Managing and Treating ITP

Because much more is known about what causes this rare disease today, new treatments continue to evolve.

By Ronale Tucker Rhodes, MS

ONCE KNOWN AS idiopathic thrombocytopenic purpura (ITP), the name for this rare condition has evolved over time as understanding about its mechanisms has advanced. ITP was first described almost a thousand years. But, it wasn't until 1915 that controversy arose regarding the mechanism of ITP. It was then that German physician Ernest Frank suggested ITP was caused by suppression of megakaryocytes (cells present in bone marrow) by a substance produced in the spleen, whereas Czech scientist Paul Kaznelson suggested it was caused due to increased destruction of platelets in the spleen. When, in 1916, Kaznelson performed a splenectomy on a patient with chronic ITP resulting in the patient's platelet count increasing and the purpura resolving, splenectomy became the prevailing treatment for ITP for years.

Then, in 1950, the Harrington-Hollingsworth experiment determined the cause of ITP was a factor in blood rather than bone marrow that destroyed platelets. Harrington and other colleagues self-infused the blood of an ITP patient, which caused their platelet count to plummet, a major seizure and bruising and petichiae. When examining the bone marrow, no effect of megakaryocytes was discovered, which suggested an effect of the platelets rather than the marrow. These results, along with other reports published in 1951, led to a name change from idiopathic thrombocytopenic purpura (meaning the cause is unknown) to immune thrombocytopenic purpura, since the role of the immune system was then recognized as the cause of the disease.[1]

In the U.S., the incidence (number of people diagnosed each year) of ITP is estimated to be 3.3 per 100,000 adults per year. The prevalence (how many people have ITP at any time) is 9.5 cases per 100,000 adults and 5.3 cases per 100,000 children (since children with ITP usually recover, the number of children who have ITP at one time is about equal to those diagnosed annually). The incidence of ITP increases with age. Among adults age 30 years to 60 years diagnosed with ITP, there are 2.6 cases among women for every male case. In older adults, about the same number of men and women are diagnosed with ITP. And, among children diagnosed with ITP, the male to female ratio is almost equal: 52 percent and 48 percent, respectively. About 40 percent of all patients diagnosed with ITP are children younger than 10

years of age. And, among children, the incidence is greatest between ages 2 years and 4 years old.[2] ITP is also more common in white than in black children, and its severity and duration may differ among geographic areas.[3]

What Is ITP?

ITP is an autoimmune bleeding disorder characterized by abnormally low levels of blood cells called platelets that maintain the integrity of blood vessel walls and help prevent and stop bleeding by accelerating clotting.[2] ITP occurs when platelets are attacked and prematurely removed by the body's immune system (with autoimmunity, the body's immune system mistakenly attacks a part of a person's own body).[3] A normal platelet count ranges from approximately 150,000 to 400,000 per microliter of blood depending on the laboratory. If a person has a platelet count lower than 100,000 per microliter of blood with no other reason for low platelets, then he or she has thrombocytopenia and may have ITP.[2]

There are three types of ITP: acute (present for less than one year), chronic (present for more than one year) and recurrent (episodes at intervals of more than three months). Eighty percent of children with ITP have the acute form that resolves six months after diagnosis independent of treatment, and the younger the child, the less risk of developing chronic ITP. In children with chronic ITP, complete remission is gained in 90 percent within three years to seven years. Recurrent ITP occurs in between 1 percent and 4 percent of children. More than 50 percent of adults have chronic ITP.[2,3]

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ITP can be further broken down into either primary or secondary. If ITP develops for no known reason, it is considered primary. On the other hand, if ITP is associated with illnesses such as an infection or other autoimmune disease, or if it occurs after a transfusion or after taking certain drugs (such as cancer drugs), it is considered secondary.[4]

Causes of ITP

While it is unclear what causes ITP, it is believed multiple factors are involved, including environmental (infections or drugs), self-marker molecules and heredity. For both primary and secondary ITP, it is known that the body's natural immune defenses inappropriately act against its own cells or tissues, which causes the destruction of the body's platelets. However, in some cases, platelet production by megakaryocytes in the bone marrow is impaired. So, the causes of ITP can be due to increased platelet destruction, reduced or inadquate platelet production, or both.[2]

