



CHAPTER

18

Specific Medical Therapy

There are several specific medical therapies available for patients with primary immunodeficiency diseases. Effective therapies for these disorders are a reality for most patients, improving their productivity and allowing most of them to lead active lives, pursue careers and have families.

Introduction

There are several specific medical therapies available for patients with primary immunodeficiency diseases. Effective therapies for these disorders are a reality for most patients, improving their quality of life and allowing them to become productive members of society. In this chapter, five established therapies (immunoglobulin replacement, stem cell transplantation, granulocyte-colony stimulating

factor, gamma interferon and adenosine deaminase replacement) and an experimental type of therapy (gene therapy) will be considered. Their specific indications, dose and treatment regimens, and risk/benefit ratios should be discussed with your physician.

Immunoglobulin Therapy

The term, immunoglobulin, refers to the fraction of blood plasma that contains “immunoglobulins” or “antibodies.” Individuals who are unable to produce adequate amounts of immunoglobulins or antibodies, such as patients with X-linked agammaglobulinemia, common variable immunodeficiency, hyper-IgM syndromes or other forms of hypogammaglobulinemia, may benefit from replacement therapy with immunoglobulin. It is important to understand that the immunoglobulin that is given partly replaces what the body should be making, but it does not help the patient’s own immune system make more. Unfortunately, the immunoglobulin only provides temporary protection. Most antibodies, whether produced by the patient’s own immune system or given in the form of immunoglobulin, are used up or “metabolized” by the body. Approximately 1/2 of the infused antibodies are metabolized over 3 to 4 weeks, so repeat doses are required at regular intervals. Depending on the route of administration, this may be done by giving small infusions under the skin as often as every 2 or 3 days, or larger intravenous infusions once every 3 or 4 weeks. Since it only replaces the missing end product, but does not correct the defect in antibody production, immunoglobulin replacement is usually necessary for the patient’s whole life.

As explained in other chapters of this handbook (see chapter titled *The Immune System and Primary Immunodeficiency Disease*), B-lymphocytes mature into plasma cells, which manufacture antibodies and release them into the bloodstream. 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 immunoglobulin will contain a wide variety of antibodies is to combine, or “pool”, blood from many individuals.

To commercially prepare immunoglobulin that can be given to patients with a primary immunodeficiency, the immunoglobulin must first be purified (extracted) from the plasma, or liquid part, of the blood of normal healthy individuals. Each donor must be acceptable as a 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. All immunoglobulin licensed in the U.S. is made from plasma collected in America. The blood or plasma from each donor is carefully tested for evidence of transmissible diseases, such as AIDS or hepatitis, and any sample that is even suspected of having one of those diseases is discarded. Plasma is collected from tens of thousands of donors, and then pooled together. The first step in immunoglobulin 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 returns the red and white cells directly back to the donor. Then, the immunoglobulins are chemically purified from the liquid plasma in a series of steps usually involving treatment with alcohol. This process results in the purification of antibodies of the immunoglobulin G (IgG) class; only trace amounts of IgA and IgM remain in the final product (see chapter titled *The Immune System and Primary Immunodeficiency Disease*). The purification process removes blood proteins other than IgG and is also very effective at killing viruses and other germs that may be in the blood.

Immunoglobulin was first used to prevent infectious diseases in World War II and it was first given for primary immune deficiency in 1952. Until the early 1980’s, the only form that was available

Immunoglobulin Therapy continued

was usually given by deep injection into muscle (intramuscular or IM). Immunoglobulin 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. The amount of immunoglobulin needed to prevent these diseases is small, only about five ml (one tsp.). Unfortunately, patients with a primary immunodeficiency require frequent injections with much larger doses of immunoglobulin. These intramuscular injections were very painful, and only modest amounts of immunoglobulin could be given in this way. There simply wasn't enough room inside the muscle for more.

In the early 1980's, new manufacturing processes were developed to make immunoglobulin preparations that could be safely injected intravenously, or directly into the vein. There are now several immunoglobulin preparations licensed in the U.S. for intravenous (IV) use. For the most part, the products are equivalent in antibody activity. However, there are some minor differences, which may make one particular preparation more suitable for a given individual. Most of the products that can be given intravenously contain some type of sugar or amino acids which help preserve the IgG molecules and prevent them from sticking together to form aggregates, which can cause severe side effects. Although these additives are harmless for most people, some of them may cause problems for specific individuals. Your doctor is your best source of information about which product is best for you. IV infusions are usually given once every three or four weeks. This results in a very high "peak" IgG level in the blood right after the dose is given and may leave a relatively low IgG level in the blood at the "trough" just before the next dose is due.

