Thrombosis & Haemostasis Research Review™

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In this issue:

Abbreviations used in this issue:

AAV5 = adeno-associated virus 5; **AF** = atrial fibrillation; **ATRA** = all-*trans* retinoic acid; **COAST** = Coagulopathy of Severe Trauma; **DOAC** = direct oral anticoagulant; **DVT** = deep vein thrombosis; **FVIII** = clotting factor VIII; **ITP** = immune thrombocytopenia; **LMWH** = low-molecular-weight heparin; **PE** = pulmonary embolism; **SVT** = superficial vein thrombosis; **VTE** = venous thromboembolism.

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

We begin this issue with the PATCH-Trauma trial of prehospital tranexamic acid for adults with severe trauma at high risk for trauma-induced coagulopathy that finds no benefit in terms of disability prevention but a short-term survival advantage. This is followed by results from ELAN that evaluated whether more prompt initiation of anticoagulation after stroke in patients with nonvalvular atrial fibrillation (AF) reduces subsequent ischemic events without increasing the risk of a haemorrhagic complication. The next two papers provide data from trials of gene therapies in haemophilia – a two-year update from GENEr8-1 reports durable endogenous factor VIII (FVIII) protein production and reduced bleeding rates in men with severe haemophilia A after a single infusion of valoctocogene roxaparvovec, and HOPE-B finds etranacogene dezaparvovec safe and efficacious in adults with moderate or severe haemophilia B. Other recently reported results for therapeutics in haemophilia include the ATLAS-A/B trial of fitusiran prophylaxis in people with severe haemophilia A or haemophilia B without inhibitors, and the HAVEN-6 trial of emicizumab in mild and moderate haemophilia A.

We hope you enjoy this update in Thrombosis & Haemostasis research, and look forward to receiving any feedback you may have.

Kind Regards,

Professor Harshal Nandurkar
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Prehospital tranexamic acid for severe trauma

Authors: The PATCH-Trauma Investigators and the ANZICS Clinical Trials Group

Summary: The Australian and New Zealand PATCH-Trauma (Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage) study evaluated the benefit of prehospitalisation antifibrinolytic therapy with tranexamic acid versus placebo in adults with suspected severe trauma at high risk for trauma-induced coagulopathy. A total of 1,310 adults (mean age 44 years), predominantly men, with Coagulopathy of Severe Trauma (COAST) score ≥ 3 were accrued within three hours of traumatic injury from emergency prehospital medical services such as ambulances and randomised 1:1 to commence tranexamic acid treatment or placebo either on scene or en route to the hospital. Tranexamic acid treatment consisted of a 1 g bolus prehospitalisation plus a 1-g infusion over eight hours after hospital admission. Coagulopathy risk was determined by paramedics or pre-hospital physicians utilising the COAST score, considering factors such as vehicle entrapment, systolic blood pressure, body temperature, major chest injury likely to require intervention and likely intra-abdominal or pelvic injury. Although tranexamic acid conferred an early survival benefit over placebo with a risk ratio of 0.79 (28-day mortality, 17.3% vs 21.8%) it failed to prevent disability in survivors – the primary trial outcome measure - with approximately half of survivors in each trial arm having a favourable functional outcome at six-months as evaluated using the Glasgow Outcome Scale–Extended (GOS-E ≥ 5, 53.7% vs 53.5%).

Comment: Prior evidence leading to this PATCH-Trauma trial showed that tranexamic acid reduces mortality among patients with bleeding trauma (CRASH-2 trial, 2010) and that early treatment was most effective, with no benefit when the drug was administered more than three hours after injury. One limitation was that the follow-up was only for 28 days in the CRASH-2 trial, while it is known that the recovery period is often longer. Hence, this PATCH-Trauma trial was designed to administer tranexamic acid prehospital and within three hours of injury and with a longer follow-up period of six months. There appeared to be a benefit in improving survival at early time points. More patients in the tranexamic acid group than in the placebo group survived, but more patients in the tranexamic acid group had severe disability. It is intuitive to hypothesise that when severely injured patients survive, there will be increased frequency of disability. The best outcomes obviously are improved survival with improved functional ability. But it will be difficult to withhold treatment that leads to improved survival in the short-term because of concerns of disability in the longer term.

