ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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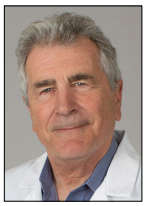
Thrombosis in Immune Thrombocytopenia



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H&O What is immune thrombocytopenia (ITP), and what causes it?

HL ITP is an autoimmune disorder that causes a significant decrease in the blood platelet count, to less than 100×10^9/L. This decrease results from increased platelet destruction and decreased platelet production, and it commonly leads to subcutaneous bleeding at platelet levels of less than 20×10^9/L. Like many autoimmune diseases, ITP can develop at any age and results from a person's genetic makeup and a triggering event.

Primary ITP occurs without any overt secondary associated disorder. In secondary ITP, which occurs in approximately 20% of cases, patients have a medical disorder that has been associated with the development of ITP. Such disorders include other autoimmune and rheumatologic diseases, such as lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and Evans syndrome. HIV infection, hepatitis C, and *Helicobacter pylori* infection have all been associated with the development of ITP,[1] as have lymphoproliferative malignancies such as chronic lymphocytic leukemia, multiple myeloma, and Hodgkin lymphoma.[2]

Genomic studies of patients with ITP have revealed underlying genetic mutations that are associated with disorders of immunodeficiency, systemic inflammatory disorders, and other autoimmune diseases. Studies of the genetics of adult and pediatric patients with Evans syndrome, a combination of ITP and autoimmune hemolytic anemia, often find that the patients have one or more genetic mutations associated with common variable immunodeficiency. The frequency of such mutations is elevated in pediatric patients, which is counterintuitive because ITP often emerges in such patients after an infection, surgery, or even pregnancy.

The International Working Group on Immune Thrombocytopenia has divided the natural history of the disease into 3 stages.[3] Acute disease, which lasts for less than 3 months, defines a period in which most spontaneous remissions occur, particularly in the pediatric population. In pediatric patients, disease onset is often triggered by a viral illness. After the viral illness ends, the immune system can right itself, and the ITP goes into spontaneous remission. On a smaller scale, the measles-mumps-rubella vaccine also can cause a transient decline in the platelet count in children. In at least 70% of cases, pediatric ITP will remit spontaneously within 1 to 5 weeks, and no treatment is required beyond the short-term avoidance of injury.

ITP that lasts from 3 to 12 months has been designated as progressive disease, a period in which treatment-associated remissions can occur with a high degree of frequency in young adult women. Chronic ITP has now been defined as disease lasting longer than 12 months. Contemporary recommendations now favor waiting at least 1 year before splenectomy is considered.

H&O How common is thrombosis in people with ITP?

HL In a meta-analysis that included 29 studies, researchers found that the incidence of thrombosis among people with ITP was 3.0% per year overall, in comparison with 1.29% per year for people without a history of thrombosis.[4] The relative risk (RR) of thrombosis was higher among people with ITP than in a matched population without ITP (1.60; 95% CI, 1.34-1.86), including an

increased RR of arterial thrombosis (1.52; 95% CI, 1.25-1.80). The increase in venous thrombosis among people with ITP was not statistically significant. However, patients who had undergone splenectomy also had an increased RR of venous events in comparison with those who had not undergone splenectomy (2.39; 95% CI, 1.61-3.17).

H&O What causes thrombosis in people with ITP?

HL We know that just having ITP increases the risk of thrombosis, with epidemiologic studies showing a 1.5- to 2-fold increased risk of venous thromboembolic events. Additional risk factors include older age, male sex, recent surgery, cancer, and prior history of either venous or arterial thrombosis. Risk factors related to ITP treatment include splenectomy and thrombopoietin receptor agonists (TPO-RAs) when they are combined with other risk factors. A retrospective cohort study from Australia concluded that older patients with ITP who have been treated with multiple agents and have secondary ITP while taking TPO-RAs are at the highest risk for thrombosis.[5]

