Thrombotic thrombocytopenic purpura directly linked with ADAMTS13 inhibition in the baboon (*Papio ursinus*)


Introduction

von Willebrand factor (VWF) is a multimeric glycoprotein that bridges platelets to injured arterial vessels through interactions with both subendothelial collagen and platelet membrane receptors. Unusually large VWF multimers (UL-VWFs) are released as VWF precursors into the bloodstream by stimulated endothelial cells. These high-molecular-weight proteins are abnormally adhesive, being able to bind and cross-link platelets in circulation even in the absence of endothelial injury. Normally, UL-VWFs are rapidly cleaved by circulating VWF-cleaving protease (ADAMTS13), which generates VWF multimers of sizes seen in normal plasma. The inability to process UL-VWF in cases of ADAMTS13 deficiency can cause disseminated platelet-rich thrombi, which block terminal arterioles, leading to hemolytic anemia with ischemic organ failure and ultimately death in patients with thrombotic thrombocytopenic purpura (TTP). Diagnosis is based on signs of concurrent thrombocytopenia with hemolytic anemia and fragmented red blood cells (schistocytes) in the absence of other identifiable primary causes.

ADAMTS13 deficiency can be hereditary by mutations in the *ADAMTS13* gene or acquired by inhibiting autoantibodies to ADAMTS13. The former is currently treated by infusion of fresh frozen plasma, which contains donor ADAMTS13 to overcome the deficiency. The latter often requires plasma exchange to both replenish the diminished proteolytic activity and remove inhibitors.

These plasma therapies could effectively reduce mortality to approximately 20%, but morbidity still is considerable and not seldom as a consequence of the plasma therapy. Safer therapeutic strategies are therefore required and could focus on the inhibition of the platelet-VWF interaction or on the reconstitution of enzyme by infusion of a recombinant ADAMTS13 preparation. However, the current *Adams13* mouse model does not consistently present with TTP features, hampering preclinical evaluation of novel potential therapeutic approaches.

Motto et al have indeed demonstrated that TTP can be triggered by injection of *Escherichia coli* derived shigatoxin in a subset of *Adams13* mice provided the “susceptible” genetic background. The authors concluded that unidentified genetic and environmental modifiers contribute significantly to the development of acute disease. This was strengthened by the variable onset of TTP in the CASA/Rk *Adams13* animals (ie, although a small number of mice spontaneously developed TTP symptoms, others did not present with TTP even after stimulation with shigatoxin).

In humans, triggers are not always distinctively identifiable, although some observations on pregnancy, infection, and surgery as precipitating factors of acute illness in the background of ADAMTS13 deficiency have been reported. On the other hand, some patients with congenital ADAMTS13 deficiency present with recurrent TTP from childhood on, without reports of a trigger (eg, papillitis, surgery, pregnancy, infection, and medications). Motto et al also found that the most frequent ineffector-related trigger was unusual and recurrent papillitis. In contrast, we could only find a single case of urogenital infection in our TTP cases.

To our knowledge, the baboon is the only nonhuman species that consistently presents with TTP after injection of shigatoxin. This paper aims to expand our knowledge of TTP in the baboon, with the ultimate goal of developing a suitable baboon model for the preclinical evaluation of potential therapeutic approaches.
proband C and proband D in Matsumoto et al21 and patient 05 I-1 in Schneppenheim et al22), so-called Upshaw-Schulman syndrome (MIM #274150). Hence, identification and classification as well as pathophysiological explanation of the exact role and mechanism of triggers remain obscure.

In this work, we have examined the effect of ADAMTS13 inhibition on primate hematology in vivo to determine whether additional triggers would be required to provoke TTP and to develop a reliable animal model for this disease.

**Methods**

**mAb characterization**

Hybridomas were generated21 from mice primed with 10 μg purified human recombinant (full-length) ADAMTS13 (rADAMTS13), and monoclonal antibodies (mAbs) were produced on large scale in a bio-incubator (Celine CL 350, Integra Biosciences). The proteins were purified using protein A coupled Sepharose FF (GE Healthcare), dialyzed to phosphate-buffered saline, pH 7.4. All preparations were controlled for purity by sodium dodecyl sulfate–polyacrylamide gel electrophoresis and Coomassie staining, for inhibitory activity against baboon plasma ADAMTS13 by FRET-SVWF73 assay and for endotoxin content using the LAL precipitation assay following instructions from the provider (Lonza Switzerland).