Reference: N Engl J Med. 2023;389(2):127-36
Abstract

Early versus later anticoagulation for stroke with atrial fibrillation

Authors: Fischer U et al., for the ELAN Investigators

Summary: The international open-label ELAN trial aimed to elucidate the optimal timing of direct oral anticoagulant (DOAC) therapy with respect to the risk: benefit profile after acute ischemic stroke in patients with nonvalvular AF. Over two thousand adult patients (median age, 77 years; 45% female) with AF who experienced an acute ischemic stroke were randomised to initiate DOAC treatment with rivaroxaban, dabigatran, apixaban or edoxaban therapy early (n=1,006), or late as per current recommendations, with treatment initiation timing dependent on stroke severity according to infarct size on imaging (i.e., mild stroke, 2 vs 3-4 days; moderate stroke, 2 vs 6-7 days; severe stroke, 6-7 vs 12-14 days). Rates of a primary composite outcome measure including recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial haemorrhage or vascular death within one month numerically favoured more prompt intervention (2.9% vs 4.1%). A trend towards benefit with early anticoagulation with respect to prevention of secondary stroke was found, with lower absolute rates of recurrent stroke at 30 and 90 days (1.4% vs 2.5% and 1.9% vs 3.1%, respectively), but did not reach statistical significance. Both strategies had a comparable safety, with a 0.2% incidence of symptomatic intracranial haemorrhage at one month in both trial arms.

Comment: Several guidelines recommend delay in the initiation of anticoagulation after ischemic stroke. For example, the European guidelines suggest delay of anticoagulation for three days after minor stroke, six days after moderate stroke, and 12 days after a serious stroke, with severity assessed by the NIHSS score. This trial studied initiation of DOACs within 48 hours after stroke onset in participants with minor or moderate stroke and on day 6 or 7 in those with major stroke. This trial also used an imaging-based definition of stroke severity rather than the NIHSS score. The results of this trial showed no major differences between the early-treatment group and the later-treatment group with respect to the primary outcome (a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial haemorrhage or vascular death within 30 days after randomization) or the secondary outcomes (which included the individual components of the composite primary outcome at 30 and 90 days). The results in the article are expressed as the potential for a 2.8-percentage-point advantage and a 0.5-percentage-point disadvantage of early initiation with respect to the composite primary outcome (on the basis of the 95% confidence interval for the difference in outcomes). The frequency of recurrent ischaemic stroke up to 30 days was 1.4% with early intervention and 2.5% with later commencement of anticoagulation and this difference of 1.1% is quite small. However, there were very few symptomatic intracranial haemorrhages (0.2% in both groups), indicating that the risk of haemorrhage with early intervention was not higher. There is still progress to be made in this area, particularly for those patients with minor haemorrhagic conversion of ischemic infarcts as these patients were excluded from trials and we do not know if minor haemorrhage will affect outcomes from early intervention.

Reference: N Engl J Med. 2023;388(26):2411-21
Abstract

Two-year outcomes of valoctocogene roxaparvovec therapy for hemophilia A

Authors: Mahlangu J et al., for the GENEr8-1 Trial Group

Summary: Previously published 52-week data from the phase 3 GENEr8-1 trial of the adeno-associated virus vector-based gene therapy valoctocogene roxaparvovec showed significantly increased endogenous FVIII protein production and reduced bleeding rates in men with severe haemophilia A on standard FVIII prophylaxis after a single infusion (Ozelo M et al. *N Engl J Med.* 2022;386[11]:1013-25). Now, two-year results demonstrate that control of bleeding is durable with estimated maintenance of mild haemophilia levels for five years. Briefly, enrolled adult patients (n=134) who had been on prophylactic FVIII replacement therapy for at least 12 months and had residual FVIII levels ≤ 1 IU/dL received a single infusion of 6×10^{13} vector genomes of valoctocogene roxaparvovec per kilogram of body weight. At two-years post-treatment, the improvement in bleeding rates was sustained, preventing a mean of four events annually for an overall 84.5% reduction in annualised treated bleeding rate versus baseline ($p<0.001$). Almost complete eradication of FVIII use was noted and mean endogenous FVIII activity at two-year analysis was 22 IU/dL increased from pre-infusion, although decreases were found after one year. Extrapolation of these data in pharmacokinetic modelling estimated a mean FVIII activity of 11.8 IU/dL at five-years post-infusion, comparable to that in patients with mild-to-moderate haemophilia A according to epidemiologic data.

