Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies

Chapter 24

There are several specific medical therapies available for patients with primary immunodeficiency diseases involving the humoral immune system. These illnesses include X-Linked Agammaglobulinemia (XLA) and Common Variable Immune Deficiency (CVID), among others, and are characterized by a lack of and/or impaired antibody function. Effective therapies for these disorders are a reality for most patients, and optimize their health, improve their quality of life and allow them to become productive members of society. In this chapter, therapy for antibody disorders will be discussed. For all of these therapies, individual risk/benefit ratios should be discussed with your healthcare provider.

Immunoglobulin Therapy

The term "immunoglobulin" refers to the fraction of blood plasma that contains immunoglobulins, or antibodies. These immunoglobulins (Ig) in the serum or plasma are IgG, IgM, IgA, IgD and IgE. Individuals who are unable to produce adequate amounts of Ig or antibodies, such as patients with XLA, CVID, Hyper-IgM Syndromes, Wiskott Aldrich Syndrome or other forms of antibody deficiency may benefit from replacement therapy with Ig. Only the IgG is purified from the plasma to produce commercial Ig products, so Ig used for treatment contains very little of any of the other Ig types.

As explained in other chapters of this handbook, B-lymphocytes mature into plasma cells, which manufacture antibodies and release them into the bloodstream. (See chapter titled "The Immune System and Primary Immunodeficiency Disease.") There are literally millions of different antibodies in every normal person, but because there are so many different germs, no one person has made antibodies to every germ. The best way to ensure that the Ig will contain a wide variety of antibodies is to combine or "pool" the plasma from many individuals.

Ig was first used to prevent infectious diseases in World War II and first given for primary immunodeficiency diseases in 1952. Until the early 1980's, the only form that was available was usually given by deep injection into muscle (intramuscular or IM), although it was also given by subcutaneous infusion rarely in the U.S. but more commonly in other parts of the world (for example, Scandinavia). Ig products for intramuscular injection continue to be used to give normal individuals a boost of antibodies after exposure to some specific diseases such as measles or hepatitis, or before they travel to areas where those diseases are prevalent. In these instances, the amount of Ig needed to prevent diseases is small, generally 5-10 cc (1-2 teaspoons).

What is Ig Replacement Therapy?

Ig is prepared from the plasma collected from a large number of normal individuals, usually between 10,000-50,000, who have been carefully screened to make sure they are healthy and do not harbor certain infectious diseases. The plasma contains a broad range of specific antibodies to many different types of bacteria and viruses. Each plasma donor must be acceptable as a

(Immunoglobulin Therapy continued)

blood donor according to the strict rules enforced by the American Association of Blood Banks and the U.S. Food and Drug Administration (FDA). Donors are screened for travel or behavior that might increase the risk of acquiring an infectious disease. Only the IgG is purified from the pooled plasma. To commercially prepare the Ig for patients with primary immunodeficiency diseases, the immunoglobulin must first be purified (extracted) from the plasma. All Ig licensed in the U.S. is made from plasma collected in the U.S.

The blood, or plasma, from each donor is carefully tested for evidence of transmissible diseases, such as AIDS or hepatitis, and any plasma sample that is even suspected of having one of those viruses is discarded. The first step in Ig production is to remove all the red and white blood cells. This is frequently done right as it comes out of the donor's arm by a process called plasmapheresis, which collects the plasma and then returns the red and white cells directly back to the donor. Plasmapheresis is done at centers specifically designated for this purpose. Then, the immunoglobulins are chemically purified from the plasma in a series of steps. This process results in the purification of antibodies of the IgG class; only trace amounts of IgA and IgM, and other plasma proteins remain in the final product.

In the early 1980's, new manufacturing processes were developed to make Ig preparations that could be safely injected intravenously, that is directly into the vein. Now multiple Ig preparations are licensed in the U.S. for intravenous use. Products developed for intravenous use have also been used successfully subcutaneously, which is administered under the skin, and in recent years products for subcutaneous use have been licensed. For the most part, the products are equivalent in antibody activity. However, there are some differences which may make one particular preparation more suitable than another for a given individual. Most products contain some type of sugar or amino acid that help preserve the IgG molecules and prevent them from sticking together to form aggregates. If aggregates were present, they could cause severe side effects. Although these sugar and protein additives are harmless for most people, some of them may cause problems for specific individuals. Your prescriber is your best source of information about which product is best for you.

Purified Ig has been used for more than 50 years and has an excellent safety record. During the purification process and with the final product, there are several steps that destroy or remove many types of viruses, including HIV, to ensure that the final Ig product cannot transmit any known infectious diseases to the patient. Thus, the final Ig product contains highly purified plasma IgG that has a broad range of specific antibodies to many types of bacteria and viruses. It is also effective in helping the white cells in the body kill bacteria, viruses and other germs that may be in the tissues or blood of the patient being treated, and is safe to administer.

