Initial experience from a double-blind, placebo-controlled, clinical outcome study of ARC1779 in patients with thrombotic thrombocytopenic purpura

ARTICLE *in* AMERICAN JOURNAL OF HEMATOLOGY · APRIL 2012

Impact Factor: 3.8 · DOI: 10.1002/ajh.23106 · Source: PubMed

Statistical analysis. Categorical variables were summarized using frequency counts and percentages. Continuous variables were summarized using one or more of the following: mean, standard deviation, median, minimum, and maximum, 75th and 90th percentile, ignoring missing data when applicable. Age at survey, age at start of chronic transfusion therapy, average weight, average pretransfusion Hb and %HbS, average transfusion volume, duration of transfusion therapy and predominant transfusion type were summarized with each patient contributing equally. Weight, pretransfusion Hb and %HbS, transfusion volume, and days late were also summarized with each transfusion contributing equally. The probability of pretransfusion %HbS less than 30% was modeled using generalized estimating equations to account for the lack of independence induced by multiple transfusions per subject. The models were used to generate estimates of the odds ratio (OR) and 95% confidence intervals. Results were considered statistically significant if the confidence interval excluded one.

Acknowledgments

The authors thank the entire TWiTCH Trial Group (members listed in "Appendix") and Rho Federal Systems Division, Inc. (Nancy Yovetich PhD, Christopher Woods, Jamie Spencer, Marsha McMurray) for their valuable contributions to the study.

[1]St. Jude Children's Research Hospital, Memphis, Tennessee; [2]Rho Inc., Chapel Hill, NC; [3]Baylor College of Medicine, Houston, Tennessee; [4]Emory University/Children's Healthcare of Atlanta, Atlanta, Georgia; [5]Children's National Medical Center, Washington, DC; [6]Medical University of South Carolina, Charleston, South Carolina; [7]University of Mississippi Medical Center, Jackson, Mississippi; [8]University of Texas Southwestern Medical Center at Dallas, Dallas, TX; [9]Wayne State University, Detroit, Michigan; [10]Children's Memorial Hospital, Chicago, Illinois; [11]Nemours Children's Clinic, Jacksonville, Florida
*Correspondence to: Banu Aygun, MD, St. Jude Children's Research Hospital, Department of Hematology, M/S 800, 262 Danny Thomas Place, Memphis, TN 38105-3678
E-mail: banu.aygun@stjude.org
Conflict of interest: Nothing to report.

Published online 29 December 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.23105

References

1. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5–11.
2. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: Rates and risk factors. Blood 1998;91:288–294.
3. Adams R, McKie V, Nichols F, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. N Engl J Med 1992;326:605–610.
4. Cohen AR, Martin MB, Silber JH, et al. A modified transfusion program for prevention of stroke in sickle cell disease. Blood 1992;79:1657–1661.
5. Miller ST, Jensen D, Rao SP. Less intensive long-term transfusion therapy for sickle cell anemia and cerebrovascular accident. J Pediatr 1992;120:54–57.
6. Aygun B, McMurray MA, Schultz WH, et alfor the SWiTCH Trial Investigators. Chronic transfusion practice for children with sickle cell anemia and stroke. Br J Haematol 2009;145:524–528.
7. Adams RJ. Lessons from the stroke prevention trial in sickle cell anemia (STOP) study. J Child Neurol 2000;15:344–349.
8. Lee MT, Piomelli S, Granger S, et al. STOP Study Investigators. Stroke Prevention Trial in Sickle Cell Anemia (STOP): Extended follow-up and final results. Blood 2006;108:847–852.
9. Adams RJ, Brambilla D. Optimizing primary stroke prevention in sickle cell anemia (STOP 2) trial investigators. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease. N Engl J Med 2005;353:2769–2778.
10. Kwiatkowski JL, Yim E, Miller S, Adams RJ;for the STOP 2 Study Investigators. Effect of transfusion therapy on transcranial Doppler ultrasonography velocities in children with sickle cell disease. Pediatr Blood Cancer 2011;56:777–782.
11. Mirre E, Brousse V, Berteloot L, et al. Feasibility and efficacy of chronic transfusion for stroke prevention in children with sickle cell disease. Eur J Haematol 2010;84:259–265.
12. Hulbert ML, McKinstry RC, Lacey JL, et al. Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease. Blood 2011;117:772–779.

