Haematology RESEARCH REVIEW™

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Issue 37 – 2021

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Abbreviations used in this issue
BU = Bethesda units
CR = complete remission
DOAC = direct oral anticoagulant
FIX/FVIII/FXI/FXII = factor IX/VIII/XI/XII
INR = international normalised ratio
MPN = myeloproliferative neoplasm
VTE = venous thromboembolism

Welcome to issue 37 of Haematology Research Review.

This issue begins with a systematic review of evidence on the optimal antithrombotic treatment of VTE in patients with MPN, which is based solely on observational studies reporting low certainty for all strategies as there were no randomised controlled trials that met the eligibility criteria. We have also included a review of new anticoagulants that target FXI and FXII. Meanwhile, a retrospective analysis of international pharmacovigilance and published literature data has reported no evidence of embryopathy associated with DOAC use during pregnancy, although shortcomings in the data and how they are currently collected were emphasised. This issue concludes with research reporting on the impact of exposure to hydroxycarbamide (hydroxyurea) before puberty for sickle cell disease on spermatogenesis.

We hope you enjoy the research selected, and we look forward to your comments and feedback.

Kind regards,

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A systematic review of antithrombotic treatment of venous thromboembolism in patients with myeloproliferative neoplasms

Authors: Hamulyák EN et al.

Summary: This was a systematic review and meta-analysis of ten observational studies (most with a high risk of bias and clinical and statistical heterogeneity) evaluating anticoagulant and/or antiplatelet therapy, with or without cytoreduction, in 1295 patients with MPNs who had a history of VTE; no eligible randomised controlled trials were found. The arterial or venous thrombotic event rate during follow-up was 23%. The recurrence risk for patients on oral anticoagulation plus cytoreduction was 16%, with risks for those receiving vitamin K antagonists and DOACs of 18% and 8%, respectively. The reported VTE recurrence rates in analysed patients (n=748) were ≤33% (median 13%), with a rate of 3.2% in 63 cytoreduction-treated patients receiving DOACs. The recurrent VTE risk was consistently lowered when cytoreduction was added to antithrombotic treatments irrespective of type.

Comment (PO): This is a useful review. It supports our local approach but highlights the lack of good-quality evidence on which our treatment strategies in patients with a MPN and a history of (venous) thrombosis are based. The analysis is based on a little over 1000 patients and taken from observational studies. There were no randomised trials. Observed recurrence rates are high and at least 20%, particularly where neither antithrombotic nor cytoreductive therapy is used. As we are already aware, with the standard of care in NZ, the lowest risks of recurrence are achieved using combinations of cytoreduction and anticoagulation. Optimal dosing regimens nonetheless remain unclear. DOACs appear to be effective, including for splanchnic thrombosis, but we lack appropriately powered clinical trials to support current decision making in this area of practice.

Reference: Blood Adv 2021;5:113–21
Abstract

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Independent commentary by Dr Paul Ockelford

Paul Ockelford is a haematologist and Clinical Associate Professor, University of Auckland School of Medicine and Director of both the Adult Haemophilia Centre and Thrombosis Unit at Auckland City Hospital. Paul has particular expertise in haemostasis and thrombosis and consults on a wide range of haematological disorders. He maintains an active research programme in the treatment of venous thromboembolism. Paul is a former chair of the New Zealand Subcommittee on Thrombosis and Haemostasis. He serves on the Medical Advisory panel of the New Zealand Haemophilia Foundation and the National Haemophilia Management Group. Paul acts as a reviewer for a number of medical journals and is an Investigator for a number of international clinical thrombosis trials. He is a former Chairman of the New Zealand Medical Association.

Real-world data demonstrate improved bleed control and extended dosing intervals for patients with haemophilia B after switching to recombinant factor IX Fc fusion protein (rFIXFc) for up to 5 years

Authors: Shapiro A et al.

Summary: These researchers reported on the real-world clinical utility of rFIXFc (recombinant FIX fusion protein) for haemophilia B in 64 patients who had been receiving this treatment on demand or as prophylaxis for a median of 2.7 years in routine clinical practice. For patients who had switched from another prophylactic factor agent with a known dosing interval (n=32), 26 had their initial dosing interval lengthened on rFIXFc. For patients who received rFIXFc prophylaxis from the beginning to the end of the chart review period (n=53), 91% maintained or lengthened their dose interval from the first through to the last rFIXFc dose. Weekly factor consumption decreased by ~50% after rFIXFc prophylaxis was started. There were also decreases in the overall annualised bleed rates, annualised spontaneous bleed rates and annualised joint bleed rates after switching to rFIXFc prophylaxis. All but one of the 31 patients with available data exhibited improved or stable compliance on rFIXFc.

