This past August, the U.S. Food and Drug Administration (FDA) reported what patients had been experiencing all year - an ongoing shortage of immune globulin (Ig) products in the United States. Over the past year PDSA has heard from many patients, caregivers, and even practitioners frustrated by this shortage. Some of you told us that you could not receive your regular IVIG treatment for ITP and were offered alternative treatments – often the "dreaded prednisone." Some told us that they had to put off dental work or surgery because of restricted access to IVIG treatments necessary to raise platelet counts to a safe level to undergo these procedures. Others worried about traveling or playing sports without their IVIG boost. PDSA would like to thank *IG Living* magazine for permission to reprint the following article, addressing many of the reasons for the plasma protein therapy shortage and offering useful advice should your IVIG treatment be unavailable. For more information about IVIG and ITP, visit https://pdsa.org/ivig.html.

What Patients Need to Know About Plasma

By Abbie Cornett

IN RECENT YEARS, the demand for plasma protein therapies used to treat rare and chronic conditions has grown at a tremendous rate. The worldwide demand for intravenous immune globulin (IVIG) and subcutaneous IG (SCIG) more than doubled between 2008 and 2016, and it is projected to continue growing at more than 8 percent per year. To keep ahead of this projected growth, manufacturers must expand collection of plasma, which is needed to produce IG products. In 2018, it was projected an additional three million plasma donations were needed to meet demand.

Patients may be surprised to learn it takes between six months and 12 months from the time plasma is donated until it is manufactured into an available IG product. This is because the production of a plasma therapy is a complex multistep process.

Unlike traditional pharmaceutical products that rely on a chemical process, plasma-based therapies rely exclusively on proteins found in human blood plasma. Plasma is the straw-colored liquid portion of blood made up of water, salts and proteins that performs a variety of functions in the body, including clotting and fighting disease.[1] It makes up 55 percent of a person's total blood volume.

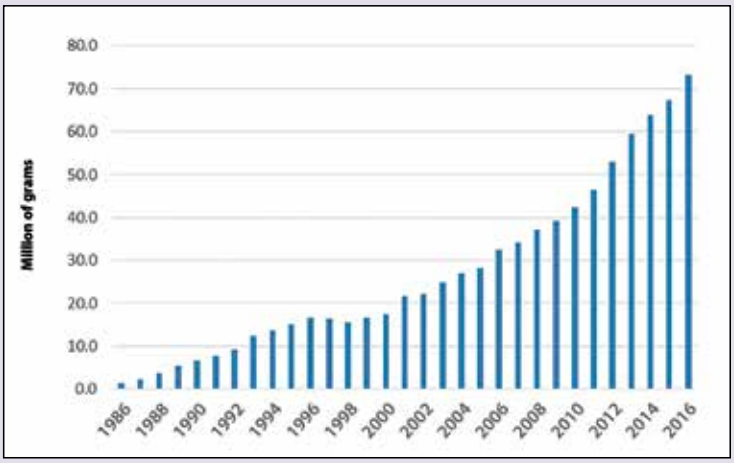
The first step in producing a plasma therapy takes place in a donation center where donors are carefully screened to ensure the quality of their plasma. Once vetted, these individuals donate their plasma through a specialized process called plasmapheresis that separates the plasma from red blood cells and other cellular components that are then returned to the donor.[1] Each individual plasma donation averages about two-thirds of a liter in volume. After an individual's plasma is collected, it is stored while it undergoes screening to guarantee its quality and safety. The plasma is then pooled with donations from thousands of other donors.[2]

The next step is fractionation, a process that isolates and purifies therapeutic proteins found in the plasma, including those used in the production of IG products. After these steps have been completed, the proteins are ready to be formulated into therapies.

Because of increasing demand and the long lead time needed to bring these products to market, there can be shortages at times. If you are a patient who has been told future treatments with your brand of IG will not be possible, here are some steps you can take:

1) If you are being treated in the home, ask if there is another brand to which you can switch. If no product is available, talk to your ordering physician about another homecare provider.
2) If you are being treated in a physician's office, ask if there is another brand to which you can switch. If no product is available, look for other sites of care. Specifically, check with the hospital where your ordering physician has privileges. Or, check with a homecare provider.
3) If you are being treated in a hospital outpatient infusion center, go back to your ordering physician and ask about another outpatient center. Or, check with a homecare provider.
4) Consider exploring the subcutaneous route of infusion if it makes sense for your condition.

The U.S. Polyvalent IG Market (IVIG/SCIG) from 1986 to 2016



Source: The Marketing Research Bureau, Inc. (Orange, CT).

IG manufacturers are making every effort to address these issues affecting shortages. In fact, every major plasma fractionator is investing in new production capacity, and manufacturers are producing IG products at top capacity. In addition, some new products are coming to market, and one previously removed from the market is being reintroduced.

