Thrombosis & Haemostasis Research Review™

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In this issue:

Abbreviations used in this issue:

alloHCT = allogeneic hematopoietic cell transplantation; **aPTT** = activated partial thromboplastin time; **CAD** = coronary artery disease; **CI** = confidence interval; **CMB** = cerebral microbleed; **COVID-19** = coronavirus disease 2019; **DOAC** = direct oral anticoagulant; **DVT** = deep venous thrombosis; **HR** = hazard ratio; **ICH** = intracranial haemorrhage; **ISTH** = International Society of Thrombosis and Haemostasis; **ITP** = immune thrombocytopenia; **LMWH** = low-molecular-weight heparin; **MRI** = magnetic resonance imaging; **OR** = odds ratio; **SWI** = susceptibility-sensitive MRI; **Tpo-RA** = thrombopoietin receptor agonist; **TTP** = thrombotic thrombocytopenic purpura; **UFH** = unfractionated heparin; **VTE** = venous thromboembolism.

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Welcome to the latest issue of Thrombosis and Haemostasis Research Review.

In this issue we look at results from the DIVERSITY trial that finds a dabigatran dosing algorithm non-inferior to standard of care anticoagulation for the treatment of acute venous thromboembolism (VTE) in paediatric patients. We review a cohort study from the Montefiore Medical Centre, United States, that analyses the effect of anticoagulation in coronavirus 2019 disease (COVID-19) on mortality and discuss the ramifications of the prospective ROADMAP-CAD trial which provides a score using coagulation parameters to predict severity of coronary artery disease (CAD) that is substantiated by angiography in patients eligible for CAD assessment and could be useful in screening patients for further intervention. We also look at a multicentre retrospective study that investigated the use of thrombopoietin receptor agonists for refractory immune thrombocytopenia (ITP) during pregnancy and a two-centre cohort study that compared the incidence of intracranial haemorrhage in cancer patients with brain metastases treated with direct oral anticoagulants (DOACs) versus low molecular weight heparin (LMWH) for VTE or atrial fibrillation. Finally, two MRI-based studies investigate the risk of cognitive impairment in thrombotic thrombocytopenic purpura (TTP) and the prevalence of occult cerebral microbleeds in adults with ITP.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Professor Harshal Nandurkar

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Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY)

Authors: Halton J et al., for the DIVERSITY Trial Investigators

Summary: The randomised, controlled, open-label, phase 2b/3, non-inferiority DIVERSITY trial investigated the suitability of a dabigatran dosing algorithm for paediatric patients with VTE. A total of 328 patients requiring anticoagulation therapy for ≥ three months following initial parenteral anticoagulation were accrued between February 2014 and November 2019 from 65 centres across 26 countries predominantly in North and South America and Europe and a total of 267 randomised. Patients were administered standard of care anticoagulation (LMWH, unfractionated heparin [UFH], vitamin K antagonists or fondaparinux; n=90) or an age- and weight-adjusted oral dabigatran dosing regimen (n=177). After a median exposure of 85 days, dabigatran met the prespecified absolute 20% difference in the primary composite endpoint (proportion of patients achieving complete thrombus resolution plus freedom from recurrent VTE and VTE-related death) to establish non-inferiority versus standard of care (standard of care vs dabigatran: 42% vs 46%; Mantel-Haenszel weighted difference, −0·04; 90% confidence interval [CI], −0.14 to 0.07; $p<0·0001$ for non-inferiority). No significant difference was found between the arms in secondary end points including on treatment bleeding events (24% vs 22%; hazard ratio [HR] 1.15; 95% CI, 0.68-1.94; $p=0.61$), major bleeding events (2% vs 2%; HR 0.94; 95% CI, 0.17-5.16; $p=0.95$) or serious adverse effects (20% vs 13%). The authors concluded that in paediatric patients with VTE requiring long-term anticoagulation age- and weight-adjusted dabigatran offers an alternative to the current standard of care.