Comment (PO): The pivotal trials for extended half-life rFIXFc (B-Long) demonstrated both effectiveness and safety in previously treated adults and children with severe haemophilia B. This product allows for more individualised dosage regimens. Flexible dosing reduces the treatment burden, improves compliance with prophylaxis and leads to improved outcomes. The benefits observed across all age groups is confirmed in this retrospective analysis funded by the manufacturer. Dose frequency was weekly or less in 93%. The observations are similar to the reported Australian experience also using Alprolix®. One difference is the factor reduction of 4 iu/kg/week reported by Australian colleagues, which reflects local NZ experience. Observed factor reduction depends on comparative baseline historical dosing intensity using short half-life recombinant FIX products. It is expected that long-term extended half-life FIX will lead to significantly improved joint health and reduced need for orthopaedic surgeries, but confirmation is awaited.

Reference: Haemophilia 2020;26:975–86
Abstract

Treatment of acquired hemophilia A, a balancing act

Authors: Schep SJ et al., the Dutch Society of Haemophilia Treaters, The Netherlands

Summary: Clinical presentations and the efficacy and safety associated with treatment over a 27-year period were reported for a retrospective cohort of 143 patients with acquired haemophilia A, followed for median of 16.8 months, in the Netherlands. Steroid monotherapy was first-line immunosuppressive therapy for 67.6% of the patients, steroids with cyclophosphamide for 11.9% and steroids with rituximab for 11.9%, and the respective success rates associated with these treatments were 35.2%, 80.0% and 66.7%. CR was achieved in 75% of the patients. Factors associated with a lower likelihood of achieving CR were a high anti-FVIII antibody titre, severe bleeding and steroid monotherapy. The most important adverse event was infection, which was more common with steroid combination therapy than steroid monotherapy (38.7% vs. 10.6% [p=0.001]). The proportion of patients who died was 38.2%, due to infections mainly (19.2% vs. 7.7% for fatal bleeds). Predictors of mortality were advanced age, underlying malignancy and ICU admission.

Comment (PO): Acquired haemophilia A has an approximate incidence of 1.5 per million population, so we expect to see 5–10 cases in NZ annually. This study reports that inhibitor titre and bleed severity are prognostic markers for CR, and that steroid combination therapy is more effective than steroid monotherapy. The drawback with combination treatment is higher infection rates, with older age being the main risk factor for adverse events. The combination of low FVIII inhibitor titre (<20BU), FVIIIc >1% and minimal bleeding identifies a better prognostic subgroup for which steroid monotherapy is probably preferable. In other patients, steroids in combination with either cyclophosphamide or rituximab are preferred because of better CR rates. In this group, prevention of infection is an essential strategy as infection is the most important cause of death, especially after successful inhibitor eradication.

Reference: Am J Hematol 2021;96:51–9
Abstract

Emicizumab for the treatment of acquired hemophilia A

Authors: Knoebl P et al.

Summary: These researchers described six males and six females (aged 64–80 years) with acquired haemophilia A (eight with severe bleeding; initial FVIII <1%; median inhibitor titre 22.3 BU/mL) who were treated with subcutaneous emicizumab 3 mg/kg/week for 2–3 doses then 1.5 mg/kg every 3 weeks to maintain their lowest effective FVIII level; a median of five injections was administered, and all the patients also received steroids and/or rituximab. The patients' activated partial thromboplastin time normalised within 1–3 days of their first emicizumab dose, and their FVIII (human reagents) were >10% after a median of 11 days. Haemostatic efficacy was obtained, and bypassing therapy was ceased after a median of 1.5 days. CR (FVIII [bovine reagents] >50%) was achieved after a median of 115 days, and emicizumab was discontinued after a median of 31 days. There were no deaths due to bleeding or thromboembolism, and there was no breakthrough bleeding after the first emicizumab injection.

Comment (PO): Emicizumab is a wonder drug that has fulfilled an unmet need for the management of haemophilia A with inhibitors. It also has exciting potential to replace standard FVIII infusions with advantages, including long half-life, enabling treatments at weekly intervals or less and subcutaneous administration. It was only a matter of time before use in acquired haemophilia A would be reported. The loading dose is the same as in the landmark Haven studies, used for 2–3 days, with the maintenance dose interval adjusted to 3-weekly based on an arbitrary chromogenic FVIII (human) target activity of 10–30%. This measures both the patient FVIII and the emicizumab effect. Improved haemostasis was seen within 3 days of starting emicizumab. Responses were based on clinical bleeding and FVIII chromogenic levels using human reagents. Dose-reduced immunosuppression with steroids (~2 weeks) was used with all patients receiving rituximab with excellent outcomes. A number of issues remain unresolved but this proves the principle.

