Pharmacodynamic Effects of Escalating Dosages of a New Recombinant Human Factor VIIa (LR769) in Congenital Hemophilia A or B Patients

J. Powell1, C. Kluft2, M. Moerland3, J. Frieling4, L. Valentino5

1 UC Davis, Sacramento, CA, USA, 2 Good Biomarker Sciences, Leiden, The Netherlands, 3 Centre for Human Drug Research, Leiden, The Netherlands, 4 rEVO Biologics, Framingham, MA, USA, 5 RUSH University Medical Center, Chicago, IL, USA

Abstract

Objective

Congenital Hemophilia A and B treatment may be complicated by the development of inhibitors to the deficient factor. In such cases factor replacement becomes ineffective, and use of a bypassing agent is needed to treat a bleeding or in the peri-operative period. A recombinant form of activated Factor VII has been available for this purpose. In this study, a new recombinant human Factor VIIa (LR769) produced by LFB/rEVO Biologics is tested. The goal is to provide patients with Hemophilia A and B who develop inhibitors a cost-effective alternative treatment option.

Methods

Three sites (2 in US and 1 in NL) participated. The study was approved by the IRB/EC of the institutions and performed consistent with the Declaration of Helsinki. Informed consent was obtained prior to any study activities. Fifteen adult hemophilia A or B patients with or without inhibitors were treated in 3 dosing cohorts. Each patient was treated in 2 cohorts on 2 separate occasions, according to one of three sequences: 25 and 75 µg/kg, 25 and 225 µg/kg, or 75 and 225 µg/kg. Each dose cohort consisted of 10 administrations.

Serial sampling to obtain plasma for performing several pharmacodynamic parameters are taken at baseline and up to and including 24-36 hours after administration. Assays reported here include a) activated partial thromboplastin time; b) prothrombin time; c) Prothrombin fragments 1+2; d) D-dimer; e) thrombin-antithrombin complex. Samples for thromboelastometry and thrombin generation assay were taken, but not yet available.

Results

Twenty patients were screened and 15 enrolled and treated. Hemophilia A/B ratio was 11/4. Twelve had severe and 3 moderate hemophilia. None of the patients currently had inhibitors. Ages ranged from 20 to 61 years. Safety and PK are presented by L. Valentino in a separate ePoster.

The figures 1-3 show the mean ± SD for the parameters for aPTT, PT and F1+2. Baseline aPTT was, as expected, high at baseline and showed a clear dose related shortening just after infusion. The highest dose decreased the aPTT to high normal values. PT also shortened with maximum effects seen that lasted longer for the highest dose. Effects on D-dimer and TAT are variable. D-dimer shows a small increase at the highest dose only. TAT increases at 75 and 225 mcg/kg with a peak in the first 5 hours to 2-2.5 times pretreatment values. Prothrombin fragments 1+2 levels increased minimally at the 25 µg/kg dose, but showed a dose dependent increase in the 75, and 225 µg/kg cohorts.

Conclusions

- LR769 is pharmacodynamically active after a single dose of 25, 75, and 225 µg/kg in hemophilia A or B patients
- Dose related effects on aPTT, PT and F1+2 were found
- These and other PD parameters will help in selecting the dose for Phase 3 trials