



Understanding Idiopathic Thrombocytopenic Purpura

By Ronale Tucker Rhodes, MS

This rare bleeding disorder often resolves on its own, but for those who develop chronic ITP, treatment and resources are available.

Try saying the words idiopathic thrombocytopenic purpura to someone and then wait for the perplexed look. The name of this disease sounds baffling enough to someone inside the medical profession, much less to a layperson who has likely never heard of a fraction of the autoimmune diseases affecting millions of people these days. So, imagine what these words sound like to someone who is told that they have the condition.

Idiopathic (immune) thrombocytopenic purpura, or ITP for short, is rare. It occurs in 50 to 150 per million people each year and affects children and adults equally.¹ According to the Platelet Disorder Support Association

(PDSA), estimates of the prevalence and incidence of ITP vary since they are often based on small population samples or the review of insurance records. However, the incidence of ITP among children is approximately 4.3 to 5.3 per 100,000 per year (equally affecting boys and girls). And, since children with ITP usually recover, the prevalence of childhood ITP is about equal to the incidence. In adults, the incidence of ITP is between 1.6 and 6.6 per 100,000, and the prevalence is approximately 9.5 cases per 100,000. While more adult women than men have the disease, the gender difference disappears in people over 60 years old.²

What Is ITP?

Idiopathic means there is an unknown cause; thrombocytopenic means the blood has a lower than normal number of platelets; and purpura refers to bruises caused by bleeding from small blood vessels under the skin. In short, ITP is a bleeding disorder caused by a low number of blood cell fragments called platelets (or thrombocytes).³ Platelets, which are made in bone marrow along with other kinds of blood cells, stick together (clot) to seal small cuts or breaks on blood vessel walls and stop bleeding. A normal platelet count ranges between 150,000/ μ L and 450,000/ μ L of blood. With ITP, the platelet count is less than 100,000/ μ L. By the time significant bleeding occurs, the platelet count is less than 10,000/ μ L. The lower the platelet count, the greater the risk of bleeding.⁴

Those with mild ITP may have few or no symptoms. Those who do experience symptoms may bruise easily; may have excessive bleeding following minor cuts; may have joint pain; may bleed in the urine, vomit, bowel movements or white parts of the eyes; and may bleed under the skin, which appears as tiny red or purple dots on the skin (known as petechiae).⁵ A lot of bleeding can cause hematomas, a collection of clotted or partially clotted blood under the skin that looks or feels like a lump. Many people who have ITP may get nosebleeds, have bleeding from the gums during dental work or other bleeding that is hard to stop. Women may have heavier than normal menstrual bleeding. And, in rare instances, bleeding in the brain can result, which can be life-threatening.³

Researchers believe that ITP is an autoimmune disorder caused when antibodies, which typically fight infection, attack and destroy the body's healthy platelets. What causes this is unknown. There are two types of ITP: acute and chronic. Acute ITP, the most common type, is temporary or short-term, generally lasting less than six months. This type occurs mostly in children between 2 and 4 years of age, and often occurs after a child has an infection or is sick with a virus. Chronic ITP is long-lasting, usually lasting six months or longer, and mostly affects adults, although sometimes teenagers or children develop it.¹

Diagnosing ITP

To diagnose ITP, doctors typically begin by excluding other possible causes of bleeding and a low platelet count, such as leukemia myelophthisic marrow infiltration, myelodysplasia, aplastic anemia and adverse drug reactions.⁶ If no other causes are found, then three other tests are typically conducted. A complete blood count

(CBC) determines the number of white and red blood cells and platelets. With ITP, white and red blood cell counts are usually normal, while the platelet count is low. A blood smear confirms the number of platelets observed in a CBC. And a bone marrow examination helps to determine the cause of a low platelet count. This exam can include a bone marrow biopsy in which a sample of solid bone marrow is removed and/or a bone marrow aspiration, in which the liquid part of the marrow is removed. Many times, both procedures are performed at the same time, as

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both the solid and liquid samples are frequently taken from the sample place on the back of one of the hipbones via a needle or through an incision. With ITP, the bone marrow will be normal because 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