Reference: Blood 2021;137:410–9
Abstract

New anticoagulants: moving beyond the direct oral anticoagulants

Authors: Fredenburgh JC & Weitz JI

Summary: These authors reviewed the rationale, development and testing of new anticoagulants that target FXII and FXI, focusing on those that have reached or completed phase 2 evaluation for one indication or more. After reviewing the basic science, epidemiological studies and animal models, and discussing issues around maximising safety, they introduce these new agents and discuss their pharmacological properties and possible clinical indications. They then presented findings of the early-phase trials of FXI inhibitors (abelacimab, osocimab, xisomab, BAY 2433334, IONIS-FXI-Rx, JNJ70033093) and an FXII inhibitor (garadacimab), the potentials of which should become clearer over the next few years.

Comment (PO): The DOACs have revolutionised the management of venous thromboembolic disorders. They are effective in a wide spectrum of clinical presentations and contraindicated in only a small number of settings. This review speculates on future anticoagulant development, focussing on inhibitors of FXII and FXI. There is proof of concept from phase 2 studies for inhibiting these contact factors as targets of interest. In view of the effectiveness of DOACs, however, large trial populations will be needed to show possible benefit of new drugs over currently available anticoagulant protocols. It is unlikely they will be trialled for standard VTE management. Potential areas of application will include medical devices and possibly secondary stroke prevention where effective options are limited. Innovative developments in the field of thrombosis management are uninspiring when compared with the game-changing agents now available for routine clinical management of malignant and bleeding disorders. This probably reflects the effectiveness of current therapies.

Reference: J Thromb Haemost 2021;19:20–9
Abstract

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Association of hemochromatosis HFE p.C282Y homozygosity with hepatic malignancy

Authors: Atkins JL et al.

Summary: These researchers estimated the incidences of primary hepatic carcinoma and death according to *HFE* variant status for a cohort of 451,186 UK patients aged 40–70 years of European ancestry followed for a median of 8.9 years. Among male p.C282Y homozygotes (n=1294), 10 of 21 incident hepatic malignancies occurred in men without haemochromatosis at baseline, and they had increased risks of hepatic malignancies and death from any cause than men with neither *HFE* variant (respective hazard ratios 10.5 [95% CI 6.6, 16.7] and 1.2 [1.0, 1.5]). The risks of primary hepatic malignancy and death among male p.C282Y homozygotes out to age 75 years were estimated at 7.2% and 19.5%, respectively, compared with 0.6% and 15.1% for men with neither variant. The risks of hepatic malignancy and death among female p.C282Y homozygotes (n=1596) did not reach statistical significance (respective hazard ratios 2.1 [95% CI 0.7, 6.5] and 1.2 [0.9, 1.5]).

Comment (LY): It is well known that iron accumulation on the basis of haemochromatosis can cause liver cirrhosis and therefore increase the risk of hepatic malignancy. However, by reducing iron burden with phlebotomy, these risks are reduced. It is unclear what the modern day incidence of such events in a homozygous population who have largely been diagnosed earlier would be. This very large GP-based analysis in the UK of patients recruited during 2006–2010 shows that there is still an increased rate of hepatic carcinoma and severe liver disease in this population. The authors have attempted to adjust for confounders such as obesity, alcohol and viral liver disease, but the obvious hole in the data is the absence of iron level measurements so it is unclear whether the damage had been done before diagnosis. Given the increased rates of hepatic malignancy identified, further follow-up of treated cohorts is of value, and ensuring that cirrhosis is diagnosed (if present) to allow screening for hepatoma.

Reference: JAMA 2020;324:2048–57
Abstract

Preservation of thrombin generation in cirrhosis despite abnormal results of international normalized ratio: implications for invasive procedures

Authors: Ferreira CM et al.

Summary: These researchers compared thrombin generation, with and without the presence of thrombomodulin, between consecutive patients with cirrhosis and INRs <1.5 (n=72), those with INRs ≥1.5 (n=25) and healthy controls (n=46). Compared with controls, the patients with cirrhosis were found to have reduced endogenous thrombin potential, with no significant difference between the lower and higher INR groups (1250 vs. 1186 nmol/l·min [p=0.3572]). Thrombin generation in both INR groups was comparable with controls after the addition of thrombomodulin. Endogenous thrombin potential without/with thrombomodulin ratio was high in 80% of the patients, but this was more marked in those with an INR of ≥1.5 vs. <1.5 (0.81 vs. 0.69 [p=0.0042]). Three patients from the lower INR group and two from the higher INR group experienced bleeding after ligation of oesophageal varices, and their endogenous thrombin potential without/with thrombomodulin ratios were 0.72–0.90, compared with 0.57 in controls.

Comment (LY): Thrombin generation potential is a tricky assay, with many permutations in terms of reagents and sample choice. In theory it should give an accurate picture of the overall balance of coagulation components, whereas standard clotting assays do not, as these artificially separate different areas of coagulation. The main point of interest in this paper is not the specifics of thrombin generation, but rather the fact that cirrhosis, with the reduction in procoagulant proteins synthesised by the liver, does not necessarily mean less thrombin generation, so the prothrombin ratio may be somewhat misleading. Correction of vitamin K deficiency in these patients should always be a priority, but the means of assessing coagulability and whether additional plasma protein administration is needed remain unclear.