Another route for giving immunoglobulin is to inject it relatively slowly, directly under the skin. This is known as subcutaneous infusion, and is done with a much smaller needle than is used for IV, and a small pump that can be worn on the belt. It is an alternative for those patients who have difficulty getting venous access and for some who have adverse reactions to intravenous immunoglobulin. Typically, subcutaneous infusions are given once or twice a week by the patient (or by a parent or partner) at home. Since small doses are given more frequently than is usually done with IV therapy, the "peaks" and "troughs" tend to level out. Subcutaneous therapy may be preferred by

patients who have side effects from the high peaks or feel "washed-out" or weak before their next IV dose would be due. Subcutaneous infusions might also be preferred by patients who have trouble getting IVs started, and by those who prefer treating themselves at home on their own schedule.

Purified immunoglobulin has been used for nearly 50 years and has an excellent safety record. There has never been a case of AIDS due to the use of immunoglobulin. However, in 1993, before we had good tests for the presence of the Hepatitis C virus, there was an outbreak of hepatitis C associated with one of the immunoglobulin preparations. Since that time, all immunoglobulin preparations are treated with special steps which are included to specifically kill viruses such as the AIDS virus and the hepatitis viruses. Some processes treat the immunoglobulin with solvent and detergent to dissolve the envelopes of the viruses. Others pasteurize with heat or use acid treatment to kill them. These methods have been shown by FDA tests to destroy all AIDS and hepatitis viruses, and most manufacturers now perform several of these steps on every batch to make the chance of any virus getting through as low as possible.

Most patients usually tolerate the intravenous immunoglobulin products very well. They can be administered either in an outpatient clinic or in the patient's own home. A typical infusion will take two to four hours from start to finish. Some patients may tolerate certain preparations more quickly, while others may take longer to receive their dose of IgG. Use of intravenous products allows physicians to give larger doses of immunoglobulin than could be given intramuscularly. In fact, doses can be given that are large enough to keep the IgG levels in the patient's serum in the normal range, even just before the next infusion when the level would be lowest. Most patients have no side effects from the IV infusions, but sometimes low-grade fever or headaches occur. These symptoms can usually be alleviated or eliminated by infusing the immunoglobulin at a slower rate and/or by giving acetaminophen, aspirin or other common medications an hour or so before infusion. 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 may occasionally be severe, especially in patients with a history of migraine. These headaches may occur during the infusion or as long as three to five

General Care During Specific Illness continued

days later. Some patients with the more severe and persistent headaches have been found to have an increase in the number of white blood cells in the cerebral-spinal fluid, which surrounds the brain. This 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 bothersome, and usually requires treatment. In some patients merely changing brands of IVIG will eliminate the problem. In some cases, it is necessary to treat with a steroid, before, during, or after the infusion. You should notify your doctor if you experience headaches that do not respond to standard medications such as acetaminophen.

The dose of immunoglobulin varies from patient to patient. In part, the dose is determined by the patient's condition and weight. It is also determined by measuring the level of IgG in the patient's blood at some interval after infusion, and by determining how well a given dose of

immunoglobulin treats or prevents symptoms in an individual patient. Studies have shown that patients with chronic sinusitis and chronic lung diseases such as bronchitis do better when given higher doses of immunoglobulin. Some patients, who lose IgG molecules from their digestive tracts or kidneys, may require more frequent doses.

It is important to remember that although our current immunoglobulin products are very good, they do not duplicate exactly what nature normally provides. The manufactured immunoglobulin is almost pure IgG, so essentially 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.

Hematopoietic Stem Cell Transplantation

Transplantation of stem cells from a normal donor to a recipient with a primary immunodeficiency is a highly specialized procedure that can be used to treat some primary immunodeficiency diseases. A "stem cell" is a type of cell that can produce descendants that branch into different types of cells, such as B lymphocytes and T lymphocytes. It can also make more stem cells and continuously regenerate the pool of stem cells. Traditionally, stem cells for the immune system were obtained from bone marrow. This process was called "bone marrow transplantation." Now, purification techniques allow separation of stem cells from peripheral blood, and blood obtained from the placenta at birth ("cord blood"). Cord blood, in particular, has been shown to provide an excellent alternative source of stem cells for the immune and blood systems. The stem cells that give rise to the lymphocytes and other cells of the immune system also make blood cells. They are called "Hematopoietic" stem cells (HSC). The process of taking stem cells from one person and putting them into another is therefore called "HSCT" or hematopoietic stem cell transplantation. The primary immunodeficiency diseases for which HSCT is most commonly performed include

those diseases that are characterized by deficient T-lymphocytes or combined deficiencies of T-lymphocytes and B-lymphocytes. HSCT is most often used to treat severe combined immune deficiency (SCID). HSCT has also been used in some patients to treat other primary immunodeficiency diseases such as the Wiskott-Aldrich syndrome, hyper-IgM syndromes, and chronic granulomatous disease.