In primary ITP, it is unknown what is causing this autoimmune reaction. But, with secondary ITP, the cause is due to another condition. These include inherited immune disorders (such as autoimmune lymphoproliferative syndrome), systemic autoimmunity (such as systemic lupus, ongoing infections such as HIV, hepatitis C and Helicobacter pylori) and lymphoproliferative disorders (such as chronic lymphocytic leukemia). In addition, some cases resembling ITP can result from the use of certain drugs, after a viral or bacterial infection or after vaccination for measles, mumps and rubella.[2]

When ITP is caused by an infection, it is believed the infection generates antibodies that cross-react with platelet antigens or immune complexes that bind to platelet receptors, thereby impairing platelet production due to infected megakaryocyte bone marrow-dependent progenitor cells, decreased production of thrombopoietin (TPO), and splenic sequestration of platelets secondary to portal hypertension (HCV). For instance, sudden and severe onset of thrombocytopenia has been observed in children after vaccination for measles, mumps and rubella or natural viral infections, including Epstein-Barr virus, cytomegalovirus and varicella zoster virus.[5]

Familial ITP (when more than one family member is affected) is rare, and its inheritance remains unclear.[3]

Symptoms of ITP

In some cases, people with ITP have no signs or symptoms. However, when symptoms do occur, they can vary greatly from person to person. In general, the lower the platelet count, the more symptoms, including:[4,6]

- Easy or excessive bruising (purpura)
- Petechiae (tiny red dots on the skin caused by broken blood vessels or leaks in a capillary wall)
- Bleeding from the nose, mouth and gums, and digestive and urinary tracts

- Blood in urine or stools
- Unusually heavy menstrual flow
- Feeling tired or fatigued

Rarely, bleeding within the brain occurs,[4] but it can be life-threatening if it does. According to a study conducted in 2001 of 2,031 children, life-threatening bleeding occurs in 0.2 percent within the first 12 months, and the risk can be greater during the initial phase of ITP and if the platelet count is below 10,000 x 10^6 per liter, but it can occur at any time in ongoing ITP.[3]

Diagnosing ITP

It's first necessary to exclude other possible causes of bleeding and a low platelet count when diagnosing ITP. Then, in addition to looking at the medical history and performing a physical exam, the following tests can be performed. A complete blood count can determine the number of blood cells, including platelets, in a sample of blood. With ITP, the white and red blood cell counts are usually normal but the platelet count is low. A blood smear, in which a sample of blood is placed on a slide and observed under a microscope, can be used to confirm the number of platelets observed in a complete blood count.[7] And, a bone marrow exam (the American Society of Hematology doesn't recommend this test for children) can verify there are adequate platelet-forming cells (megakaryocytes) in the marrow to rule out other diseases such as metastatic cancer and leukemia.[4]

In some cases, a bone marrow biopsy (in which a sample of bone tissue and the enclosed marrow is removed) and/or a bone marrow aspiration (in which the liquid portion of the marrow is removed) are performed. These can determine if the bone marrow is normal, which will signal the low platelet count is caused by the destruction of platelets in the bloodstream and spleen, rather than due to a problem with the bone marrow.[7]

Treating ITP

While there is no cure for ITP, treatment is determined by the severity of symptoms. The key is to find a treatment that works without unwanted side effects.

In some cases, treatment is not needed. Most children with acute ITP do not require treatment because their condition resolves spontaneously. The American Society of Hematology (ASH) recommends children who have no bleeding or mild bleeding be managed with observation alone regardless of platelet count. This recommendation is based on a study that found observation alone did not lead to an increase in later treatment or an increase in delayed bleeding symptoms. For pediatric patients requiring treatment, ASH recommends a single dose of 0.8 g/kg to 1.0 g/kg of intravenous immune globulin (IVIG) if a more rapid increase in the platelet count is desired, or a short course of corticosteroids, as first-line treatment.[8]