Because ITP is a diagnosis of exclusion, it is important that the patient and physician communicate well to arrive at the correct diagnosis so that the wrong disease is not treated. Patients who experience an episode of low platelets can help in this process by providing as much information as possible, such as a history of platelet count; certain food ingestions (i.e., wood ear mushrooms, quinine water and bitter melon); new prescription or nonprescription medications; vaccines; chemical exposure; other diagnoses (i.e., lymphoma, lupus, hepatitis C, HIV); recurrent stomachaches, fevers or ulcers; insect or animal bites; poison ivy exposure; travel outside the country; family history of autoimmune disease or bleeding disorders; easy bruising; frequent colds or flus; hearing problems; swelling

or aching joints; thyroid gland problems; recent stress; hospitalizations; new diets or exercise programs; excessive alcohol consumption; and periodic cycles of low platelets.⁸

Treating ITP

While there is no cure for ITP, there are a number of treatments that usually help boost platelet levels. Prednisone, administered orally, usually results in a gradual increase in platelet levels and helps strengthen the walls of veins and arteries, which helps prevent unwanted bleeding. After tapering off of prednisone after weeks or months, some people's increase in platelet levels is permanent. However, those whose platelet levels drop as the prednisone dosage is reduced may require long-term low-dose prednisone to keep platelets at acceptable levels. The problem with prednisone is its side effects, which include water retention, mood changes, weight gain, gastrointestinal tract irritation and suppressed immune response, all of which increase in number and severity the longer prednisone is taken.⁹

Today, IVIG is the drug of choice to treat severe or chronic ITP.

Intravenous immune globulin (IVIG) was initially shown to be effective in treating ITP in 1981, when it was noted that dose administration of IVIG promoted a rapid recovery in children with ITP.¹⁰ Today, it is the drug of choice to treat severe or chronic ITP. There are five IVIG products that are FDA-approved, including CSL Behring's Carimune NF and Privigen, Baxter Healthcare's Gammagard S/D, Kedrion's Gammaked and Grifols' Gamunex-C.¹¹ Nobody knows precisely how IG treatment works, but it is believed that it blocks platelet removal and, thus, increases the number of platelets. Side effects are typically rare and minor, but very rarely (in one-tenth of 1 percent), a severe anaphylactic reaction may occur. IVIG is used during pregnancy because of the decreased risk to the health of the mother and the baby as compared with other treatments.⁹

All five IVIG products were approved by the FDA as a result of pivotal clinical studies. In one study of Privigen, conducted in Europe, 57 subjects with a platelet count of

less than or equal to $20 \times 10^9/L$ received 1 g/kg of Privigen twice on each of two consecutive days and were observed for 29 days. A total of 46, or 80.7 percent of subjects, responded to Privigen therapy with an increase of platelet count to greater than or equal to $50 \times 10^9/L$ within seven days after drug administration. Hemolysis occurred in eight subjects, and all cases resolved uneventfully.¹²

Anti-D antibodies in the Rho(D) immune globulin WinRho SDF work similarly to IVIG. Also administered intravenously, its effects are short-term (lasting about one month), and it is effective only for people who are Rh positive (up to 85 percent of people are) and have a spleen. Occasionally, anti-D antibodies result in a long-term platelet count increase. Unlike IVIG, it may not be suitable for some pregnant women.⁹

Splenectomy (removal of the spleen) has been used to treat ITP since the middle of the 20th century, and it works in two-thirds of ITP patients. However, doctors usually do not resort to splenectomy before trying other treatments. And, since the spleen plays an important role in cleaning the body of infection, those undergoing splenectomy are usually at a higher risk of infections. In addition, a lot of people relapse after a splenectomy and their platelet counts go down again. Some studies suggest that people age 40 and under usually fare better with splenectomy.⁹

Other drugs and treatments used for ITP include chemotherapy drugs, antibiotics, Danazol, Rituxan and immunosuppressant drugs.⁹

The American Society of Hematology (ASH) has published its *2011 Clinical Practice Guideline on the Evaluation and Management of Immune Thrombocytopenia (ITP)*, which was published in *Blood* on April 21, 2011. In addition, ASH has developed a pocket-sized quick reference guide to provide physicians with an easy reference tool for its practice guideline, which can be obtained by contacting Patrick Irelan at pirelan@hematology.org.¹³

Living with ITP

ITP patients can prevent complications by avoiding medications such as aspirin or ibuprofen that can affect platelets and increase bleeding; protecting themselves from injuries that can cause bruising or bleeding; and seeking treatment immediately for infections or symptoms of infection. Lifestyle changes also can be made to prevent complications. For instance, contact sports or other sports that can cause injury, especially head injuries, should be avoided. And certain precautions should be taken such as

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immune globulin injection (human), 10%
caprylate/chromatography purified

Take Care with GAMMAKED

WARNING: ACUTE RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

- Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IGIV) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs.
- Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. [1] GAMMAKED does not contain sucrose.
- For patients at risk of renal dysfunction or failure, administer GAMMAKED at the minimum concentration available and the minimum infusion rate practicable. (see *Warnings and Precautions*)

Please see the **GAMMAKED Brief Summary of Prescribing Information** on the following page for additional prescribing details.