Administration of Ig Replacement Therapy

It is important to understand that the Ig that is given partly replaces what the body should be making, but it does not stimulate the patient's own immune system to make more Ig. Since Ig only replaces the missing end product, but does not correct the patient's defect in antibody production, Ig replacement is usually necessary for the patient's lifetime. In addition, the Ig only provides temporary protection. Most antibodies, whether produced by the patient's own immune system or given in the form of Ig replacement, are used up or "metabolized" by the body and must be constantly replenished. Approximately half of the infused antibodies are metabolized over three to four weeks, so repeat doses of Ig are required at regular intervals.

Ig replacement therapy is generally administered either intravenously (abbreviated IVIG), or subcutaneously (abbreviated SCIG). IVIG infusions are usually given every three or four weeks. SCIG infusions may be given as often as daily, weekly, or as infrequently as every

(Immunoglobulin Therapy continued)

three to four weeks (similar to IVIG), depending on the specific SCIG product that is being prescribed, the patient's age and the preferences of the patient and the prescriber.

Since IVIG infusions are usually given once every three or four weeks directly into a vein, there is a very high "peak" IgG level in the blood right after the dose is given and a lower IgG level in the blood at the "trough" just before the next dose is due.

SCIG is injected relatively slowly, directly under the skin. Because small amounts of Ig are given (often) more frequently and because the Ig is absorbed more slowly, the peak and trough associated with IVIG are very blunted or eliminated when giving SCIG. Patients who have side effects from high peaks of IgG or feel "washed out" or weak before their next IVIG dose is due may prefer SCIG.

SCIG therapy may be an alternative for those patients who have difficulty getting venous access and/or who have systemic adverse reactions to IVIG. Collaborating with their healthcare provider, patients have the flexibility to develop a dosing regime that is tailored to their lifestyle. The number of infusions per week or month, when the infusions are done, the number of needles used, using an infusion pump or manually pushing the drug, and the rate of infusion are all variables that can be considered to design an individual patient's SCIG regimen. Patients must be committed to this therapy and should not "skip" doses or change their regimen without consulting their provider.

Side Effects from Ig Replacement Therapy

Most patients tolerate Ig very well. Infusions can be administered either in an outpatient clinic or, after tolerability and safety is demonstrated in a controlled setting, in the patient's own home. A typical IVIG infusion will take two to four hours from start to finish. Some patients may tolerate more rapid infusion while others may require longer times. Use of intravenous products allows physicians to give larger doses of Ig at one time than could be given subcutaneously. In fact, doses can be given that are large enough to keep the IgG levels in the patient's serum in the protective range, even just before the next infusion when the level would be lowest.

There is a potential for some side effects associated with IVIG. These can include low-grade fever, aching muscles or joints or post-infusion headaches occur. These symptoms can usually be alleviated or eliminated by infusing the immunoglobulin at a slower rate and/or by giving acetaminophen, non-steroidal anti-inflammatory drugs like ibuprofen, or even small amounts of short-acting systemic steroids. Sometimes saline infusions may be given before IVIG, and/or infusions may be run more slowly to help minimize side effects. Less often, patients experience hives, chest tightness or wheezing. These symptoms usually respond to antihistamines such as diphenhydramine (Benadryl™) and/or asthma medications like albuterol.

Headaches associated with Ig are not uncommon and may occasionally be severe, especially in patients with a history of migraine headaches. These headaches may occur during the infusion or as long as three days later. Some patients with severe and persistent headaches have been found to have an increase in the number of white blood cells in the cerebral-spinal fluid. This condition is known as aseptic meningitis. The cause of this apparent inflammation is not known, but it is not an infection and patients have not had permanent injury. It is important to note that every patient who develops a post-infusion headache does not necessarily have aseptic meningitis. You should notify your prescriber if you experience headaches that do not respond to standard medications such as acetaminophen or non-steroidal anti-inflammatory drugs like ibuprofen.

It may take several infusions to develop a tolerable specific IVIG regimen for each patient. Variables include the product used, the rate of infusion, and the need for any pre-medications. Once a regimen that is well tolerated has been found, it should be followed with EVERY infusion. While all Ig products provide necessary antibody replacement, each has subtle differences and

(Immunoglobulin Therapy continued)

thus are NOT interchangeable. Switching from one brand to another is one of most common causes for side effects. Patients need to know what their product is, the dose, and their specific infusion protocol. IDF ePHR is a good place to keep this information (www.idfephr.org).

Patients who experience significant side effects from IVIG infusions may benefit from changing to SCIG. Because the doses given at any one time are usually (not always) smaller, and because the Ig is slowly absorbed, there are fewer systemic side effects associated with SCIG. Side effects associated with SCIG tend to be localized skin reactions that tend to decrease over time. Changes to the individual infusion regimen, including the number of sites used, the length of the subcutaneous needle(s) used, the amount of drug given into each site and the rate of infusion are all things that can be modified to decrease the incidence of localized reactions to SCIG.

