Haematology Research Review™

Making Education Easy

Issue 25 - 2017

In this issue:

Abbreviations used in this issue

CR = complete response
FVIII = factor VIII
GI = gastrointestinal
HIT = heparin-induced thrombocytopenia
HR = hazard ratio
ICH = intracerebral haemorrhage
Ig = immunoglobulin
INR = international normalised ratio
JAK = Janus kinase
PPI = proton-pump inhibitor
PR = partial response
RBC = red blood cell
TIA = transient ischaemic attack
TTP = thrombotic thrombocytopenic purpura

Welcome to issue 25 of Haematology Research Review.

Prophylactic emicizumab significantly reduced bleeding events compared with no prophylaxis in patients with haemophilia A with inhibitors in the first study selected for this issue. Other research showed that targeting antithrombin with fitusiran, an RNA interference therapy, dose dependently reduced antithrombin levels and increased thrombin generation in patients with haemophilia A or B without inhibitors. Research published in the Lancet reporting increased major bleeding in older patients receiving aspirin-based antiplatelet therapy without a PPI (proton-pump inhibitor) prompted the authors to recommend greater concomitant PPI use in this patient group. This issue concludes with research, which included a number of NZ participants, reporting rapid, durable and safe reversal of dabigatran-induced anticoagulation for emergency scenarios.

We hope you are enjoying these updates in haematology research. Please continue to send us your comments and suggestions.

Kind regards,

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Emicizumab prophylaxis in hemophilia A with inhibitors

Authors: Oldenburg J et al.

Summary: Males aged ≥12 years with haemophilia A with FVIII inhibitors who had received episodic treatment with bypassing agents were randomised 2:1 to receive prophylactic subcutaneous emicizumab once weekly (n=35) or no prophylaxis (n=18). Compared with placebo, emicizumab recipients experienced a significantly lower annualised bleeding rate (primary endpoint; 2.9 vs. 23.3 events; difference 87% [p<0.001]), with a notably greater proportion experiencing no bleeding events (63% vs. 6%). A further 24 males who had previously received prophylactic treatment with bypassing agents received emicizumab prophylaxis, which led to a 79% reduction of their prior bleeding rate (p<0.001). There were 198 adverse events reported, mostly injection-site reactions (15%). One participant developed thrombotic microangiopathy and another experienced a thrombotic event; both had received multiple infusions of activated prothrombin complex concentrate for breakthrough bleeding. There were no antidrug antibodies detected.

Comment (PO): The development of FVIII inhibitors is the most feared complication of haemophilia A treated with factor replacement. It occurs in 20–30% of patients. Management is difficult, especially in those failing immune tolerance. Bypass agents (FEIBA or NovoSeven) are used, but are much less effective than factor replacement in the noninhibitor patient. A novel bispecific FVIII mimetic immunoglobulin (emicizumab), administered once weekly subcutaneously, was used in this well-designed international study, which included three NZ subjects. The zero bleed rate on treatment in a population with an average of two bleeds per month speaks for itself. Quality of life was dramatically improved in most patients. Side effects were minimal, provided there was no exposure to FEIBA at doses exceeding 100 U/kg for more than 1 day when on emicizumab therapy. This treatment is a game changer for those with haemophilia. Studies in paediatric patients and those without inhibitors are ongoing.

Reference: N Engl J Med; Published online July 10, 2017
Abstract

Impact of red blood cell transfusion strategies in haemato-oncological patients

Authors: Hoeks MPA et al.

Summary: This was a systematic review and meta-analysis of 15 studies (n=2636) reporting clinical outcomes and blood use in haemato-oncological patients for restrictive versus liberal RBC transfusion strategies. A trend for a lower mortality risk was found for restrictive (versus liberal) RBC transfusion strategies (relative risk 0.68 [95% CI 0.46, 1.01]), with less mean RBC use (1.40 units per transfused patient per therapy cycle) and no difference for safety outcomes.