Comment: Anticoagulation in children is extrapolated from adult clinical trial data. Prior trials with dabigatran using an age-adjusted and weight-adjusted dosing nomogram to account for renal function in children showed similar safety, pharmacokinetics and pharmacokinetic–pharmacodynamic relationships to those seen in adults with VTE. Standard of care comprised LMWHs, UFH, vitamin K antagonists or fondaparinux, used according to investigators' judgment and standard clinical practice. Dabigatran (capsules, pellets or oral solution) was dosed per an age-adjusted and weight-adjusted nomogram according to Hayton, whereby estimated renal function is derived from age and weight to achieve similar exposure to adult populations treated with dabigatran. The study treatment period was three months, and patients were followed up for an additional month. The composite primary endpoint (complete thrombus resolution, freedom from recurrent VTE and freedom from VTE-related death) was significant for non-inferiority. Therefore, dabigatran could be considered as an alternative to standard of care for treatment of acute VTE in children.

Reference: Lancet Haematol 2021;8(1):e22-33

Abstract

Prospective assessment of biomarkers of hypercoagulability for the identification of patients with severe coronary artery disease

Authors: Gerotziafas G et al.

Summary: Results from the ROADMAP-CAD study published in *Clinical and Applied Thrombosis/Hemostasis* indicate that two measures of hypercoagulability - phospholipid-dependent clotting time and thrombin peak - are potential biomarkers of the severity of coronary artery disease (CAD). The pilot study analysed three markers of hypercoagulability in platelet-poor plasma from patients referred to coronary angiography (n=66). Significantly reduced thrombin generation lag time (4.7 vs 2.5 min; $p<0.0001$), shorter phospholipid-dependent clotting time (55.0 vs 62.8s; $p=0.0001$) and higher D-dimer levels (0.509 vs 0.309 µg/ml; $p=0.038$) were observed in patients with CAD compared to controls.

Comment: ROADMAP-CAD (pROspective risk Assessment anD bioMArkers of hypercoagulability for the identification of Patients with severe CAD) was a prospective study in patients who were eligible for coronary angiography for CAD assessment. The primary study end-point was the presence of significant CAD (luminal diameter stenosis ≥ 50%). This study is noteworthy as it creates a score using coagulation parameters to predict severity of CAD that is substantiated by angiography. The data led to the derivation of a new score which combines phospholipid-dependent clotting time and thrombin generation parameters and accurately stratifies patients as high or intermediate/low risk for significant CAD. The sensitivity and the specificity of the new score is 71.4% and 61.8%. Markers of coagulation activation represent cellular derived hypercoagulability and could be useful in screening patients for further intervention.

Reference: Clin Appl Thromb Hemost 2020;26:1076029620964590
Abstract

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Independent commentary by Prof Harshal Nandurkar, who is the Director of the Alfred Cancer Program and Clinical Haematology, Head of the Australian Centre for Blood Diseases. He is the past President of the Thrombosis and Haemostasis Society of Australia and NZ and past Vice President of the International Union of Angiology (Australian Chapter).

Anticoagulation in COVID-19: Effect of enoxaparin, heparin, and apixaban on mortality

Authors: Billett H et al.

Summary: This single-centre, cohort study from the Montefiore Medical Centre, New York, United States, investigated the association between anticoagulation and survival in patients with COVID-19. Analysis was based on a total of 3,625 hospitalised patients with moderate or severe COVID-19 who received anticoagulation within 48 hours of hospitalisation. The prophylactic use of apixaban and enoxaparin were associated with significant reduction in the odds of mortality with reductions of 54% and 51%, respectively (odds ratio [OR] 0.46; $p=0.001$ and OR 0.49; $p=0.001$) whilst therapeutic apixaban decreased the odds of death by 43% (OR 0.57; $p=0.006$) compared to no use of anticoagulant. Subgroup analysis showed a linear relationship between D-dimer levels and magnitude of benefit with anticoagulation therapy with no benefit observed in patients with D-dimer levels < 1 µg/mL and the greatest advantage seen in patients with D-dimer levels > 10 µg/mL.

Comment: It is now well known that activation of coagulation is a prominent feature of COVID-19, particularly in severe illness and is a predictor of poor outcomes. There has been a lot of emphasis on anticoagulation, particularly as prophylaxis to improve survival. Generally, heparin has been the intervention of choice. In this large retrospective analysis, 58.8% received standard thromboprophylaxis, 4.0% received high-dose prophylaxis, and 19.6% received therapeutic anticoagulation. UFH was preferred for prophylaxis and apixaban for therapeutic anticoagulation (this could be specific to Montefiore Medical Centre Hospital in the Bronx). When compared with no anticoagulation at baseline, apixaban prophylaxis, apixaban therapy, and enoxaparin prophylaxis were all associated with a significant decrease in mortality. UFH was not associated with significant benefit, either as prophylaxis or therapy. Raised D-dimer levels maintained an association with poor outcomes. Interestingly, for D-dimer levels < 1 µg/mL, there was no benefit associated with any anticoagulation. The benefit on mortality with enoxaparin as prophylaxis and apixaban both as prophylaxis and therapy (but not UFH and enoxaparin as therapy) was seen only in patients with D-dimer > 1 µg/mL.

