Haematology Research Review™

Making Education Easy

Issue 31 - 2019

In this issue:

Abbreviations used in this issue

ET = essential thrombocythaemia
ITP = immune thrombocytopenia
MI = myocardial infarction
MPN = myeloproliferative neoplasm
OR = odds ratio
PE = pulmonary embolism
PEX = plasma exchange
PMF = primary myelofibrosis
PV = polycythaemia vera
QOL = quality of life
RBC = red blood cell
TTP = thrombotic thrombocytopenic purpura
VWF = von Willebrand factor
VTE = venous thromboembolism

Welcome to issue 31 of Haematology Research Review.

Our first issue of the year begins with a report on patients aged ≤40 years who have been treated for MPNs (myeloproliferative neoplasms) at the Mayo Clinic. Other selected research includes an assessment of health-related QOL, using four validated instruments, for patients receiving long-term eltrombopag for persistent/chronic ITP (immune thrombocytopenia). Also on the topic of ITP, another paper reported that lower thrombopoietin levels were predictive of better responses to eltrombopag and romiplostim. This issue concludes with research reporting outcomes for patients with acute PE who either did not receive anticoagulation or received it for only <90 days.

The start of a new year of haematology research updates is an excellent time to let us know how we are doing, so please feel free to send us your feedback and comments.

Kind regards,

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Myeloproliferative neoplasms in the young

Authors: Szuber N et al.

Summary: These authors report the Mayo Clinic's experiences of managing 361 patients aged ≤40 years with MPNs; this population constituted 12% of all the clinic's patients with MPNs seen during the same time period. The incidence of PV (polycythaemia vera) was 12%, the incidence of ET (essential thrombocythaemia) was 20% and the incidence of PMF (primary myelofibrosis) was 5%. Compared with older patients, these younger patients were significantly more likely to present with low-risk disease, those with ET were more likely to be female, and they had a significantly lower incidence of arterial events and a higher incidence of venous thrombosis in PV. This younger group was also significantly more likely to express *CALR* mutations in ET and PMF, have a normal karyotype in PV and PMF, and they had a lower incidence of high molecular risk mutations in PMF. The respective median follow-up durations for patients with PV, ET and PMF were 11.3, 13 and 7.1 years, during which the respective rates of leukaemic transformation were 4%, 2% and 10%. Due to longer survival, the younger patients with PV and ET had higher incidences of fibrotic progression (22% and 16%, respectively). The respective median survival durations for the younger patients with PV, ET and PMF were 37, 35 and 20 years, compared with 22, 22 and 8 years for those aged 41–60 years and 10, 11 and 3 years for those aged >60 years (p<0.001).

Comment (PO): The median age for MPNs is the sixth decade, with patients <40 years representing up to 20%. This analysis evaluates the natural history and long-term outcomes of young MPN patients (aged ≤40 years at diagnosis) from a single institution collected over approximately 50 years. The population represents 12% of the source database and provides comparisons with patients presenting at ages 41–60 years and >60 years. The phenotype in the younger group tended to be more indolent, with fewer arterial events prior to diagnosis and fewer total thrombotic episodes in those with ET and PMF. However, the venous thrombolic rates were higher in the young PV patients. Higher platelet counts are more frequently associated with *CALR* mutations in the young patients with ET, who together with those with PV more often have palpable splenomegaly. Compared with older age groups, the young MPN patient has a longer life expectancy. Recognition of PMF is also very important for counselling.

Reference: Am J Hematol 2018;93:1474–84
Abstract

CLICK HERE to read previous issues of Haematology Research Review

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.**

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.**

Changes in health-related quality of life with long-term eltrombopag treatment in adults with persistent/ chronic immune thrombocytopenia

Authors: Khelif A et al.