Two mAbs were selected for further study: 3H9 as an inhibitor to ADAMTS13 and 5C11 as a noninhibiting control. Measurement of ADAMTS13 activity in the presence of various concentration of either mAb was with 2μM FRET-SVWF73 and baboon plasma as a source of ADAMTS13 at 3% (vol/vol) as described.24 Reactions contained Pefabloc SC (Roche Diagnostics) to inhibit serine proteases. Animals injected with the ADAMTS13 inhibitor 3H9 are in the so-called “subject” group, and animals injected with control 5C11 are in the “control” group.

Binding of rADAMTS13 to 5C11 and 3H9 was assessed by enzyme-linked immunosorbent assay (ELISA). mAbs were immobilized onto an 96-well plate followed by incubation with serial dilutions of rADAMTS13. Detection of bound enzyme was with horseradish peroxidase-labeled anti-V5 (anti-V5–HRP; Invitrogen) and α-phenylenediamine as chromogenic substrate. All rADAMTS13 proteins contain a V5 epitope fused to the C-terminus. Apparent dissociation constants were calculated by iterative fitting to the quadratic binding equation using Prism Version 5 software (GraphPad).

3H9 and 5C11 epitopes were mapped to rADAMTS13 metalloprotease domain and a rADAMTS13 mutant lacking the second thrombospondin-1 repeat, respectively, using immunoprecipitation. Hereeto, 10nM of recombinant protein was mixed with 5nM of mAb. Recombinant protein A coupled to Sepharose beads was used to precipitate the complexes by centrifugation. Bound domains were visualized by sodium dodecyl sulfate–polyacrylamide gel electrophoresis followed by Western blotting with anti-V5–HRP and chemiluminescence.

**Baboon treatment, injections, and sampling**

Housing, treatment, phlebotomy, and care for the Cape baboons (Papio ursinus) as well as the final protocol were approved by the Control Committee on Animal Experimentation of the University of the Free State (Bloemfontein, South Africa) in accordance with the National Code for Animal Use in Research, Education, Diagnosis and Testing of Drugs and Related Substances in South Africa before engaging any experimentation. All animals were male, weighed between 10 and 20 kg, and were disease-free for at least 6 months. Animals were anesthetized by intramuscular delivery of 10 mg/kg ketamine hydrochloride. Injections and blood sampling were performed by venipuncture of the femoral vein while under anesthesia. All antibody injections were at 600 μg/kg in physiologic phosphate buffer.

**Blood analysis**

All common blood parameters were determined blindly by automated and standardized methods in the Tertiary National Health Laboratory Service, Universitas Hospital, Bloemfontein, South Africa.

Schistocytes were counted by an expert hematologist not involved in this study. Samples were blinded, and counting was done manually. When less than 1% schistocytes were observed, the smear was considered normal.

ADAMTS13 antigen was measured by ELISA as described25 using normal human pooled plasma (n = 20) as a reference set at 100%. The concentration of murine mAbs in baboon plasma was determined by a sandwich ELISA as previously described.26 Residual ADAMTS13 activity in baboon plasma was determined by FRET-SVWF73 as described27 with modifications.28 ADAMTS13 activity at baseline (before mAb injection) was taken as a standard set to 100%. To control for antibody-antigen dissociation as a consequence of diluting the samples, measurements were carried out at room temperature, and the initial velocity (first 20 minutes) was measured every 30 seconds. Effects of antibody-antigen dissociation were, however, never observed as both antibodies have a small koff.

**Tissue preparation and analysis**

Animals were killed by intravenous injection of 200 mg/kg pentobarbital (Euthapent, Kyron Laboratories) immediately followed by dissection and macroscopic inspection of lung, liver, heart, brain, kidney, and spleen. Wedges of lung, heart, brain, kidney, and spleen were dissected and fixed in 10% buffered formaldehyde for 24 hours. Liver sections were not included for microscopic analysis. A Tissue Tek microtome/cryostat device (Bayer Healthcare) was used for processing and embedding. Hematoxylin and eosin staining was by standard techniques. Staining for VWF and platelets was with a polyclonal anti-VWF (P0226) and the mAb antihuman glycoprotein IIb/IIIa clone Y2/51 (M0753), respectively, both peroxidase labeled (Dako Denmark). 3-3′-Diaminobenzidine was used as a chromogenic substrate. The Martius Scarlet Blue (MSB) technique was used for staining fibrin. This stain colors erythrocytes yellow, connective tissue blue, nuclei black to violet, and muscle and fibrin red. We used an Olympus BX41 microscope with a 100×/1.25 numeric aperture oil immersion objective. Digital image acquisition was with a Colorview IIIu camera and analySIS LS Report software (Version 2.6).