Reference: Thromb Haemost 2020;120(12):1691-99
Abstract

Ciraparantag, an anticoagulant reversal drug: mechanism of action, pharmacokinetics, and reversal of anticoagulants

Authors: Ansell J et al.

Summary: This study by Ansell et al in *Blood* examined the characteristics of ciraparantag, a novel anticoagulant reversal drug. Pre-clinical research using dynamic light-scattering methodology demonstrated the specificity of the noncovalent bond between ciraparantag and UFH, LMWH and DOACs in aqueous solution. Animal (rat) and phase 1 first in-human (n=70) pharmacokinetic analysis of ciraparantag at doses of between 5 mg and 300 mg revealed a rapid onset of action, widespread distribution and a 12-19-minute half-life. *In vivo* rat models of bleeding (tail transection and liver laceration) showed significantly reduced blood loss when ciraparantag was used to reverse bleeding from heparin, enoxaparin, dabigatran, apixaban, edoxaban or rivaroxaban. Ciraparantag has progressed to phase 2 trials in healthy volunteers.

Comment: Ciraparantag is a small molecule under development as an anticoagulant reversal agent. Ciraparantag binds to heparins and the DOACs through noncovalent charge-charge interactions. Ciraparantag arose from a program of intentional molecular design that searched for molecules that would bind to free UFH through a noncovalent, charge-charge interaction and modelling predicted binding to dabigatran, apixaban, edoxaban and rivaroxaban. There was no binding with coagulation factors and several commonly used drugs in cardiology, diabetes and epilepsy. Ciraparantag is administered as an intravenous infusion. Pharmacokinetic data from 70 subjects shows dose-proportional increment in blood levels. Maximum serum ciraparantag concentrations occurred within 5 to 9 minutes, then rapidly declined below the limit of quantification by two hours after drug administration. The half-life of ciraparantag ranged from 12 to 19 minutes across cohorts. Pharmacodynamic activity was tested by the ability to control bleeding after tail tip transection in rats after exposure to anticoagulants and demonstrated dose-dependent reduction of bleeding after fixed-dose exposure to edoxaban, dabigatran, rivaroxaban and apixaban. After a dose of 1 mg/kg IV UFH and enoxaparin (10 mg/kg IV), ciraparantag significantly reduced blood loss, whereas protamine sulphate did not. Interestingly, protamine significantly reduced activated partial thromboplastin time (aPTT) to baseline, whereas ciraparantag did not significantly decrease aPTT levels. Thus, the lack of effect on coagulation assays (anti-FXa activity assay and aPTT) of ciraparantag is discordant with the noted effect of achieving haemostasis. These and other data indicate that some assays may not be appropriate for monitoring the effectiveness of ciraparantag. Haemostatic reversal effect of ciraparantag was also confirmed in a rat model of liver trauma and bleeding post edoxaban exposure. Additional phase 2 trials are in progress before phase 3 studies to reverse anticoagulation in the context of bleeding or urgent surgery.

Reference: Blood 2021;137(1):115-25
Abstract

Use of thrombopoietin receptor agonists for immune thrombocytopenia in pregnancy: results from a multicentre study

Authors: Michel M et al.

Summary: This observational multicentre study provides preliminary evidence to support the temporary off-label use of thrombopoietin receptor agonists (Tpo-RAs) for severe and/or refractory ITP during pregnancy. A total of 15 women (17 pregnancies) with either primary or secondary ITP who received eltrombopag (n=8; median dose 50 mg) or romiplostim (n=7; median dose 7 µg/kg) during pregnancy were included in the study. Patients had received a median of three prior lines of therapy including five who had received a splenectomy. All patients were refractory to at least corticosteroids and intravenous immunoglobulin. No serious adverse events were reported and there were no clinically symptomatic thromboembolic events. There was no foetal loss and 71% of pregnancies were carried to term. One baby with Trisomy 8 died at seven days of age but the death was not attributed to Tpo-RA exposure. The response rate was 77% and included six complete responses. Three patients did not respond to Tpo-RA treatment. The authors acknowledged a possible underestimation of placental thrombosis due to the small sample size but concluded that the use of Tpo-RA during pregnancy may be an option for women with refractory ITP who require treatment due to bleeding, profound thrombocytopenia or in preparation for delivery.