As mentioned in the chapter titled *The Immune System and Primary Immunodeficiency Diseases*, bone marrow is the organ in which immature cells of the immune system, the stem cells, divide and begin the developmental journey on the road to becoming mature T-lymphocytes, B-lymphocytes, and macrophages and neutrophils. In the normal fetus, there are so many stem cells that they spill out of the bone marrow which makes fetal blood and umbilical cord blood rich sources of stem cells. The transplantation of HSCs from a "normal" individual to an individual with a primary immunodeficiency has the potential to replace the deficient immune system of the patient with a normal immune system.

Hematopoietic Stem Cell Transplantation continued

There are two potential obstacles that must be overcome for this to succeed. The first obstacle is that, except for the children with the most complete form of severe combined immunodeficiency, the patient (the recipient or host) will have enough immune function remaining to recognize the transplanted marrow as foreign, react against it and reject it. This first problem is called graft rejection. Thus, most patients other than those with SCID must be treated with chemotherapy and/or radiation therapy, even if they do not have cancer, in order to further weaken their own residual immune system to prevent it from rejecting the transplanted HSCs. Another similar situation occurs when the recipient's bone marrow is full of its own, defective stem cells. In that case, the grafted cells may not find any place to establish themselves and there may be a "failure of engraftment." In this situation, chemotherapy and/or radiation must also be given to reduce the number of defective stem cells in the recipient's bone marrow to "make room" for the new stem cells to engraft. Although the chemotherapy and/or radiation therapy prevents the patient (recipient) from rejecting the transplanted HSCs, it may cause serious side effects. These include loss of all of the cells of the bone marrow, including the red cells that carry oxygen, the white cells that help fight infection, and the platelets that help the blood clot. There is a very high risk of contracting a serious infection during the weeks immediately after a transplant. The chemotherapy also may cause severe blistering of the mouth or other mucus membranes that makes eating and drinking impossible. It is because of these serious complications that transplantation is reserved for those patients with the most severe immune defects.

The second obstacle arises from the fact that the transplanted stem cells (or graft) carry the immune system of the donor. Mature T-cells may be carried along with the stem cells and/or may develop from the graft and may recognize the recipient (host) patient's tissues as foreign. The grafted immune system can react against and attack tissues in the recipient (or "host"). This problem is called "graft vs. host disease (GvHD)." Often, medicines such as steroids and cyclosporine, which suppress inflammation and T-cell activation, are given to prevent and/or treat GvHD. In order to overcome the dual problems of graft rejection by the host and, more importantly, graft versus host disease, doctors try to find a "match" in which certain proteins called "transplantation," "HLA," or

"histocompatibility" antigens are the same on the cells of the donor and recipient (see paragraph below). Alternatively, the bone marrow or other HSC preparation can be treated to remove most of the mature T-lymphocytes, which are the ones that cause most GvHD. Unfortunately, depletion of T-cells may cause delays in the development of the new immune system or incomplete engraftment.

Selection of the Donor

A "matched" HSCT is one that uses a donor whose tissue (or transplantation) antigens are very similar or identical to those of the recipient. These transplantation antigens are called histocompatibility antigens because they determine whether the transplanted tissue is "compatible" with the donor. In humans, these histocompatibility antigens are referred to as HLA antigens.

Each of us has our own collection of these histocompatibility antigens on most of our cells including the cells of our immune system and bone marrow, as well as on cells in most other tissues including skin, liver and lungs. The exact structure of these HLA antigens is determined by a series of genes clustered on the sixth (6th) human chromosome. Since the genes for histocompatibility antigens are closely clustered on the chromosome they are usually inherited as a single unit called a haplotype. There are so many different forms of these histocompatibility antigens that each person's haplotype (or collection of HLA antigens) is relatively unique. Since people who are closely related (like brothers and sisters) share many genes, they may also share their gene clusters (their haplotypes) which determine their histocompatibility antigens.

Since all of us have two number 6 chromosomes, we each have two haplotypes encoding the HLA antigens. Within each haplotype the histocompatibility gene cluster contains four major groups (or loci) designated HLA-A, HLA-B, HLA-C and HLA-D, with many different specificities possible in each of these four different groups or loci. There are so many different specific antigens possible for each of the four different HLA groups the chance that two unrelated individuals would have identical haplotypes is low. However, since haplotypes tend to be inherited as a unit, the chance that an individual's brother or sister would have the same haplotype is relatively high.

