XIII concentrate does not require this step. The inactive factor XIII molecule circulates in the person's blood, and then—in the presence of fibrin that is produced during bleeding—gets activated by thrombin and calcium. This results in the release of subunit B and the exposure of the active (catalytic) site of the subunit A (shown as light blue hexagons), forming active factor XIII (A<sub>2</sub>). The active A subunits are designated with an asterisk (A\*).

FXIII, factor XIII; rFXIII, recombinant factor XIII.

rare disorders and are able to do more extensive testing, I think that health care delivery will change to accommodate this need. In the meantime, clinicians will need to get into the habit of seeking out specialized centers where they can send their less-usually performed tests.

### H&O What are the benefits of getting the results of these tests?

**MC** The most important benefit is making the diagnosis, which allows the clinician to institute appropriate therapy. Test results are also important to confirm that the patient has subunit A deficiency rather than subunit B deficiency. The assumption is generally that a particular patient has subunit A deficiency, simply because it is so much more

prevalent than subunit B deficiency. Depending on the therapy, however, the clinician may need proof of that before starting the patient on treatment.

Another benefit of genetic testing is that it serves as the starting point for genetic counseling for the patient's family, especially if the parents of the patient are considering having another child. Testing can also be done prenatally, based on amniocentesis or chorionic villus sampling.

### H&O How much of an advance in treatment did the approval of human factor XIII concentrate (Corifact, CSL Behring) represent?

**MC** Human factor XIII concentrate is plasma-derived, virally inactivated factor XIII. It was approved by the

US Food and Drug Administration (FDA) in 2011. Human factor XIII concentrate, although until recently unlicensed in Canada, has been available in this country through a special access program for well over 12 to 13 years. We have had a very good experience with this product in Canada, where it is known as Fibrogammin P. Human factor XIII concentrate is not known to have transmitted any infections and has made it relatively easy to manage patients with factor XIII deficiency, which was very difficult to manage before we had this product.

**H&O** What was the treatment before human factor XIII concentrate was available?

**MC** Our choices were fresh frozen plasma or cryoprecipitate. Neither of these products is virally-inactivated, and a large volume must be administered in order to give a sufficient amount of factor XIII. These products are no longer used to treat human factor XIII deficiency in countries where the newer agents are available.

**H&O** What are the advantages of recombinant coagulation factor XIII A subunit (Tretten, Novo Nordisk) over human factor XIII concentrate?

**MC** Recombinant coagulation factor XIII A subunit was approved in Canada in 2012 and in the United States in 2013. The advantages of this product are a lower volume and the fact that it is a recombinant product. It is a highly concentrated agent and only a small amount is needed to give patients an adequate amount of factor XIII. The one limitation is that it contains only subunit A, so it will not help people with a subunit B deficiency. Consequently the use of this product requires that we obtain more information about the patient than we used to need.

Along with Inbal and colleagues, I performed a single-arm study of 41 patients with congenital factor XIII subunit A deficiency, all of whom were treated prophylactically with recombinant factor XIII concentrate. What we found was a bleeding rate that was significantly lower than the historic bleeding rate using on-demand treatment: a crude mean of 0.138 vs 2.91 bleeds per patient per year, respectively.

**H&O** Are patients sometimes first placed on human factor XIII concentrate, and later placed on recombinant coagulation factor XIII A subunit after testing has been completed and a subunit A deficiency is confirmed?

**MC** We certainly can do that. Alternatively we can put patients on recombinant factor XIII A subunit, and then

a few days later follow up with pharmacokinetic testing to ensure it is effective in the patient.

**H&O** Which of these agents do you see US physicians using more often going forward?

**MC** If the price is not an issue, I think that most patients will receive recombinant factor XIII because it is a recombinant product with a very low volume. If there is a price differential between the 2 agents, then it depends what the differential is. [Editor's note: the Medicare average sales price of Corifact is \$6.74 per unit for the first quarter of 2014, and is not available for Tretten as of press time.]

**H&O** Is there anything that you would like to emphasize?

**MC** I think it is important to emphasize that factor XIII deficiency, although a devastating, life-threatening condition with a very high risk of bleeding, is one of the least problematic bleeding disorders to have because treatment is so effective and convenient. As soon as we start appropriate treatment with factor XIII, whether that be with human factor XIII concentrate or recombinant coagulation factor XIII A subunit, the patient is completely protected from bleeds. In addition, because these agents have such a long half-life and stay in the patient's blood for such a long period, the patient requires therapy only once a month. As such, every patient with factor XIII deficiency should be on prophylactic treatment to prevent bleeding episodes.

**Suggested Readings**

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