Kinetics of Recombinant Von Willebrand Factor (rVWF) Clearance and ADAMTS13-mediated Multimer Proteolysis in Severe Von Willebrand Disease (VWD)

Bettina Ploder,[1] Peter Chen,[2] Miranda Chapman,[3] Bruce Ewenstein,[3]

[1*]Shire, Vienna, Austria; [2*]Shire, Bannockburn, IL; [3*]Shire, Cambridge, MA

INTRODUCTION

- Knowledge of VWF proteolysis kinetics due to *in vivo* ADAMTS13-mediated cleavage and subsequent projected loss of VWF ristocetin cofactor activity (VWF:RCo) is critical for successful treatment with VWF replacement therapies.
- VWF:RCo loss is affected by: 1) the clearance of VWF antigen (VWF:Ag), and 2) ADAMTS13- mediated proteolytic cleavage of VWF and resultant reduction in multmeric size.
- A highly purified recombinant von Willebrand factor (rVWF, vonicog alfa, Vonvendi®, BAX111), which retains a higher content of the more hemostatic, intact ultra large VWF multimers (ULM), and with a higher specific activity compared to plasma-derived products,[1,2] could present an alternative treatment option for VWD patients.

OBJECTIVE

- Evaluate the ULM patterns and associated kinetics of rVWF in a prospective Phase 3 trial[1] in adults with severe VWD.
- Examine the possible effect of the variance of ADAMTS13 levels on VWF:RCo or ULM proteolysis of rVWF.

METHODS

- A qualitative approach was used to describe the relative influence of the 2 factors contributing to the loss of VWF:RCo after infusion with rVWF.
- VWF:RCo was determined using a modification of the Dade Behring coagulation analyzer (BCS) method with plasma samples from adult patients with severe, predominantly type 3, VWD taken at pre-specified time points over 96 hours post-infusion with a single dose of rVWF: 50 IU VWF:RCo/kg (N = 15) [PK50_rVWF]; 50 IU VWF:RCo/kg together with 38.5 IU/kg rFVIII (1.3:1 ± 0.2 ratio) (N = 16) [PK50_rVWF:rFVIII], or 80 IU VWF:RCo/kg rVWF (N = 14) [PK80_rVWF]. 80 IU PK was repeated after 6 months of treatment (N = 13).
- ADAMTS13 levels (% of normal) were determined at baseline using an ELISA-based chromogenic assay (Technoclone).
- VWF multimer content was evaluated using low-resolution sodium dodecyl sulfate (SDS) agarose gel electrophoresis adjusted to equalize VWF:Ag content, followed by a luminescence western blot imaging system.
- Loss of ULM and VWF:RCo clearance in relation to ADAMTS13 levels were explored using Spearman's rank order correlation.

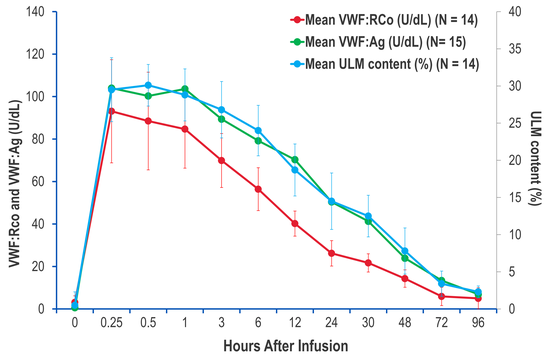
REFERENCES

1. Gill JC, Castaman G, Windyga J et al. Hemostatic efficacy, safety, and pharmacokinetics of a recombinant von Willebrand factor in severe von Willebrand disease. *Blood.* 2015 Oct 22;126(17):2038-46.