**Statistics**

Significance between datasets was assessed by the Student t test or the Mann-Whitney U test depending on the result of the Kolmogorov-Smirnov test for normality. Welch correction to the Student t test was performed if parametric datasets were found not to have equal variances by F test (Prism Version 5, GraphPad). P values were calculated comparing mean values of 3H9 with 5C11-injected animals using .05 as a cutoff for significance.

**Results**

3H9 is an inhibitory anti-ADAMTS13 monoclonal antibody

A series of mAbs was developed using purified full-length human rADAMTS13 as an antigen in Balb/C mice. The anti-ADAMTS13 mAb 3H9 binds an epitope in the metalloprotease domain of ADAMTS13 (supplemental Figure 1, available on the Blood Web site; see the Supplemental Materials link at the top of the online article). 3H9 inhibits human ADAMTS13 function (not shown) and cross-inhibits ADAMTS13 in baboon plasma (Figure 1A). The noninhibitory anti-ADAMTS13 mAb 5C1125 binds to the second thrombospondin type 1 repeat (supplemental Figure 2) and serves as a control. Both mAbs have comparable affinity for rADAMTS13 with apparent dissociation constants of 2.4 ± 0.4nM and 2.2 ± 0.4nM (mean ± SD; n = 3) for 3H9 and 5C11, respectively (Figure 1B).
Systemic inhibition of ADAMTS13 in baboons injected with 3H9

Two boluses of 600 μg/kg 3H9 and 5C11 were administered intravenously to 6 and 5 baboons, respectively, over a course of 2 days with a 96-hour follow-up regimen (Figure 1C). Antibody injections resulted in a mean initial plasma mAb concentration of more than 50 nM, which declined similarly for both mAbs (Figure 1D). Consequently, plasma ADAMTS13 activity fell below detection limit (< 5%, Figure 2A), and antigen decreased to approximately 40% in subject animals (Figure 2B). ADAMTS13 activity was reduced to approximately 50% in control animals despite normal antigen levels and no measurable functional inhibition in vitro (Figures 1–2). Neither VWF antigen (supplemental Figure 3) nor multimer patterns (supplemental Figure 4) changed significantly over the course of the study in either group.

Inhibition of ADAMTS13 consistently causes thrombocytopenia and schistocytic hemolytic anemia

All subject animals developed thrombocytopenia within 24 hours, with platelet counts decreasing further to 12 ± 7 × 10^9/L after 48 hours (Figure 3A). As a consequence, some animals had minor bleeding events, which spontaneously resolved (supplemental Figure 5). Intravascular hemolysis became apparent as haptoglobin decreased to below the detection limit of the assay 72 hours after injection (Figure 3B) coinciding with a decrease in hemoglobin less than 70% of baseline (Figure 3C). Schistocytes were observed in peripheral blood smears, confirming the presence of fragmentation hemolysis (Figure 4A). The schistocyte count increased over time (Figure 4B), indicating that fragmentation was taking place continuously. Serum lactate dehydrogenase (LDH) levels, as a marker for tissue damage29 and hemolysis, increased approximately 3-fold (Figure 3D) with no signs of intravascular coagulation (supplemental Table 1). None of the animals had signs of renal bleeding events, which spontaneously resolved (supplemental Figure 5). Intravascular hemolysis became apparent as haptoglobin decreased to below the detection limit of the assay 72 hours after injection (Figure 3B) coinciding with a decrease in hemoglobin less than 70% of baseline (Figure 3C). Schistocytes were observed in peripheral blood smears, confirming the presence of fragmentation hemolysis (Figure 4A). The schistocyte count increased over time (Figure 4B), indicating that fragmentation was taking place continuously. Serum lactate dehydrogenase (LDH) levels, as a marker for tissue damage29 and hemolysis, increased approximately 3-fold (Figure 3D) with no signs of intravascular coagulation (supplemental Table 1). None of the animals had signs of renal

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between inhibition of ADAMTS13 activity and TTP.

