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

174 patients, 132 (75.9%) were enrolled in the extension study. Approximately half of the 174 patients were enrolled in Europe, 12.6% in the United States, 5.7% in Japan, and 32.2% from the rest of the world. The ethnic origins of the patients were white for 126 (72.4%), Asian for 31 (17.8%), black or African American for 14 (8.0%), and others for 3 (1.7%). Fourteen patients (8.0%) were adolescents.

The pharmacokinetic profile was further determined in 27 patients who received either rVIII-SingleChain 50 IU/kg or octocog alfa. Samples were collected at the following time points: before dosing; at 30 minutes, 1 hour, 4 hours, 8 hours, 10 hours, 24 hours, 32 hours, and 48 hours; and 72 hours after receiving the drug. Comparing rVIII-SingleChain with octocog alfa, the former had lower clearance, a greater area under the curve, and a longer half-life.

A total of 848 bleeds were treated during the study period. The treatment was rated as excellent or good in 93.8% of bleeds. A single injection controlled 81% of bleeds, and 94% of bleeds were controlled with 1 or 2 injections.

Eighty-six percent of patients were on prophylactic dosing with a 2- or 3-times-per-week regimen (median doses 30 and 36 IU/kg, respectively). The median annualized bleeding rate in the prophylaxis arm was 1.14, significantly less ($P<.0001$) than 19.64 in the on-demand arm. The annualized bleeding rates for the 2-times-weekly or 3-times-weekly groups were similar. Patients who received rVIII-SingleChain for prophylaxis before a total of 16 surgeries had a 100% success rate. A median dose of 89.4 IU/kg (range, 40.5 to 108.6) was used on the day of surgery.

Over 99% of injections were administered without reactions, and no inhibitors or anti-CHO antibodies were observed. The most frequent adverse events were nasopharyngitis, arthralgia, and headache. There were 10 serious adverse events, including 1 hypersensitivity reaction that was adequately managed with steroids and antihistamines. Overall, rVIII-SingleChain was considered well tolerated and effective in this study population.

PADIS-PE Identifies Risk Factors for Residual Perfusion Defects After Pulmonary Embolism

Written by Muriel Cunningham

Published reports suggest that 30% to 50% of patients experiencing a pulmonary embolism (PE) have perfusion defects 6 to 12 months later [Cosmi B et al. *Intern Emerg Med.* 2011; Sanchez O et al. *J Thromb Haemost.* 2010; Nijkeuter M et al. *Chest.* 2006]. An increased risk of dyspnea and greater pulmonary artery pressure can accompany these residual perfusion defects [Sanchez O et al. *J Thromb Haemost.* 2010]. The PADIS-PE study [NCT00740883] was a randomized, double-blind, multicenter study conducted to determine the rate of residual perfusion defects and associated risk factors in patients who had experienced a single episode of unprovoked PE. The study results were presented by Olivier Sanchez, MD, PhD, Georges Pompidou European Hospital, Paris, France.

The study was conducted from 2007 to 2012 at multiple centers in France. Patients having their first unprovoked PE received 6 months of anticoagulation therapy, then underwent a lung ventilation/perfusion (V/Q) scan, echocardiography, and a leg ultrasound. Patients with a normal or near-normal V/Q lung scan at baseline were classified as having no perfusion defect, and those with a pulmonary vascular obstruction ≥10% were classified as having a perfusion defect. Patients were randomized to 18 months of warfarin treatment (n=184) or placebo (n=187), evaluated at 18 months, and followed for another 24 months. Risk factors associated with the presence of residual perfusion defects were identified using univariate and multivariate analyses of the patients' baseline data.

PE was initially diagnosed via positive spiral computed tomography in 285 patients (77%) and via high-probability V/Q lung scan in 86 patients (23%). Proximal deep vein thrombosis and right ventricular dysfunction were diagnosed in 112 (30%) and 123 (33%) patients, respectively. A total of 234 patients received low-molecular-weight heparin (LMWH), 370 patients received vitamin K antagonists, 6 had fibrinolysis, and 1 patient was treated with rivaroxaban.

In this study, 124 patients (33%) had residual perfusion defects, 61 patients (16%) had residual deep vein thrombosis, and 95 (27%) had thrombophilia. The mean±SD D-dimer level was 352±459 µg/L. Univariate analysis indicated that patients with a perfusion defect were significantly older (66 vs 53 years; OR, 1.05; 95% CI, 1.03 to 1.06; $P<.0001$), and that significantly higher proportions of patients with a perfusion defect had chronic respiratory disease (39 vs 34%; OR, 2.77; 95% CI, 1.64 to 4.67; $P<.001$) and chronic cardiac disease (9 vs 4%; OR, 4.60; 95% CI, 1.39 to 15.2; $P=.013$). Independent risk factors for residual perfusion defects identified in the multivariate analysis included age >65 years (OR, 3.28; 95% CI, 1.91 to 5.63; $P<.0001$), chronic respiratory disease (OR, 2.10; 95% CI, 1.12 to 3.93; $P=.021$), and right ventricular dysfunction at diagnosis (OR 1.96; 95% CI, 1.14 to 3.37; $P=.014$). Initial treatment with LMWH vs unfractionated heparin or pentasaccharide was associated with a decreased risk of residual perfusion defects (OR, 0.50; 95% CI, 0.29 to 0.86; $P=.013$).