Comment: This is follow-up safety and efficacy data at a two-year time point from a previously published phase 3 trial of valoctocogene roxaparvovec for haemophilia A. The median FVIII activity was between 6%-39% of normal, correlating with a mild haemophilia phenotype, which was confirmed with an 84.5% reduction in bleeding events. Modelling by the authors based on prior phase 1-2 data predicts that FVIII activity would decrease to 10% of normal (as in mild haemophilia) by three-to-five years depending on the assay used to quantify FVIII levels. Anti-AAV antibodies developed in all recipients, precluding retreatment but there was no obvious relationship between the development of antibodies and FVIII activity. The principal adverse effect is a hepatocellular pattern of liver function test abnormalities seen in laboratory analyses in 88.8% of participants. These abnormalities were largely grade 1, lasted a median of 21.0 days and are related to the effects of adeno-associated virus used to carry the FVIII genome into the hepatocytes. In a minority of patients, abnormal liver function tests were still noted at the two-year time point. These two-year data will inform world-wide therapeutic approval by various medical licensing agencies.

Reference: N Engl J Med. 2023;388(8):694-705
Abstract

Gene therapy with etranacogene dezaparvovec for hemophilia B

Authors: Pipe S et al.

Summary: Data from HOPE-B (Health Outcomes with Padua gene; Evaluation in Hemophilia B) demonstrates superior prevention of bleeding episodes with the gene therapy etranacogene dezaparvovec compared to routine coagulation factor IX replacement in men with moderate-to-severe haemophilia B. Men with congenital haemophilia B classified as severe or moderately severe (n=54) with endogenous factor IX activity ≤2% of normal were accrued from sites in the US and Europe and received a single etranacogene dezaparvovec infusion at a dose of 2×10^{13} genome copies/kg following a six-month period of factor IX prophylaxis. The presence/absence of pre-existing adeno-associated virus 5 (AAV5) neutralising antibodies was not a trial entry criterion. Results included a 64% reduction in the relative risk of bleeding episodes with gene therapy between months seven to 18 compared to factor IX prophylaxis in the lead-in period (annual bleeding rate reduced from 4.19 to 1.51; rate ratio, 0.36). Other benefits with gene therapy included significant reductions in rates of spontaneous bleeding, joint bleeding, usage of factor IX concentrate and a significant increase in factor XI activity from one month sustained up to 18-months post-infusion. A favourable safety profile was reported.

Comment: The Padua-IX variant used in this gene transfer study has factor IX activity that is six-to-eight times higher than the normal variant. Presence of pre-existing anti-AAV5 antibodies was not taken into account for trial inclusion. The primary endpoint of annualised bleeding rate during months seven-18 after treatment decreased significantly to 1.51 as compared against 4.19 during the lead-in period of the preceding six months. The mean increase in factor IX activity was ~36% in this population of patients with baseline factor IX activity ≤2% of the normal value. The reduction in bleeding correlated with a decrease in the mean usage of factor IX by approximately 250,000 IU per participant per year. Abnormal liver function tests, such as ALT elevation in 20%, were mostly mild to moderate. All patients developed anti-AAV antibodies and there was no development of factor IX inhibitors. This data places gene therapy as an advancement in improving care and quality of life in patients with haemophilia B.