Appendix

TWiTCH Trial investigators and coordinators:

TWiTCH Trial investigators and key contributors include the following: Brigitta Mueller and Bogdan Dinu (Baylor College of Medicine, Houston, TX); Kusum Viswanathan and Natalie Sommerville-Brooks (Brookdale Hospital Medical Center, Brooklyn, NY); Clark Brown and Betsy Record (Children's Healthcare of Atlanta, Atlanta, GA); Matthew Heeney and Meredith Anderson (Children's Hospital Boston, Boston, MA); Janet L. Kwiatkowski, Jeffrey Olson and Martha Brown, (Children's Hospital of Philadelphia, Philadelphia, PA); Lakshmanan Krishnamurti and Regina McCollum (Children's Hospital of Pittsburgh, Pittsburgh, PA); Kamar Godder and Jennifer Newlin (Children's Hospital of Richmond, Richmond, VA); William Owen (Children's Hospital of the King's Daughters); Stephen Nelson (Children's Hospitals and Clinics of Minnesota, Minneapolis, MN); Alexis A. Thompson and Katie Bianchi (Children's Memorial Hospital, Chicago, IL); Lori Luchtman-Jones and Sheronda Brown (Children's National Medical Center, Washington, DC); Margaret Lee (Columbia University, New York, NY); Courtney Thornburg (Duke University Medical Center, Durham, NC); Charles Daeschner and Cynthia Brown (East Carolina University, Greenville, NC); Sherron Jackson and Lisa Kuisel (Medical University of South Carolina, Charleston, SC); Ramamoorthy Nagasubramanian (Nemours Children's Clinic Orlando, Orlando, FL); Cynthia Gauger (Nemours Children's Clinic, Jacksonville, FL); Brian Berman and Mary DeBarr (Rainbow Babies and Children's Hospital, Cleveland, OH); Sharon Singh and Antonella Farrell (Schneider Children's Hospital, New Hyde Park, NY); Banu Aygun and Eileen Hansbury (St. Jude Children's Research Hospital, Memphis, TN); Scott Miller and Kathy Rey (SUNY Downstate, Brooklyn, NY); Isaac Odame, Nagina Parmar, and Manuella Merelles-Pulcinni (The Hospital for Sick Children, Toronto ON Canada); Zora R Rogers and Leah Adix (The University of Texas Southwestern Medical Center, Dallas, TX); Lee Hilliard and Jeanine Dumas (University of Alabama, Birmingham, AL); Michelle Neier and Stephanie Farias (University of Medicine and Dentistry of New Jersey, New Brunswick, NJ); Ofelia Alvarez and Patrice Williams (University of Miami, Miami, FL); Rathi Iyer and Mary T. Walker (University of Mississippi Medical Center, Jackson, MS); Hamayun Imran and Stephanie Durggin (University of South Alabama, Mobile, AL); Elizabeth Yang (Vanderbilt University, Nashville, TN); Sharada Sarnaik and Mary Murphy (Wayne State University, Detroit, MI).

Initial experience from a double-blind, placebo-controlled, clinical outcome study of ARC1779 in patients with thrombotic thrombocytopenic purpura

Spero R. Cataland,[1]* Flora Peyvandi,[2] Pier M. Mannucci,[2] Bernhard Lämmle,[3] Johanna A. Kremer Hovinga,[3] Samuel J. Machin,[4] Marie Scully,[4] Gail Rock,[5] James C. Gilbert,[6] Shangbin Yang,[1] Haifeng Wu,[1] Bernd Jilma,[7] and Paul Knoebl[8]

Despite advances in our understanding of the pathophysiology of thrombotic thrombocytopenic purpura (TTP), there remains significant room for improvement in the treatment of acute TTP. A novel approach to the treatment of TTP using ARC1779 to target the A1-domain of von Willebrand Factor (VWF) to prevent the formation of microthombi has been developed. Preliminary data suggests that blockade of the A1-domain of VWF by ARC1779 can inhibit VWF activity, resulting in clinically significant improvements in the platelet count and lactate dehydrogenase [1–5]. **ARC1779 is a nucleic acid macromolecule, or aptamer, that inhibits the prothrombotic function of VWF by binding to**

the A1-domain of VWF, blocking its interaction with the platelet GPIb receptor. It has been hypothesized that ARC1779 prevents the formation of new microthrombi in patients with acute TTP, and may result in shorter courses of plasma exchange (PEX) and fewer end organ complications via the more rapid inhibition of microthrombotic disease. Prior to the premature closure of the study, nine patients were treated with either ARC1779 of placebo as an adjunct to PEX. Although limited, these data support the safety of this targeted approach to the treatment of TTP, providing the basis for continued study of this unique approach to therapy.