Summary: The EXTEND study evaluated open-label eltrombopag, administered for a median of 2.37 years, in 302 adults with persistent/chronic ITP who had completed a prior eltrombopag trial. This paper reported changes in patient-reported health-related QOL over time and its association with platelet response. Four health-related QOL instruments used all returned results indicating positive mean changes from baseline over time after adjustments for patient baseline characteristics and rescue therapy use, as well as positive associations with platelet response. The improvements from baseline were noted within 3 months and persisted through 2.5–5 years of treatment depending on health-related QOL instrument.

Comment (PO): Eltrombopag has been available for use in NZ since 2014. Funding changes gazetted in October 2018 have been broadened now, allowing its use in eligible patients with a significant and well-documented contraindication to splenectomy, after failure of initial immunosuppressive therapy, with renewal in those for whom continued use is indicated to maintain a response. The open-label EXTEND study demonstrated at a median 2.4 years an 86% sustained platelet response in 302 patients, with reduced bleeding and a good safety profile. This health-related QOL analysis uses the EXTEND patient population to show improved QOL in patients on long-term eltrombopag. Using multiple definitions of response, a positive association was seen between platelet improvement and QOL. Fatigue, bleeding concerns and physical functioning all improved in most, although not all, using several measuring tools.

Reference: Am J Hematol 2019;94:200–8
Abstract

Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura

Authors: Scully M et al., for the HERCULES Investigators

Summary: Patients with TTP (thrombotic thrombocytopenic purpura; n=145) were randomised to receive intravenous caplacizumab 10mg bolus followed by 10 mg/day subcutaneously or placebo during PEX (plasma exchange) and a further 30 days in this trial. Compared with placebo, caplacizumab recipients had: i) a shorter median time to platelet count normalisation (primary outcome; 2.69 vs. 2.88 days [p=0.01]), and they were 1.55 times more likely to achieve this outcome; ii) a lower event rate for the composite outcome of TTP-related death, TTP recurrence or thromboembolic event during the treatment period (12% vs. 49% [p<0.001]); and iii) a lower TTP recurrence rate during the trial (12% vs. 38% [p<0.001]). There were no cases of refractory disease among caplacizumab recipients, whereas there were three in the placebo group. Caplacizumab recipients also required less PEX and had shorter hospital stays than placebo recipients. Mucocutaneous bleeding (the most common adverse event) occurred in 65% and 48% of caplacizumab and placebo recipients, respectively. There were three deaths in the placebo arm and one (due to cerebral ischaemia, after treatment) in the caplacizumab arm.

Comment (PO): About half of the patients with acquired TTP are immune-mediated with antibody-mediated inhibition of ADAMTS13. A severe reduction of ADAMTS13 (<5%) is present in approximately 80% of cases, with inhibitory activity detected in about half. Current treatments with PEX and immunosuppressives have reduced mortality rates, primarily due to microvascular thrombosis, to less than 20% by restoring ADAMTS13 functional activity. Refractory disease and poor outcomes are still seen in ~15% of cases with persistent thrombocytopenia. Caplacizumab significantly reduces time to platelet recovery, TTP-related death, major thromboembolic events and TTP recurrence. It appears to add value to standard therapy by reducing the duration of PEX and hospital stay. It may be particularly beneficial to prevent post-PEX recurrences, after platelets normalise, in those with persisting ADAMTS13 activity of <10%. Rituximab, however, has also been used as salvage therapy in those with a suboptimal response.

Reference: N Engl J Med 2019;380:335–46
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

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Preemptive rituximab prevents long-term relapses in immune-mediated thrombotic thrombocytopenic purpura

Authors: Jestin M et al., on behalf of the French Thrombotic Microangiopathies Reference Center

Summary: Long-term outcomes were reported for 92 patients with immune TTP in clinical remission treated with pre-emptive rituximab after severe ADAMTS13 deficiency was detected during follow-up; 37 patients had experienced >1 episode of immune TTP. The median cumulative relapse incidence before pre-emptive rituximab was started was 0.33 episodes per year, and this fell to zero after pre-emptive rituximab. Recovery of ADAMTS13 activity was sustained in 37% over 31.5 months of follow-up on pre-emptive rituximab, while severe ADAMTS13 deficiency recurred in 49% after an initial improvement. Additional courses of rituximab usually resulted in improvements in ADAMTS13 activity. Undetectable ADAMTS13 activity persisted for 14% of patients after their first rituximab course, although 60% of re-treated patients improved. The overall clinical relapse rate was 15%, and the overall adverse event rate was 20.7%. Patients who responded to pre-emptive rituximab treatment experienced a change in ADAMTS13 conformation. Among 23 historical patients with immune TTP and persistently undetectable ADAMTS13 activity, the 7-year clinical relapse rate was 74%.

