Highlights in Disorders of Coagulation and Thrombosis From the 2014 American Society of Hematology Meeting

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ACE910 Appears Safe and Effective in Phase 1 Study of Hemophilia A

Prophylactic ACE910, a factor VIII–mimetic bispecific antibody, had a favorable safety profile and a promising efficacy profile in an open-label phase 1 trial of patients with hemophilia A. The efficacy of ACE910 appeared to be unaffected by the presence of factor VIII inhibitors.

Dr Midori Shima of Nara Medical University in Kashihara, Nara, Japan, presented data from the trial, in which 18 patients aged 12 to 59 years received ACE910 subcutaneously once a week for 12 successive weeks. The 6 patients in the low-dose cohort received 0.3 mg/kg per week following a loading dose of 1 mg/kg, the 6 patients in the medium-dose cohort received 1 mg/kg per week following a loading dose of 3 mg/kg, and the 6 patients in the high-dose cohort received 3 mg/kg per week. Each cohort contained at least 2 patients with and without factor VIII inhibitors.

ACE910 appeared to be safe, with a total of 8 mild adverse events (AEs) and 2 moderate AEs. The moderate AEs—a respiratory tract infection and headache—occurred in the medium-dose and high-dose cohorts, respectively. The researchers found no evidence of AEs related to hypercoagulation, and no anti-ACE910 antibodies were detected.

Compared with the 6 months prior to study enrollment, the annualized bleeding ratio (ABR) during the 12 weeks of treatment decreased in patients both with (by 64.7%-100%) and without (by 22.8%-100%) factor VIII inhibitors. The ABR also decreased in the medium-dose cohort for patients with (by 88.9%-100%) and without (by 100%) factor VIII inhibitors. Similarly, ABR in the high-dose cohort decreased in patients with (by 100%) and without (by 0%-100%) factor VIII inhibitors. Pharmacokinetic and pharmacodynamic studies showed a dose-dependent increase of ACE910 concentration in plasma. All patients had shortened activated partial thromboplastin time and promotion of thrombin generation with ACE910 dosing.

According to the researchers, this was the first study to demonstrate that once-weekly prophylactic treatment using subcutaneous ACE910 has a favorable safety profile and a promising efficacy profile for patients with severe hemophilia A, including those with factor VIII inhibitors. The researchers emphasized that this drug could be particularly useful for patients with factor VIII inhibitors or venous access difficulty.

Shima M, Hanabusa H, Taki M, et al. Safety and prophylactic efficacy profiles of ACE910, a humanized bispecific antibody mimicking the FVIII cofactor function, in Japanese hemophilia A patients both without and with FVIII inhibitors: first-in-patient phase 1 study [ASH abstract 691]. *Blood*. 2014;124(21)(suppl).

ALN-AT3 Increases Peak Thrombin Generation in Phase 1 Trial

The investigational agent ALN-AT3, which reduces levels of antithrombin through interference with RNA, was effective at increasing peak thrombin generation in a small phase 1 trial. ALN-AT3 is being developed with the goal of restoring hemostatic balance in patients with hemophilia A and B.

For the first part of the study, which was presented by Dr Benny Sorensen of Alnylam Pharmaceuticals in Cambridge, Massachusetts, researchers randomly assigned 4 healthy volunteers to receive either a single subcutaneous dose of ALN-AT3 0.03 mg/kg (3 people) or a placebo (1 person). The maximum allowable level of relative reduction in antithrombin was set at 40%. For the second part of the study, the researchers administered 3 weekly doses of ALN-AT3 to 3 patients with hemophilia A or B. Dosing began at 0.015 mg/kg.

After a follow-up of at least 70 days, patients in the first part of the study experienced a reduction in antithrombin activity of up to 32%. This decrease was statistically significant compared with placebo, and caused a statistically significant increase in peak thrombin generation that was consistent with the degree of knockdown in antithrombin. The reduction in antithrombin was durable, lasting up to 70 days after a single dose of ALN-AT3. In the second part of the study, patients with hemophilia experienced a knockdown in antithrombin of up to 57%.

The researchers concluded that RNA interference with ALN-AT3 is a "promising approach for restoring hemostatic balance in hemophilia" and possibly other bleeding disorders. Advantages of RNA interference include the subcutaneous route of administration, infrequent dosing, and the potential for use in hemophilia patients who have inhibitors.

Sorensen B, Mant T, Akinc A, et al. A subcutaneously administered RNAi therapeutic (ALN-AT3) targeting antithrombin for treatment of hemophilia: interim phase 1 study results in healthy volunteers and patients with hemophilia A or B [ASH abstract 693]. *Blood*. 2014;124(21)(suppl).