Comment (LY): It has historically been a natural assumption that boosting haemoglobin levels to higher levels with RBC transfusions would make patients feel better and result in better outcomes. Over the last 10 years, a plethora of studies in surgical and critically ill patients has confirmed this is not the case, and that the majority of these patient groups do better with restrictive transfusion protocols. High-quality studies for haematological malignancy are lacking, but this meta-analysis attempts to synthesise them. Most are of treatment for acute leukaemia and in general restrictive policies (lower threshold, 1 vs. 2 units) at least were no worse than more liberal policies, with a definite trend to improved outcomes. It is reasonable for acute haematology units to follow the same RBC transfusion policies as the rest of the hospital.

Reference: Br J Haematol 2017;178(1):137–51
Abstract

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Bendamustine plus rituximab for chronic cold agglutinin disease

Authors: Berentsen S et al.

Summary: Forty-five patients with primary chronic cold agglutinin disease received four 28-day cycles of rituximab 375 mg/m^2 on day 1 and bendamustine 90 mg/m^2 on days 1 and 2 in this Nordic prospective multicentre trial. The overall response rate was 71%, with respective CR and PR rates of 40% and 31%. The response rate among participants who had previously received rituximab or fludarabine plus rituximab (n=14) was 50%, with three CRs and four PRs. Haemoglobin level increased by a median of 3.7 g/dL, with median increases of 4.4 g/dL and 3.9 g/dL in participants with CRs and PRs, respectively. After 32 months, the tenth percentile of response duration had not been reached. The grade 3–4 neutropenia rate was 33%, but the rate of infections with or without neutropenia was only 11%. Bendamustine dose reductions were required by 29% of participants.

Comment (PO): Primary cold agglutinin disease accounts for approximately 15% of autoimmune haemolytic anaemia. The IgM (k) antibody, directed against the I antigen on red cells and binding at low temperatures, results in C3b-mediated predominantly extravascular haemolysis in the liver as well as intravascular red cell destruction. The disorder causes significant morbidity in an older population with seasonal exacerbation of symptoms, a requirement for transfusion support and thrombotic events in about 20% of patients. Management guidelines are mainly based on expert opinion and usually recommend single-agent rituximab or in combination with fludarabine. Overall response rates with rituximab plus fludarabine are 70%, with a 20% CR rate and a median response duration of more than 5 years. The CR rate reported using rituximab plus bendamustine is double that with rituximab plus fludarabine, with a similar or longer response duration. Importantly the clinical infection rate appears appreciably lower (11% vs. 59%) making rituximab plus bendamustine more attractive as first-line therapy.

Reference: Blood 2017;130(4):537–41
Abstract

Presenting ADAMTS13 antibody and antigen levels predict prognosis in immune-mediated thrombotic thrombocytopenic purpura

Authors: Alwan F et al.

Summary: Using data from the United Kingdom TTP registry, these researchers prospectively investigated the impact of presenting anti-ADAMTS13 IgG antibody and ADAMTS13 antigen on mortality. The investigation included 312 episodes of TTP affecting 292 patients over an 87-month period. The overall mortality rate was 10.3%, and was greater in participants: i) with a raised versus normal troponin level at presentation (12.1% vs. 2.0% [p=0.04]); ii) with a low versus normal Glasgow Coma Score at presentation (20% vs. 2.2% [p>0.0001]); iii) in the upper versus lower quartile for anti-ADAMTS13 IgG antibody level (16.9% vs. 5.0% [p=0.004]); and iv) in the lower versus upper quartile for ADAMTS13 antigen level (18% vs. 3.8% [p=0.005]). The mortality rate was highest at 27.3% for participants who were within both the highest anti-ADAMTS13 IgG antibody quartile and the lowest ADAMTS13 antigen quartile.

Comment (PO): Acquired TTP is a rare life-threatening disorder (4–13 per million per year), which is more common in women (3-fold) with a mortality untreated approaching 90%. Deficiency of the protease ADAMTS13 (<10%) is due to inhibitory antibodies and results in abnormal amounts of very large von Willebrand factor multimers within the circulation. Mortality with treatment occurs in 20–30% of patients. Poorer prognosis is associated with lower ADAMTS activity level, older age, high lactate dehydrogenase level, increased troponin level and lower Glasgow Coma Score. These registry-based UK data confirm that higher ADAMTS antibody levels also correlate with other clinical predictors of adverse outcome, but those with high antibody levels do not universally do poorly. Using an in-house ADAMTS13 antigen assay, the poorest outcome occurs when antibody levels are highest and antigen levels are lowest. It remains to be seen how this might impact on the prediction of treatment-related survival in these patients.

