Thrombosis & Haemostasis Research Review™

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Issue 26 - 2023

In this issue:

Abbreviations used in this issue:

ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; **AF** = atrial fibrillation; **CI** = confidence interval; **DOAC** = direct-acting oral anticoagulant; **DVT** = deep vein thrombosis; **FVIII** = coagulant factor VIII; **HR** = hazard ratio; **ITP** = immune thrombocytopenia; **iTTP** = immune-mediated TTP; **OR** = odds ratio; **PE** = pulmonary embolism; **QALY** = quality-adjusted life year; **SCT** = stem cell transplant; **TRA** = thrombopoietin receptor agonist; **TTP** = thrombotic thrombocytopenic purpura; **VKA** = vitamin-K antagonist; **VTE** = venous thromboembolism.

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

This issue includes results from the German phase 3 AXADIA–AFNET 8 trial of anticoagulation with apixaban versus phenprocoumon in patients with nonvalvular atrial fibrillation (AF) and end-stage renal disease on chronic haemodialysis. We have also included data regarding the efficacy of allogeneic stem cell transplant (SCT) for sickle cell disease with regard to reduction in vaso-occlusive events that provides a baseline for evaluation of novel therapies including autologous transplant with gene therapy; and a retrospective analysis from the UK reports the long-term effectiveness of pre-emptive anti-CD20 treatment for relapse prevention in immune-mediated thrombotic thrombocytopenic purpura (iTTP). Finally, a cost-effective analysis from the US health system perspective suggests that in the second-line treatment setting earlier use of splenectomy or rituximab and delayed thrombopoietin receptor agonists (TRAs) may be a favourable strategy for adults with chronic immune thrombocytopenia (ITP) and findings from the prospective Vienna Cancer and Thrombosis Study suggest that certain cancer patients with non-O blood types may have an increased risk of blood clots.

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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Risk and timing of venous thromboembolism in patients with gastrointestinal cancer: a nationwide Danish cohort study

Authors: Tønnesen J et al.

Summary: A research group from Herlev and Gentofte Hospital in Copenhagen, Denmark conducted a retrospective analysis of nationwide registries to elucidate the risk and timing of venous thromboembolism (VTE) in patients with a first diagnosis of gastrointestinal cancer. A total of 87,069 adult patients (median age range, 68.2 to 72.4 years) diagnosed with gastrointestinal cancer over an 11-year period spanning 2008 to 2018, inclusively, were identified and followed for one year (mean 271 days). The most common location of malignancy was colorectal, accounting for over 60% of all gastrointestinal cancers, followed by pancreas (12%), oesophagus (7.3%), stomach (6.9%), liver (5.8%), gallbladder (3%) and small intestine (1.9%). A 4.4% absolute one-year risk of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), was found in the overall study cohort with risk ranging from 3.6% to 7.8% in liver/colorectal cancer and pancreatic cancer, respectively. The greatest risk for VTE was observed in the four-month period following index gastrointestinal cancer diagnosis with up to three-quarters of cases occurring in this time frame. Factors identified as elevating the risk of VTE on Cox proportional-hazard modelling analysis included prior VTE, heart failure, chronic obstructive pulmonary disease, liver disease, chronic kidney disease and diabetes. One-third of patients with a gastrointestinal tumour died in the first year after diagnosis but one-year mortality rate by cancer type ranged from 20% to 70.3% with pancreatic cancer the most lethal malignancy and colorectal the least lethal.

Comment: The strength of this report is that it is based on high quality Danish registry data from over 87,000 patients with gastrointestinal cancer. The primary outcome was first incident VTE event. All VTE events on the date of cancer diagnosis and within one year thereafter were identified. Baseline use of oral anticoagulant therapy ranged from 7.5% to 9.3%, probably related to approximately 8%-10% history of atrial fibrillation and a prior VTE event that ranged from 1.9% to 4.1% in small intestinal and pancreatic cancer patients, respectively. The take home messages were that most episodes of VTE occurred within the first 120 days of diagnosis with higher rates amongst patients with pancreatic, gastric and gallbladder cancers. Other patient factors and comorbidities that increased the risk of VTE were age over 79 (hazard ratio [HR] 1.58), prior VTE (HR 1.09), heart failure (HR 1.14), chronic obstructive pulmonary disease (HR 1.12), liver disease (HR 1.40), chronic kidney disease (HR 1.23) and diabetes (HR 1.08). Mortality was increased at 33% and mortality was highest in patients with pancreatic cancer (70.3%) and lowest in patients with colorectal cancer (20.6%), respectively. This paper raises question about the increased awareness for prophylaxis in patients with higher cancer-VTE scores (e.g., Khorana score).