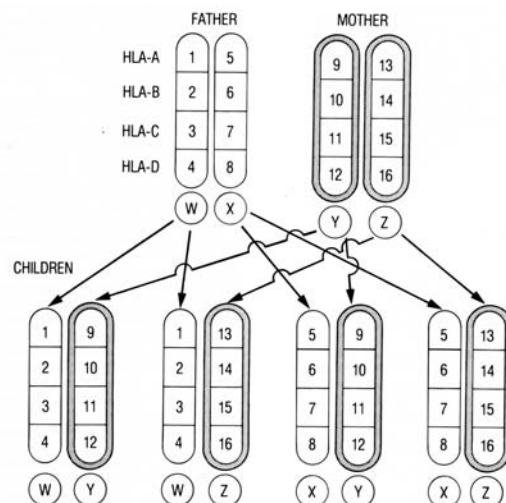
Hematopoietic Stem Cell Transplantation continued

The four loci in each haplotype are clustered together on each of the 6th chromosomes (see *Figure 1* below). The ways that parents could pass them on to their children are also shown in the diagram. In almost all cases, the four genes making up the haplotype on one chromosome stay together when the paired chromosomes are separated and one member of each pair goes into one individual egg or sperm cell. Like any other genetic characteristic, the choice of which of the two number 6 chromosomes goes into any given sperm or egg cell occurs in a random fashion. Whichever one of each parent's chromosomes is passed on to a child determines each of the two haplotypes the child will have.

As with any other genetic characteristic, each parent passes on only one chromosome and only one set of transplantation genes (haplotype) to each child. There are only four possible combinations of haplotypes in the children. Each of the four combinations is represented in *Figure 1*.

In the usual situation, a brother or sister of the patient is selected as the donor. Each sibling has a 25% chance of having the same transplantation genes and being a perfect match for the patient since there are only four possible combinations of genes. Due to the laws of probability and the fact that most families have limited numbers of children, fewer than 25% of patients have a sibling which is a "match." There has been a major effort to develop alternative methods for giving transplants to patients who do not have a matched donor in their own family.

CHAPTER 18; FIGURE 1 Selection of the Donor



Matched Unrelated Donors

If an HLA identical matched sibling donor is not available, one alternative is to try to find a suitable "matched" donor through one of the worldwide computer-based registries of individuals who have volunteered to serve as bone marrow donors. The National Marrow Donor Program in the United States has listings of hundreds of thousands of individuals who have provided a blood sample to have their HLA type measured. Successful transplants for patients with a primary immunodeficiency using donors found through this and other registries have saved the lives of many patients over the past 20 years with results using a fully matched unrelated donor (MUD donor) now approaching the success rate for transplants using sibling matches. There have also been many patients successfully transplanted using donors that were not fully matched. The success rate for such transplants has not been as high as with those full matches and diminishes with the greater the degree of mismatch between donor and patient. With mismatched transplants, other measures must be added to the transplant procedure in effort to protect the patient from graft versus host disease or GvHD that may occur when the T-cells in the graft recognize the new host as foreign and begin to attack.

Another source of HSC that may be used for transplantation in patients with primary immunodeficiency is umbilical cord blood. In the growing fetus, the HSC frequently leaves the marrow and are found circulating in high numbers in the blood. At the time of birth, the placenta is recovered, the blood that is remaining is removed and the HSC isolated and banked. These cord blood HSC may then be HLA typed and used for transplantation. Since cord blood contains fewer mature T-lymphocytes than the marrow or blood of adult donors, sometimes cord blood transplants have been successful even though the degree of match between donor and patient was not very good. A limitation of cord blood HSC transplantation is if only a small amount of cord blood is obtained, there may not be a sufficient number of HSC to treat a larger child or adult.

T-cell Depletion

Another alternative approach for the transplantation of a patient who does not have a matched sibling donor is to remove the mature T-lymphocytes from the stem cells before infusing them into the patient. In this way, the infused cells are less able

Hematopoietic Stem Cell Transplantation continued

to recognize the patient (host) as foreign, and the graft versus host reaction is markedly reduced and sometimes eliminated. Although the mature T-lymphocytes have been removed from the grafted stem cells, T-lymphocytes of donor origin can still develop from those stem cells and reconstitute the patient's T-lymphocyte immunity. The risk of graft versus host disease from these T-lymphocytes is markedly reduced because these cells develop inside the new host from immature precursor cells in the grafted marrow. Like a person's own T-cells, they are "educated" during their maturation to ignore or "tolerate" the histocompatibility antigens on the cells of the recipient (host). Since it takes longer for new T-cells to mature and learn to work with other cells in the recipient, engraftment from T-cell depleted HSCTs is usually slower than with matched HSCTs, and complete immunologic reconstitution may not occur. Occasionally, more than one transplant has to be performed to help create a fully functioning new immune system in the recipient. Unmatched donors for this kind of transplant will usually be one of the recipient's parents (called haploidentical transplants), since they share one half of the transplantation antigens of their child (see *Figure 1*). Some centers use this approach frequently for treatment of SCID babies while other centers believe that the search for a matched unrelated donor is the first choice option. It is also possible to do T-cell depletion in situations where less than fully matched unrelated donors are used.