ITP is associated with both arterial and venous thrombosis. Patients with ITP can have the same underlying risk factors for thrombosis as the general population, independently of their ITP diagnosis. Arterial clots are related to interactions between platelets and the vascular wall. People who have common genetic risk factors—the factor V Leiden mutation or the prothrombin G20210A mutation—are more likely to experience venous thrombosis, whereas people with obesity or lipid abnormalities will have an increased risk of both arterial and venous thrombosis. Ethnicity can also play a role in thrombosis risk; the factor V Leiden and prothrombin G20210A mutations are found predominantly in individuals of Indo-European descent. Individuals of African descent have elevated factor VIII as their major risk factor, combined with obesity. Inflammation can further increase their risk because it further increases factor VIII activity, increasing the risk of pulmonary embolism (PE). People of East Asian descent have a much lower risk of thrombosis than people of European descent, even when they have adopted an American lifestyle.

ITP is a Th1 and Th17 autoimmune inflammatory disorder leading to an increased risk of thrombosis. Inflammatory increases in interleukin 6 (IL-6) result in increases in factor VIII and fibrinogen, further promoting thrombosis.

Some people with ITP may have an autoimmune condition, called antiphospholipid antibody syndrome, that causes excess antiphospholipid antibodies to form, increasing the risk of thrombosis. The risk of thrombosis is especially high among people who have markers for 3 antibodies: lupus anticoagulant, anticardiolipin, and anti-beta$_2$ glycoprotein.

Finally, we know that removal of the spleen, which has been used historically as a treatment for ITP, makes patients more susceptible to thrombosis for the rest of their life. In a study of nearly 10,000 people with ITP, of whom 1762 underwent splenectomy, the cumulative incidence of abdominal venous thromboembolism (VTE) was 1.6% among those who underwent splenectomy vs 1.0% among those who did not undergo splenectomy.[6] The cumulative incidence of deep vein thrombosis or PE was 4.3% among those who underwent splenectomy vs 1.7% among those who did not undergo splenectomy. In addition, splenectomy was associated with a higher adjusted risk of sepsis, both early (hazard ratio [HR], 3.3; 85% CI, 2.4-4.6) and late (HR, 1.6 or 3.1, depending on comorbidities).

Airplane travel also increases the risk of thrombosis. Dr Frits Rosendaal, the expert on clotting who discovered factor V Leiden, showed that airplane travel increases the risk of thrombosis through a combination of hypoxia from reduced air cabin pressure, dehydration from low air humidity, and immobilization.[7] The immobilization that occurs during long drives can also lead to venous thrombosis.

The use of high-dose intravenous immunoglobulin (IVIG) has been linked to arterial thrombosis and, to a lesser degree, VTE. Therefore, we are hesitant about using high doses of IVIG to boost platelet counts in individuals with ITP who are at high risk for thrombosis. If a patient is older, is obese, or has elevated lipids, we would recommend using a dose of 400 mg/kg daily for 5 days rather than a higher dose. Another option is to use pulsed dexamethasone rather than IVIG. One of the problems with dexamethasone is that it can lead to glucocorticoid-induced hyperglycemia, so it should be used with caution in patients who are diabetic or prediabetic.

H&O What steps should be taken to ensure a prompt diagnosis of thromboembolic events in patients with ITP?

HL When we see swelling of the legs, we use compression ultrasound to assess for venous thrombosis. We also use D-dimer testing to look for excess thrombin generation in the blood. If the D-dimer level is high, this further assists in confirming a possible thrombosis. If a patient presents with shortness of breath and poor oxygenation by pulse oximetry, we perform computed tomography angiography to see if a PE has developed. If the patient cannot receive contrast agents because of significant renal problems, we can use a ventilation perfusion scan to look for a PE. However, if platelet counts permit, we begin anticoagulation as soon as possible.

H&O How does the management of thrombosis for patients with ITP differ from the management for patients without ITP?