Reference: BMJ Open 2023;13(1):e062768

Abstract

A randomised controlled trial comparing apixaban with the vitamin K antagonist phenprocoumon in patients on chronic haemodialysis: The AXADIA-AFNET 8 study

Authors: Reinecke H et al.

Summary: The German AXADIA–AFNET 8 (Compare Apixaban and Vitamin K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease; NCT02933697) phase 3b trial failed to demonstrate improved safety or efficacy of anticoagulation with the factor Xa inhibitor apixaban versus the vitamin-K antagonist (VKA) phenprocoumon in patients with nonvalvular AF and end-stage renal disease on haemodialysis. A total of 97 patients (mean age 75 years; 30% women) with chronic (paroxysmal, persistent or permanent) AF and end-stage kidney disease requiring chronic haemodialysis, indicated for oral anticoagulation by virtue of increased risk of stroke or systemic embolism (CHA_2DS_2-VASc score ≥2) were accrued to the trial. Patients received open-label apixaban (2.5 mg twice-daily; n=48) or phenprocoumon (international normalised ratio, 2.0 to 3.0; n=49). At a median follow-up exceeding 14 months there was no significant difference between arms in the primary safety or efficacy outcome measures, both composite outcomes comprised of major and clinically relevant non-major bleeding or death (45.8% vs 51%; hazard ratio [HR] 0.93; 95% confidence interval [CI], 0.53-1.65); and ischemic stroke, all-cause death, myocardial infarction and DVT or PE (20.8% vs 30.6%; *p*=0.51), respectively. The authors noted the high rate of cardiovascular events in this population even with anticoagulation.

Comment: While direct-acting oral anticoagulants (DOACs) for AF are efficacious and safe in patients with mild to severe renal failure (chronic kidney disease stage II through IV), their safety in AF in the context of chronic haemodialysis is unknown. The primary goal of this study was to compare the safety of apixaban with VKA therapy (phenprocoumon is the most common VKA in Austria, Germany). Prior data has established that in patients on haemodialysis apixaban dosage of 2.5 mg twice-daily was associated with identical plasma levels compared with individuals with normal kidney function receiving 5 mg twice-daily. The median follow-up time was 429 days on apixaban therapy and 506 days on phenprocoumon for a total of 97 patients. The primary safety outcome measure occurred in 22 events in patients randomised to apixaban and 25 events occurred in patients randomised to VKA with 18 on-treatment events in both groups. The median time in target range in patients randomised to VKA was 50.7% while of 48 patients randomised to apixaban, 44 adhered to the intake of medication according to protocol. There were no differences in all-cause mortality between the two groups (18.8% vs 24.5%). With regard to secondary efficacy outcomes regarding prevention of thromboembolic events, 10 events occurred on apixaban treatment and 15 events occurred on VKA treatment, most events were cardiovascular deaths. It is important to note that while no differences were observed in safety or efficacy outcomes between apixaban and VKA, patients on chronic haemodialysis with AF remain at high risk of thromboembolic and bleeding events on oral anticoagulation and so other interventions may be required in this high-risk cohort.

Reference: Circulation 2023;147(4):296-309
Abstract

Long-term risk of relapse in immune-mediated thrombotic thrombocytopenic purpura and the role of anti-CD20 therapy

Authors: Doyle A et al.

Summary: Doyle et al retrospectively analysed data from the United Kingdom Thrombotic Thrombocytopenic Purpura (TTP) registry to explicate the natural history of iTTP and the effectiveness of pre-emptive anti-CD20 treatment for a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) relapses (ADAMTS13 activity of <20% without thrombocytopenia). More than 400 patients (n=443) with at least three years follow-up were identified (median follow-up, 8.6 years) and included in the study. Almost one-third of patients experienced at least one relapse over the study period for a five-year relapse rate of 40% (~60% ADAMTS13 relapse and ~40% clinical relapses with a recurrence of thrombotic microangiopathy). A significant reduction in clinical relapses (11.1% vs 22.6%; *p*=0.0004) but increase in ADAMST13 relapses (8% vs 16%) was noted in cases diagnosed after 2012, attributed by the authors to the introduction of regular monitoring and pre-emptive anti-CD20 therapy. More than half of the study population received front-line anti-CD20 therapy, predominantly rituximab, which was effective at preventing progression to clinical relapse in 96% of patients and retained efficacy on subsequent retreatments. A subgroup of patients (6%) was identified who experienced early and frequent relapses (average time to first relapse 1.7 years). A propensity for relapse with a greater than two-fold likelihood was found in patients with Black Caribbean ethnicity (odds ratio [OR] 2.66). It was concluded that pre-emptive anti-CD20 treatment has long-term effectiveness for ADAMTS13 relapse.