The experiment with 2 injections of ADAMTS13 inhibitor and 96-hour follow-up induced TTP with limited organ damage except to the myocardium in one of the animals, but without evidence of discomfort. We hypothesized that prolonged inhibition of ADAMTS13 would increase the chance of advanced ischemic organ damage and raise the model to advanced or end stage. One animal continuously received injections of 3H9 every 48 hours for 12 days with blood analysis every 24 hours. The immunoglobulin titer continuously received injections of 3H9 every 48 hours for 12 days.

Baboons injected with 3H9 have immunohistochemical features characteristic of TTP

Histologic sections of kidney, heart, spleen, and brain revealed numerous cosinophilic (hyaline) inclusions in small vessels of a subject but not control animal killed after 96 hours of treatment (Figure 5; supplemental Figure 6). Immunohistochemical staining confirmed that the thrombi were characteristic of TTP as these were enriched in VWF and platelet antigen CD61, whereas fibrin was lacking. Thrombi were not detected in lungs, which is consistent with postmortem pathologic studies of human TTP. The combination of the hematologic and histologic findings provides sufficient evidence for TTP in all subject animals, suggesting a direct link between inhibition of ADAMTS13 activity and TTP.

Advanced TTP by continuous injections of 3H9

The experiment with 2 injections of ADAMTS13 inhibitor and 96-hour follow-up induced TTP with limited organ damage except to the myocardium in one of the animals, but without evidence of discomfort. We hypothesized that prolonged inhibition of ADAMTS13 would increase the chance of advanced ischemic organ damage and raise the model to advanced or end stage. One animal continuously received injections of 3H9 every 48 hours for 12 days with blood analysis every 24 hours. The immunoglobulin titer showed a cyclic pattern corresponding to the bolus infusions but without accumulation (supplemental Figure 7). As expected, all initial hematologic indications characteristic of TTP gradually increased during the study. The animal remained thrombocytopenic with an average platelet count of $34 \times 10^9/L$ (supplemental Figure 8A), serum LDH levels increased further to approximately 5-fold, and haptoglobin remained undetectable (supplemental Figure 8B). Severe anemia set in from day 6 but then leveled at 5 g/dL (supplemental Figure 8C). Blood smears became increasingly indicative for severe schistocytic hemolysis with a large number of reticulocytes and eventually Howell-Jolly bodies (supplemental Figure 8D). The latter were thought to indicate functional hyposplenism probably because of widespread microvascular thrombosis of the spleen with autosplenectomy. At day 6, a sudden but transient increase in troponin-T (0.41 μg/L with cutoff < 0.03; supplemental Figure 9) suggested some myocardial ischemic necrosis. Cardiac ischemia is observed in the majority of TTP patients and is associated with increased mortality and morbidity according to a recent study. However, this animal never became noticeably ill, and 4 days after cessation of injections all parameters returned to baseline with no further complications.

Discussion

Our data show that inhibition of ADAMTS13 in baboons consistently causes the characteristic hematologic picture of TTP without the requirement of additional inciting triggers. Consequently, ADAMTS13 function is essential for maintaining microvascular integrity in nonhuman primates. This is in contrast to common laboratory mice where congenital deficiency of ADAMTS13 is prothrombotic but insufficient to cause spontaneous TTP. Differences between murine and primate physiology may account for this. For instance, certain modifiers, including other proteases, that can substitute for ADAMTS13 activity, may process VWF more efficiently in mice than in primates.

