Highlights in hemostasis

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SUMMARY

This article will briefly summarize the key data presented at ASH 2017 related to hemostasis. In total, seven abstracts will be discussed.

(BELG J HEMATOL 2018;9(1):19-21)

A RANDOMIZED, OPEN-LABEL, BLINDED OUTCOME ASSESSMENT TRAIL EVALUATING THE EFFICACY AND SAFETY OF EDOXABAN VERSUS DALTEPARIN FOR VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER: HOKUSAI VTE-CANCER STUDY

Treatment of cancer-associated venous thromboembolic events (VTE) is challenging because of a high risk of recurrent VTE and major bleeding events in these patients. Current guidelines recommend the use of low molecular weight heparin (LMWH) for 6 months, but the benefit-risk profile after 6 months is uncertain. This randomized, open-label, non-inferiority clinical trial aims to evaluate the hypothesis that edoxaban is non-inferior to dalteparin in cancer patients with acute symptomatic or incidental VTE.[1] Patients were randomized to receive either LMWH during a minimum of 5 days followed by edoxaban 60 mg once daily or dalteparin 200 units per kg once daily for one month followed by 150 units per kg. 1,050 patients were enrolled and randomized to receive edoxaban (525 patients) or dalteparin (525 patients). At entry, 63% had a pulmonary embolism whereas the remainder had isolated deep-vein thrombosis. 67% had symptomatic VTE. Recurrent VTE or major bleeding occurred in 67 of 522 patients (12.8%) on the edoxaban arm and in 71 of 524 patients (13.5%) in the dalteparin arm (HR with edoxaban [non-inferiority], 0.97; 95%CI, 0.70 to 1.36; P=0.0056). Analyzed separately, recurrent VTE occurred less frequently in the edoxaban arm compared to the dalteparin group (-3.8%; 95%CI, -7.1 to -0.4), whereas bleeding events occurred more frequently with edoxaban compared to dalteparin (3.1%, 95%CI, 0.5 to 5.7). However, the frequencies of severe major bleeding events were similar between arms (12 patients in each group). Finally, survival at 12 months free of major bleeding events or VTE was similar between arms (edoxaban 55.0%; dalteparin 56.5%). In summary, oral edoxaban for up to 12 months was shown to be non-inferior to dalteparin in cancer-patients with VTE.[1]

HAVEN 2: EFFICACY, SAFETY AND PHARMACOKINETICS OF ONCE-WEEKLY PROPHYLACTIC EMICIZUMAB (ACE910) IN PEDIATRIC PATIENTS (<12 YEARS) WITH HEMOPHILIA A WITH INHIBITORS: INTERIM ANALYSIS OF SINGLE-ARM, MULTI-CENTER, OPEN-LABEL, PHASE 3 STUDY

Emicizumab is a bispecific-humanized monoclonal antibody that bridges FIXa to FX and restores FVIIIa function. Earlier clinical data with emicizumab have been promising and demonstrated its efficacy and safety. During ASH 2017, updated results of the HAVEN 2 trial were presented. The HAVEN 2 trial (NCT02795767) analyzes the use of emicizumab as prophylaxis treatment, in patients with hemophilia A with inhibitors aged 2-12 years, previously treated with bypassing agents.[2] This updated analysis includes 60 patients with a median observation time of 9 weeks. Overall, 54 of 57 patients (94.7%) had no treated bleeds. Only 3 treated bleeds were reported and only one of the 3 bleeds was spontaneous. In total, 37 of 57 patients (64.9%) reported

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Conflict of interest: The selection of the abstracts discussed here is the sole responsibility of the author and was not influenced by third parties.

no bleeds. 23 patients were followed for more than 12 weeks and were included in the annualized bleed rate population. The annualized bleed rate was 0.2 (95%CI 0.06; 0.62) for treated bleedings. Health related quality of life and caregiver burden were also considerably improved. Emicizumab was well tolerated (most common side effects: viral upper respiratory tract infection, injection site reaction). As such, HAVEN 2 is the largest clinical trial in pediatric patients with hemophilia A with inhibitors. This updated analysis demonstrates that emicizumab prophylaxis reduces the incidence of bleeding and that the treatment was well tolerated in this population.[2]

SEX MATTERS: THE HORMONAL MILIEU REGULATES THROMBOSIS

Analyses of platelet mRNA of participants of the Framingham study revealed a relationship between cardiovascular risk factors and platelet mitochondrial related transcripts in humans. A correlation has been particularly highlighted between the mitochondrial protein optic atrophy-I (OPA1) transcript and the occurrence of coronary heart disease and diabetes. OPA1 mRNA was also found to be increased in females, particularly during the 3rd trimester of pregnancy, in correlation with increased platelet aggregation. These results suggest a relationship between OPA1 activity, estrogens and platelet activation. A murine model with platelet-restricted deletion of OPA1 was used to further elucidate this association.[3] Research demonstrated a decreased risk of thrombosis in female mice with OPA1 deficient platelet that was reversed by gonadectomy. In contrast, OPA1 deletion in mice increased the risk of thrombosis but the transfer of OPA1-deficient platelets into a platelet-depleted female reversed the pro-thrombotic risk. To conclude, experiments in a murine model support the hypothesis that a direct interaction exists between the platelet genotype and the systemic milieu. Additionally, preserving OPA1 might be protective in males, whereas OPA1 expression in females might promote platelet hyper-activation.[3]