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In one newly completed study, mini-pools of IVIG from as few as 20 donations have been found just as significant in treating pediatric ITP as standard high IVIG doses (see Study Shows Mini-Pools of IVIG as Effective as Standard IVIG to Treat Pediatric ITP, p.14). With the high cost of IVIG, the study suggests this first-line treatment can be much more cost-effective for patients and payers.[9]

Because of the significant risk of hemolysis (destruction of red blood cells) with IV Rho(D) immune globulin (RhIG, anti-D immune), ASH advises against its use in children with a hemoglobin (protein found in red blood cells) concentration that is decreased because of bleeding, or in those with evidence of autoimmune hemolysis. However, a single dose of IV RhIG can be used as first-line treatment in Rh-positive, nonsplenectomized children with a negative direct antiglobulin test who require treatment.[8]

Children who have significant ongoing bleeding despite treatment with IVIG, RhIG or conventional doses of corticosteroids can be treated with rituximab or high-dose dexamethasone as second-line treatment. Rituximab or high-dose dexamethasone may also be considered as an alternative to splenectomy or as treatment for children who do not

respond favorably to splenectomy.[8] It should be noted that splenectomy as a therapeutic option in children is restricted to those with uncontrollable bleeding.[3]

Recommended treatment for adults is similar to that for children by using drugs that alter the immune system's attack on platelets. First-line treatment initially consists of high-dose corticosteroids with a goal of impairing the production of antiplatelet antibodies so platelet count will remain elevated after ceasing treatment. If corticosteroids fail to improve platelet levels or if severe bleeding persists, patients are treated with monthly IVIG infusions. IV RhIG can also be administered in patents who are Rh positive and who have not received a splenectomy.[2]

Second-line therapy includes rituximab (anti-CD antibody), which reduces IgG antibody production; splenectomy, which improves platelet count in approximately 70 percent of cases and can achieve remission in 50 percent to 60 percent of patients; imuran (azathioprine); Cytoxan (cyclosphosphamide); Sandimmune (cyclosporine); Danocrine (danazol); Cellcept (mycophenolate mofetil); and Vincristine (vinca alkaloids).[2]

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Thrombopoietic receptor agonists (TPO-RAs), a new treatment form, stimulate platelet production by megakaryocytes in the bone marrow. Two TPO-RAs are available. Promacta (eltrombopag), manufactured by GlaxoSmithKline and later acquired by Novartis Pharmaceuticals, was approved by FDA in 2008 to treat adult patients with chronic ITP. In 2015, FDA expanded the indication for eltrombopag to include treatment of chronic ITP in patients 6 years of age and older who have not achieved an appropriate response with other medical therapy or splenectomy. Nplate (romiplostim), manufactured by Amgen, was also approved by FDA in 2008 to treat ITP patients who have had insufficient response to corticosteroids, IVIG or splenectomy.[2,3,8] And, in April, FDA approved romiplostim to treat pediatric patients ages 1 year and older with ITP for a minimum of six months and who have had an insufficient response to corticosteroids, IVIG or splenectomy (see Romiplostim Approved to Treat Pediatric Patients with Immune Thrombocytopenia on p.17).[10]

The most recent drug approved by FDA to treat adults with chronic ITP who have had an insufficient response to a previous treatment is Tavalisse (fostamatinib disodium hexahydrate) in 2018. Tavalisse, manufactured by Rigel Pharmaceuticals, belongs to a class of drugs known as spleen tyrosine kinase inhibitors that work by increasing platelets in the blood.[11]

Lifestyle adjustments may also be required for managing ITP. For instance, those whose platelet counts are less than 50,000 are recommended to wear protective gear such as helmets and to avoid contact sports such as boxing or football that carry a high risk of injury. Alcohol should also be consumed in moderation because it slows production of platelets. Over-the-counter medications such as aspirin and ibuprofen should be avoided as they can impair platelet function. And, those who have had their spleen removed need to watch for signs of infection, including fever, and seek immediate medical attention.[7]