Factor XI Agent Reduces Venous Thromboembolism After Surgery

Patients with a severe deficiency in factor XI are known to be at reduced risk for venous thromboembolism (VTE). Now, a study finds that lowering factor XI levels using the investigational antithrombotic agent ISIS 416858 (FXI-ASO) in patients undergoing total knee arthroplasty reduces the incidence of VTE without increasing the risk of bleeding. FXI-ASO is a second-generation, single-stranded antisense oligonucleotide that reduces expression of mRNA in the liver.

For the open-label, parallel group study, which was presented by Dr Harry Büller of the Academic Medical Center in Amsterdam, the Netherlands, researchers randomly assigned 274 patients undergoing total knee arthroplasty to either 200 mg of FXI-ASO (134 patients), 300 mg of FXI-ASO (71 patients), or 40 mg of enoxaparin (69 patients). FXI-ASO was given subcutaneously in 9 injections beginning 36 days before surgery and ending 3 days after surgery. Enoxaparin was given once daily for at least 8 days after surgery. VTE was diagnosed based on symptomatic events or on bilateral venography conducted on days 8 to 12 after surgery.

The researchers found that the rate of VTE was significantly lower with 300 mg of FXI-ASO (4.2%) than with enoxaparin (30.4%), and that the 200-mg dose of FXI-ASO was statistically noninferior to enoxaparin, with a 26.9% rate of VTE. Mean factor XI levels were lower with 200 and 300 mg of FXI-ASO (0.38 and 0.20 U/mL, respectively) than with enoxaparin (0.93 U/mL), whereas levels of factors XII, IX, and VIII were not changed by FXI-ASO. The risk of bleeding was no higher with FXI-ASO 200 or 300 mg (2.8% and 2.6%, respectively) than with enoxaparin (8.3%). Hemoglobin levels before and after surgery were similar among the 3 treatment groups, as were transfusion requirements.

The researchers concluded that FXI-ASO appears to be an effective agent for reducing the risk of VTE after surgery by reducing factor XI levels. Although the agent appeared to be safe in this study, they emphasized that additional studies are needed to confirm the safety and efficacy of FXI-ASO.

Büller HR, Bethune C, Bhanot S, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis [ASH abstract LBA-1]. *Blood*. 2014;124(21)(suppl).

Anticoagulants Linked to Decreased Risk of VTE in Patients With Cancer-Associated Pulmonary Embolism

The use of anticoagulants in cancer patients with incidental pulmonary embolism (PE) is associated with a reduction in risk of recurrent VTE, according to a recent meta-analysis. The analysis also found that mortality at 6 months was significantly higher in patients whose thrombus was located centrally rather than peripherally, and that major bleeding was lower in patients treated with low-molecular-weight heparin (LMWH) than in those treated with a vitamin K antagonist (VKA).

Dr Tom van der Hulle of Leiden University Medical Center in Leiden, the Netherlands, and colleagues analyzed data on 926 cancer patients from 11 observational studies and registries who had incidental PE, meaning that it was diagnosed on a computed tomography (CT) scan performed for reasons other than suspected PE.

The researchers found that the risk of symptomatic recurrent VTE at 6 months was lower in patients treated with a VKA (6.4%; 95% CI, 2.2%-12%) or LMWH (6.2%; 95% CI, 3.5%-9.6%) than in those who did not receive an anticoagulant (12%; 95% CI, 4.7%-23%). Overall mortality at 6 months was not significantly different among the 3 groups: 37% (95% CI, 29%-44%) in patients treated with LMWH, 28% (95% CI, 18%-40%) in those treated with a VKA, and 47% (95% CI, 28%-66%) in those who did not receive an anticoagulant. The risk of major bleeding was significantly lower in patients treated with LMWH (3.9%; 95% CI, 2.3%-5.9%) than in those treated with a VKA (13%; 95% CI, 6.4%-20%).

From these results, the researchers concluded that the use of anticoagulants is linked to a reduced risk of VTE recurrence in patients with incidental PE associated with cancer. They emphasized that the findings of this observational study should be examined in a randomized trial, although they acknowledged that conducting a placebo-controlled trial might not be feasible.

van der Hulle T, den Exter PL, Meyer G, et al. Risk of recurrent venous thromboembolism and major bleeding in cancer-associated incidental pulmonary embolism amongst treated and untreated patients: a pooled analysis of 926 patients [ASH abstract 590]. *Blood*. 2014;124(21)(suppl).

Enoxaparin Not Linked to Intracranial Hemorrhage in Patients With Brain Metastases

VTE affects approximately 1 in 5 patients with brain metastases, but evidence has been limited on whether anticoagulants are safe for use in these patients. Now, a retrospective study finds that the use of enoxaparin in patients with brain metastases is not associated with an increase in measurable or significant intracranial hemorrhage or a decrease in overall survival.