Reference: Blood 2017;130(4):466–71
Abstract

Intracranial hemorrhage in patients with atrial fibrillation receiving anticoagulation therapy

Authors: Lopes RD et al.

Summary: These researchers identified 174 ARISTOTLE trial participants who experienced ICH (intracranial haemorrhage) from the 18,140 who received ≥1 dose of study drug. Spontaneous ICH accounted for 71.7% of the events, with the remainder being traumatic. Apixaban recipients had a significantly lower rate of ICH than warfarin recipients, regardless of type and location (0.33% vs. 0.80% per year). Independent predictors of ICH were enrolment in Asia or Latin America, older age, prior stroke/TIA and baseline aspirin use. The median time from most recent INR measurement to ICH among warfarin recipients was 13 days, and their median INR before the ICH was 2.6, with 78.5% having an INR of <3.0. After ICH, 55.7% of participants had a discharge modified Rankin scale score of ≥4 and 43.3% died within 30 days, with no difference between apixaban and warfarin recipients.

Comment (PO): ICH is associated with significant morbidity and mortality in patients receiving anticoagulant treatment. In atrial fibrillation trials, the direct (nonvitamin K/novel) oral anticoagulants have a 36–43% 30-day mortality rate after ICH. All direct oral anticoagulants have a reduced ICH rate compared with warfarin, but it is lowest with apixaban (58% compared with warfarin). This is a secondary analysis of the ARISTOTLE (apixaban versus warfarin atrial fibrillation) trial (18,201 patients). The lower observed ICH with apixaban (0.33% vs. 0.8% per year for warfarin) was independent of ICH type (spontaneous or traumatic), or bleed location (intraparenchymal, subdural or subarachnoid). Nearly 80% of warfarin-related ICH episodes were associated with a therapeutic INR in the recent fortnight, suggesting that better INR control is unlikely to further decrease warfarin-related brain bleeds. Aspirin, older age and previous stroke or TIA further increase the ICH risk. All-cause mortality after ICH approaches 50% and is similar for both apixaban and warfarin.

Reference: Blood 2017;129(22):2980–7
Abstract

Targeting of antithrombin in hemophilia A or B with RNAi therapy

Authors: Pasi KJ et al.

Summary: Four healthy volunteers received a single subcutaneous injection of fitusiran (RNA interference therapy targeting antithrombin) 0.03 mg/kg or placebo, and 25 patients with moderate or severe haemophilia A or B without inhibitory alloantibodies received three injections of fitusiran 0.015, 0.045 or 0.075 mg/kg/week, 0.225, 0.45, 0.9 or 1.8 mg/kg/month or a fixed 80mg dose. There were no thromboembolic events during the study. Mild injection-site reactions were the most common adverse events. Plasma fitusiran concentrations increased in a dose-dependent manner, with no accumulation on repeated administration. Monthly administration was associated with a dose-dependent reduction in mean maximum antithrombin level of 70–89% from baseline. A reduction in antithrombin level of >75% from baseline led to median peak thrombin levels at the lower end of the range seen in healthy participants.

Comment (PO): The theme we can apply to this safety report is 'beyond factor'. It is the first of what are likely to be numerous reports aimed at resetting the haemostatic balance, which is disturbed in favour of bleeding in patients with congenital coagulation disorders. This non-factor subcutaneous weekly-monthly therapy is agnostic to the type of coagulation defect and whether or not there are inhibitors complicating factor replacement. The approach is based on the observation that coinheritance of a prothrombotic phenotype can ameliorate the severity of haemophilia and improve thrombin generation, which is defective in congenital disorders of coagulation. In this case, a small inhibitory RNA specifically targets antithrombin messenger RNA and suppresses antithrombin production in the liver, causing a dose-dependent decrease in antithrombin levels and increased thrombin generation without any thromboembolic complications. No significant side effects were observed. Efficacy data are now awaited with interest.