The Procedure of Bone Marrow Transplantation

Bone marrow transplantation is accomplished by removing bone marrow from the pelvic bones. Bone marrow is removed by drawing the marrow up through a needle which is about 1/8 of an inch in diameter. Only two teaspoons are taken from each puncture site because, if more is taken, the sample is diluted with the blood which flows through the bone marrow space. Bringing blood with the bone marrow increases the risk of carrying over the mature T-cells which cause GvHD. Usually, two teaspoons are taken for each two pounds of the recipient's body weight. The average donor might have only a few punctures performed to get enough stem cells for a baby, but over 100 punctures may be required to get enough stem cells for a teen or full sized adult. The procedure may be performed under general anesthesia or under spinal anesthesia.

The discomfort after the procedure varies from donor to donor. Nearly everyone will require some type of pain control medication for two to three days, but most are not required to stay in the hospital overnight, and are able to return to full activity shortly. Due to the ability of stem cells to regenerate them, being a donor does not deplete or damage one's immune system.

After removal from the donor, the bone marrow is passed through a fine sieve to remove any small particles of bone and then placed in a sterile plastic bag. The cells are given to the patient with a primary immunodeficiency through a needle into a vein in the same manner as a blood transfusion.

Results of Bone Marrow Transplantation

Bone marrow transplantation between HLA matched siblings has been successfully employed in the treatment of immunodeficiency since 1968. The first child to receive a transplant, a patient with SCID, is still alive, healthy and has a family of his own. This case suggests that, as best as can be determined, the graft is very long lasting and appears to be permanent. In the usual patient with a primary immunodeficiency, bone marrow transplantation involving a "matched" marrow has minimal graft versus host disease and is associated with an overall success rate of as high as 90%. Many of these recipients can be considered cured and will be free from any signs of their primary immunodeficiency. However, a great deal depends on the health of the patient at the time of the transplant. If the patient is in relatively good health, free from infection at the time of the transplantation and does not have lung damage from previous infections, the outlook is very good. The chances of a successful transplant in SCID with full recovery by the recipient will be best if the transplant is done within the first month of life. Many patients who have diseases such as Wiskott-Aldrich syndrome, chronic granulomatous disease, or hyper IgM syndromes who require chemotherapy before the transplant to allow engraftment of the new bone marrow can also be cured by HSCT. Here again, the initial health of the patient is extremely important and the best survival is in children transplanted under the age of five who are relatively free of infections and who do not have pre-existing lung or liver damage.

Granulocyte-Colony Stimulating Factor (G-CSF)

Cells that are derived from stem cells in the bone marrow can take several different paths or “lineages” as they develop into mature cells in the blood. The particular pathway any given cell will follow is partly determined by its exposure to “growth factors” or chemical signals from other cells that tell the bone marrow what is needed. For example, a growth factor called “erythropoietin” is necessary for production of the red blood cells that carry oxygen in the blood.

The types of white blood cells that eat and kill bacteria are called granulocytes. The most important type of granulocyte is the neutrophil or poly. If a patient does not make enough of this kind of white blood cell, or if they are destroyed in the blood stream or the spleen, the condition is called neutropenia. The most important growth factor which helps stem cells in the bone marrow produce neutrophils is called granulocyte-colony stimulating factor (G-CSF). It got this name because it was first discovered as a protein which caused stem cells to develop into colonies of granulocytes in laboratory culture

experiments. The gene for G-CSF has been isolated, replicated and put into cells in test tubes, which then produce the human protein. This is purified and can be injected into patients to raise their white blood cell counts. G-CSF is available as Neupogen® and in a slightly modified form called Neulasta®. These growth factors are most commonly used for cancer patients whose bone marrow has been suppressed by chemotherapy. They are also used in patients with a primary immunodeficiency that have had bone marrow transplants, in order to get the new marrow to produce white blood cells faster. G-CSF is also used in patients who do not make enough granulocytes because of defects in their own bone marrow or autoimmune diseases. Neupogen® is usually kept in the refrigerator and is given by subcutaneous injection at home, several times a week, or everyday in some cases. The dose must be adjusted according to the resulting rise in the white blood cell count. Side effects may include local reactions at the injection sites, pain in the bones, and potentially, serious allergic reactions.

