



Long-Term Effects of PIDDs

By Annaben Kazemi

While patients are at risk for long-term complications due to primary immunodeficiencies, these can be mitigated through early diagnosis and treatment.

Many primary immune deficiency disease (PIDD) patients express concern about whether they may experience long-term complications from their disease. And while it's reassuring to know that the majority of patients do not suffer long-term effects, it's important to be knowledgeable about what the effects are, as well as the risk factors involved.

Most long-term effects occur due to two reasons: frequent infections and/or the presence of autoimmune

complications. PIDD patients have an increased susceptibility to infections both before diagnosis and during follow-up, some of which can lead to permanent organ damage, disability and possibly even death if left untreated. The most common infections include pneumonia, acute diarrhea, acute sinusitis and otitis media.¹ These patients also are susceptible to respiratory infections of the lungs and bronchial tubes, which can cause permanent damage to organs, as well as acute and recurrent infections, particularly those that involve the gastrointestinal system. In fact, respiratory, acute and recurrent infections are a common thread that binds a large cross section of common variable immune deficiency (CVID) patients.

PIDD patients often also develop autoimmune diseases, which can cause long-term complications. The presence of autoimmune complications is recognized in up to two-thirds of CVID patients. Among the autoimmune manifestations reported, cytopenias are the most common, including thrombocytopenia, anemia and neutropenia.²

Risks of Organ Damage

“Timely diagnoses and proper treatment, such as immunoglobulin replacement therapy, are the most effective ways to reduce the risk of organ damage in immune-deficient patients,” says Dr. Marc Riedl, section head of clinical immunology and allergy in the Department of Medicine and the director of clinical trials for the UCLA Food and Drug Allergy Care Center at UCLA Medical Center. But, as Dr. Riedl explains, diagnostic delay remains common due to the limited awareness of the presenting features of PIDD. While immunologists are trained specifically to diagnose and treat PIDD, patients often are initially referred to other specialists. And, since immunology is a very complex area of medicine, diagnosis of PIDDs by other specialists has been difficult and protracted.

Particular types of PIDDs pose greater risks for permanent organ damage; therefore, it’s important to recognize those conditions and be proactive in seeking treatment from a specialist. According to Dr. Riedl, “Certain immune deficiencies such as CVID and XLA [X-linked agammaglobulinemia] can result in permanent organ damage because of the risks of recurrent infection due to antibody deficiency.” CVID and XLA are multisystem disorders and, thus, present to physicians in diverse specialties. As a result, diagnosis is often delayed until the second or third decade of life, which results in irreversible organ damage.

In a 2009 study³ of 62 newly diagnosed PIDD patients in immunology departments across the United Kingdom, 79

percent of patients had suffered repeated upper- and lower-respiratory infections before diagnosis, and of those patients, 27 percent who waited more than seven years for a diagnosis had suffered permanent lung damage. In the two years before diagnosis, 85 percent of patients had been referred to other specialists before being referred to an immunologist. More than half of this group had been admitted as hospital in-patients prior to diagnosis. The most common diagnosis (56 percent of patients) was CVID, followed by specific antibody deficiency (10 percent). The most common symptoms experienced by patients included chest infections/pneumonias (79 percent), lower-respiratory tract infections (40 percent), chronic diarrhea (13 percent), eye infection (9 percent), abscesses/boils (9 percent), failure to thrive (in pediatric patients) (7 percent), urinary infection (7 percent) and sepsis (7 percent). Thirty-four percent of patients also had suffered other serious infections.

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Risks of Physical Disability and Death

While the risk of physical disability and/or even death is increased with late diagnoses, there is good news. Replacement therapy with immunoglobulins (IGs) is proved to increase life expectancy and reduce the frequency, as well as the severity, of infections. Whether IG is administered intravenously or subcutaneously, the results demonstrate a lower risk of severe infections that could result in morbidity or even death. Replacement therapy is not only effective, but safe. According to Michael A. Friedman, MD, formerly with the U.S. Food and Drug Administration (FDA): “A five-layer system of overlapping safeguards forms the core of the blood safety system established by FDA. This system starts at the blood collection center and extends to manufacturers and distributors of blood products.... In addition to these layers of protections, many plasma derivative products also are processed to inactivate viruses that may be present.”⁴

Problematically, PIDD patients generally have a lower level of daily activity as a result of their condition.⁵

Disability resulting from total loss of hearing, gastrointestinal problems, pulmonary dysfunction, as well as a multitude of other issues can severely limit daily and life activities. In addition, PIDD patients have a higher mortality rate as a result of multiple and reoccurring infections⁶ and organ damage as a result of nontreatment. Death is associated with major organ failure and/or wide systemic infections that are diagnosed too late.