Patient enrollment. A total of nine subjects (seven ARC1779, two Placebo) were enrolled at six sites when the study was closed. Demographic and clinical details of the enrolled subjects are shown in Table I. ADAMTS13 activity was available from 6/7 ARC1779-treated subjects and both placebo subjects.

Clinical response. Clinical response criteria were achieved by 4/7 subjects on the ARC1779 arm, and 0/2 placebo subjects prior to the end of the 14-day infusion period. For the 4 ARC1779-treated subjects, the median number of PEX procedures to achieve response criteria was 7 (range, 6–9). Three ARC1779-treated patients did not meet clinical response criteria by 14 days. Of these one met the clinical response criteria on Day 17, and one additional subject met the criteria at the 6-week follow-up visit, after judged to be refractory to ARC1779 after 9 days of therapy and receiving treatment with rituximab, vincristine, and cyclophosphamide. One additional ARC1779-treated patient achieved a normal platelet count on Day 4, but on Day 6 PEX was held as a part of the tapering of PEX while the ARC1779 was continued without tapering given that the platelet count was normal for only 2 consecutive days. He became thrombocytopenic on the following day after holding PEX for 1 day and while receiving ARC1779 alone and was never able to achieve a normal platelet count before the end of the 14-day infusion period despite the resumption of daily PEX. Two days after the discontinuation of ARC1779 (after tapering completed, but continuing daily PEX) the patient was noted to have a rising troponin-I [9.79 and 17.14 ng mL^{-1} on 2 consecutive days (normal <0.11 ng mL^{-1})] as measured in the local clinical laboratory. Three days after the ARC1779 infusion was stopped his troponin-I remained elevated at 14.52 ng mL^{-1} and he suffered a cardiac arrest and died. One of the two placebo-treated patients achieved a normal platelet count after 14 daily PEX procedures, but the other placebo-treated patient remained severely thrombocytopenic on day +3, eventually achieving a normal platelet count at the 6-week follow-up visit after therapy with rituximab. For the five subjects who achieved a normal platelet count on ARC 1779 (including the subject who achieved a normal platelet count but did not meet response criteria), the median number of daily PEX procedures to achieve a platelet count of $>150 \times 10^9$/L was 5 (range, 4–14).

ARC1779 concentration and VWF activity. Serial VWF activity and ARC1779 concentrations were studied to judge the efficacy of ARC1779 in terms of free A1 domains as a surrogate for VWF activity (Fig. 1). These data demonstrated the sustained suppression of VWF activity (decreased available A1 domain sites) throughout the 14-day infusion with recovery to normal levels after the tapering and discontinuation of the infusion.

Adverse events. Subjects randomized to ARC1779 arm of the study experienced the following serious adverse events: mental status changes (2), seizure disorder (1), catheter-related thrombosis (1), and catheter-related sepsis (1). The mental status changes in both subjects were determined to not be related to the study drug. In the case of the first patient, they occurred 30 days after her last dose of ARC1779 and in the context of multiple acute infarctions of the cerebral hemispheres and cerebellum. Given the recurrent thrombocytopenia at the time of presentation, a recurrence of TTP was felt to be the most likely etiology of the acute infarctions and the subsequent mental status changes. In the second patient, the mental status changes and a seizure disorder were noted to occur coincident with a recurrent thrombocytopenia consistent with a recurrence of TTP. Imaging of his brain by CT showed no abnormalities, and symptoms improved with the reinitiation of PEX therapy. In the opinion of the treating physicians, these serious adverse events were not thought to be related to ARC1779, but rather were related to the diagnosis of TTP and the related therapy (catheter-related complications). No serious adverse events were reported on the placebo arm of the study. No ARC1779-treated subjects

TABLE I. Demographic and Clinical Data (Median) at Presentation and Responses to Therapy for all Nine Enrolled Subjects

	Median age (range)	Sex (M/F)	Race (AA/C)	Pretreatment ADAMTS13%[a]	Platelet count ($\times$109/L)	LDH (U/L)	Creatinine (mg dl^{-1})	Clinical response ($\leq$14 days)	Immune suppressive therapy	Adverse events
ARC1779 ($n = 7$)	44 (33–51)	4/3	3/4	72 ($<$2.5–100)	16	1,063 (263–1,804)	1.31 (0.8–2.46)	4/7	Corticosteroids (4); Rituximab (1); CSA (1); Vincristine (1)	Mental status changes (2)[a], catheter-related Sepsis (1)[a]; catheter-related DVT (1)[a]
Placebo[b] ($n = 2$)	32, 70	0/2	0/2	$<$2.5, 42%	16	647, 1,258	4.54, 0.99	0/2	Corticosteroids (1)	None

All adverse events reported were judged to not likely be related to the study drug.[a]Four of 8 ADAMTS13 measurements were obtained after the first PEX procedure but prior to the first dose of ARC1779.
[b]Given that there were only two subjects in the placebo arm, data for both subjects rather than the median data are presented.