Comment: The strength of this study is that it followed a large cohort of iTTP patients over 10 years in the setting of a registry. This was before caplacizumab was accessible as a treatment for iTTP. The important messages are that despite effective initial treatment, the relapse rate is 40%, which supports the argument for close monitoring of ADAMTS13 levels. There were fewer 'clinical relapses' (i.e., overt phenotypes of iTTP with thrombocytopenia) and more 'ADAMTS13 relapses' (manifested with ADAMTS13 activity level of <20% without thrombocytopenia) due to frequent monitoring. It was also reassuring to note that relapses responded again to anti-CD20 therapies. The authors noted a small group (6%) of patients with frequent relapses but who also continued to response to pre-emptive treatment. Another point to note by the authors was that there was higher incidence of iTTP amongst Black Caribbean and Black African populations in the UK with more frequent relapses.

Reference: Blood 2023;141(3):285-94
Abstract

Reduction in vaso-occlusive events following stem cell transplantation in patients with sickle cell disease

Authors: Leonard A et al.

Summary: In order to explicate the efficacy of allogeneic SCT for sickle cell disease with regard to vaso-occlusive events an analysis of electronic medical chart data from patients enrolled in one of 11 US National Institutes of Health or Children's National Hospital clinical trials was undertaken. The study included 163 patients (60% male; 91% HbSS genotype; average age 21 years, range 7 months-64 years) with sickle cell disease who received an allogeneic SCT between 2005 and 2019 and had complete records for two years prior to and at least two years following transplant. Pre-transplant conditioning was predominantly nonmyeloablative and most patients received transplants from a human leukocyte antigen (HLA)-matched sibling donor. The average time to death after transplant was almost seven years (range, 4.5-11.4 years). Results showed a significant mitigation of vaso-occlusive events after SCT with an 84% reduction in the mean number of events in the two years prior versus the two years following transplant (5.6 vs 0.9; *p*<0.001) and the greatest reduction in events observed in the second year after transplant (mean vaso-occlusive events: 0-12 months, 0.8; 12-24 months, 0.1). This benefit was consistent regardless of graft-versus-host disease or engraftment (graft rejection, 12%).

Comment: Recurrent acute painful vaso-occlusive events are a devastating feature of sickle cell disease. This report follows 163 patients post allogeneic transplant with 75% undergoing nonmyeloablative conditioning and most (72%) with matched sibling donor. The incidence of acute and chronic graft-versus-host disease was 13% and 8%, respectively. Average myeloid chimerism at two years was 81% and graft rejection was noted in 12%. The principal conclusion from this paper was about the reduction of vaso-occlusive events in all patients from 1.7 events per 100 patient-years versus 0.3 events per 100 patient-years in the two years after HSCT. There was no difference in pre- and post- vaso-occlusive event frequency based on the type of conditioning (myeloablative vs nonmyeloablative). In patients who had graft rejection, VOEs were reduced from 2 events per 100 patient-years before transplant to 0.7 events per 100 patient-years at 12 months and 0.5 events per 100 patient-years at 24 months after transplant, respectively (*p*<0 .001) and there was no correlation between the total number of vaso-occlusive events and percentages of HbS or HbF at two years after transplant. Hopefully, this benefit in the reduction of painful vaso-occlusive events will guide further treatments for sickle cell disease including autologous SCT with gene therapy.

Reference: Blood Adv 2023;7(2):227-34
Abstract

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Targets of autoantibodies in acquired haemophilia A are not restricted to factor VIII: data from the GTH-AH 01/2010 study

Authors: Oleshko O et al.