Comment: This was an observational multicentre international study established by the French reference centre for adult immune cytopenias. In total, data from 15 women, 17 pregnancies, and 18 neonates were analysed. Ten of 15 patients had pre-existing chronic ITP; 1 patient had persistent ITP at pregnancy onset; and ITP was diagnosed during pregnancy in four cases. The median number of treatment lines before the use of Tpo-RAs was 3.0 (range, 2-7 lines), including splenectomy for five patients. Patients were exposed during pregnancy to either eltrombopag (n=8; median dose, 50 mg [range, 25-100 mg]) or romiplostim (median dose, 7 µg/kg [range, 3-10 µg/kg]). One patient was successively treated with romiplostim during a first pregnancy and was receiving eltrombopag when a second unexpected pregnancy occurred; eltrombopag was continued for 39 weeks until delivery and beyond. Median time of exposure to Tpo-RAs during pregnancy was 4.4 weeks (range, 1-39 weeks). In 10 out of 17 pregnancies, Tpo-RAs were started beyond week 32 of gestation in preparation for delivery, because platelet count was $<20x10^9$/L. Four patients with chronic ITP were receiving Tpo-RAs when they became pregnant, and in three cases, Tpo-RAs were started early in the third trimester for symptomatic ITP not responding to standard therapy. Apart from mild headache, no clinically symptomatic thromboembolic events occurred and there was no foetal loss. Thrombocytopenia was found in six of 14 neonates. Ten patients responded with complete response in six. Thrombocytosis was observed in only one neonate. There were no differences between eltrombopag and romiplostim. The note of caution in the interpretation of this study is that Tpo-RAs were initiated in only two women at eight weeks of pregnancy (for 12 weeks of romiplostim) and in one woman at four weeks pregnancy (for 9 weeks romiplostim) and the remaining women were around 30 weeks gestation at initiation. So, the impact on foetal development is still an open question.

Reference: Blood 2020;136(26):3056-61
Abstract

Cerebral MRI findings predict the risk of cognitive impairment in thrombotic thrombocytopenic purpura

Authors: Alwan F et al.

Summary: This study by Ferras Alwan and colleagues utilised cerebral magnetic resonance imaging (MRI) to elucidate the long-term impact of acute neurological symptoms and their etiology in patients with congenital or idiopathic TTP. Analysis of 131 patients following an acute episode of TTP who were experiencing severe headaches or neurological symptoms found atypical imaging in over half the patients (56%). Atypical imaging was significantly more common in patients experiencing neurological symptoms than in patients with headaches (80% vs 18%; $p<0.0001$) and was associated with cognitive impairments including decreased verbal and performance IQs (85 vs 99; $p=0.02$ and 83 vs 100; $p=0.02$; respectively). Abnormalities in the frontal lobe including hyperintense white matter lesions were more common in patients with intellectual impairments (67% vs 19%; $p=0.02$). Self-reported mental health comorbidities were common in this population with 65% suffering from depression and 55% anxiety.

Comment: The results of this study highlight the importance of recognising cognitive impairments as long-term comorbidities and suggests the importance of following neuropsychiatric status in TTP patients with cerebral MRI abnormalities at the first presentation. This is the largest study to review the neuro-radiological findings seen in TTP and to correlate these with a comprehensive neuropsychology assessment for patients with persisting cognitive symptoms. Eighteen percent of patients whose only symptom was headaches had an abnormal cerebral MRI, in comparison to 80% of patients who presented with more quantifiable symptoms such as seizures or visible neurological symptoms. The MRI findings at the acute phase and neuropsychology assessments at the remission phase revealed a link between hyperintense white matter lesions, mainly seen in the frontal and supratentorial regions in MRI images, and severe cognitive impairment. When considering all patients who underwent neuropsychological evaluation, patients with a normal cerebral MRI scan were found to have scores similar to those seen in normal controls with significantly lower IQ values were seen in patients who had an abnormal MRI. Another point to make is that all patients in this study were managed with plasma exchange and immunosuppressors such as steroids and rituximab. Its hopeful that newer treatments such as von Willebrand factor blockage with caplacizumab early in the disease could reduce thrombosis and ischaemic cell damage in the brain thereby preventing cognitive impairment in remission.