Reference: N Engl J Med. 2023;388(8):706-18
Abstract

Heparin for women with recurrent miscarriage and inherited thrombophilia (ALIFE2)

Authors: Quenby S et al., for the ALIFE2 Block Writing Committee & ALIFE2 Investigators

Summary: An international open-label, randomised controlled trial – ALIFE2 – reports no improvement in the live birth rate with low-molecular-weight heparin (LMWH) use during pregnancy in women with a history of multiple miscarriages and inherited thrombophilia. The international trial accrued a total of 326 pregnant women 42 years or younger from hospitals in the UK, the Netherlands, the US, Belgium and Slovenia. All women had confirmed inherited thrombophilia (most commonly heterozygosity for factor V Leiden, prothrombin 20210A mutation or protein S deficiency) and a history of at least two pregnancy losses (median, 3). Standard obstetric care was provided to all women throughout their pregnancy ± anticoagulation with once-daily subcutaneous LMWH initiated before seven weeks' gestation. LMWH did not improve miscarriage rates with just over 70% of women in each trial arm delivering a live infant. Incidence of adverse events were similar, at 24% in the LMWH cohort and 23% in the control cohort. There were no cases of serious adverse events or heparin-induced thrombocytopenia. The study authors recommended that LMWH not be used in this population.

Comment: This trial covered the unmet need of clarity about the effect of anticoagulant treatment for recurrent pregnancy loss in women with hereditary thrombophilia. Inherited thrombophilia types were factor V Leiden mutation, prothrombin gene mutation (G20210A), antithrombin deficiency, protein C deficiency, or protein S deficiency. Women were administered a number of LMWH formulations at a prophylactic dose (e.g., enoxaparin 40 mg) regardless of body weight. LMWH was continued throughout pregnancy. The only additional relevant intervention was with low-dose aspirin in women with a higher risk of preeclampsia. This trial has taken over eight years to complete with the recruitment of 326 participants. The data is convincing that there was no impact on live birth rates. The numbers were too low for subgroup effects. This leads to the recommendation of not screening for inherited thrombophilia in women with recurrent pregnancy loss as the standard intervention with LMWH had no benefit. One criticism of the trial is that it evaluated LMWH alone, while combination aspirin plus LMWH is more commonly used in this setting.

Reference: Lancet. 2023;402(10395):54-61
Abstract

Effectiveness and safety of apixaban vs warfarin in patients with venous thromboembolism with risk factors for bleeding or for recurrences

Authors: Cohen A et al.

Summary: This retrospective analysis of pooled data from five US claims databases investigated the relative efficacy and safety of apixaban compared to warfarin in patients with venous thromboembolism (VTE) with risk factors for bleeding or for recurrences. Over 150 thousand patients who initiated apixaban (n=94,333) or warfarin (n=60,786) for an index VTE event between 2014 and 2019 and were at risk of bleeding due to thrombocytopenia or a history of bleeding, or at risk for recurrent VTE due to thrombophilia, chronic liver disease or an immune-mediated disorder were identified. Stabilised inverse probability treatment weighting analysis found a diminished risk of VTE recurrence, major bleeding and clinically relevant non-major bleeding in the apixaban treated cohort versus the warfarin treated cohort (hazard ratios, 0.72, 0.70 and 0.83, respectively).

Comment: Patients with VTE and increased risk of bleeding were excluded or underrepresented in the phase 3 clinical trials on DOACs. Similarly, the major DOAC studies trials required testing for primary hypercoagulable state and the proportions of patients with thrombophilia in these trials were low. This study covers several insurance datasets plus Medicare and Medicaid for patients with at least one pharmacy claim for warfarin or apixaban during the 30-day period following the index VTE event. The two subgroups with risks of bleeding that were evaluated were those with known history of bleeding and of thrombocytopenia. Three subgroups were included with increased VTE risk - those with known thrombophilia, chronic liver disease or immune conditions. Overall, the study noted that the risk of major bleeding and clinically relevant non-major bleeding was lower with apixaban compared to warfarin amongst patients with VTE with and without a history of bleeding. An additional observation for major bleeding was that for patients with thrombocytopenia, apixaban and warfarin had a similar risk of major bleeding, whereas for patients without thrombocytopenia apixaban had a lower risk of major bleeding versus warfarin.