Reference: Blood Coagul Fibrinolysis 2021;32:1–7
Abstract

The incidence of venous thromboembolic events in trauma patients after tranexamic acid administration

Authors: Rivas L et al.

Summary: The EAST multicentre, retrospective study reported on patients aged 18–80 years who required ≥5 units of blood in the first 24 hours after sustaining a traumatic injury, according to whether they received tranexamic acid (n=887) or not (n=446); patients who did not receive tranexamic acid had a greater injury severity score, but otherwise the groups were similar. The incidences of VTE, myocardial infarction and cerebrovascular accident were similar between the groups, but the tranexamic acid group required significantly fewer transfusions and they were less likely to die (adjusted odds ratio 0.67 [95% CI 0.45, 0.98]). These findings were similar when only patients who had sustained blunt injuries were evaluated, despite higher extremity/pelvis abbreviated injury scores.

Comment (LY): This is a multicentre retrospective review, so not great-quality data, but still useful as there are always lingering questions about VTE risk with tranexamic acid given its mechanism of action. In this large trauma cohort, administration of tranexamic acid did not increase the rate of thrombotic events. Once again, this is a reassuring result in this patient context. The study suggests benefits in terms of transfusion requirements, supporting the high-quality randomised data supporting tranexamic acid administration within the first 3 hours following major trauma.

Reference: Blood Coagul Fibrinolysis 2021;32:37–43
Abstract

Safety of direct oral anticoagulant exposure during pregnancy

Authors: Beyer-Westendorf J et al.

Summary: This retrospective cohort study compiled case reports and reviewed the literature to identify 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 to be major birth defects possibly related to DOAC exposure.

Comment (LY): As DOACs are now the first-line treatment option for VTE, there will naturally be a cohort of women of childbearing age who are treated. Embryopathy is well described with vitamin K antagonist exposure later in the first trimester, with rates in live births from 5% to 10% depending on the medication and the length of exposure into the first trimester. There is also a higher rate of miscarriage. This paper reporting risks in women exposed to DOACs is therefore important, as the molecules will cross the placenta. The data sources are varied, including direct reports to the investigators and pharma databases. There is no control group because of this. The mean duration of exposure was short, 5 weeks, with an upper CI of 7 weeks. The 4% rate of birth defects compares to a usual population rate of 3% with no particular pattern of anomalies. The study supports the ISTH recommendation not to electively terminate exposed pregnancies. We currently aim to identify pregnancy as soon as possible and transition to LMWH (low-molecular-weight heparin), and that recommendation is supported by the authors.

Reference: Lancet Haematol 2020;7:e884–91
Abstract

Independent commentary by Dr Laura Young

Laura is a haematologist specialising in thrombosis and haemostasis. Having trained at the University of Auckland, School of Medicine, she completed her training in haematology in Auckland, and then completed a period of research at the University of Auckland as part of a PhD focusing on coagulation inhibitors. She is now employed at Auckland Hospital as part of the Thrombosis Unit and Haemophilia Centre, and is involved in hospital based clinical trials and also preclinical research at the University of Auckland. She also has a part time lecturing position in the Department of Molecular Medicine and Pathology at the University School of Medicine.

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Effect of hydroxyurea exposure before puberty on sperm parameters in males with sickle cell disease

Authors: Joseph L et al.

Summary: These researchers analysed and compared sperm parameters in 26 samples from 15 men with sickle-cell disease exposed to hydroxycarbamide before puberty (median age at initiation, 6 years; median exposure duration, 4 years; mean dosage, 22.4 mg/kg/day) with 46 samples from 23 men who had not been exposed to hydroxycarbamide. All hydroxycarbamide-exposed men and 52% of the hydroxycarbamide-naïve men had received transfusion therapy at the time of semen analysis. Substantial quantitative and qualitative semen abnormalities were detected in all the men, with no significant differences between the hydroxycarbamide-exposed and hydroxycarbamide-naïve men for semen volume, sperm concentration, total sperm count or spermatozoa motility, morphology or vitality.

Comment (LY): The safety of hydroxycarbamide has been contentious in haematology. In sickle-cell anaemia, the benefits are clear, but given the disease is benign, giving a chemotherapeutic agent to children has caused disquiet. This study is small but demonstrates no difference in sperm quality for those boys receiving hydroxycarbamide before puberty and those who did not, although sperm quality overall was impaired for all patients. New therapies for sickle-cell anaemia are being developed, but none are likely to overtake hydroxycarbamide in terms of cost/benefit for severe disease in the immediate future.

Reference: Blood 2021;137:826–9
Abstract