For the study, Dr Jessica Donato of Harvard Medical School in Boston, Massachusetts and colleagues used an online medical records database to identify 184 patients with confirmed brain metastases. The study included 93 patients who had received enoxaparin and 91 matched controls who had not. Approximately half the patients had been diagnosed with non–small cell lung cancer; other cancer types included breast cancer,

melanoma, renal cell carcinoma, colorectal cancer, and small cell lung cancer.

The researchers found no difference between the 2 groups in the 12-month cumulative incidence of either measurable intracranial hemorrhage (which was 20.7% in the enoxaparin group and 19.7% in the control group; *P*=.52) or significant intracranial hemorrhage producing symptoms or requiring surgery (which was 18% in the enoxaparin group and 25% in the control group; *P*=.67). The incidence of confirmed or possible intracranial hemorrhage, however, was higher in the enoxaparin group than in the control group (41% vs 30%; *P*=.04). No difference in survival was found between the 2 groups (*P*=.26). A subanalysis of patients with renal cell carcinoma or melanoma found a trend toward a higher incidence of intracranial hemorrhage in the enoxaparin group (43%) compared with the control group (23%); the difference was not statistically significant (*P*=.07).

This is the largest clinical study to assess the risk of intracranial hemorrhage in patients with brain metastases treated with anticoagulation, according to the researchers. Although the data support the use of enoxaparin to treat VTE in patients with brain metastases, survival does not appear to be affected. There was a trend toward an increased risk of intracranial hemorrhage with enoxaparin in patients with renal cell carcinoma or melanoma that should be examined in future studies.

Donato J, Campigotto F, Coletti E, Neuberg D, Weber G, Zwicker J. Risk of intracranial hemorrhage associated with enoxaparin administration in patients with brain metastasis [ASH abstract 348]. *Blood*. 2014;124(21)(suppl).

Prothrombin Complex Concentrates Halt Bleeding From Apixaban

Two 4-factor prothrombin complex concentrates (PCC) appear to be effective for halting severe bleeding in people taking apixaban (Eliquis, Bristol-Myers Squibb), according to a study in 15 healthy adults. Apixaban is a novel oral anticoagulant that inhibits factor Xa. It is used to treat VTE and prevent it from recurring after joint replacement surgery of the knee or hip, and to prevent blood clots in people with nonvalvular atrial fibrillation.

Dr Charles Frost of Bristol-Myers Squibb in Princeton, New Jersey, presented the results of the open-label, randomized, placebo-controlled, 3-period crossover study of 15 people with an average age of 33 years. In each period, participants received apixaban 10 mg twice per day on days 1 to 3, followed by a final dose on the morning of day 4. Three hours after the final dose, participants received a 30-minute infusion of either 50 U/kg of Cofact (a heparin-free PCC), 50 U/kg of Beriplex P/N (a PCC containing heparin), or saline solution. Each participant moved on to a different treatment after an 11-day washout period.

The study investigators found that during the saline solution period, changes in endogenous thrombin potential (ETP) and other measures of apixaban pharmacodynamics followed the expected apixaban plasma concentration-time profile. The greatest changes in ETP occurred near the time of maximum concentration of apixaban in plasma, and returned to baseline as the concentration of apixaban in plasma decreased. During the Cofact period, the average ETP immediately following infusion was similar to that right before the final dose of apixaban was given on day 4. Within 3.5 hours, it had returned to the baseline value. During the Beriplex period, the average ETP after 30 minutes was similar to that right before the final dose of apixaban was given on day 4. Within 5.5 hours, it had returned to the baseline value. In the case of both Cofact and Beriplex, average ETP continued to increase beyond the baseline value for approximately 15 hours before returning to baseline.

According to the investigators, this was the first study to investigate the effect of 4-factor prothrombin complex concentrates on the pharmacodynamics of apixaban and to demonstrate that both Cofact and Beriplex P/N reverse the steady-state pharmacodynamic effects of apixaban in several coagulation assessments. Further evaluation of these agents in both healthy participants and those treated with apixaban is required.

Reversal of apixaban anticoagulation by 4-factor prothrombin complex concentrates in healthy subjects [ASH abstract 345]. *Blood*. 2014;124(21)(suppl).

Promoter Methylation May Affect Severity of Von Willebrand Disease

Family members who share the same mutation in the *VWF* gene display a wide variation in von Willebrand disease (VWD) severity, with some people never developing the disease. A new study supports the hypothesis that methylation in the *VWF* gene may affect the severity of VWD.

For the study, which was presented by Dr Susan Kuldanek of Children's Hospital Colorado in Aurora, Colorado, researchers conducted laboratory studies using blood samples from 821 members of a multigenerational Amish family. Four CpG sites were analyzed for each participant.