Reference: Br J Haematol 2020;191(5):868-74
Abstract

Safety of direct oral anticoagulant exposure during pregnancy: a retrospective cohort study

Authors: Beyer-Westendorf J et al.

Summary: This retrospective cohort study, published in *The Lancet Haematology* by Beyer-Westendorf et al, found no evidence to support the hypothesis that DOAC exposure in pregnancy confers a high risk of embryopathy. Compilation of case reports from physicians, the International Society of Thrombosis and Haemostasis (ISTH) registry, pharmacovigilance databases of the DOAC manufacturers (Bayer, Boehringer Ingelheim and Daiichi Sankyo), the Teratology Information Service, the German drug authority, the Risk Evaluation and Mitigation Strategy Review, the European Medicines Agency and a literature review identified 614 unique cases of DOAC exposure (rivaroxaban 82%, apixaban 8%, dabigatran 6% and edoxaban 4%) during pregnancy between February 2007 and July 2020. The median duration of exposure was 5.3 weeks into pregnancy. Analysis of pregnancy outcome data on just over half the cases (55%) found a 6% rate of foetal abnormalities, 4% of which were adjudicated by the European Concerted Action on Congenital Anomalies and Twins classification as major birth defects that may be related to DOAC exposure.

Comment: This is the largest and most detailed dataset on this topic and may guide patient counselling in situations of DOAC exposure. This report has to be placed in the context of the incidence of coumarin embryopathy, which is estimated to be about 7% and abnormalities include midface hypoplasia, ocular malformations, and skeletal abnormalities. But the true rates of coumarin-associated embryopathy are not clear as cases of miscarriage or elective termination are not known. Here, the rates of any foetal abnormality were 6% and abnormalities potentially attributable to DOACs were 4% (95% CI, 2-6). The embryotoxic effects of DOACs were very variable and did not follow a distinct pattern, which would be expected from harmful drug exposures in the first or second trimester, as shown in the case of warfarin embryopathy. There were 74 (22%) miscarriages overall of which 28% were in the first trimester, 7 (9%) occurred in the second trimester, and there were 46 miscarriages (62%) for which information on the trimester was not available. Reasons for 28 (38%) of the 74 elective terminations of pregnancy were attributed to: social reasons (n=12; 16%), fear of DOAC embryopathy (n=6; 8%), and medical reasons (n=10; 14%). The 2016 ISTH guidance is against elective pregnancy termination for fear of DOAC embryotoxicity and the recommendation in favour of close pregnancy surveillance. Obviously, social and other medical reasons also influence the frequency of pregnancy termination.

Reference: Lancet Haematol 2020;7(12):e884-91
Abstract

Intracranial haemorrhage with direct oral anticoagulants in patients with brain metastases

Authors: Leader A et al.

Summary: This international two-centre retrospective cohort study reported in *Blood Advances* found no difference in the incidence of intracranial haemorrhage (ICH) in cancer patients with brain metastases treated with DOAC versus LMWH for venous thromboembolism or atrial fibrillation. Analysis of 96 patients (41 treated with DOACs and 55 with LMWH) found a lower absolute incidence of the 12-month cumulative incidence of any ICH and major ICH in patients treated with DOACs that was not statistically significant (10.1% vs 12.9%; HR 0.77; 95% CI, 0.23-2.59 and 5.1% vs 11.1%; HR 0.45; 95% CI, 0.09-2.21).

Comment: There is increasing use of DOACs in the management of thrombosis occurring in the context of active cancer. VTE may occur due to the thrombophilic effect of cancer and due to immobility, that may go with manifestations of cancer. DOACs are as effective as LMWH; the question of safety - i.e., risk of bleeding - dominates making a preference. Bleeding in brain metastasis due to anticoagulation can independently dictate cancer outcome due to poor reversibility. This is two-centre retrospective cohort study in Petah Tikva, Israel and Amsterdam, The Netherlands. More DOAC-treated patients had a high PANWARDS (platelets, albumin, no congestive heart failure, warfarin, age, race, diastolic blood pressure, stroke) risk score than LMWH patients (26 of 41 [63.1%] and 25 of 55 [45.5%], respectively; p=0.097). Interestingly, most DOACs were started prior to brain metastases diagnosis, and most LMWH treatments were initiated thereafter. It is likely that physicians may prefer to continue DOACs than initiate DOAC treatment in this setting indicating the physicians' preference of LMWH for acute events that warrant anticoagulation. While this study was not powered to detect bleeding risk with DOACs, it does show that DOACs and LMWH have comparable safety and that DOACs are an acceptable option in patients with metastatic brain tumours. One caveat is that this study included few patients with metastatic melanoma or renal cell carcinoma, which are associated with a higher risk of ICH.