Summary: This study employed an autoantibody screening strategy to elucidate whether the pathogenesis of acquired haemophilia A involves a specific pathogenic autoantibody response against endogenous clotting factor VIII (FVIII) or a more general breakdown of self-tolerance with generation of autoantibodies against a range of targets. The researchers investigated the presence and concentration of antinuclear and anticytoplasmic autoantibodies plus seven autoantibodies against extractable nuclear antigens in plasma samples from patients with acquired haemophilia A (n=69) and controls using human epithelial cell (HEp-2) immunofluorescence and enzyme immunoassays. A significantly greater proportion of patients with acquired haemophilia A were positive for antinuclear autoantibodies (64% vs 30%; OR 4.02; *p*=0.0002), anticytoplasmic autoantibodies (30% vs 19%; *p*=0.166) and anti-α-fodrin immunoglobulin A autoantibodies (12% vs 0%; *p*=0.006) compared to controls. In addition, antinuclear autoantibody titres were higher in patients versus controls. Almost 80% of patients with acquired haemophilia A had detectable non-FVIII targeted autoantibodies, significantly more than controls (78% vs 46%; OR 4.16; 95% CI, 1.98-8.39). Findings were consistent across sensitivity analyses and in multivariable binary logistic regression analysis. The authors concluded that the diverse pattern of autoantibodies found in haemophilia supports a role for immune tolerance aberrations in its pathology.

Comment: This paper demonstrates that autoantibody production in acquired haemophilia A is not solely against FVIII but is a part of a wider autoimmune spectrum containing higher percentage positivity for antinuclear autoantibodies (64% versus 30% in age-matched controls). Patients with acquired haemophilia A also had increased presence of concomitant autoimmune diseases including rheumatoid arthritis and systemic lupus erythematosus. The antinuclear staining of HEp-2 cells was not an incidental cross reactivity of anti-FVIII autoantibodies as a well characterised panel of anti-FVIII monoclonal antibodies did not show HEp-2 cell binding. This work concludes that a more general failure of peripheral self-tolerance control mechanisms underlies acquired haemophilia A pathogenesis with consequent proliferation and differentiation of FVIII-specific B cells to produce high-affinity FVIII-neutralising autoantibodies.

Reference: Blood Adv 2023;7(1):122-30
Abstract

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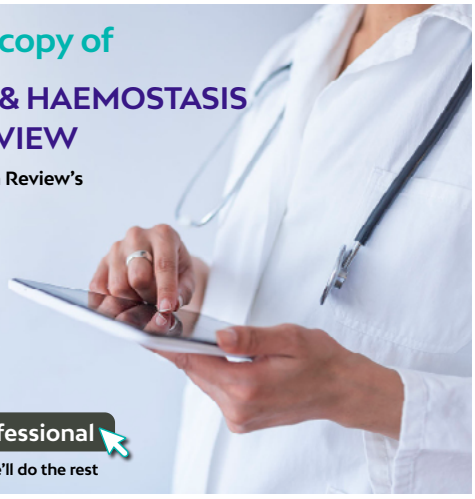

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Real-world effectiveness of caplacizumab vs the standard of care in immune thrombotic thrombocytopenic purpura

Authors: Izquierdo C et al., on behalf of Spanish Apheresis Group (GEA) and the Spanish Thrombotic Thrombocytopenic Purpura Registry (REPTT)

Summary: This retrospective study from the Spanish Thrombotic Thrombocytopenic Purpura Registry (Registro Español de PTT) examined the effectiveness of the addition of caplacizumab to standard of care in patients with iTTP treated outside a clinical trial. Data on 77 patients who accessed caplacizumab (57% as part of a front-line therapeutic regimen) through the Sanofi Medical Access Program between June 2018 and November 2020 were identified and clinical outcomes compared to 78 patients who received standard of care therapeutics including plasma exchange and immunosuppression (prednisone 1 mg/kg per day ± rituximab). Caplacizumab treatment was initiated at a median of five days from plasma exchange therapy and had a median duration of 35 days. While rates of clinical remission were high and comparable between cohorts (95.5% vs 93.6%; p=0.65), significantly fewer disease exacerbations and cases of refractoriness were found in the caplacizumab treated cohort (exacerbations, 5.2% vs 20.5%; refractoriness, 6.5% vs 14%; both p<0.05) and a trend towards lower mortality was also observed although statistical significance was not reached (3.8% vs 7.7%). Efficacy was improved and faster responses were elicited by front-line use of caplacizumab compared to after refractoriness or exacerbation. Caplacizumab treatment within three days of plasma exchange was associated with a significantly greater odds of fewer plasma exchanges and reduced duration of hospitalisation (OR 7.5 and OR 11.2; both p≤0.05) on multivariate analysis. No severe adverse events were reported in the caplacizumab treated cohort.