Reference: Adv Ther. 2023;40(4):1705-35
Abstract

Venous thromboembolism recurrence among patients who abandon oral anticoagulant therapy in the USA

Authors: Alberts M et al.

Summary: A retrospective longitudinal study utilising data from the Symphony Health database emphasises the importance of continuous DOAC use after primary VTE event (deep vein thrombosis [DVT] or pulmonary embolism [PE]) to mitigate severe and potentially fatal sequelae. A cohort of over 306 thousand patients with balanced baseline characteristics who initiated DOAC treatment between April 2017 and October 2020 and filled at least one repeat prescription or abandoned treatment at/before the first refill comprised the study population. Weighted Kaplan–Meier and Cox proportional hazard models revealed a significantly increased probability of VTE recurrence in DOAC abandoners, with the risk estimated to be elevated by 72% at three months (7.74% vs 4.65%; hazard ratio 1.72) and 53% at 12 months compared to patients who continued DOAC therapy (9.91% vs 6.89%; hazard ratio, 1.53).

Comment: This report confirms existing literature that DOAC discontinuation is associated with increasing VTE recurrence. The power of this study is the real-world experience in the survey of over 300,000 patients of whom 8.4% abandoned their first prescription for a DOAC, based on pharmacy and insurance data. These 'abandoners' were compared against those who continued anticoagulation. Patients were covered by commercial insurance (almost 50%) and then Medicare and Medicaid. Just about half of the patients in both groups had DVT as their index VTE diagnosis, followed by PE in ~35% and the remaining patients had both DVT plus PE. After three months of follow-up, the probability of VTE recurrence as a composite outcome of DVT or PE was 7.74% in the abandoner cohort compared to 4.65% in the non-abandoner cohort and this progressively increased to 11.76% and 8.56%, respectively, at 24 months. This provides evidence about the importance of continuing anticoagulation, especially in the initial period after VTE diagnosis.

Reference: Adv Ther. 2023;40(4):1750-64
Abstract

Fitusiran prophylaxis in people with severe haemophilia A or haemophilia B without inhibitors (ATLAS-A/B)

Authors: Srivastava A et al.

Summary: A multicentre, open-label, randomised, phase 3 trial – the international ATLAS-A/B trial – reports promising results for prophylactic use of the investigational small interfering RNA therapeutic fitusiran in men with severe haemophilia A or B. Adolescent patients at least 12 years of age and adults accrued to the trial (n=120) had severe haemophilia A with FVIII < 1% or haemophilia B with factor IX level ≤ 2%, had experienced at least six bleeding episodes in the previous six months requiring factor concentrate treatment and had no inhibitory antibodies to FVIII or factor IX. Patients were allocated to treatment with on-demand factor concentrates for bleeding/breakthrough bleeding episodes ± monthly 80 mg subcutaneous fitusiran. At a median follow-up of almost eight months fitusiran prophylaxis elicited a significant reduction in the annualised bleeding rate versus on-demand clotting factor concentrate (median: 0 vs 21.8; mean, 3.1 vs 31). In addition, fitusiran obviated factor replacement therapy in half of patients, with zero breakthrough bleeds. The same endpoint was achieved in 5% of patients in the on-demand arm. The most common adverse event in the fitusiran prophylaxis group was increased alanine aminotransferase, reported in 23% of patients. There were no deaths or cases of treatment-related thrombosis. The ATLAS-INH trial is evaluating fitusiran in haemophilia A/B with inhibitors.

Comment: Antithrombin is an endogenous 'brake' that restricts the coagulation cascade to the site of injury proportional to the haemostatic need. Its pivotal role is underscored by the high incidence of VTE in those with antithrombin deficiency. This paper explores the hypothesis that suppression of endogenous anticoagulant will switch the balance towards maintaining haemostasis in those with inherited bleeding disorders such as severe haemophilia A/B. In this study, the effects of reduction of antithrombin with the small interfering RNA therapeutic fitusiran in patients with severe haemophilia A/B was evaluated in terms of annualised bleeding rates. In the comparator arm, patients received on-demand coagulation factors. Fitusiran use was associated with a significant reduction in the annualised bleeding rates, a result associated with an improvement in quality of life. Increased concentrations of alanine aminotransferase in 23% of 79 participants was the most common treatment-emergent adverse event in the fitusiran group. It is important to note that there were no thrombotic episodes with fitusiran usage. In this study, the benefit of fitusiran was not compared with regular coagulation factor prophylaxis, which is known to significantly decrease bleeding episodes but at the inconvenience of frequent intravenous injections and risk of development of inhibitors.