Reference: Blood Adv 2020;4(24):6291-97
Abstract

Identification of occult cerebral microbleeds in adults with immune thrombocytopenia

Authors: Cooper N et al.

Summary: Nichola Cooper and colleagues from Hammersmith Hospital, London, United Kingdom, conducted a single-centre, cross-sectional prospective study to examine occult cerebral microbleeds (CMBs; also known as microhaemorrhages) in adults with ITP (nadir platelet counts < 30x 10^9/L). Analysis was based on a total of 50 patients with ITP and 18 healthy controls with microbleeds detected noninvasively in the brain using susceptibility-sensitive MRI (SWI; protocol, repetition time/echo time= 28 ms/20 ms; flip angle=15; 0.5x0.5 mm in-plane resolution; 1 mm slice thickness; 35x45 cm FOV). Occult CMBs, mostly between one to five mm in diameter, were detected variably distributed through the brain in 43% of patients with ITP and 0% of healthy controls. There was an inverse relationship between proportion of patients with CMBs and nadir platelet count with 60% of patients with a nadir platelet count of < 5x10^9/L having a CMB (0% CMBs in patients with nadir platelet count ≥ 15x10^9/L; 22%, 10-14x10^9/L, 36%, 5-9x10^9/L). The presence of CMBs was significantly associated on univariable and multivariable analysis with longer disease duration (p= 7x 0^{-6}), lower platelet count, both nadir and at time of MRI (p=0.005 and p=0.029) and higher organ bleeding score (p=0.028). The authors concluded that CMBs may constitute a biomarker of bleeding risk in ITP.

Comment: This study used SWI to document CMBs. Hemosiderin-laden macrophages (that phagocytise escaped red cells) may persist indefinitely and are detected by SWI as small black dots. In most patients, significant bleeding is rare unless the platelet count is, <20x10^9/L and may be absent or minimal even with a count as low as 5-10x10^9/L; while in other patients, similar counts may be associated with extensive purpura and mucosal haemorrhage, particularly at diagnosis. Intrinsic haemostatic activity of platelets, endothelium damage, and inflammation contribute to the unpredictability of the bleeding risk and to the weak correlation with the actual platelet count. The overall bleeding mortality rate in adults is estimated to be approximately 1% to 2%. However, the risk is much higher, up to 10% to 15%, in older unresponsive patients. The absence of CMBs in patients with a platelet nadir ≥15x109/L and in all 18 healthy controls clearly substantiates ITP as the causative or permissive factor for CMBs. Prevalence of CMBs was also associated with lower platelet counts at the time of SWI and with higher organ bleeding scores, but not with mucosal and skin bleeding scores or with the number of previous treatments, age or gender. There was no correlation with neurological outcomes. It lays the foundation for more longitudinal studies and clinical correlation.

Reference: Blood 2020;136(25):2875-80
Abstract

A coagulation defect arising from heterozygous premature termination of tissue factor

Authors: Schulman S et al.

Summary: Sol Schulman et al report the discovery and pre-clinical evaluation of a novel coagulation defect in tissue factor. A patient with unexplained bleeding but normal haematological laboratory evaluation underwent whole genome sequencing where a heterozygous frameshift variant (p.Ser117HisfsTer10) in the tissue factor gene *F3* was found. *In vitro* characterisation of the variant in differentiated CRISPR-edited human induced pluripotent stem cells revealed that translation resulted in a truncated tissue factor protein that was incapable of inhibition of factor Xa and thrombin generation. Tumour factor was also shown to be haploinsufficient. Excessive bleeding times, impaired clot formation and increased mortality following injury were observed in *in vivo* studies of F3+/– mice. The authors estimated that heterozygous tissue factor deficiency is present in 1:25,000 people (based on the F3 null allele frequency of $2x10^{-5}$ in the gnomAD database). They concluded that coagulation initiation is impeded by tissue factor deficiency, which cannot be identified by routine clinical laboratory tests.