Comment: The standard first-line therapies for iTTP includes plasma exchange and concomitant immunosuppressive therapy (corticosteroids ± rituximab). Immunosuppressive treatments take days to weeks to be effective, thereby creating a high-risk period for mortality. Caplacizumab is a novel humanised nanobody targeting von Willebrand factor (vWF) that blocks platelet–vWF aggregation. Hence, it is effective immediately after administration. This paper reports real-world experience in the utility of caplacizumab from the Spanish TTP registry. All patients were treated with standard therapy ± caplacizumab. Caplacizumab was commenced as initial treatment in 57% and also for refractoriness (in 24.7%) and post exacerbation (in 18.2%). In 84%, rituximab was used together with caplacizumab. For the patients who received initial caplacizumab treatment, only 4.5% experienced exacerbations, compared with 20.5% of those not treated with caplacizumab. Moreover, the incidence of refractoriness was lower with the use of caplacizumab than without it (4.5% versus 14.1%). There were fewer deaths with caplacizumab that without (3/77 versus 6/78). Caplacizumab had a shorter median time to response than standard treatment alone (8.5 vs 14 days). Initial use of caplacizumab demonstrated quicker response as compared to when it was given as second line (5 vs 15 days). Other advantages were in the domain of health care resource utilisation with caplacizumab reducing the number of plasma exchanges and length of hospitalisation. Amongst the rituximab treated cohort, those who also received caplacizumab had a quicker response versus those with rituximab alone. Caplacizumab does not change the underlying autoimmune biology of iTTP and hence, it was interesting to note that no differences were observed in the median time to relapse between patients treated with caplacizumab plus rituximab versus patients treated with caplacizumab alone. Median time to ADAMTS13 >10% was also not different between caplacizumab plus rituximab versus patients treated with caplacizumab alone. The best effect of caplacizumab is at the initial presentation and its use together with immunosuppression and plasma exchange needs further cost analysis studies.

Reference: Blood Adv 2022;6(24):6219-27
Abstract

Surgical outcomes in people with haemophilia A taking emicizumab prophylaxis: experience from the HAVEN 1-4 studies

Authors: Kruse-Jarres R et al.

Summary: This post hoc analysis of pooled data from Hoffmann-La Roche's international phase 3 HAVEN suite of studies was performed to evaluate the safety of surgery in patients with haemophilia A on emicizumab prophylaxis. Analysis included a cohort of 126 patients (median age 33 years; median emicizumab exposure time before surgery, 278 days; 55.6% FVIII inhibitors) who underwent at least one unplanned surgery (65.9% one procedure; 34.1% ≥ 2 procedures for a total of 233 surgeries). Most surgeries (92%) were minor procedures such as dental work, central venous access device insertion/removal or endoscopic while the major surgeries (n=18) included arthroplasty and synovectomy. Due to the absence of established procedures for the management of surgical bleeding in this population the decision to employ additional prophylactic factor concentrate was left to treating physicians. Almost two-thirds of minor procedures were performed without additional prophylactic factor concentrate while most (83.3%) of the major procedures did employ additional prophylaxis. Rates of intra- and post-operative bleeds were low (18% in the minor surgical group and 17% in the major surgical cohort). More evidence is required to establish surgical guidelines.

Comment: Emicizumab is a bispecific humanised monoclonal antibody that replaces the function of coagulation factor VIII by forming a bridge activated FIX and FX. It is useful in all patients with haemophilia A, with or without inhibitors. A series of studies (HAVEN 1-4 phase 3 clinical trials) have demonstrated the efficacy and safety of emicizumab in adults, adolescents, and children with haemophilia A, with or without FVIII inhibitors. This publication reports data from these studies pertaining to the use of emicizumab for surgical prophylaxis (minor surgeries 215, major operation 18). In this cohort, 56% had FVIII inhibitors. Of the 62 minor dental procedures, 35.5% were managed with additional prophylactic factor concentrate. Those with inhibitors 5/29 procedures required rFVIIa (a single dose in most situations). Out of the 33 dental procedures in those without inhibitors, 14 (42.4%) required standard half-life and two (6.1%) needed extended half-life FVIII, mostly as a single dose. Antifibrinolytic agents (tranexamic acid or aminocaproic acid) were used in 32 (51.6%) dental procedures. There were similar successes in the management of central venous access device, minor endoscopic and joint procedures. Four arthroplasties and four synovectomies were included in the 18 major surgeries. Of these, 15 operations were managed with prophylactic FVIII concentrates with no postoperative bleeds in 12 procedures. All five participants who underwent arthroplasty received pre- and postoperative factor concentrate prophylaxis with one person experiencing a postoperative bleed. There were no safety issues and no deaths, thrombosis, thrombotic microangiopathy or new FVIII inhibitor development. The summary is that major and minor procedures can be effectively and safely managed for those on emicizumab prophylaxis with additional FVIII or rFVIIa.