Gamma-Interferon

Phagocytic cells (neutrophils, monocytes, macrophages and eosinophils) of patients with chronic granulomatous disease (CGD) are not able to kill certain types of bacteria and fungi (see chapter titled *Chronic Granulomatous Disease*). Gamma Interferon is a protein the immune system uses to stimulate the phagocytes to kill bacteria more efficiently, amongst other effects (see next paragraph). CGD patients who are given gamma interferon three times weekly by subcutaneous injection have approximately 70% fewer serious infections than patients not receiving gamma interferon. When patients taking gamma interferon do have infections, they require less time in the hospital. Benefit from gamma interferon is most evident in children under ten years of age, but all age groups benefit to some degree.

Interferon is a substance that is found naturally in the body. It is called “interferon” because it was originally discovered to interfere with virus growth. Several different types of interferon have been identified and it has been shown that they exert numerous effects on the immune system. The types of interferons are named alpha, beta

and gamma. Gamma interferon is related to alpha and beta interferon for its antiviral activities. In addition, gamma interferon is a potent stimulus for phagocytic cells and can help make up for the fact that CGD cells do not make hydrogen peroxide properly. Gamma interferon improves the bacterial killing by the phagocytic cells.

Gamma interferon is supplied in a single dose vial of 0.5 ml. The dose for each patient is determined by body surface area, which means that both height and weight are considered. For small children, the surface area is not a reliable method, so their dose is based only on their weight. The vials must be kept refrigerated, but not frozen, and should not be shaken. There is no preservative in the gamma interferon preparation, so opened vials should be discarded after twelve hours at room temperature. Expired vials should not be used. Gamma interferon is given at home as a subcutaneous (under the skin) injection three times a week (such as Monday, Wednesday, and Friday). The preferred sites for injection are in the thighs and arms. These injections are similar to giving insulin to diabetics. Used syringes should

Gamma-Interferon continued

be disposed of in an approved needle waste box and the full box returned to the physician or local emergency room for proper disposal. Needles and syringes should not be discarded in your household trash.

Common side effects of gamma interferon include fever, muscle aches, headaches, and occasionally chills. Taking the interferon at bedtime can minimize side effects. If headaches persist the next morning, the drug should be given earlier in the evening. If the severity of the side effects is unacceptable, it may be appropriate to reduce the dose, but this should be determined

by the physician. If no other side effects are seen but fevers suddenly follow the gamma interferon injection, this should be reported to the physician. In some instances fevers following gamma interferon can be a sign of a sub-clinical (or hidden) infection. A few patients experience symptoms of depression from gamma interferon, and if depression occurs, consult your physician. Patients with a history of seizures should not take gamma interferon.

PEG-ADA

Deficiency of the enzyme adenosine deaminase (ADA) causes a rare, life threatening form of severe combined immunodeficiency disease (SCID) (see chapter titled *Severe Combined Immunodeficiency*). About one in a million children are born with ADA deficiency. Cells of the immune system (lymphocytes) are more dependent on ADA for their development and proper functioning than are most other types of cells. When ADA is missing, a substance called deoxyadenosine builds up. This is toxic to the developing immune system, but it does not hurt other types of cells as much. Most ADA deficient infants lack both T- and B-lymphocytes and begin to get repeated, serious infections of the skin, respiratory and digestive tracts soon after birth. However, there are milder cases, in which the onset of serious illness may be delayed for months or even a few years. The complete deficiency of ADA results in SCID. Although antibiotics and regular treatment with intravenous gamma globulin are helpful, ADA-deficiency SCID that is not treated specifically is usually fatal by two years of age if immune function is not restored. Like other forms of SCID, ADA deficiency can be cured by HSCT from a matched donor with the same tissue type as the patient (usually a brother or sister). Although some experts may differ, most now recommend that ADA SCID patients receive chemotherapy “conditioning” prior to their transplant. This is because in many cases there is significant resistance to the transplanted HSC from engrafting in this form of SCID that may be overcome by the “conditioning” treatment.

There are three approaches to treating ADA deficient SCID patients who do not have a “matched” donor: “partially matched” or haploidentical HSCT, enzyme replacement, and experimental gene therapy. The various methods of carrying out bone marrow transplantation and some experimental approaches to gene therapy are discussed earlier in this chapter. This section will deal with enzyme replacement therapy. The rapid elimination of purified enzymes by the body made enzyme replacement for ADA deficiency impractical until it was discovered that linking a large molecule called polyethylene glycol, or PEG, to the enzyme could greatly prolong its life and therefore its effectiveness after injection. A clinical trial of PEG-ADA (ADAGEN®), using ADA purified from cows, was begun in April 1986 in a critically ill child who had failed to benefit from two haploidentical marrow transplants. Based on the results with this patient and others treated subsequently, PEG-ADA was approved for treatment of ADA deficiency by the US Food and Drug Administration in March 1990. A teaspoon of PEG-ADA has as much ADA activity as a billion normal T-lymphocytes. Intramuscular injection of this amount or less of PEG-ADA once or twice a week maintains enough ADA activity in the bloodstream of patients to largely eliminate the toxic effects of deoxyadenosine that cause the immune deficiency. This gives the immune system a chance to recover over a period of several weeks to a few months. Continued weekly injections of PEG-ADA are then necessary to maintain clinical improvement.