Reference: Lancet Haematol. 2023;10(5): e322-32
Abstract

Thrombosis & Haemostasis Research Review™

Independent commentary by Professor Harshal Nandurkar

Professor Harshal Nandurkar 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).

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Incidence and prognosis of superficial vein thrombosis during pregnancy and the post-partum period

Authors: Wiegers H et al.

Summary: A Danish nationwide cohort study analysed population-level data to explicate the incidence of lower extremity superficial vein thrombosis (SVT) in women in the antepartum/postpartum periods and the risk of subsequent VTE. Data on more than 1.3 million deliveries over a 21-year period spanning 1997 to 2017 derived from the Danish Medical Birth Register, the National Patient Registry and the National Prescription Registry. The incidence of SVT of the legs was low overall, found in a total of 710 women (70% during pregnancy; 30% in the first three months after birth) for an incident rate of 0.6 per 1,000 person-years. Incidence rates of SVT were low during pregnancy but increased with gestation duration (first, second and third trimesters: 0.1, 0.2 and 0.5 per 1,000 person-years, respectively). The highest incidence of lower leg SVT was found in the postpartum period (1.6 per 1,000 person-years). VTE was 100-times more common in pregnant women with, versus without, lower extremity SVT with the risk estimated on Cox proportional hazards modelling to be more than 80-fold elevated (10.4% vs 0.1%; hazard ratio, 83.3).

Comment: Incidence of VTE is four-five-fold higher in pregnancy and especially so in the three months post-delivery. There is a paucity of data regarding the incidence of SVT during pregnancy and the post-partum period and hence, no consensus on treatment. This report describes the incidence of SVT in over 1,270,000 deliveries over a 21-year period in Denmark. The incidence of SVT was observed to be 0.06%. However, the risk of progression to VTE was quite high, with the cumulative incidence of VTE in women with SVT 13.0% (95% CI, 8.3–20.0) versus 0.2% (0.1–0.3) in women without SVT and the median lag between the diagnosis of SVT and DVT ~49 days. Women with prior history of VTE were excluded from the study, and also those developing DVT within a week of SVT diagnosis, in order to avoid misclassification of SVTs that were actually related to DVTs at presentation. This data supports the American Society of Haematology guideline of treating SVT with LMWH. The overall incidence of pre-existent varices was 0.6% in the entire cohort but the association of varices with the risk of SVT was not explored.

Reference: Lancet Haematol. 2023;10(5): e359-66
Abstract

Emicizumab in people with moderate or mild haemophilia A (HAVEN 6): a multicentre, open-label, single-arm, phase 3 study

Authors: Négrier C et al.

Summary: Emicizumab may be a therapeutic option for any severity haemophilia A with the bispecific monoclonal antibody exhibiting efficacy and a safe profile in patients with non-severe disease without FVIII inhibitors in the HAVEN 6 trial, consistent with the other HAVEN suite of studies in severe haemophilia A with/without inhibitors. Trial criteria allowed entry to any age patient with a body weight of at least 3 kg for whom prophylaxis was deemed appropriate with a diagnosis of mild or moderate congenital haemophilia with FVIII activity levels between ≥1% and <40%, a negative test for inhibitor (<0.6 Bethesda Units/mL) and quantified bleeding episodes in the six months prior to trial inclusion. The study population (n=72) included a minority of female patients (4%), the median age was 23.5 years, disease was predominantly of moderate severity (mild, 29%) and half of participants were receiving FVIII prophylaxis at study entry. Patients received a one-month loading dose of 3 mg/kg/week emicizumab followed by monthly maintenance with emicizumab dosed at between 1.5 to 6 mg/kg. At a median follow-up of over 55 weeks the annualised bleed rate for treated bleeds was 0.9 and all-bleed annualised bleed rates were reduced significantly compared to pre-study (2.3 vs 10.1). Two-thirds of patients had no treated bleeds during emicizumab treatment. A favourable safety profile was reported with headache, injection-site reaction and arthralgia the most common adverse events but none resulting in treatment cessation, modification or interruption. No treatment-related serious adverse events, deaths of microangiopathies were reported.