Comment (PO): More about TTP and rituximab. A major challenge with TTP is life-threatening recurrences. Up to 50% of patients will relapse with unpredictable severity. Although most occur within the first 1–2 years, it can be delayed a decade or more. Longitudinal testing has established ADAMTS13 deficiency as a strong risk factor for recurrence. Recurrence rates of 38% (1 year) and 59% (5.4 years) have been reported with levels <10%. These impressive French registry data confirm a high cumulative recurrence in an historical untreated cohort and show that rituximab infusions are effective in 85% of those treated with an acceptable safety profile. An estimated number needed to treat of 1.6 prevents one relapse and32 prevents one death, assuming a 5% mortality rate with relapse. Long-term follow-up is recommended in all immune TTP patients, although the optimal testing schedule (~3 monthly) and rituximab dosing regimen (375 mg/m^2 weekly ×4) are undefined. A conformational change in ADAMTS13 is associated with relapse.

Reference: Blood 2018;132:2143–53
Abstract

The von Willebrand factor Tyr2561 allele is a gain-of-function variant and a risk factor for early myocardial infarction

Authors: Schneppenheim R et al.

Summary: These researchers investigated the impact of the common VWF (von Willebrand factor) variant p.Phe2561Tyr on haemostasis in 865 genotyped patients with coronary artery disease, 915 with MI (myocardial infarction) and 417 controls. A univariate analysis revealed that carriers of the Tyr2561 allele aged ≤55 years had an increased risk of repeat MI (OR 2.53 [95% CI 1.07, 5.98]), especially females (5.93 [1.12, 31.24]). Compared with Phe2561, Tyr2561 was associated with a larger platelet aggregate size, both in probands' blood and with the recombinant variants, and a halving of the critical shear rate for inducing aggregate formation. Tyr2561-associated differences in C-domain circular dichroism spectra suggested an increased shear sensitivity of VWF secondary to altered associations of the C domains that disrupt the normal dimer interface.

Comment (PO): Does VWF play a role in vascular events? High VWF levels are associated with increased arterial thrombosis risk in epidemiological studies, and genetic variants associated with increased VWF activity have been linked to MI but not stroke. It is unknown if there is a causal link between these higher levels and thrombosis. Conversely patients with von Willebrand disease have lower rates of stroke and MI than the general population. Evidence is provided in this report showing for the first time that a gain of function mutation in the C4 domain increases platelet aggregation and cardiovascular disease risk. The exon 45 variant resulting from a Tyr substitution at position 2561 occurs in 10% of the normal population. It alters intravascular shear thresholds and enhances GPIIb/IIIa-mediated platelet receptor binding and platelet aggregation. In a modest study of patients with coronary artery disease, the mutation was associated with an increased MI risk in women aged ≤55 years, but the confidence limits were wide.

Reference: Blood 2019;133:356–65
Abstract

Common conditions associated with hereditary haemochromatosis genetic variants

Authors: Pilling LC et al.