References: 1. GAMMAKED [prescribing information]. Fort Lee, NJ: Kedrion Biopharma, Inc. 2012

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Brief Summary

See full Prescribing Information for complete information

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Indications

GAMMAKED consists of immune globulin injection (human) 10% liquid that is used:

- As replacement therapy of Primary Humoral Immunodeficiency (PI).
- To treat patients with Idiopathic Thrombocytopenic Purpura (ITP) to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery.
- To treat Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.

Contraindications

- GAMMAKED is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- GAMMAKED is contraindicated in IgA deficient patients with antibodies against IgA and history of hypersensitivity.

Warnings and Precautions

- Severe hypersensitivity reactions may occur with IGIV products, including GAMMAKED. In this case, discontinue GAMMAKED infusion immediately and institute appropriate treatment. Medications such as epinephrine should be available for immediate treatment of acute hypersensitivity reaction.
- Assure that patients are not volume depleted prior to the initiation of the infusion of GAMMAKED. Periodic monitoring of renal function and urine output is particularly important in patients judged to have a potential increased risk for developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN)/serum creatinine, prior to the initial infusion of GAMMAKED and at appropriate intervals. If renal function deteriorates, consider discontinuation of GAMMAKED. For patients judged to be at risk for developing renal dysfunction (e.g., any degree of pre-existing renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs) administer GAMMAKED at the minimum infusion rate practicable.
- Do not administer GAMMAKED subcutaneously in patients with ITP because of the risk of hematoma formation.

- Hyperproteinemia, increased serum viscosity and hyponatremia may occur in patients receiving IGIV treatment, including GAMMAKED. It is clinically critical to distinguish true hyponatremia from a pseudohyponatremia that is associated with concomitant decreased calculated serum osmolality or elevated osmolar gap.
- Thrombotic events have been reported following IGIV treatment and may occur in patients receiving IGIV treatment, including GAMMAKED. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilization and/or known or suspected hyperviscosity. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity. For these patients, administer GAMMAKED at the minimum rate of infusion practicable.
- Aseptic Meningitis Syndrome (AMS) may occur infrequently with IGIV treatment, including GAMMAKED. Discontinuation of IGIV treatment has resulted in remission of AMS within several days without sequelae. The syndrome usually begins within several hours to two days following IGIV treatment. AMS is characterized by the following symptoms and signs: severe headache, nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, nausea and vomiting. Cerebrospinal fluid (CSF) studies are frequently positive with pleocytosis up to several thousand cells per cu mm, predominantly from the granulocytic series, and with elevated protein levels up to several hundred mg/dL, but negative culture results. Conduct a thorough neurological examination on patients exhibiting such symptoms and signs including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV.
- IGIV products, including GAMMAKED, may contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Delayed hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration, and acute hemolysis consistent with intravascular hemolysis, has been reported. Monitor patients for clinical signs and symptoms of hemolysis. If signs and/or symptoms of hemolysis are present after GAMMAKED infusion, perform appropriate confirmatory laboratory testing.
- Noncardiogenic pulmonary edema may occur in patients following treatment with IGIV products, including GAMMAKED. Transfusion-related Acute Lung Injury is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically occur within 1 to 6 hours after treatment. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil and anti-HLA antibodies in both the product and patient serum. TRALI may be managed using oxygen therapy with adequate ventilatory support.
- The high dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.
- Because GAMMAKED is made from human blood, it may carry a risk of transmitting infectious agents. No cases have ever been identified for GAMMAKED. ALL infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Talecris Biotherapeutics, Inc. [1-800-520-2807]

- After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens may cause a positive direct or indirect antiglobulin (Coombs') test.