Reference: N Engl J Med; Published online July 10, 2017
Abstract

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Independent commentary by Dr Laura Young, a haematologist specialising in thrombosis and haemostasis at Auckland Hospital as part of the Thrombosis Unit and Haemophilia Centre. She also has a part-time lecturing position in the Department of Molecular Medicine and Pathology at the University School of Medicine. **For full bio CLICK HERE.**

Independent commentary by Dr Paul Ockelford, a haematologist and Clinical Associate Professor at the University of Auckland School of Medicine and Director of both the Adult Haemophilia Centre and Thrombosis Unit at Auckland City Hospital. He serves on the Medical Advisory panel of the New Zealand Haemophilia Foundation and the National Haemophilia Management Group. **For full bio CLICK HERE.**

Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1)

Authors: Mesa RA et al.

Summary: This paper reported final data from the phase 3 PERSIST-1 trial, which stratified patients with higher risk myelofibrosis by risk category, platelet count and region, and randomised them to receive oral pacritinib 400mg once daily (n=220) or best available therapy (excluding JAK2 inhibitors; n=107) until disease progression or unacceptable toxicity. The participants were followed for a median of 23.2 months. Compared with best available therapy, a greater proportion of pacritinib recipients had achieved a reduction in their spleen volume of ≥35% at week 24 (primary endpoint; 19% vs. 5% [p=0.0003]). Pacritinib was well tolerated.

Comment (LY): The pacritinib story is an interesting one. Myelofibrosis, the JAK2 positive myeloproliferative neoplasm with the worst outcome, is challenging to manage, particularly with significant cytopenias. Ruxolitinib, an inhibitor of JAK1 and JAK2, has predominantly been trialled with platelet counts above 100 × 10^9/L and cytopenias have been dose-limiting. The PERSIST series of studies of pacritinib, a JAK2-specific inhibitor (and also other tyrosine kinases such as FLT-3), included higher risk patients with severe thrombocytopenia; however, the trials were abruptly temporarily suspended by the US FDA because of survival and bleeding concerns that do not appear to have been significant in the final analysis. Spleen volume was reduced with pacritinib versus standard care, and some disease-related symptoms were reduced, although importantly, the total symptom score in the intent-to-treat analysis was not improved significantly. The role of this agent is still unclear, with a trial to commence of those with ruxolitinib failure. Currently in NZ none of these agents are funded.

Reference: Lancet Haematol 2017;4(5):e225–36
Abstract

Clinical outcomes in a cohort of patients with heparin-induced thrombocytopenia

Authors: Kuter DJ et al.

Summary: The benefits and risks of non-heparin anticoagulants for treating HIT (heparin-induced thrombocytopenia) were investigated in patients with a positive heparin-platelet factor-4 antibody test and recent heparin exposure. For the study population of 284 patients with HIT without thrombosis, 71 with HIT with thrombosis and 87 without HIT, the respective proportions with an intermediate or high '4T' score were 58%, 85% and 8%, the respective proportions who started non-heparin anticoagulation were 56%, 80% and 45%, and the respective proportions who experienced a primary outcome event (death, limb amputation/gangrene or new thrombosis) were 36%, 48% and 17%, of whom 38%, 61% and 40% were receiving non-heparin anticoagulation. Compared with participants without HIT, those with HIT with thrombosis were significantly more likely to experience a primary outcome event (HR 2.48 [1.35, 4.55]), whereas for those with HIT without thrombosis, the likelihood was marginally increased (1.66 [0.96, 2.85]). The risk of a primary outcome event was also significantly increased following a platelet transfusion (HR 1.77 [p=0.02]). The respective major bleeding rates in the HIT without thrombosis, HIT with thrombosis and no HIT groups were 36%, 48% and 16% (p=0.005). There was no reduction in primary outcome events with non-heparin anticoagulation in either of the groups with HIT.

Comment (LY): HIT is feared by all clinicians who use heparin as being a challenge both to diagnose and manage, with high rates of thrombosis. This large multicentre cohort from 2008 unfortunately does nothing to allay these concerns. The criteria were practical: evidence of antibodies (rather than a functional test for HIT) and thrombocytopenia (both found in 80%). Those who developed HIT with thrombosis unsurprisingly did worse. The cohort included a large number of patients with positive antibodies and no thrombosis at diagnosis – they also did quite badly, with 20% dying and/or developing thrombosis. Around half this group (without initial thrombosis) received non-heparin anticoagulants. Major bleeding was very common, affecting almost half the HIT with thrombosis group. This study emphasises that managing this condition remains a difficult juggling act and did not really show clear benefits for non-heparin anticoagulants, although these remain standard care in HIT.