Looking Ahead

Efforts to understand more about ITP are ongoing. As of this writing, there were 234 studies listed on ClinicalTrials.gov. Following is a brief look at some of these:

- Researchers are studying whether intravenous corticosteroids and IVIG administered together will increase platelet count faster, minimize adverse effects of IVIG and lead to a more sustained increase in platelet count. If it is shown the combined therapy results in a quicker rise in platelet count, this would support and justify the use of the combination therapy in emergency situations, which is often used today when children present with a life-threatening bleed.[12]
- Another study is researching whether eltrombopag can be used instead of IVIG in patients with ITP to adequately raise their platelet count when undergoing minor or major surgery. The randomized controlled trial will involve 74 adult patients in Canada. In addition to evaluating the efficacy and safety of eltrombopag bridging therapy compared with IVIG bridging therapy, the study will evaluate bleeding, adverse events and patient-reported treatment satisfaction.[13]
- Eltrombopag is also being studied to determine the Fc

gammaRIIIA gene (V158F) genetic predisposition with treatment outcome of the drug in ITP refractory patients. Patients will be assessed by collection of blood samples from 50 controls (treated with standard immunosuppressive first- and second-line treatments) and 25 steroid-refractory patients at the time of enrollment to the trial and then subsequently at three months and six months after treatment.[14]

- A two-phase study known as the PROLONG Trial will evaluate if low-dose rituximab maintenance therapy may prolong the effect of the drug in ITP. In the first phase, patients will be randomized into a rituximab-only or rituximab-plus-dexamethasone group to determine if the response to rituximab can be improved by the addition of dexamethasone. In the second phase, patients will be randomized into a low-dose rituximab or placebo group to determine if the response achieved in the first phase can be prolonged by administering maintenance treatment with low-dose rituximab.[15]
- And, an observational registry study will document serious adverse events in ITP patients treated off-label with rituxumab.[16]

Because ITP is a rare disorder, information about patients with ITP is being collected in many registries with the help of medical centers. One of these is the ITP Natural History Study Registry, an international patient-consented registry that aims to collect, store and retrieve data on the natural progression of ITP, enabling collection of data on diagnosis and treatment, management of care, quality of life, clinician reporting and characterization of the ITP population as a whole. It is hoped these registries will provide useful information that can lead to a greater understanding of the disease and help to design future studies.[17]

ITP's Impact on Patients

ITP is a rare autoimmune disorder that leads to easy or excessive bruising and bleeding caused by increased platelet destruction, reduced or inadequate platelet production, or both. In some cases, it is unknown why this occurs, yet in others, it can be linked to another condition. Symptoms vary among those affected, with some requiring no treatment and others requiring extensive treatment. While much has been learned about the disease since its first description more than 1,000 years ago, research is ongoing to find additional more effective treatments.

Despite advances in our knowledge and treatments, however, ITP has a significant impact on patients' quality of life. In June, Novartis, which markets Promacta, released results of its survey titled I-WISh (ITP World Impact Survey). Findings from more than 1,300 ITP patients across 13 countries showed the disease had especially high impact for many patients on emotional well-being (36 percent) and ability to work (28 percent). About two-thirds of patients reported fatigue as the most severe symptom at diagnosis (71 percent) and survey completion (64 percent). Overall, two main treatment goals reported by patients were achieving healthy blood counts (79 percent) and increasing their energy levels (55 percent).

"These initial data from the I-WISh survey reveal how a rare blood disease like ITP can significantly affect a patient's ability to live and function in their day-to-day life," said Samit Hirawat, MD, head of Novartis oncology global drug development. "We believe these results demonstrate that, even beyond medicine, ITP patients are seeking compassion, support and understanding from family, friends so they can strive to live the best lives they can. These are important insights, and we will look to build them into the programs and services we develop to better support this community."[18]

RONALE TUCKER RHODES is the editor of *IG Living* magazine.