Summary: Using 2006–2010 UK Biobank data (n=451,243), these researchers compared morbidity and mortality between cohorts of patients of European descent with the *HFE* p.C282Y genetic variant of hereditary haemochromatosis and those with no such mutation. Among individuals who were homozygous for p.C282Y (n=2890; 0.6%), 21.7% of men and 9.8% of women had been diagnosed with haemochromatosis by end of follow-up (mean 7 years). Compared with men in the 40- to 70-year age bracket with no p.C282Y mutation, those who were p.C282Y homozygous were more likely to be diagnosed with haemochromatosis (OR 411.1 [95% CI 299.0, 565.3]), liver disease (4.30 [2.97, 6.18]), rheumatoid arthritis (2.23 [1.51, 3.31]), osteoarthritis (2.01 [1.71, 2.36]) and diabetes mellitus (1.53 [1.16, 1.98]), with a greater proportion developing ≥1 of these conditions over the follow-up period (15.7% vs. 5.0% [p<0.001]); a similar pattern was seen for women (10.1% vs. 3.4% [p<0.001]). Individuals who were p.C282Y/p.H63D heterozygotes also had more haemochromatosis diagnoses, although excess morbidity was modest.

Comment (LY): Historically *HFE* haemochromatosis was diagnosed on the basis of evidence of iron overload; however, with the understanding of the genetics and mechanism of the disease, diagnosis based on screening and family studies is now much more common. Recent cohorts have suggested a low prevalence of clinical manifestations; however, this study of a large number of generally well volunteers shows that clinical features associated with the disease are significantly more common in the homozygote population. Unfortunately, the results cannot be correlated with iron levels, which would be of interest, nevertheless the results suggest that early diagnosis and subsequent treatment with venesection are definitely worthwhile.

Reference: BMJ 2019;364:k5222
Abstract

Long-term outcomes among patients discharged from the hospital with moderate anemia

Authors: Roubinian NH et al.

Summary: These researchers reported the prevalence of anaemia at and after discharge from a total of 21 US hospitals, along with associated morbidity and mortality events, for a retrospective cohort of 445,371 adult survivors who had been hospitalised a total of 801,261 times during 2010–2014. The prevalence of moderate anaemia (haemoglobin level 7–10 g/dL) at discharge increased significantly from 20% in 2010 to 25% in 2014 while RBC transfusions fell significantly from 39.8 to 28.5 units per 1000 patients. There was also a significant decrease in the proportion of patients whose moderate anaemia resolved within 6 months of discharge (from 42% to 34%), with concurrent significant decreases in RBC transfusions and re-admissions from 19% to 17% and from 37% to 33%, respectively. The adjusted 6-month mortality rate for patients with moderate anaemia fell significantly from 16.1% to 15.6% during this period, with a parallel decrease seen for all other patients.

Comment (LY): Worldwide there has been a shift to less RBC transfusions, as it has become clear that liberal transfusion thresholds in a wide range of acute scenarios do not improve and may harm outcomes. However, it is reassuring to see that in this large cohort, such a change in practice does not adversely affect longer term outcomes. However, as elegantly summarised in the editorial with this paper, it also highlights that patient blood management programmes also need to incorporate other therapies for anaemia to try and improve the haemoglobin result subsequently, such as appropriate investigation for cause, and iron infusions.

Reference: Ann Intern Med 2019;170:81–9
Abstract

Thrombopoietin level predicts response to treatment with eltrombopag and romiplostim in immune thrombocytopenia

Authors: Al-Samkari H & Kuter DJ

Summary: This retrospective analysis of patients with ITP sought to determine the predictive ability of baseline thrombopoietin level on response to treatment with eltrombopag (n=37) or romiplostim (n=46). Significant predictive relationships were seen between thrombopoietin level and the likelihood of an overall response, a moderate response and a superior response, with significant inverse correlations seen between thrombopoietin level and each of these response types; e.g. each 10 pg/mL increase in thrombopoietin level was associated with an overall response to eltrombopag (OR 0.524 [95% CI 0.327, 0.837]) and romiplostim (0.905 [0.844, 0.970]). Thrombopoietin level thresholds of ≤136 pg/mL among eltrombopag recipients and ≤209 pg/mL among romiplostim recipients were found to be optimal for differentiating responders from nonresponders. Most nonresponders had high thrombopoietin levels, but the addition of low-dose prednisone usually led to a response.

