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

SIPPET STUDY

Survey of **I**nhibitors in **P**lasma-**P**roduct **E**xposed **T**oddlers

" 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."

Peyvandi F *et al. N Engl J Med 2016;374:2054-64*

GRIFOLS

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

METHODOLOGY

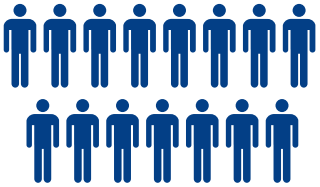
Study Design

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



1:1 BLOCK RANDOMIZATION
one brand of pdFVIII/VWF and one of rFVIII per country
303 screened/264 randomized

n= 251 analyzed

125 to pdFVIII/VWF

126 to rFVIII

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*

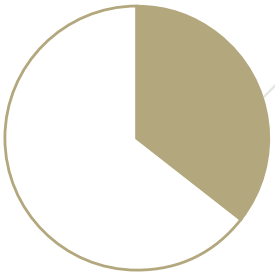
***BU**=Bethesda Units; **CI95**=95% confidence interval; **ED**=exposure day; **HR**=hazard ratio.*

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)



35.4% Cumulative Incidence of all inhibitors

Inhibitor
No Inhibitor

pdFVIII/VWF *vs* rFVIII

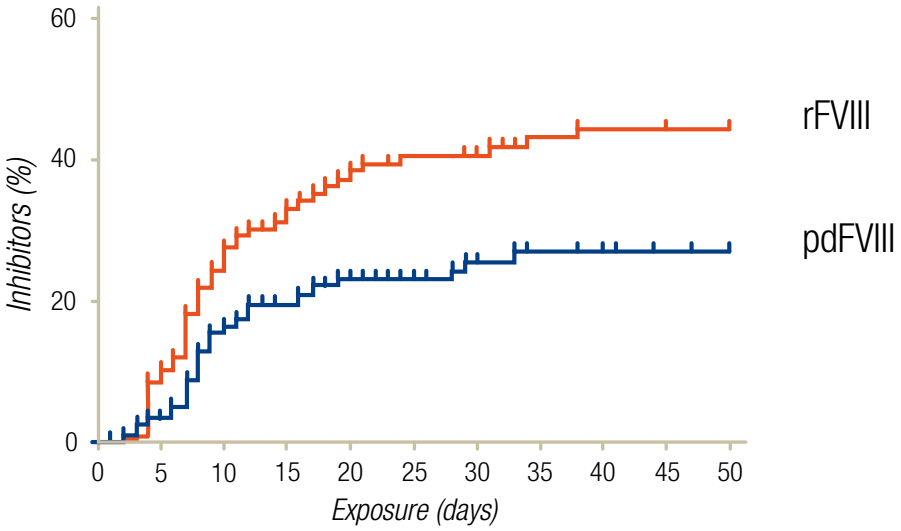
pdFVIII/VWF: cumulative incidence **26.8%** (CI95 18.4-35.2).

29 developed an inhibitor

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

47 developed an inhibitor

Cumulative incidence of all inhibitors



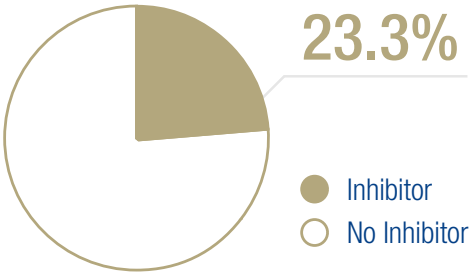
rFVIII 87% higher incidence of inhibitors than pdFVIII/VWF

(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

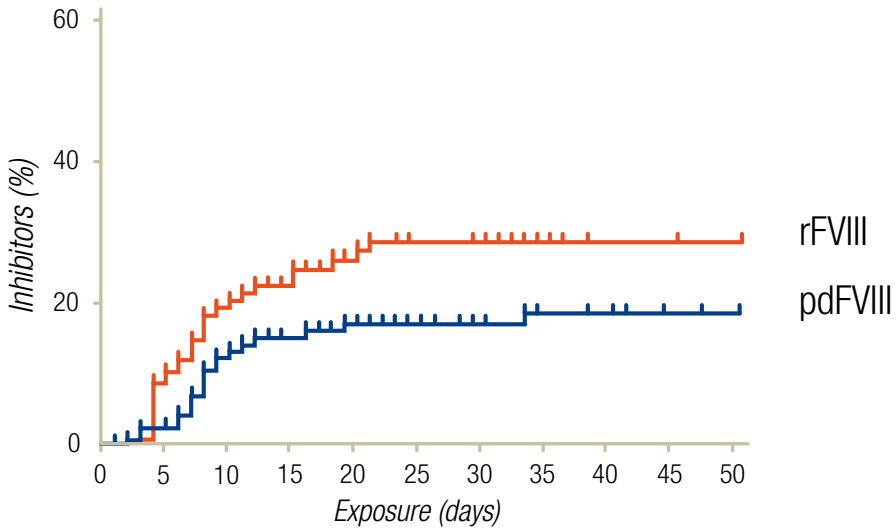
pdFVIII/VWF: cumulative incidence **18.6%** (CI95 11.2-26.0).

20 of 29 inhibitors were high-titer

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

30 of 47 inhibitors were high-titer

Cumulative incidence of high-titer inhibitors



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

(HR 1.69, CI95 0.96-2.98)

RESULTS

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