References

1. History Cooperative. Idiopathic Thrombocytopenia Purpura: A History. Accessed at historycooperative.org/idiopathic-thrombocytopenic-pupura-a-history.
2. National Organization for Rare Disorders. Rare Disease Database: Immune Thrombocytopenia. Accessed at rarediseases.org/rare-diseases/immune-thrombocytopenia.
3. ITP Foundation. Guide to Understanding ITP (Immune Thrombocytopenia). Accessed at www.itpfoundation.org/Assets/ITP+Foundation$!27s+Guide+to+Understanding+ITP.pdf.
4. ITP Foundation. What Is ITP? Accessed at www.itpfoundation.org/itpdefined.htm.
5. Cines, DB, Liebman, H, and Stasi, R. Pathobiology of Secondary Immune Thrombocytopenia. *Seminars in Hematology*, 2009 Jan; 46(1 Suppl 2): S2–14. Accessed at www.ncbi.nlm.nih.gov/pmc/articles/PMC2682438.
6. Platelet Disorder Support Association. What Is ITP? Accessed at www.pdsa.org/about-itp/causes.html.
7. Mayo Clinic. Idiopathic Thrombocytic Purpura Diagnosis and Treatment. Accessed at www.mayoclinic.org/diseases-conditions/idiopathic-thrombocytopenic-purpura/diagnosis-treatment/drc-20352330.
8. Kessler, CM. Immune Thrombocytopenic Purpura (ITP) Treatment & Management. Medscape, April 23, 2018. Accessed at emedicine.medscape.com/article/202158-treatment.
9. Garbutt, T. Mini-Pools of IVIG Just as Effective as Standard IVIG in Pediatric Immune Thrombocytopenia. *Oncology Nurse Advisor*, Dec. 26, 2018. Accessed at www.oncologynurseadvisor.com/hematologic-cancers/mini-pool-ivig-as-effective-as-standard-ivig-in-pediatric-itp/article/823430.
10. FDA Approves Romiplostim for Pediatric Patients with Immune Thrombocytopenia. U.S. Food and Drug Administration press release, Dec. 14, 2018. Accessed at www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm628525.htm.
11. FDA Approves Fostamatinib Tablets for ITP. U.S. Food and Drug Administration press release, April 17, 2018. Accessed at www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm604956.htm.
12. CenterWatch. A Randomized Study of IVIG vs. IVIG with High-Dose Methylprednisolone in Childhood ITP. Accessed at www.centerwatch.com/clinical-trials/listings/33573/immune-thrombocytopenic-purpura-randomized-study-ivig-vs/?&radius=50.
13. CenterWatch. A Trial of Eltrombopag or Intravenous Immune Globulin Before Surgery for Immune Thrombocytopenia Patients. Accessed at www.centerwatch.com/clinical-trials/listings/131475/immune-thrombocytopenic-purpura-trial-eltrombopag-or-intravenous/?&radius=50.
14. CenterWatch. Association of Fc RIIIA Polymorphism and THPO Expression With Response to Eltrombopag in Refractory ITP Patients. Accessed at www.centerwatch.com/clinical-trials/listings/99856/immune-thrombocytopenic-purpura-itp-association-fc-riiia/?&radius=50.
15. CenterWatch. The PROLONG Trial - Rituximab Maintenance Therapy in ITP. Accessed at www.centerwatch.com/clinical-trials/listings/189794/purpura-thrombocytopenic-idiopathic-prolong-trial--rituximab/?&radius=50.
16. CenterWatch. The ITP-RITUX Cohort: Rituximab in Immune ThrombocytoPenia. Accessed at www.centerwatch.com/clinical-trials/listings/128325/purpura-thrombocytopenic-idiopathic-itp-ritux-cohort-rituximab-immune/?&radius=50.
17. Platelet Disorder Support Association. ITP Natural History Study Patient Registry. Accessed at pdsa.org/healthcare-professionals-researchers/hcp-registry.html.
18. Novartis Survey Uncovers Real-World Impact of Immune Thrombocytopenia or ITP, a Rare Blood Disease, on Patients' Quality of Life. Novartis press release, June 15, 2018. Accessed at www.novartis.com/news/media-releases/novartis-survey-uncovers-real-world-impact-immune-thrombocytopenia-or-itp-rare-blood-disease-patients-quality-life.