Adverse Reactions

Clinical Trials

- PI - The most common adverse reactions ($\geq 5\%$) with intravenous use of GAMMAKED were headache, cough, injection site reaction, nausea, inflammation of the throat, and hives. Vomiting was reported more frequently in pediatric patients. The most common adverse reactions ($\geq 5\%$) with subcutaneous use of GAMMAKED were infusion site reactions, headache, fatigue, joint pain, and fever.
- ITP - The most common adverse reactions during clinical trials (reported in $\geq 5\%$ of subjects) were headache, vomiting, fever, nausea, back pain and rash.
- CIDP - The most common adverse reactions during clinical trials (reported in $\geq 5\%$ of subjects) were headache, fever, chills, hypertension, rash, nausea and weakness.

Postmarketing Experience

- Hemolytic anemia and aseptic meningitis have been identified and reported during the post marketing use of GAMMAKED.

The following adverse reactions have been reported during the overall post marketing use of IGIV products:

- Respiratory: Apnea, Acute Respiratory Distress Syndrome (ARDS), TRALI, cyanosis, hypoxemia, pulmonary edema, dyspnea, bronchospasm
- Cardiovascular: Cardiac arrest, thromboembolism, vascular collapse, hypotension
- Neurological: Coma, loss of consciousness, seizures/convulsions, tremor
- Integumentary: Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous dermatitis
- Hematologic: Pancytopenia, leukopenia, hemolysis, positive direct antiglobulin (Coombs test)
- General/Body as a Whole: Pyrexia, rigors
- Musculoskeletal: Back pain
- Gastrointestinal: Hepatic dysfunction, abdominal pain

Drug Interactions

- Passive transfer of antibodies may transiently interfere with the response to live viral vaccines, such as measles, mumps and rubella. This may confound serologic testing. Inform the immunizing physician of recent therapy with GAMMAKED so that appropriate measures may be taken.

Use in Specific Populations

- Pregnancy Category C. There is no human or animal data. It should only be given to a pregnant woman only if clearly needed.
- Geriatric: In patients over 65 years of age, do not exceed the recommended dose, and administer GAMMAKED at the minimum infusion rate practicable.

Rx Only

Manufactured by:

Talecris Biotherapeutics, Inc.
Research Triangle Park, NC 27709

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Fort Lee, NJ 07024

wearing seatbelts and wearing gloves when working with knives or other tools.

If bleeding does start, ITP patients should sit or lie down and apply pressure to the wound if it can be seen. An ice pack also can slow the bleeding. If the wound is to an arm or leg, that limb should be elevated above heart level. If there is blood in the urine, increased fluids should be ingested. If there is vaginal blood, tampons should not be used; instead, the number of sanitary pads should be kept track of and clots should be watched for. A physician should be contacted if the patient has a headache, confusion or dizziness; if there is blood when coughing or difficulty breathing; if there is blood in the urine, vomit or bowel movement; and if there is unusually heavy vaginal bleeding or vaginal bleeding after menopause.⁵

ITP is a serious disease, but the prognosis is good.

For pregnant women with ITP, treatment is not usually needed. However, treatment is needed for those with very low platelet counts to prevent serious heavy bleeding during delivery and afterward. And, while babies of women with ITP aren't usually affected, some babies are either born with low platelet levels or develop low platelets soon after birth. These babies' platelet counts almost always return to normal without any treatment.¹⁴

The PDSA (www.pdsa.org) has a variety of resources for ITP patients, including a 26-page booklet titled *Coping with ITP* and online discussion groups.¹⁵

The ITP Prognosis

ITP is a serious disease, but the prognosis is good. More than 80 percent of children with untreated ITP have a spontaneous recovery with complete normal platelet counts in two to eight weeks. Fatal bleeding occurs in only 0.9 percent of children upon initial presentation of ITP, and fatal intracerebral hemorrhage occurs rarely in children with ITP who have been treated with prednisone and anti-D antibodies or IVIG for at least two days. In adults with ITP, 60 percent to 90 percent respond with an increased platelet count after treatment with prednisone, a combination of prednisone and anti-D antibodies, or

IVIG. And, of those who don't maintain an increased platelet count and who require splenectomy, approximately two-thirds have a sustained response and 10 percent to 15 percent have a partial response.⁶

There is no question that ITP is a more chronic, persistent disorder in adults, but almost all patients do well. With a correct diagnosis, proper treatment and use of available resources, ITP patients can live relatively normal lives. ■

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

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