A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A

SIPPET STUDY
Survey of Inhibitors in Plasma-Product Exposed Toddlers

"Patients treated with plasma-derived factor VIII containing von Willebrand factor had a lower incidence of inhibitors than those treated with recombinant factor VIII"

"These findings may have clinical relevance because the development of factor VIII alloantibodies is currently the major therapeutic complication in hemophilia A."

SIPPET is the first randomized trial specifically designed to compare the immunogenicity of FVIII products

**METHODOLOGY**

**Study Design**
An investigator-initiated, multicenter, randomized open-label clinical trial in previously untreated or minimally treated patients with severe hemophilia A

14 countries

42 Sites

303 patients screened

**Objective**
Assess the incidence of FVIII inhibitors in patients treated with plasma-derived FVIII containing von Willebrand factor (pdFVIII/VWF) or recombinant FVIII (rFVIII).

**Eligibility criteria**
Male sex, age < 6 years, severe hemophilia A (FVIII:C < 1 IU/dl), previously untreated with any FVIII concentrate, not or minimally treated (<5 times) with blood components*, no treatment with investigational drugs and negative for FVIII inhibitors.

**Observation period**
Randomized patients were followed for 50 consecutive EDs, or 3 years, or until the development of a confirmed inhibitor, whichever occurred first.

**OUTCOME MEASURES**

**Primary Endpoint**
The development of an inhibitor ≥ 0.4 BU by Bethesda assay with the Nijmegen modification.

**Secondary Endpoint**
High-titer inhibitors defined by peak levels ≥ 5 BU during 6 months observation.

* whole blood, fresh frozen plasma, packed red blood cells, platelets, cryoprecipitate

BU = Bethesda Units; CI95 = 95% confidence interval; ED = exposure day; HR = hazard ratio.
OUTCOME MEASURES

Primary Endpoint: overall incidence of inhibitors

All inhibitors

- 76 patients developed an inhibitor
- 73% of inhibitors were persistent
- All inhibitors occurred before 39 exposure days (range 2-38)

pdFVIII/VWF vs rFVIII

pdFVIII/VWF: cumulative incidence **26.8%** (CI95 18.4-35.2).

29 developed an inhibitor

rFVIII: cumulative incidence **44.5%** (CI95 34.7-54.3).

47 developed an inhibitor

Cumulative incidence of all inhibitors

rFVIII 87% higher incidence of inhibitors than pdFVIII/VWF

(HR 1.87, CI95 1.17-2.96)
**OUTCOME MEASURES**

Secondary Endpoint: high-titer inhibitors

High-titer inhibitors

- **66%** (50 of 76) of inhibitors were high-titer
- **89%** of high-titer inhibitors were persistent
- All high-titer inhibitors occurred **before 34 exposure days** (range 2-33)

**pdFVIII/VWF vs rFVIII**

**pdFVIII/VWF:** cumulative incidence 18.6% (CI95 11.2-26.0).

20 of 29 inhibitors were high-titer

**rFVIII:** cumulative incidence 28.4% (CI95 19.6-37.2).

30 of 47 inhibitors were high-titer

**rFVIII 69% higher incidence of high-titer inhibitors than pdFVIII/VWF**

(HR 1.69, CI95 0.96-2.98)
Patients treated with pdFVIII containing VWF experienced significantly lower incidence of inhibitors than with rFVIII

Recombinant FVIII products had NEARLY TWICE the rate of inhibitor development of pdFVIII containing VWF

69% higher rate of HIGH-TITER inhibitor development with rFVIII than pdFVIII containing VWF