Table 1. Multivariate Analysis (Adjusted for Treatment Effect)

Variable	OR (95% CI)	*P* Value
Age	2.38 (1.30 to 4.38)	.005
Residual perfusion defect at inclusion[a]	2.22 (1.23 to 4.01)	.009
Residual deep vein thrombosis at inclusion	2.02 (1.06 to 3.85)	.03

[a]Residual perfusion defect on ventilation/perfusion lung scan, >10%.

ANNEXA-A: Andexanet alfa Reduces Anti-fXa Activity in Apixaban-Treated Subjects

Written by Muriel Cunningham

Andexanet alfa is an agent developed to reverse the activity of factor Xa (fXa) inhibitors. Phase 2 proof-of-concept studies in patients taking rivaroxaban, apixaban, edoxaban, and enoxaparin have been completed and andexanet is now being studied in phase 3 confirmatory trials. In part 2 of the phase 3 ANNEXA-A trial [NCT02207725], subjects were treated with apixaban, dosed to steady state, and randomized 3:1 to receive an andexanet bolus plus an infusion or placebo. Mark Crowther, MD, McMaster University, Hamilton, Ontario, Canada, presented the study results.

Because of the difficulty in conducting trials in actively bleeding patients, the ANNEXA-A study was designed to enroll older subjects (50 to 75 years) who were otherwise healthy and to utilize biomarker end points. The primary end point was the percentage change in anti-fXa activity from baseline to the nadir after infusion. Baseline was defined as the measurement at peak anti-Xa before the start of bolus, and the nadir was the lowest anti-Xa value between 10 minutes prior to and 5 minutes after the end of infusion.

A total of 32 subjects were enrolled, 24 to the andexanet arm and 8 to placebo. Twenty-two patients (68.8%) were male and 29 patients (90.6%) were white with a mean age of approximately 59 years (range, 50 to 73). Subjects who were randomized to active treatment received an andexanet bolus of 400 mg followed by 480 mg for a 2-hour continuous intravenous infusion (4 mg/min).

The safety results were consistent with those observed in earlier studies of andexanet. One subject discontinued during the andexanet infusion after experiencing mild hives; there were no other allergic symptoms or cardiorespiratory effects. Six subjects had mild infusion-related reactions, 4 (16.7%) in the andexanet group and 2 (25.0%) receiving placebo. None experienced severe or serious adverse events. Transient elevation of prothrombin fragment 1+2 was seen in most subjects who received andexanet but it returned to ≤2 times the upper limit of normal by the fourth day after treatment. D-dimer did not increase for more than 1 day. Dr Crowther commented that no thrombotic events were noted in anyone infused with this product across all studies. No clinically important antibodies to factor X or fXa were reported.

Subjects in part 2 of the ANNEXA-A study met its primary study end point. The mean anti-fXa significantly decreased by 92% from baseline, which was also significantly lower than the placebo group ($P<.001$). In addition, andexanet significantly reduced free apixaban ($P=.0002$ vs placebo). Thrombin generation was restored to preapixaban levels in all andexanet-treated subjects ($P<.0001$). A large, multicenter, open-label phase 4 study of andexanet is now being conducted at centers in North America and Europe. This study will enroll subjects with acute bleeding who are taking fXa inhibitors to determine the change in anti-fXa activity as well as the number of patients who can achieve effective hemostasis.

AFFINITY: rVIII-SingleChain Efficacious and Well Tolerated in Pivotal Study

Written by Muriel Cunningham

rVIII-SingleChain is an investigational recombinant, single-chain factor VIII being studied in adolescents and adults with hemophilia A. Johnny Mahlangu, MD, University of the Witwatersrand, Johannesburg, South Africa, presented the pharmacokinetic, efficacy, and safety results from the phase 1 rVIII-SingleChain AFFINITY trial [NCT01486927].

This was a large, international, open-label study. Based on investigator judgment, patients were assigned to either prophylaxis or on-demand therapy. For prophylaxis, patients received 20 to 40 IU/kg rVIII-SingleChain every second day or 20 to 50 IU/kg rVIII-SingleChain 2 to 3 times per week. For prophylaxis prior to surgery the regimen was individualized based on the type of surgery. Dose and frequency of rVIII-SingleChain could be adjusted at the investigator's discretion. The World Federation of Hemophilia recommendation was used to guide the treatment of bleeds.

A total of 174 patients were enrolled, 146 (83.9%) for prophylaxis and 27 (15.5%) for on-demand therapy. These included 120 subjects (68.9%) with >50 exposure days (EDs) and 52 subjects (29.9%) with >100 EDs; as a result, there were a total of 14306 EDs. Among the