Qualifying for Ig Replacement Therapy and Appropriate Dosage

Before starting Ig replacement therapy, it is important that your provider completes all the immune studies to demonstrate that your immunoglobulins are not only low but that you do not make specific antibodies normally following natural infections or immunization with vaccines. An exception to this rule is those patients that have extremely low serum immunoglobulins, like a serum IgG of 200 mg/dl or less. Immunologists generally use tetanus toxoid and pneumococcal vaccines (Pneumovax) to test the ability of the patient to make specific antibodies. Blood is drawn before giving the vaccine to measure the vaccine specific antibody levels. After vaccination, a second blood sample is drawn four to six weeks later to determine how well specific antibodies are made to these vaccines. It is important that you follow through with this second blood draw to determine your response to vaccines within this four to six week timeframe. Insurance companies often review this information before approving Ig therapy.

The dose of Ig varies from patient to patient. In part, the dose is determined by the patient's condition and weight. The dose by the intravenous route generally starts at 400-600 mg/kg per month, and 100-175 mg/kg/week by the SC route. However, some patients require higher doses, especially those with chronic lung disease. Recent studies have shown that an optimal trough level (if given by the intravenous route) or steady state IgG plasma level (if given by the subcutaneous route) is approximately 850 mg/dL to insure adequate prophylaxis (infection protection). Your prescriber will measure your Ig levels and monitor your clinical status (such as how you are feeling, if you are having infections) to insure that you are receiving an adequate dose of replacement therapy.

Choice of Route

The choice of route of administration of Ig therapy (IVIG or SCIG) should be a decision based on discussions between the patient and provider. This decision is usually based on a number of factors including the clinical characteristics of each patient, the patient's preferences for therapy, appropriate site of care (home, hospital, infusion center), and sometimes, even insurance coverage.

Some patients with chronic sinusitis and chronic lung diseases, such as bronchitis, do better when given higher doses of Ig. Some patients, who lose IgG molecules from their digestive tracts or kidneys, may require more frequent doses and/or higher doses.

Remember that although our current Ig products are very good, they do not duplicate exactly what nature normally provides. The manufactured Ig is almost pure IgG, so no IgA or IgM is transferred to the patient. The specific protective functions of these immunoglobulins are therefore not replaced. The IgA on the mucosal surfaces of the respiratory tract is not being replaced, which may be part of the reason that antibody deficient patients remain somewhat more susceptible to respiratory infections, even though they are receiving enough immunoglobulin to maintain normal or near-normal blood levels of IgG.

Prophylactic Antibiotic Therapy

Some providers may prescribe prophylactic antibiotics for patients with a history of sinus or pulmonary disease in order to cover against bacterial infections of the sinuses and lungs. Prophylactic doses of antibiotics are low dose antibiotics generally given at about half the daily full dose. Common prophylactic antibiotics are amoxicillin, Bactrim/Septra (trimethoprim/sulfamethoxazole) or azithromycin.

Generally, antibiotics used for treatment of active infection are not used as prophylaxis. Some providers rotate prophylactic antibiotics with the goal of reducing the development of bacterial resistance, although there is no true evidence that this approach is necessary. Some prefer to treat with a single drug. Depending on the specific circumstances of the individual case and the type of antibiotic and the microbe needing prophylaxis, the prophylactic antibiotic may be stopped temporarily during the treatment of an active infection with a different antibiotic and resumed after the resolution of the infection and completion of the new treatment. There is no true evidence that this approach is necessary. Some prefer to treat with a single drug. There is some controversy regarding the use of prophylactic antibiotics, as some providers believe that the potential for developing drug resistant pathogens is a risk that outweighs the benefit. The decision needs to be discussed with a specialist. In patients with sinus infections the provider may also recommend a topical nasal steroid and/or saline nasal washes.

Summary of Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies

The goal of Ig therapy for antibody disorders is to provide protection from infection. Patient compliance with therapy is paramount to achieving this goal. Any barriers to therapy, real or potential, need to be addressed appropriately. It is also important to remember several things:

- Not all infections can be prevented. After starting Ig therapy, you may still get infections. However, it is hoped that the frequency and severity of infections will be significantly decreased so that permanent organ damage, like bronchiectasis can be prevented.
- "One size does not fit all." An individualized regimen must be developed for each patient and modified as necessary to achieve treatment goals and the needs of each person.
- Once a diagnosis has been made, therapy will probably be needed life long. In some instances, reevaluation of the diagnosis may be undertaken. This will be done by taking the patient off of therapy and reevaluating humoral immunity.