Reference: Am J Hematol 2017;92(8):730–8
Abstract

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Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events

Authors: Li L et al., on behalf of the Oxford Vascular Study

Summary: The risk, time course and outcomes of bleeding during antiplatelet treatment for secondary prevention were prospectively investigated in a population-based cohort of 3166 patients with a first TIA, ischaemic stroke or myocardial infarction treated with, mainly aspirin-based, antiplatelet drugs without routine PPI use. There were 218 GI, 45 intracranial and 142 other first bleeding events over 13,509 patient-years of follow-up. Of the 314 patients with bleeds who were hospitalised, 37% were missed by administrative coding. Nonmajor bleeding risk was not related to age, but major bleeding was, with patients aged ≥75 years being particularly high-risk (HR 3.10 [95% CI 2.27, 4.24]), especially for fatal bleeds (5.53 [2.65, 11.54]); this was sustained during long-term follow-up. Similarly, patients aged ≥75 years had an increased risk of upper GI bleeds (HR 4.13 [2.60, 6.57]), particularly disabling or fatal bleeds (10.26 [4.37, 24.13]), which most major upper GI bleeds were in this age group, outnumbering disabling or fatal ICH (absolute risk, 9.15 per 1000 patient-years). Patients aged ≥85 years had a significantly lower estimated number needed to treat with routine PPIs in order to prevent one disabling or fatal upper GI bleed over 5 years compared with those aged <65 years (25 vs. 338).

Comment (LY): Aspirin is considered a rather low-risk strategy for vascular disease. This very large, well-conducted observational study has confirmed this is the case for patients aged under 75 years, where bleed rates were similar to randomised trials. However, in older patients this was not the case, with an annualised rate of major bleeds as high as 4% in the extreme elderly. In addition, the proportion of bleeds that were fatal or disabling rose significantly, including GI bleeding, which is frequently thought to be less significant. The authors comment that given the proven reduction of GI bleeding by PPIs in such patients (in other studies), these should be prescribed routinely, given the frequency and severity of GI bleeds in the over 75-year age group.

Reference: Lancet 2017;390(10,093):490–9
Abstract

Idarucizumab for dabigatran reversal

Authors: Pollack CV et al.

Summary: This paper reported the full cohort analysis for an open-label trial of intravenous idarucizumab 5g for anticoagulation reversal following dabigatran administration in 301 patients with uncontrolled bleeding (137 GI and 98 ICH) and 202 about to undergo an urgent procedure. Based on either the diluted thrombin time or the ecarin clotting time, median maximum percentage reversal of dabigatran was 100% with idarucizumab. Among the group with uncontrolled bleeding who could be assessed, the median time to bleeding cessation was 2.5 hours. In the urgent procedure group, the intended procedure was started in a median of 1.6 hours; 93.4%, 5.1% and 1.5% had periprocedural haemostasis assessed as normal, mildly abnormal and moderately abnormal, respectively. The respective 90-day thrombotic event rates in the uncontrolled bleeding and urgent procedure groups were 6.3% and 7.4%, and their respective mortality rates were 18.8% and 18.9%. No serious adverse safety signals emerged.

Comment (LY): Because of the funding arrangements, dabigatran is a very commonly used oral anticoagulant in NZ. It is therefore perhaps not surprising that hospitals in NZ contributed approximately 20% of the participants in the definitive reversal study of patients presenting with major bleeding or requiring emergency surgery. It is reassuring that this single-arm trial showed that the monoclonal antibody idarucizumab is highly effective for dabigatran reversal, with a rate of thrombotic complications typical of these types of high-risk patients. Clinicians need to be aware of the possibility of some rebound effect after 24–48 hours, which can be managed with further doses of idarucizumab for the very small minority with rebound high levels and ongoing bleeding.

Reference: N Engl J Med 2017;377(5):431–41
Abstract