Comment (LY): ITP that fails first-line therapy is a challenge. Internationally, thrombopoietin receptor agonists are more likely to be second-line. These agents are expensive and have some disadvantages, such as dietary restrictions associated with eltrombopag and the requirement for long-term use. Prediction of those where benefit is more likely may be of value in deciding treatment algorithms. This retrospective single-centre analysis used a commercially available thrombopoietin ELISA, showing lower levels are more likely to respond. If the results are confirmed in larger numbers, this approach may be clinically valuable – also of interest is the increase in response using combinations of agents to target this immune disorder by more than one mechanism simultaneously.

Reference: Am J Hematol 2018;93:1501–8
Abstract

Predictive value of venous thromboembolism (VTE)-BLEED to predict major bleeding and other adverse events in a practice-based cohort of patients with VTE

Authors: Klok FA et al.

Summary: Data from the XALIA study were used to validate the VTE-BLEED score for predicting major bleeding during chronic anticoagulation for VTE. Prognostic indices of VTE-BLEED for major bleeding at days 30 and 90 were calculated for 4457 participants, who had a median at-risk time of 190 days. Compared with participants who were low risk according the VTE-BLEED, those at high risk had greater 30- and 90-day major bleeding rates (respective treatment-adjusted hazard ratios 2.3 [95% CI 1.1, 4.5] and 3.2 [1.3, 7.7]). VTE-BLEED provided similar predictive utility for selected patients with unprovoked VTE and those treated with rivaroxaban. A high VTE-BLEED score was also associated with a significantly increased risk of death from any cause (treatment-adjusted hazard ratio 11 [95% CI 4.8, 23]), but not recurrent VTE (1.5 [0.85, 2.7]).

Comment (LY): Over recent years, the focus has been largely on the risk of VTE recurrence in terms of selection of long-term anticoagulation. However, risk of major bleeding complications is an important consideration. This score includes factors that are well known to carry increased bleeding risk, such as active cancer, renal disease, anaemia and older age. There is certainly reassurance in the high negative predictive value of a low score, although it is not surprising; the rate of significant bleeding in the younger, relatively healthy adult population with VTE is low in clinical practice, and confirmed in this large real-world cohort study.

Reference: Br J Haematol 2018;183:457–65
Abstract

Thirty-day outcomes in patients with acute pulmonary embolism who discontinued anticoagulant therapy before 90 days

Authors: Nieto JA et al., RIETE Investigators

Summary: The 30-day rate of PE-related death, sudden death or recurrent VTE was evaluated in patients with PE from the RIETE database (n=34,447) who were not anticoagulated (n=47) or had received anticoagulation for <90 days (n=1348). Among patients who had not received anticoagulation, the fatal PE rate was 53% and the sudden death or nonfatal recurrent VTE rate was 0.45%; the respective rates for those who stopped anticoagulation prematurely were 3.33% and 1.48%. The incidence of the composite of the three outcomes declined logarithmically from 6.36 per 100 patient-days in patients who did not receive anticoagulation to 0.13–0.32 per 100 patient-days in those who received anticoagulation for 8–90 days; during the first week of follow-up, the respective incidence rates were 13.9 and 0.31–0.60 per 100 patient-days. Untreated patients had a 27-fold higher adjusted likelihood of one of the outcomes than treated patients; this declined progressively to 2.5- to 7-fold higher in patients treated for ≥7 days.

Comment (LY): In these days when anticoagulation is easily and readily administered for PE, it is of value to collect data on patients for whom it is not feasible to better inform these decisions. As might be expected, the risk of death and fatal PE is very high. It was however particularly high in those who did not receive any treatment, or were treated for less than 1 week. Therefore, attempting anticoagulation where possible seems important, even short-term. Intensity of anticoagulation is not discussed in this paper, but in our experience even reduced doses have some benefit. The relative benefit of inferior vena cava filters is also not addressed, but would often be considered in this cohort.

Reference: Am Heart J 2018;206:1–10
Abstract