PEG-ADA continued

Immune function (as measured in the laboratory) improves in nearly all patients, but the degree of improvement varies, ranging from very little to nearly normal. However, clinical benefit is more uniform and is evident within a few weeks of treatment even in the 20% of patients whose lymphocyte counts remain most depressed. Pneumonia, diarrhea and other serious infections present at the start of therapy usually resolve, and growth, which may be severely impaired initially, resumes. Over the longer term, most treated children have responded well to ordinary childhood infections, allowing them to have normal contact with other children. Older patients are attending school. Thus far, IGIV has been able to be discontinued in about half the children receiving PEG-ADA. Those who have caught chicken pox and other viral infections, which can be fatal to untreated patients with SCID, have recovered uneventfully and developed long-lasting, normal levels of antibody to the virus.

Aside from the discomfort of the intramuscular injections, PEG-ADA has had few side effects. Initially there was concern that, because a nonhuman source of ADA was being used, patients might develop antibodies that could neutralize the enzyme or cause allergic reactions. Antibodies to bovine ADA can be detected by sensitive tests in most patients, but there have been no serious allergic reactions, and in only a few cases has the development of antibody against the ADA necessitated an increase in the dose of PEG-ADA. Since ADA deficiency is so rare, and the first patients to be treated with ADAGEN are just now surviving into young adulthood, we are still learning about this disease and PEG-ADA treatment. Recently it has been recognized that the improved laboratory tests of immune function seen early after PEG-ADA is instituted usually decline over time and may return to levels comparable to what they were before PEG-ADA treatment was begun. Despite these disturbing laboratory observations, most patients continue to have a clinical course that remains improved.

It is clear that PEG-ADA can be a lifesaving treatment that is effective at preventing infections and their complications in ADA deficient patients. Its use has reversed the dire clinical outlook associated with SCID due to ADA deficiency for many of those patients not given an HLA identical sibling donor marrow transplant. If the diagnosis of ADA deficiency is delayed and the child develops serious lung disease, PEG-ADA may not be able to reverse that damage nor prevent its progression. Early diagnosis and, if a suitable HSC donor cannot be found quickly, institution of PEG-ADA therapy is extremely important. There are some ADA SCID patients with a milder delayed onset form of the disease where PEG-ADA therapy alone may be sufficient. Unfortunately, the high cost of this drug may deplete that individual's lifetime cap for insurance payments before they reach adulthood and leave them uninsurable thereafter. It can be a difficult decision in these cases where the balance lies between the potential risks and benefits of stem cell transplantation combined with conditioning treatment and the unknown continued future success of PEG-ADA treatment. For the ADA deficient infant with classic early onset SCID, there is little disagreement that HSC transplantation from a matched donor is the treatment of choice since it can provide a cure for this disease. In addition, the use of gene therapy for ADA SCID has improved to the degree that it should also be seriously considered in a patient where a matched donor cannot be found. If gene therapy is under consideration, it may be important not to begin PEG-ADA treatment since this may interfere with the successful use of gene therapy.

Gene Therapy

Most of the primary immunodeficiency diseases are caused by “spelling” defects (mutations) in specific genes. It has long been the dream of physicians that one day it would be possible to cure these diseases by fixing the mutation that causes the disease and restore the patient to normal health. As a result of the human genome project and similar efforts to map all of the genes present in human beings, we now know the identities of the specific genes involved in many diseases, including the majority of primary immunodeficiency disorders, with more genes being identified nearly every week. Finally, we have reached the stage where that long held dream is becoming reality with the cure of a few patients with primary immunodeficiency diseases leading the way, just as these diseases were the first disorders cured by bone marrow transplantation when it was introduced in the late 1960s.

Not every genetic disorder will eventually be correctable by gene therapy and this is also probably true for some primary immunodeficiencies, but primary immunodeficiency diseases as a general rule are better suited for this therapy than almost any other class of genetic disease. Transplantation of bone marrow taken from a normal donor has been successful in curing many of these disorders, so it should also be possible to take the patient’s own bone marrow and correct the genetic defect in those cells by adding a normal copy of the gene that is causing the disease. We should always have the patient’s own bone marrow so the absence of a suitable matched marrow donor will not be a problem for the gene therapy approach. Similarly, GvHD should not be a problem when the patient’s own HSC are used for the transplant. Also, since bone marrow cells are readily removed from the body and worked on in the laboratory, it is much easier to deliver the corrective gene to these cells in the test tube than it would be if we needed to deliver the genes to cells still remaining in the body like the liver, heart, lungs or muscles.