INITIATION OF SURFACE-MEDIATED THROMBOSIS EVENTS

Factor XII (FXII) and prekallikrein (PK) bind on biological and non-biological surfaces and trigger contact activation by reciprocal activation. Activated FXII and activated kallikrein are respectively involved in the coagulation cascade (activation of FXI) and in inflammation. The contact activation pathway is of interest given its contribution to thrombosis and inflammation. However, currently little is known on the triggers that initiate FXII and PK reciprocal activation. FXII contains a protease domain that is homologous to the protein domain of tPA and urokinase, two molecules that have activity in their precursor forms (i.e. in contrast to trypsin-like serine proteases in which activation requires at least one internal proteolytic events). These findings form the basis for the hypothesis that FXII expresses activity in its precursor form and that activity could be a trigger for contact activation.[4] To assess this hypothesis, FXII and PK variants that cannot be activated were created by replacing residues involved in their activation. The FXII variant was shown to activate prekallikrein, FXI and FXII, with weaker activity than normal FXII. Similarly, the PK variant activated FXII. These experiments demonstrate that FXII and PK have intrinsic activities and can trigger contact activation without pre-existing activated FXII or activated kallikrein.[4]

POLY-P: MODULATOR OF HEMOSTASIS, THROMBOSIS AND INFLAMMATION

Polyphosphates (poly-P) are ubiquitously found in biology and have been highly studied in microorganisms (but less in humans). Recent studies demonstrate a role for poly-P in many processes, with a particular funtion in the modulation of hemostasis and inflammation. In fact, it has been demonstrated that poly-P is a major component of dense granules in human platelets that are secreted during platelet activation.[5] After secretion, Poly-P has numerous functions on hemostasis: it accelerates factors V and XI activation, inhibits anticoagulant activity of TF pathway inhibitor and enhances fibrin clot structure. Therefore, poly-P could be a potential antithrombotic drug target and which might provide a novel mechanism to inhibit blood coagulation. Of note, a potential benefit of this anticoagulation pathway might be a reduction of bleeding risk compared to conventional anticoagulants.[5]

PHE174-MUTATED-HUMAN FACTOR X AS BYPASSING AGENT TO THE DIRECT FXA INHIBITORS

Activated factor X (FXa) inhibitors have rapidly emerged as preferred anticoagulation therapy. However, to date, no reversal agents are available to restore hemostasis in case of bleeding events. Direct FXa inhibitors block catalytic activity by high affinity occupation of the FXa active site. Analyses of the X-ray crystal structure of the complexes apixaban-FXa and rivaroxaban-FXa demonstrate the occupation of the FXa substrate binding S1 and S4 subsites.[6] Molecular Dynamics simulation of the complex FXa-apixaban confirmed the stabilization of apixaban in the S4 subsite and identified two residues (Tyr99 and Phe174) of the S4 pocket that have close range contacts with apixaban. To assess the impact of these 2 residues to apixaban binding, different human FXa variants were created. The mutation of Tyr99 or Phe174 led to a de-

creased sensitivity for apixaban by approximately 8-fold. A FX clotting activity assay demonstrated a marked decrease in FX activity with the Tyr99 mutant, whereas the clotting activity was almost unaffected by the Phe174 substitution. Therefore, human FXa variants with Phe174 mutation represent a promising target to abrogate binding of inhibitors and restore impaired hemostasis following FXa inhibition.[6]

MAGNETICALLY POWERED MICROBOTS: A NOVEL APPROACH TO THROMBOLYSIS?

The current treatment for thrombotic strokes includes fibrinolytic drugs and thrombectomy using a catheter. These two strategies are successful, but also have their limits. Fibrinolytic drugs come with a risk of intracranial hemorrhages, whereas catheter-based thrombectomy is invasive and can leave residual prothrombotic material. Additionally, these 2 methods have limited/restricted efficacy in small vessel occlusions. Recent experiments describe a new approach to treat thrombotic events: the injection of individual super-paramagnetic particles functionalized with fibrinolytic drugs (tPA).[7] After application of a rotation magnetic field, these particles self-assemble *in situ* by rolling into microbots similar to microwheels, capable of translating to thrombi. In this method, the functionalized particles can be introduced at sub-therapeutic concentration because particles accumulate to therapeutic levels at the thrombus periphery. In addition to the biochemical action, microwheels possess a mechanical action by drilling into thrombi (both in platelet-rich and fibrin-rich thrombi). Results are promising and demonstrate faster reperfusion by the functionalized microwheels than what is seen with soluble tPA. This method combines mechanical and biochemical actions and could reduce the risk of bleeding compared to classical fibrinolytic agents.[7]

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