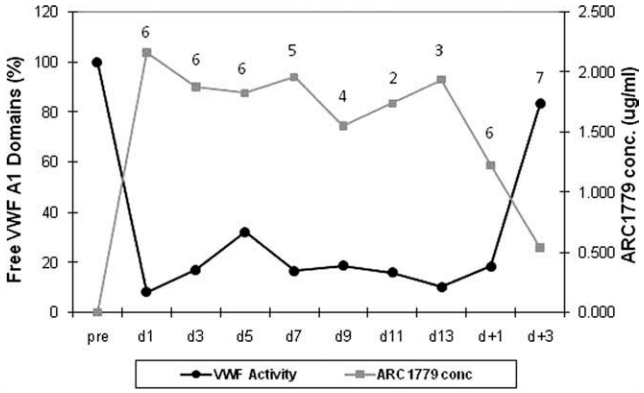

Figure 1. Shown in the figure above are the median ARC1779 concentrations and free VWF A1 domains ("VWF activity") for the ARC1779-treated patients throughout the 14-day dosing period. The number above each data point reflects the number of samples studied at each time point. Day +1 and +3 represent the first 50% tapering of ARC1779 and the time of discontinuing ARC1779 respectively.

experienced bleeding symptoms including cutaneous purpura or petechiae during the infusions despite sustained suppression of "VWF activity" in subjects with platelet counts as low as 6×10^9/L.

Despite the premature closure of this study, there are significant observations that can be made from these nine patients that were enrolled. With the bolus primed continuous infusion of ARC1779, sustained suppression of VWF activity (free A1 domain sites) relative to pretreatment activity was achieved. The suppression of VWF activity correlated with plasma concentrations of ARC1779, and recovered with tapering and discontinuing the ARC1779 infusion. Clinical responses were also consistent with what has been reported previously with ARC1779. It is not clear if a more sustained inhibition of VWF activity below the goal of 10% of baseline VWF activity would improve the efficacy, but it is worth noting that there were no hemorrhagic complications seen in the pilot study where the mean VWF activity during the ARC1779 infusion was 5%.

The most important conclusion that could be drawn from these preliminary data would be that the drug was well-tolerated by the patients studied. Concern would be justified regarding the potential for bleeding complications that might arise from inhibiting VWF activity in patients already severely thrombocytopenic (median platelet count 16×10^9/L at presentation). However, despite achieving sustained suppression of VWF activity throughout the continuous infusion of ARC1779, no patient experienced bleeding complications. Despite the absence of any observed bleeding complications, additional study is required to confirm the safety of sustained reductions to <10% VWF activity in severely thrombocytopenic TTP patients.

These data suggest that the addition of ARC1779 to PEX may have decreased the number of exchanges to achieve a normal platelet count, but with only two patients in the placebo group it is not possible to draw definitive conclusions. It is clear that ARC1779 does not alter the basic disease process that results in the initiation of microthrombus formation in patients with TTP, but rather prevents the formation of VWF-mediated microthrombi. The patient described who achieved a normal platelet count, but developed a recurrent thrombocytopenia while receiving ARC1779 but holding PEX for one day provides an illustration of this point. Despite continued therapy with ARC1779 at the intended dose, the patient clinically deteriorated, developing recurrent thrombocytopenia consistent with an acute exacerbation of TTP. Effective suppression of the ADAMTS13 inhibitory antibody via PEX or adjuvant immune suppressive therapy is still required to achieve a sustained remission of TTP. With this approach, ARC1779 or a similar agent could provide more immediate protection until the disease process can be suppressed by PEX and/or immune suppressive therapy.

While limited in number and longitudinal follow-up, these data provide support for the continued study of VWF A1 inhibition as an adjunct to PEX in the treatment of TTP. These therapies should however be viewed as protective agents that do not alter the underlying pathophysiology, and therefore should be administered as an adjunct to PEX and/or immune suppressive therapy in patients with acquired TTP.