Although it is beyond the scope of this chapter to describe the technology of gene transfer in detail, in the first cases successfully treated by gene therapy, the corrective genes were packaged inside a modified virus (called a vector). These modified viruses were then used to deliver the disease fighting gene to the patient’s lymphocytes or HSC in laboratory culture. After two to four days, to allow the viruses to insert the genes, these cultured cells were washed and then given to the patients just as if they were receiving a blood or bone marrow transfusion. The particular viruses used were from a class of viruses (retroviruses) that normally insert their own genetic material directly into the chromosomes of the cells that they infect. The viral genetic material becomes part of the genetic inheritance of the cells that they infect including the characteristic that the viral genes then get transmitted to the cell’s daughters when cell division occurs. For use in gene therapy, the viruses own genes are discarded and replaced with the genes that we want delivered, but by using the machinery of the virus—now the disease correcting gene becomes part of the inheritance of the vector treated cells and this results in cure that is transmissible to all of the daughter cells that normally develop from the originally treated cell. As we know, relatively few HSC can give rise to all of the blood and immune system cells in the body for life and because these stem cells divide and reproduce, the genetic correction added to the stem cells will spread widely to many different blood and immune system cells and also last for life.

The first clinical trial of gene therapy was in 1990 and treated a four-year-old girl with ADA deficiency. In this first use of gene transfer the ADA gene was inserted into T-lymphocytes grown from the girl’s blood using a combination of T-cell growth factor and T-cell receptor stimulation. After the cells were treated with the ADA vector and expanded in culture by several dozen fold they were infused into her vein periodically for a total of twelve infusions over two years. Now, this girl is clinically well and still has about 25% of her circulating T-cells carrying the corrective ADA gene. The design of this first trial did not attempt to correct the defective HSC and therefore gene correction has been limited to the T-cells.

Gene Therapy continued

The next primary immunodeficiency to be treated by gene therapy did target the HSC using a retrovirus to deliver the gene for the gamma chain of the major cytokine receptor family, the gene defect in X-SCID. Beginning with a groundbreaking study in France, there now have been nearly 20 X-SCID babies around the world cured using this strategy for gene therapy of X-SCID, but a major complication also developed in three infants treated by this technique. About three years after the treatment was completed and the immune system had shown complete recovery, these three children developed an unusual type of leukemia that appeared to be caused by where the inserted gene happened to splice itself into the chromosomes of the treated HSC. This complication is called "insertional mutagenesis" and it is still not clear why these three infants developed the problem while the others are healthy and appear cured. Two of these children are in remission after treatment for the leukemia, but the leukemia treatment was unsuccessful in the third. After an evaluation period when no additional patients were treated by gene therapy, clinical trials have now cautiously resumed using modified vector designs and preparations and there is optimism that this curative treatment will soon become the standard of care for X-SCID.

Attempts to treat ADA SCID using a similar approach targeting the HSC were disappointing with very low rates of engraftment of the gene-corrected cells and no sustained cures. In another important breakthrough, a trial was undertaken in Milan which in addition to the gene therapy using ADA gene treated HSC, PEG-ADA was discontinued and the patients were also given chemotherapy conditioning, although less intensive conditioning than is used if allogeneic bone marrow transplantation was been performed. Now, these ADA SCID children also have shown full recovery of both T-and B-cell function and appear to be cured as well. In another clinical trial, a small group of patients with the X-linked form of CGD have received HSC gene therapy combined with chemotherapy conditioning and also have shown remarkable improvement with clearing of deep seated infections and restoration of granulocyte function. These trials are too recent to tell us if this will result in cure for CGD, but the data is clearly very encouraging that gene therapy may be effective treatment for yet another of the primary immunodeficiency diseases.

There is great potential as well as many risks involved in gene therapy, which must still be regarded as an experimental therapy whose "kinks" have not been completely worked out. Some diseases, such as SCID, are close to the point where gene therapy may become the treatment of choice. Other diseases are more complex and the perfection of gene therapy will be farther off. Among the factors complicating the development of gene therapy for other diseases include the need to use genes that require tight physiologic regulation, genes that are needed only very early during embryonic development before a critical window of opportunity closes, dominant gene defects where the presence of a single normal gene copy is already known not to reverse the disease process or genes that must be expressed in the majority of immune system cells and do not by themselves give a selective advantage to the corrected cell population. Despite these problems, we are hopeful that one day, gene therapy will be the procedure of choice for the majority of immunodeficiency diseases.