RESULTS

ULM Content, VWF:Ag and VWF:RCo

Figure 1: Mean ULM Content, VWF:Ag and VWF:RCo and After First PK Infusion (PK50_rVWF)



- A rapid, post-rVWF infusion increase in VWF:Ag and ULM was observed, followed by ADAMTS13-mediated proteolysis.
- VWF:RCo kinetics followed a similar pattern, rising significantly within 15 minutes and sustained until a substantial decrease between 12h and 24h and returning to near baseline levels by 96h post-infusion.
- Congruent patterns of VWF:Ag and ULM loss appear to contribute to a similar extent to the rate of loss of VWF:RCo.

CONCLUSION

- These results confirm that VWF:RCo kinetics of rVWF are influenced by both the clearance of rVWF:Ag and alteration in ULM content.
- No difference in either the rate of ULM proteolysis nor loss of VWF:RCo could be linked to variances in endogenous ADAMTS13 levels within the normal physiologic range (> 100%).

DISCLOSURES

*Authors are employees of Baxalta ([1]Baxalta Innovations GmbH; [2,3]Baxalta US, Inc.), now part of Shire. The study was sponsored by Baxalta US, Inc. and Baxalta Innovations GmbH; Baxalta, now part of Shire.

VWF:RCo Clearance and Decrease of Relative Frequency of ULM in Relation to Baseline ADAMTS13 Levels

Figure 2: VWF:RCo Clearance vs. Baseline ADAMTS13 Level

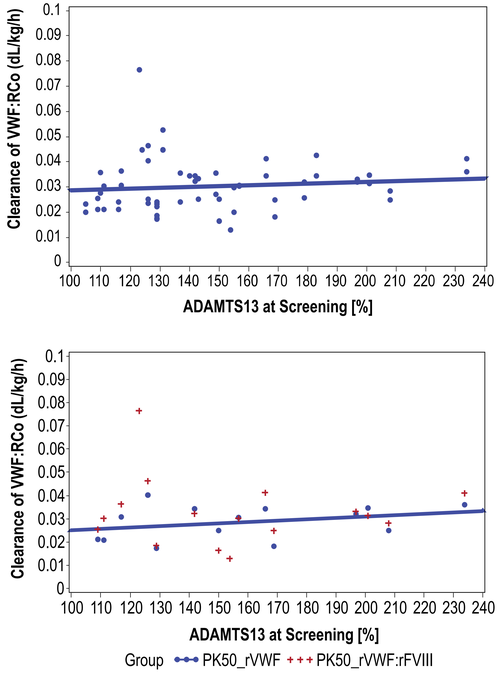
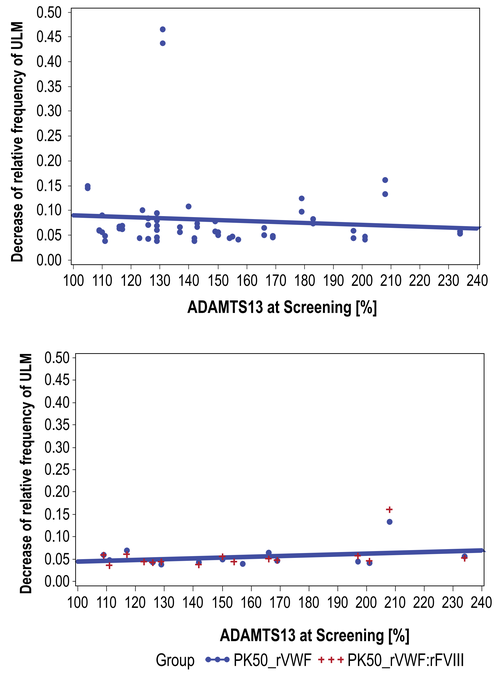


Figure 3: ULM Content Over Time vs. Baseline ADAMTS13 Level



- As expected in this non-ADAMTS13-deficient population (median 140%; range: 105% to 234%) neither ULM degradation (Spearman correlation for the 3 dose groups ranged from -0.11 to 0.28), nor VWF:RCo clearance (Cl) correlated with baseline ADAMTS13 levels irrespective of dose (Spearman correlation ranged from -0.02 to 0.44).