Methods

Study methodology. ARC1779-006 was a randomized, double-blinded, placebo controlled multicenter, international study in patients with TMA with a planned randomization ratio of ARC1779 to placebo of 3:1(ClinicalTrials.gov Identifier: NCT00726544). The objectives of the study were to evaluate: (1) the safety and tolerability of ARC1779, (2) the concentration-response of ARC1779 in terms of efficacy and safety related effects, and (3) the ability of ARC1779 to prevent or minimize short-term neurologic, cardiac, and renal injury from an acute episode of TTP. The study was intended to enroll 100 subjects, but was terminated prematurely by the sponsor after enrolling nine subjects for financial reasons.

Eligible subjects included adults 18–75 years of age with a diagnosis of a TMA (platelet count of $<100 \times 10^9$/L and microangiopathic hemolytic anemia without an alternative explanation). Patients with pregnancy-associated TMA were eligible if no longer pregnant or breast-feeding. Patients with both initial and relapsed events were eligible. The volume of PEX and decision regarding adjuvant immune suppressive therapy were left to the discretion of the treating physician. Subjects randomized to ARC1779 received an initial loading dose of 0.21 mg kg^{-1} followed by a continuous infusion at a rate of 0.6 μg/kg/min. After each PEX, a repeat loading dose at 50% of the initial loading dose was administered to rapidly restore ARC1779 concentrations after the removal of drug by PEX. ARC1779 or placebo was continued until achieving a clinical response (platelet count $=150 \times 10^9$/L on 3 consecutive days) or for a maximum of 14 days. The infusion (ARC1779 or placebo) was then decreased by 50% on day +1, by an additional 50% on day +2, and discontinued on day +3. PEX was tapered at the discretion of the treating physician.

Efficacy was assessed by the serial measurement of complete blood counts (CBC) and the lactate dehydrogenase (LDH). Bleeding complications were monitored and reported by the treating physician who reported any clinical bleeding symptoms and findings including minor skin bleeding, both during therapy and the planned 6-week follow-up.

[1]Department of Medicine and Pathology, Ohio State University, Columbus, Ohio; [2]U.O.S. Dipartimentale per la Diagnosi e la Terapia delle Coagulopatie, A. Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Cà Granda Foundation Maggiore Policlinico Hospital, Milan, Italy; [3]Department of Hematology, University Hospital Bern, Bern, Switzerland; [4]University College London Hospitals, London, United Kingdom; [5]Department of Pathology, University of Ottawa, Ottawa, ON, Canada; [6]Archemix Corp., Cambridge, Massachusetts; [7]Department of Clinical Pharmacology, Medical University of Vienna, Wien, Austria; [8]Department of Internal Medicine, Medical University of Vienna, Vienna, Austria
Contract grant sponsor: Archemix Corp
Bernd Jilma and Paul Knoebl are senior authors.
**Correspondence to: Spero R. Cataland, M.D., Department of Internal Medicine, Ohio State University, A361 Starling Loving Hall, 320 W. 10th Ave., 306B Starling Loving Hall, Columbus, OH 43210*
E-mail: spero.cataland@osumc.edu
Conflict of interest: SRC, FP, PMM, BL, JKH, SJM, MS, GR, BJ, and PK all served as consultants to the Archemix Corp. JCG was employed by the Archemix Corp
Published online 29 December 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.23106

References

1. Bouchard PR, Hutabarat RM, Thompson KM. Discovery and development of therapeutic aptamers. Annu Rev Pharmacol Toxicol 2010;50:237–257.
2. Knobl P, Jilma B, Gilbert JC, et al. Anti-von Willebrand factor aptamer ARC1779 for refractory thrombotic thrombocytopenic purpura. Transfusion 2009;49:2181–2185.
3. Gilbert JC, DeFeo-Fraulini T, Hutabarat RM, et al. First-in-human evaluation of anti von Willebrand factor therapeutic aptamer ARC1779 in healthy volunteers. Circulation 2007;116:2678–2686.
4. Diener JL, Daniel Lagasse HA, Duerschmied D, et al. Inhibition of von Willebrand factor-mediated platelet activation and thrombosis by the anti-von Willebrand factor A1-domain aptamer ARC1779. J Thromb Hemost 2009;7:1155–1162.
5. Jilma-Stohlawetz P, Gorczyca ME, Jilma B, et al. Inhibition of von Willebrand factor by ARC1779 in patients with acute thrombotic thrombocytopenic purpura. J Thromb Hemost 2011;105:545–552.