As the patient advocate for *IG Living*, I am ready to answer your questions about IG therapy, as well as your concerns if you have been told your product is not available.■

ABBIE CORNETT is the patient advocate for *IG Living* magazine. She can be reached at patient advocate@igliving.com or (800) 843-7477 x1366.

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Alternative Treatments to IVIG in ITP Patients

By James Bussel, MD

Because ITP has many possible treatments that can increase the platelet count, in the current setting of an IVIG shortage, it is probably the disease most targeted for the use of other treatments instead of IVIG. In general, the major benefit of IVIG in treatment of ITP is the high response rate combined with the ability to rapidly increase the platelet count (days) to very high levels. The major drawbacks are reactions, primarily headaches, the time to infuse (hours), and the temporary nature of the response.

What can be used in place of IVIG?

1. IV anti-D: if your blood type is Rh+ (85% of patients), you have not had your spleen removed, and you do not have antibodies on your red blood cells (an easy blood test called the coombs test or direct antiglobulin test), then you might likely respond well to IV anti-D (the leading brand is Winrho). When a higher dose (75 micrograms per kilogram bodyweight) is used, the response is very similar to that of IVIG in rapidity, frequency and height of response. The last time there was a major IVIG shortage in the United States (late 1990's early 2000's) the use of Winrho increased dramatically. Currently, its use has greatly decreased because of a 1:1000 (slightly less) serious reaction called "intravascular hemolysis". However, if high dose steroid premedication is given eg 30mg/kg of methylprednisolone IV right before giving Winrho, the chance of a serious (or any reaction) is greatly decreased. Winrho can be given in 5-30 minutes IV.

2. Dexamethasone: high dose dexamethasone (dex) brings up the platelet count faster than does prednisone. Furthermore, it is only given for 4 days at a time and has many of the response characteristics of IVIG and IV anti-D except that it is several days slower. By virtue of its being given for only 4 days, it is believed to have less side effects than continuous prednisone. However, the 4 days of taking it (especially days 3 and 4) and the 1-2 days after stopping it (no taper) can be difficult to deal with. It can be given for 4 days and then repeated weeks to months later as needed.

3. TPO agents: in the US, three are available for patients with ITP: romiplostim (nplate), eltrombopag (promacta, revolade), and avatrombopag (doptelet); a fourth (lusutrombopag) is only licensed for low platelets in patients with liver disease (a fifth agent, 3S Bio TPO, is only available in China and several other adjacent countries). The difficulty with the TPO agents (well known to have high response rates and to be relatively safe and easy to tolerate) is deciding on the initial dose in view of the response requiring 5-7 days if a patient receives a dose to which they will respond. Romiplostim has dosing of 1-10 micrograms/kg once a week administered subcutaneously by a health care professional. If one starts at the bottom and works up slowly it can take over a month to find an effective dose. Therefore, depending upon urgency, one might start at 3 mics/kg and increase to 5, 7 and then 10 mics/kg. If there is more urgency, the progression can be the same but starting with 5 or even 7 mics/kg. Eltrombopag is recommended for non-Asian adults to stat at 50 mg/day and then increase to 75 mg/day in 2 weeks if the count does not increase sufficiently. In a more urgent situation one can start with 75mg daily. Avatrombopag has a recommended starting dose of 20mg daily with the ability to increase as high as 40mg daily; intermediate steps would suggest taking avatrombopag 40mg 3 or 4 days per week and 20mg the other 3-4 days of the week. Unlike eltrombopag which requires an empty stomach, avatrombopag can be (is encouraged to be) taken with food.

If one is using a TPO agent or dexamethasone, it is important to plan ahead if the use is for an elective surgery or specific known situation in the future eg trip that will not have medical care available, the "big game" (whatever that is). IV anti-D will increase the count very quickly if it works which is most but not all the time.

Depending upon urgency and the past history of patient responses, an appropriate choice of IVIG replacement treatment can be made. Sometimes a combination may be used. In this setting we believe a TPO agent should be part of the combination because of their unique mechanism of effect. it is also important to consider that even if another treatment is started that might take effect more quickly, the advantage of using a simultaneous TPO agent is the ability to prevent relapse and manage the count after the emergency has passed. IV anti-D can be used in maintenance if needed analogous to the use of repeated infusions of IVIG. TPO agents use in maintenance of the platelet count by continued usage is well-described. Dex can be given several times but not usually more than 3 times 4 days. It may be harder to put up with on successive uses.

For any questions, contact your hematologist. There are many other treatments of ITP and they certainly can be used to increase the platelet count. This may require considerable additional time to achieve a response and/or be more toxic. Usage of any of the treatments of ITP in place of IVIG depends on expectation of response to the considered treatment.

To learn more about the wide variety of ITP treatments, visit the PDSA website here: https://pdsa.org/treating-itp.html ■