Comment: This is very elegant paper that takes identification of a putative defect in the tissue factor gene and conducts a thorough laboratory analysis to identify mechanisms of coagulopathy; it uses a number of *in vitro*, cellular and mouse studies. The summary of this work for the clinical audience is as follows. Tumour factor is cryptic, hidden under the endothelium and hence not visible to normal circulation, unless there is trauma. Hence, it is not quantifiable by a traditional coagulation assay. The identification of a mutation in the tumour factor gene was a result of sequencing 983 individuals with unexplained bleeding disorders. The data presented is from one individual. The genetic defect is a two-nucleotide deletion that results in a premature stop codon and results in a truncated form of tumour factor that has no coagulation activity and the representative mRNA is degraded. This individual was effectively heterozygous for functional tumour factor having one allele generating wild-type tumour factor and one allele generating truncated non-functional tumour factor. The history included menorrhagia, epistaxis, easy bruising and an episode of bleeding following a dental extraction, but was otherwise healthy. Factor VII deficiency is probably the closest comparator to heterozygous tumour factor deficiency (homozygous deficiency of both tumour factor and VII is lethal). FVII deficiency is heterogeneous in its presentation with only a minority of individuals developing bleeding phenotype. Hence, mutations in other genes influence the phenotype. As there are no laboratory tests to screen individuals for tumour factor deficiency, the take-home message is to include the tumour factor gene in any sequencing panels for investigating unexplained bleeding.

Reference: J Clin Invest 2020;130(10):5302-12
Abstract

HIGH-2-LOW risk model to predict venous thromboembolism in allogeneic transplant patients after platelet engraftment

Authors: Martens K et al.

Summary: This publication in *Blood Advances* details the creation and validation of a novel risk assessment model to identify patients who will derive the most benefit from early thromboprophylaxis after allogeneic hematopoietic cell transplantation (alloHCT). A modelling cohort of 1,703 patients who underwent alloHCT at Fred Hutchinson Cancer Research Centre between 2006 and 2015 and had not received anticoagulation at day 30 constituted the study cohort for the risk assessment model. Seven predictors of VTE - history of catheter-related deep venous thrombosis (DVT), inpatient at day 30, grade 3-4 graft-versus-host disease, history of pulmonary embolism or lower-extremity DVT, lymphoma diagnosis, obesity with body mass index ≥35 kg/m^2, and white blood cell count ≥11 × 10^9/L – constituted the HIGH2-LOW model to stratify patients into three categories according to risk. At day 30-100 post-transplant the incidence of VTE in high-, intermediate- and low-risk patients was 10.25%, 3.58% and 1.54%, respectively.

Comment: VTE is relatively common post alloHCT and difficult to manage due to co-existing thrombocytopenia and graft-versus-host disease. As severe thrombocytopenia occurs in the first 30-days post-transplant, pharmacologic thromboprophylaxis is generally not recommended by most consensus guidelines and the use of low-dose anticoagulation for thromboprophylaxis after 30 days, when the majority of patients achieve platelet engraftment, varies significantly. The authors have created a risk assessment model by retrospective analysis of a single institution cohort. Day 100 was taken as the primary time of interest for outcome assessment as most patients are discharged home at this time point but potential VTE outcomes were assessed for 365 days post stem cell infusion. Catheter associated thrombosis was also enumerated along with pulmonary embolism and lower limb DVT. The overall incidence (and rate) of VTE at 100 and 360 days was 4.9% (18.60 per 100 patient-years; n =95) and 8.0% (10.26 per 100 patient-years; n=151), respectively. The risk assessment model used VTE events occurring between day 30 and day 100 (n=56). The variable constituting the risk assessment model are listed above; all were given one point except for history of pulmonary embolism or lower limb DVT, which was given two points. Further validation demonstrated that the observed versus predicted VTE curves overlaid each other in the time-to- event analysis. Incidence of VTE at day 100 was 10.25% in the high-risk cohort (score=2+), 3.58% in the intermediate-risk cohort (score=1) and 1.54% in the low-risk (score=0).

Reference: Blood Adv 2020;5(1):167-75
Abstract

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