Reference: Blood Adv 2022;6(24):6140-50
Abstract

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ABO blood group type and risk of venous thromboembolism in patients with cancer

Authors: Englisch C et al.

Summary: In an effort to explicate the relationship between ABO blood type and VTE risk in patients with cancer an Austrian research group from the Comprehensive Cancer Centre in Vienna analysed data from the prospective Vienna Cancer and Thrombosis Study. Two-year incidence of VTE in 1,708 patients (46% female; median age 61 years) with newly diagnosed or recurrent cancer (lung, 19%; breast 16%; brain, 14%; lymphoma, 13%) were evaluated according to blood type. The two-year incidence of VTE was 8.8% in the study population and two-year mortality was 38%. Restricted cubic spline analysis revealed an elevated risk of VTE in patients with non-O blood types versus those with O blood type from three months to two years (cumulative VTE incidence: six months, 6.5% vs 5.7%; 12 months, 8.4% vs 7%; 24 months, 10.2% vs 7.6%; time-restricted subdistribution HR 1.79). Subgroup analysis by thrombotic risk tumour type found the elevated VTE risk associated with non-O blood type was confined to intermediate and low-risk tumours (HR 1.75), with no excess risk in very high VTE risk tumour types such as pancreatic, gastroesophageal and glioblastoma.

Comment: This report extends the observation from the general population that non-O blood groups are associated with a higher VTE risk than O blood group. The causative mechanisms include higher levels of vWF and FVIII. The Vienna Cancer and Thrombosis Study prospectively follows patients with cancer for the development of VTE. Of the 1,708 patients followed up, VTE occurred in 151 patients during a median follow-up of 24 months. The spread of blood groups was 653 (38%) O, 682 (40%) A, 262 (15%) B, and 111(7%) AB. Between three to 24 months of follow-up after cancer diagnoses, non-O blood group was associated with increased risk of VTE. This association held up after adjustments for age, gender, disease stage, platelet count, sP-selectin levels, and D-dimer. An interesting observation on subgroup analysis was that the increased risk of VTE for non-O blood group was valid for cancers with intermediate or low VTE risk but not in high VTE risk tumour types. Patients with non-O groups had higher vWF and FVIII levels and the increased VTE risk may be due to higher FVIII activity. This information could help us guide VTE risk assessment and intervention in the context of cancer diagnoses.

Reference: Blood Adv 2022;6(24):6274-81
Abstract

Cost-effectiveness of second-line therapies in adults with chronic immune thrombocytopenia

Authors: Goshua G et al.

Summary: This study utilised Markov modelling to examine the cost-effectiveness of three second-line therapies for chronic ITP from a US health system perspective. Data from prospective, observational and meta-analyses were employed to estimate costs for six treatment strategies, each comprised of different sequences of the three second-line therapy options - rituximab, TRAs (romiplostim and eltrombopag) and splenectomy. Cost estimates were based on wholesale drug prices in 2020 in US dollars (TRAs, $114 thousand per year; rituximab, $8,000 per dose). The cost estimate for a laparoscopic splenectomy included a four-day hospital stay ($20,000) with optional imaging and/or repeat procedure and indefinite post-surgical anticoagulation with apixaban costs ($6,000 per year) also factored in. Strategies that sequenced TRAs as the final option behind rituximab and splenectomy were found to be the most cost-effective with total costs of approximately US$380,000, almost three-times less expensive than treatment sequencing commencing with TRAs (both over one million dollars; difference exceeding US$687,000). Quality-adjusted life years (QALYs) were fairly similar across strategies (range, 12.08-12.30). It was noted that the most cost-effective strategy of first-line splenectomy followed sequentially by rituximab then TRAs does not align with current therapeutic guidelines.