Comment: Prior studies with emicizumab (HAVEN 1-4) focussed on its efficacy in severe haemophilia A with or without inhibitors where it was found to be at least as effective as standard prophylaxis. While the severity and frequency of bleeding in haemophilia correlates with baseline factor levels, there are patients with non-severe haemophilia A (defined as FVIII ≥1% of normal levels) with a significant bleeding phenotype. This study - HAVEN 6 - explores its effectiveness in mild and moderate haemophilia deemed by their haematologist as needing prophylaxis. This was a single-arm, open-label, non-controlled study with the comparison being bleed data in the 24 weeks before the study collected retrospectively. All of the three dosing schedules achieved a mean FVIII level ≥ 50%. There was a significant decrease in the annualised bleeding rates with emicizumab as compared to the 24 weeks prior to the study. This data is not surprising given the efficacy of emicizumab in severe haemophilia A. There were no significant thrombotic adverse events. Even if emicizumab turns out to be equally effective as intravenous prophylaxis with clotting factors, it is certainly more convenient given the subcutaneous route and one-to-four weekly administration.

Reference: Lancet Haematol. 2023;10(3): e168-77
Abstract

All-trans retinoic acid added to treatment of primary immune thrombocytopenia

Authors: Yang J et al.

Summary: A systematic review and meta-analysis analysed the evidence for the benefit of adjunct all-*trans* retinoic acid (ATRA) in Chinese patients with primary immune thrombocytopenia (ITP). Five observational studies and four randomised clinical trials, all Chinese, including 760 patients were identified from a search of online databases. The pooled overall response rate from observational studies was 59.5%, including 20.6% with a complete response. Meta-analysis of clinical trial data indicated that the addition of ATRA to standard therapy outperformed standard therapy alone, associating with a significantly increased likelihood of a response, complete response and durable response with odds ratios of 3.21, 2.12 and 3, respectively. A protective effect against relapse and the need for salvage therapy was also noted (odds ratios, 0.30 and 0.36). The findings support the adjunct use of ATRA in patients with ITP.

Comment: While the role of ATRA in the treatment of acute promyelocytic leukaemia is well established, there has been recent interest in the usefulness of ATRA in ITP. This draws on the roles that ATRA plays in inducing megakaryocyte differentiation, maturation and immune regulation. There have been several observational studies and randomised clinical trials published between 2010-2022 and this paper provides a timely systematic review and meta-analysis. Five studies were from multiple centres and four studies were from single centres. The meta-analysis included 760 participants (187 patients in the observational studies and 573 in randomised controlled trials). Amongst the four randomised controlled trials, there were 132 patients with newly diagnosed ITP and 441 patients with relapsed or refractory ITP. The median age of the patients was 32–46 years, and approximately 38%–53% of patients were men. The median baseline platelet count was from 11.9 x 10^9/L to 20 x 10^9/L. The dose of ATRA varied from fixed doses of 10 mg twice-daily, 10 mg three times per day and 20 mg/m^2 daily. ATRA was given variably with prednisolone, dexamethasone, danazol or low-dose rituximab and the comparison was with these four drugs on their own. The individual trials demonstrated variability in the effect of ATRA. However, in this combined analysis, as shown in the data above, all parameters of sustained response rate, overall response rate and complete response rate favoured the use of ATRA. There was also a significant reduction in the frequency of use of salvage treatment. The commonest side effects were the expected ones of dry skin, headache, dizziness and rash. Work to follow would be the use of ATRA together with, or in comparison to, thrombopoietin receptor agonists.

Reference: Ann Hematol. 2023;102(7):1695-704
Abstract

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