The consistency of the response to inhibition of ADAMTS13 in baboons is rather unexpected because TTP in human cases with congenital ADAMTS13 deficiency as well as in the susceptible mouse strain (CASA/Rk) has a variable time of onset. One possible explanation for this heterogeneity in human congenital TTP is that numerous ADAMTS13 mutations may result in diverse plasma ADAMTS13 activities below the detection limit of currently available assays (~5%), which would still be sufficient to prevent spontaneous recurrent TTP. This is substantiated by the observation that women with a specific hereditary congenital TTP variant that spontaneously sets in immediately after birth and is characterized by a chronic relapsing course requiring prophylactic infusion of donor plasma to constantly replenish the deficient enzyme. Taken together, this implies that a threshold ADAMTS13 activity, probably less than 5%, underlies spontaneous precipitation of disease (ie, in the absence of an obvious external inciting trigger). We assume that ADAMTS13 inhibition in the subject baboons is below this critical level because the 3H9 plasma concentrations achieved in these animals exceed the dissociation constant of the antibody-antigen interaction by far, indicating all ADAMTS13 molecules are occupied with inhibitor. This does not, however, rule out that TTP can be incited when ADAMTS13 activity levels are above threshold because patients...
with measurable ADAMTS13 activity may still develop TTP.\textsuperscript{37} Although in that context, triggers such as pregnancy or infection probably play a substantial role by precipitating acute illness through a currently unknown mechanism. Therefore, our results do not exclude supplementary roles for triggers; rather, they situate them in a specific context.

Another significant difference with the current \textit{Adams1}\textsuperscript{3,4} mouse model is that half of the shigatoxin-treated CASA/Rk mice died,\textsuperscript{15} whereas all baboons in our experiment survived. Even systemic inhibition of ADAMTS13 for as long as 2 weeks in a selected animal did not cause death. Before plasma exchange treatment, the average duration of hospitalization of TTP patients was 14 days before death,\textsuperscript{45,46} not taking into account a potential presymptomatic period. This could mean that the human and primate organs tolerate the process of ongoing thrombosis for a relatively long time. This may be because thrombi in TTP are disseminated in multiple organs\textsuperscript{7,48} and there allocate to terminal arterioles rather than to large afferent vessels. It is, therefore, possible that additional exogenous triggers accelerate the disease.

Lifting it to an advanced stage by acting synergistically with the ADAMTS13 deficiency and rendering organs more susceptible to the consequences of microangiopathy. This has been observed in a patient homozygous for the 4314insA \textit{ADAMTS13} mutation who presented with mild TTP symptoms, which however exacerbated during pregnancy.\textsuperscript{49} In that respect, certain triggers may not function merely to incite disease, and it therefore remains difficult to speculate how much longer the one animal with long-term ADAMTS13 inhibition could have survived the ongoing TTP.

Our model particularly reflects the early stages of acute acquired idiopathic TTP. In humans, this phase is poorly described, mostly because patients who seek medical assistance generally already have signs of organ damage (ie, advanced-stage TTP).\textsuperscript{50} Our data confirm that the early stages do not cause considerable discomfort, which is in line with the minor signs of organ dysfunction in the baboons with TTP. In addition, in humans, TTP has been suggested to present mildly\textsuperscript{36,50,51} before precipitating as an acute perceptible bout with symptoms of failing organs. Our study thus confirms and justifies the newly adapted diagnostic standard for TTP,\textsuperscript{45} including thrombocytopenia with schistocytic hemolytic anemia in the absence of a primary illness but no longer requiring former criteria of advanced disease, such as neurologic and renal dysfunction. Consequently, our baboon model of TTP is ideally suited for preclinical testing of new treatment strategies because it provides consistency without animal discomfort. Moreover, the model can be used to address the role, effect, and nature of reported triggers.

Taken together, our results show that ADAMTS13 activity is essential for microvascular integrity in primates as TTP spontaneously and quickly occurs after ADAMTS13 inhibition in the absence of additional triggers. We are the first to demonstrate the initial stages of acquired idiopathic TTP, suggesting that these may go by relatively unnoticed as measurable organ failure and/or death are not seen before 96 hours of ADAMTS13 inhibition. Consequently, our model offers an opportunity for clinical and basic research on TTP by providing a framework for alternative therapies and novel insights.

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### Authorship

Contribution: H.B.F. and J.R. designed research, performed experiments, and interpreted data; H.B.F. provided essential reagents and wrote the paper; J.R. and V.J.L. were responsible for the animal study design and supervised animal experimentation; J.R. coordinated the animal experimentation; K.V. designed research, provided essential reagents, interpreted data, coordinated tool development, and wrote the paper; H.D. designed research and provided essential reagents; I.P., N.V., S.L., and W.J.v.R. performed experiments; V.J.L. and P.N.B. assisted as experts in clinical hematology and pathology; P.J.A. provided essential reagents and revised the manuscript; U.B. performed VWF multimer analysis; and all authors critically reviewed the manuscript.

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