Comment: Second-line treatments are often required in adults with ITP and three widely used treatments are rituximab, splenectomy and TRAs. The question is about preference or sequential order between these modalities. The 2019 American Society of Haematology (ASH) guidelines recommend TRA over rituximab, and rituximab over splenectomy, with splenectomy being the least preferred treatment. Thus, as per ASH guidelines, the use of splenectomy in adult patients with chronic ITP is often reserved for patients who fail TRA or rituximab therapy, at least in North America. In Australia, until recently, splenectomy (unless medically contraindicated) was a prerequisite to the use of TRAs. This health economics report puts the cost-effectiveness of these therapies in perspective. It will be important to validate these conclusions for the Australian setting as the purchase price for TRAs for PBS use is most likely different from North America. The authors created a Markov model that examined the six possible treatment strategies incorporating different sequences of the three treatments. The assumption was that the only reason for changing treatments was ineffectiveness without considerations for toxicity, cost or other factors. All costs were estimated in 2020 US Dollars. To put this in the Australian perspective and without getting into too many details about cost attribution, it is interesting to note that the cost assumption of laparoscopic splenectomy with a median four-day hospital stay was $20,449 (costs of vaccination, investigations for an accessory spleen and anticoagulation for post splenectomy thrombosis are all extra). The assumption of willingness-to-pay was $195,300/QALY. The sequence of splenectomy followed by rituximab and then TRA therapy represented the cost-effective treatment strategy with a total cost of $376,350 and accrual of 12.08 QALYs. The most expensive schedule was TRA followed by rituximab and then splenectomy - $1,063,416 with accrual of 12.28 QALYs. The authors note that the treatment pathways that incorporate TRAs as the first or second sequential therapy do not represent a cost-effective strategy as they substantially exceed the willingness-to-pay threshold. The early use of TRAs was cost-ineffective largely due to the high cost of the drugs and the need for ongoing therapy in most patients. An annual price reduction of more than 80% in TRAs is needed for any strategy with early TRA utilisation to begin to become cost-effective. The early use of splenectomy was cost-effective largely because of high response rates without need for ongoing therapy in most patients.

Reference: Am J Hematol 2023;98(1):122-30
Abstract

Pre-emptive cyclosporin A in immune-mediated thrombotic thrombocytopenic purpura

Authors: Comparon C et al.

Summary: Pre-emptive cyclosporin A may be a viable therapeutic option for patients with iTTP unresponsive or intolerant to rituximab according to this small analysis from the national registry of the French reference centre for thrombotic microangiopathies. A total of 14 adult patients in persistent clinical remission in whom an ADAMTS13 relapse could not be resolved by rituximab (n=11) or who were precluded further administrations by virtue of adverse reactions (n=11) and received cyclosporin A (median treatment duration 17.5 months) were identified from the registry and included in the study. ADAMTS13 activity was normalised in all except one patient at a median time of 2.5 months. Five patients experienced subsequent ADAMTS13 relapses, three of which were resolved with rituximab or cyclosporin A retreatment. Two patients discontinued cyclosporin A due to severe side effects. It was concluded that cyclosporin A elicits durable restoration of ADAMST13 activity in this population with an acceptable safety profile.

Comment: This report is about the utility of cyclosporin A in 14 patients either relapsing after an initial response to rituximab (n=11) or those who were intolerant of rituximab (n=3). Before commencing cyclosporin A, patients were received treatments comprising corticosteroids, cyclophosphamide, bortezomib, rituximab, ofatumumab, and splenectomy. All patients were in clinical remission at the time of cyclosporin A initiation, but ADAMTS13 activity was persistently undetectable. Cyclosporin A was given twice daily, with a trough level ranging from 100 to 150 mg/L. Median duration of cyclosporin A treatment was 17.5 months. The results showed that ADAMTS13 activity normalised in almost all patients (13/14) after a median time of 2.5 months. During follow up, ADAMTS13 activity decreased in five patients needing reintroduction of rituximab, azathioprine or cyclosporin A. Cyclosporin A-related side effects included tremor, gum hypertrophy, and nausea that did not result in a dose change. Febrile neutropenia and hypertension were reported in two patients. These results support that conversion of an asymptomatic low ADAMTS13 activity to a clinical relapse state can be prevented by treatment with cyclosporin A.

Reference: Eur J Haematol 2023;110(2):157-60
Abstract

Thrombosis & Haemostasis Research Review™

Independent commentary by Prof Harshal Nandurkar

Prof 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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