A total of 121 family members had an autosomal-dominant C4120T mutation in the A1 domain of the mature von Willebrand factor (VWF) molecule. The researchers found a significant variation in levels of VWF antigen, which ranged from 9 to 76 in the individuals with the C4120T mutation and from 46 to 483 in the individuals without the mutation. Among those with the C4120T mutation, there was a trend toward increased methylation at each of the 4 CpG sites for samples in the low-antigen group compared with the high-antigen group. These results approached statistical significance at CpG1 (*P*=.1) and CpG2 (*P*=.063). Among those without the

C4120T mutation, there was a trend in the low-antigen group toward increased methylation at CpG2 and CpG3, and decreased methylation at CpG1 and CpG4; the difference in CpG4 approached statistical significance (*P*=.053). There also was a near-significant trend between VWF antigen level and methylation percentage within the mutation-bearing, low-expression subset at CpG4 (*P*=.064).

The researchers concluded that this is the first study to demonstrate a possible epigenetic explanation for variance in the severity of VWD. Although the data did not achieve statistical significance, there was a trend toward higher methylation associated with low antigen levels in individuals with the C4120T mutation at 2 CpG sites. The researchers emphasized that studies with larger numbers of individuals are needed.

Kuldanek SA, Venkataraman S, Randall W, et al. Epigenetic regulation of von Willebrand factor gene expression may contribute to von Willebrand disease severity [ASH abstract 470]. *Blood*. 2014;124(21)(suppl).

Risk of Ischemic Stroke Elevated With Low ADAMTS13 Activity

The risk of ischemic stroke is elevated in patients with low ADAMTS13 activity, according to a recent study, and further elevated in those who also have high levels of VWF antigen. ADAMTS13 is a metalloprotease enzyme that cleaves VWF multimers, downregulating their activity in platelet aggregation.

Dr Michelle Sonneveld of Erasmus University Medical Center in Rotterdam, the Netherlands, and colleagues conducted a prospective study of the relationship between ADAMTS13 activity, VWF antigen levels, and ischemic stroke among participants in the Rotterdam Study, a cohort study of adults aged 55 years and older. The researchers included 5941 people who did not have a history of stroke or transient ischemic attack. Blood drawn at baseline was used to measure ADAMTS13 activity with the FRETS-VWF73 assay and VWF antigen levels with the enzyme-linked immunosorbent assay (ELISA).

After an average follow-up of 9.5 years, 306 patients were definitively diagnosed with an ischemic stroke. After adjusting for cardiovascular risk factors, the researchers found that the risk of ischemic stroke was higher for people whose ADAMTS13 activity was in the lowest quartile than in the highest quartile (hazard ratio [HR], 1.65; 95% CI, 1.16-2.23). The risk of ischemic stroke was even higher in people with low ADAMTS13 activity and high VWF antigen levels compared with those who had high ADAMTS13 activity and low VWF antigen levels (HR, 3.51; 95% CI, 1.60-7.70).

The researchers concluded that low ADAMTS13 activity predicts the risk of ischemic stroke, independently of age, sex, and established cardiovascular risk factors. This risk was further elevated in individuals who had both low ADAMTS13 activity and a high VWF antigen level.

Sonneveld MAH, de Maat M, Portegies MLP, et al. 113 Low ADAMTS13 activity is a strong risk factor for ischemic stroke: a prospective cohort study - the Rotterdam study [ASH abstract 113]. *Blood*. 2014;124(21)(suppl).

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Waldenström Macroglobulinemia
Pashtoon Murtaza Kasi, MD, Stephen M. Ansell, MD, PhD, and Morie A. Gertz, MD, MACP

Optional Link

Mantle Cell Lymphoma: State of the Art
Alan P. Skarbnik, MD, and Andre H. Goy, MD

Optional Link

January Columns

In Situ Vaccination as a Therapy for Low-Grade Lymphoma
Joshua Brody, MD

Extending Endocrine Therapy in Women With Hormone Receptor–Positive Breast Cancer
Paul E. Goss, FRCP, MB BCh, PhD

Use of Predictive Biomarkers in Phase 2 Trials
Janet E. Dancey, MD

Understanding Bleeding in Ebola Virus Disease
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Video of the Week

EDITOR'S CORNER

I had brought a red from Maremma and a lovely prosecco to celebrate the stars coming into alignment—those being the Star of David and that of Bethlehem, given that Hanukkah and Christmas abut this year. It was time for our book club. I selected the volume after reading an interview in the New York Times Book Review with Francis Collins, director of the National Institutes of Health, who cited The Creative Destruction of Medicine by cardiologist Eric Topol as his favorite book of the year. READ MORE

In This Issue

Waldenström Macroglobulinemia
Mantle Cell Lymphoma
Fetal and Neonatal Immune Cytopenias
Low-Grade Lymphoma
Hormone Receptor–Positive Breast Cancer
Predictive Biomarkers in Phase 2 Trials
Ebola Virus Disease

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