HL The main treatment for VTE is systemic anticoagulation. Treatment is used as soon as possible in life-threatening circumstances, such as a major symptomatic PE, which can be life-threatening if untreated. If the patient does not have significant thrombocytopenia and the condition does not require emergent treatment, we also have the option of mechanical clot extraction in place of clot lysis, which should be avoided in patients with ITP and a platelet count of less than 80×10^9/L. Because the use of anticoagulants can lead to bleeding, even in patients with a normal platelet count, we recommend holding antithrombotic therapy if the platelet count is less than 30×10^9/L and avoiding full-dose therapeutic heparin or direct oral anticoagulation for a platelet count of less than 50×10^9/L.

Researchers at McMaster University in Canada have proposed the Thrombosis and Thrombocytopenia 2 (TH2) risk score, which depends heavily upon physician assessment of a patient's risks for thrombosis and bleeding.[8] The score is adapted for assessing continuation of anticoagulation during treatment for a thrombotic event in a patient with ITP whose platelet count drops to less than 50×10^9/L while on anticoagulation. Its overall clinical utility would have to be proved in a multicenter study.

For arterial thrombotic complications, we use a single antiplatelet agent when the platelet count falls to between 30 and 50×10^9/L. We begin corticosteroids to increase the platelet count. As much as 35 g of IVIG may be used, followed by TPO-RAs to a target platelet count above 100×10^9/L. The final agent to be used is rituximab.

We used to use low-molecular-weight heparin in all patients with acute VTE, but now we tend to favor direct oral anticoagulation with factor Xa inhibition or direct thrombin inhibition. Rivaroxaban (Xarelto, Janssen), apixaban (Eliquis, BMS/Pfizer), and edoxaban (Savaysa, Daiichi Sankyo) are examples of oral factor Xa inhibitors, and dabigatran (Pradaxa, Boehringer Ingelheim) is a direct thrombin inhibitor. Initial treatment of VTE requires full doses of these agents as determined in clinical trials, but lower doses can be used in selected circumstances and after 3 to 6 months of initial treatment. For secondary prophylaxis after initial treatment of VTE, we use approximately half the dose of the agent that we initially used to treat the thrombosis.

To use anticoagulants for antithrombotic prophylaxis at the time of high-risk procedures, such as after major surgery, the platelet count needs to be higher than 30×10^9/L, and preferably at least 50×10^9/L. The goal is to increase the platelet count to at least 50×10^9/L. Increasing the platelet count may require the use of TPO-RAs, IVIG, or corticosteroids. Prophylaxis dosing of rivaroxaban is 10 mg daily and of apixaban is 2.5 mg twice daily. Anticoagulation should continue for approximately 10 days to 4 weeks, depending on the procedure.

H&O What do you tell patients with ITP who are concerned about the risk of thrombosis with vaccines?

HL We know that the risk of thrombosis is higher from the flu than from the flu vaccine, and from COVID than from the mRNA COVID vaccine. The risk of thrombosis appears to be higher with the mRNA COVID vaccine than with other vaccines. For a patient who is at especially high risk of thrombosis on the basis of factors such as obesity and personal history, we can use a prophylactic dose of anticoagulant and confirm that their platelet count is higher than 50×10^9/L before vaccination. But either way, it is certainly safer for them to get the COVID vaccine than to get COVID itself. Antiviral therapy can be useful if a patient at high risk for thrombosis does get COVID, but that is an individual decision.

Another important point regarding vaccination is that vaccines are ineffective, or only minimally effective, in patients who have taken rituximab within the past 6 months because rituximab depletes B cells. In these cases, vaccines should be scheduled at least 6 months out from rituximab administration.

Disclosures

Dr Liebman has received research support from Novartis, Rigel, Janssen, and Syntimmune; and has served as a consultant for Amgen, BMS, GSK, Momenta, Novartis, Pfizer, and Rigel.

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