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In a study at Mount Sinai Medical Center,⁷ 473 patients in New York with CVID were followed over four decades. Ninety-four percent of patients had a history of infections, and 68 percent also had noninfectious complications, which included hematologic or organ-specific autoimmunity, 28.6 percent; chronic lung disease, 28.5 percent; bronchiectasis, liver damage, 15.4 percent; lymphoma, 8.2 percent; other cancers, 7 percent. Reduced survival was associated with age at diagnosis, lower baseline IgG, higher IgM and fewer peripheral B cells. The risk of death was 11 times higher for patients with noninfectious complications. And, 19.6 percent of patients died, which was a significantly shorter survival than age- and sex-matched population controls. The study's authors concluded that mortality was associated with lymphoma, any form of hepatitis, functional or structural lung impairment and gastrointestinal disease, but not with bronchiectasis, autoimmunity, other cancers, granulomatous disease or previous splenectomy.

Preventing Permanent Organ Damage and Physical Disability

The importance of receiving early preventive care to limit negative effects of the disease can't be overemphasized. While there is no guarantee that patients won't suffer long-term effects, awareness and early diagnoses are the most effective ways of preventing adverse conditions. "The longer a patient goes untreated, the higher the risk,"

says Dr. Riedl. "In order to navigate treatment, the patient needs a good team." Periodic follow-up with a specialist and developing a team of doctors who can work together to treat the patient are crucial to maintaining optimal health.

Both intravenous IG (IVIG) and subcutaneous IG (SCIG) treatments appear to be safe, with comparable efficacy. A starting dose of 300 to 400 mg/kg/month for IVIG and 100 mg/week for SCIG is recommended. The goal is to achieve IgG trough levels greater than 5 g/L for patients with agammaglobulinemia and 3 g/L greater than the initial IgG level for patients with CVID;⁸ however, clinical response should be foremost in choosing the dose and trough level. With either infusion method, adverse reactions are generally mild owing to improved manufacturing processes of the IG products.

In addition to IG replacement therapy, other medications such as antibiotics, anti-inflammatories or other immunomodulatory medication may be necessary depending on the associated conditions in individuals with PIDD.

It is important to note that parents can play a key role in early diagnosis and, as such, reduce the risk of organ damage. There is some evidence of genetic susceptibility, with 20 percent of patients having a dominantly inherited disorder with variable expression of symptoms. Therefore, knowing the family history and sharing it with an individual's pediatrician or doctor can help with early diagnosis. Preventive care and regular doctor visits are key in diagnosis.⁹

Long-Term Risks of Medical Therapies

While the most common long-term risks of medical therapies are overuse of antibiotics and the negative effects of steroid treatment, the effects of long-term IG replacement therapy are still generally unknown.

Patients with chronic sinusitis or chronic lung disease may require long-term treatment with broad-spectrum antibiotics in addition to IG therapy. Due to the nature of their reduced immunity, these patients need higher doses and longer courses of antibiotics than other adults. If mycoplasma or chlamydia infections are suspected, antibiotics specific for those organisms may be indicated. Prophylactic antibiotics can be used in PIDD patients, but the concern is that too much use of an antibiotic can cause bacteria to become increasingly antibiotic resistant, and that the resistant bacteria will not respond to the antibiotic in the future when this therapy may truly be needed. Diarrhea also can be a common side effect of antibiotic therapy.

Prednisone is a corticosteroid commonly used to treat PIDD patients with inflammatory conditions because of its anti-inflammatory effects. Corticosteroids have a rapid onset of action and profoundly affect many parts of the immune system, as well as most other body systems. Prednisone is not without side effects, most commonly weight gain, hypertension, bone thinning, easy bruising and glucose intolerance. However, not all side effects occur in every patient. Many of the side effects of steroids are predictable and related to the amount of steroid a patient takes in his/her daily dose and the length of time the patient remains on the medication. Despite the numerous potential side effects of steroids, when used properly, these drugs save lives and avert threats to the function of important organs.¹⁰

IG replacement therapy is a growing field of study. While new therapies are being tried and multiple disciplines are experiencing a raised level of awareness of PIDD, there are few long-term studies that show its effects. However, IG replacement therapy is proved to increase life expectancy and reduce the frequency and severity of infections. Both IVIG and SCIG are safe when dosed appropriately and monitored.⁵

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A five-year multicenter prospective study looked at 201 patients with CVID and 101 patients with XLA to identify the effects of long-term IG treatment and the IgG trough level to be maintained over time required to minimize infection risk.¹¹ Overall, 21 percent of the patients with CVID and 24 percent of patients with XLA remained infection-free during the study. However, the effect of IG therapy at replacement dosage for noninfectious comorbidities (autoimmunity, lymphocytic hyperplasia and enteropathy) remains to be established.

An Encouraging Prognosis

While the prognosis is encouraging for PIDD patients who are treated with IG replacement therapy, the best

outcome is produced through the formation of partnerships between medical professionals and PIDD patients. Early detection and treatment are the primary keys to reducing long-term organ damage and avoiding disability and death.

The medical community across multiple disciplines needs to have a heightened awareness of PIDD and evaluate patients for an immune deficiency if suspicion is raised. The nature of the disease and the fact that it is multisymptom and multidiscipline lends itself to widespread information-sharing across the medical community, as well as between patients and the medical community.

Patient outreach programs can play a key role in mitigating the effects of organ damage by raising awareness in the general population, thus helping in early detection and diagnosis of PIDDs. ■

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