

Comparative effectiveness research in the United States and primary immunodeficiency diseases

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The United States enacted legislation in 2010 that will promote the use of comparative effectiveness research in the making of healthcare decisions. Of concern with this relatively new mandate is the possibility of using comparative effectiveness research as a means only to mitigate costs rather than to focus on quality of care. This is of particular concern for patients with rare and chronic conditions, such as primary immunodeficiency diseases. The Immune Deficiency Foundation (IDF) uses their survey research to advocate for the needs of patients with primary immunodeficiency diseases to ensure that their unique medical concerns are not overlooked but instead, integrated within an overall healthcare emphasis on personalized medicine and differences in patient treatment response. IDF research shows the efficacy of treatment with immunoglobulin replacement therapy (IG therapy) for many patients with primary immunodeficiency diseases, that IG therapy is underused in the primary immunodeficient community, and that IG therapies are unique and not interchangeable.

Keywords: Comparative effectiveness research, primary immunodeficiency diseases, Immune Deficiency Foundation, IDF, immunoglobulin therapy, IG therapy

1. Background

Primary immunodeficiency diseases (PID) represent a class of disorders in which there is an intrinsic defect in the immune system (rather than immune disorders that are secondary to infection, chemotherapy, or some other external agent). In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular, phagocytic or complement defenses against infection fail to work properly. There are more than 150 different primary immunodeficiency diseases currently recognized by the World Health Organization [1]. In 2005, the Immune Deficiency Foundation (IDF) commissioned a survey to help establish an estimated prevalence of PID in the United States. A national probability sample of 10,000 households was sampled by random digit dialing and screened by telephone to identify how many of the nearly 27,000 household members had been diagnosed with a PID. This study yielded an estimated population prevalence of diagnosed primary immunodeficiency diseases at 1 in 1,200 persons in the United States. When applied to the U.S. population of 311,656,000 persons, this suggests approximately

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250,000 persons have a diagnosed primary immunodeficiency disease in the United States [2]. Many individuals with a PIDD receive treatment through infusions of immunoglobulin therapy, an effective replacement therapy for the antibody deficiency forms of the disease. Today, immunoglobulin replacement therapy is available in intravenous (IVIG) and subcutaneous (SCIG) modes of administration.

2. Comparative effectiveness research in the United States and the PIDD population

The Patient Protection and Affordable Care Act (PPACA), enacted in March 2010, established the Patient-Centered Outcomes Research Institute (the Institute), a private, non-profit entity that will establish research priorities, fund comparative clinical effectiveness research, train researchers in comparative effectiveness research methods, communicate results to the public, and in general provide for the conduct of comparative effectiveness research. The legislation requires that the Institute ensure that diversity in populations is accounted for in research designs. The law also prohibits any findings of comparative effectiveness research to be construed as practice guidelines or coverage decisions and contains safeguards for patients against discriminatory coverage decisions [3]. The Institute is operational and currently conducting a schedule of public meetings.

IDF is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with PIDD in the United States. During federal legislation negotiations, IDF actively advocated for the legislation to appropriately leave key health care decisions up to patients and their physicians, and not to their insurers, by ensuring that the Institute's research focused on quality care rather than on cost. Due to the complex health care needs of persons with PIDD, a "one size fits all" approach is never appropriate for this patient population. Rather, health care should focus on the patient's needs and specific concerns and medical issues, which may be affected by that individual's co-morbidities, sex, race, or other key factors.

As patient advocates, IDF, in collaboration the American Plasma Users Coalition (A-PLUS), worked with the United States Congress to ensure that the law provides patients with key information for making health care decisions, including provisions to ensure that funding is available to disseminate key research findings. A-PLUS is a coalition of rare disease patient organizations whose patients rely on plasma-derived products to live relatively healthy and productive lives with chronic conditions. IDF and A-PLUS appreciate that the law assures that the key research elements – from the beginning of the design phases – are publicly available for review. It is hoped that this open, transparent process will provide a research avenue on key issues specific to patients, especially those with rare diseases, before proceeding with comparative effectiveness research.

Importantly, IDF and the rare disease community worked with Congress to ensure that the Institute is required to establish and consult with an Expert Advisory Panel for

Rare Diseases. The Panel will assist in the design of research studies and determine the relative value and feasibility of conducting particular research studies.

An ongoing concern in the United States related to comparative effectiveness research is its potential use to limit care. This is of particular concern to patients with rare, chronic diseases who have especially complex medical needs and resulting high medical costs. To address this concern, the law states that the Institute may not mandate coverage, reimbursement, or other policies for any public or private payer. Also, the U.S. Secretary of Health and Human Services is prohibited from using the Institute's research in determining coverage, or creating reimbursement or incentive programs for a treatment in ways that (1) treat extending the life of an elderly, disabled, or terminally ill patient of lower value than extending the life of others or (2) preclude or discourage an individual from choosing a health care treatment based on how the individual values the tradeoff between extending the length of their life and the risk of disability [3].

In the United States Congress, legislation continues to be introduced to protect against rationing of care linked to the Institute. For example, Senator Kyl (R-AZ) introduced S. 660, the "Preserving Access to Targeted, Individualized, and Effective New Treatments and Services (PATIENTS) Act of 2011," with the stated purpose to "protect all patients by prohibiting the use of data obtained from comparative effectiveness research to deny or delay coverage of items or services under Federal health care programs and to ensure that comparative effectiveness research accounts for advancements in personalized medicine and differences in patient treatment response" [4].

3. Medical characteristics of patients with PIDD

IDF is concerned with the lack of research conducted on behalf of rare and chronic disease populations, particularly for patients with primary immunodeficiency diseases. The major health surveys conducted by the government in the United States—the National Health Interview Survey and the National Health and Nutrition Examination Survey—do not collect information on primary immunodeficiency diseases. No comprehensive population survey has ever been undertaken by the federal government to estimate the prevalence or the population characteristics of these diseases in the United States. Thus, research conducted by IDF has focused on filling the data gap with regard to individuals with PIDD so that information on the characteristics and what constitutes quality of care for this population is available. IDF has conducted a series of surveys including three *National Patient Surveys* and three *Treatment Experiences and Preferences of Patients with Primary Immune Deficiency Diseases Surveys* in the effort to create a comprehensive portrait of the primary immunodeficient patient, their medical condition and their treatment.

The majority of patients with a diagnosis of a PIDD who respond to IDF surveys have an antibody deficiency for which immunoglobulin therapy is the standard of care.

The IDF treatment surveys are based on a large sample of persons known to IDF who use immunoglobulin replacement therapy in the treatment of their PIDD. All three of these are nationally distributed surveys, each with more than 1,000 completions. These cases provide a relatively large national sample of persons with PIDD who have been treated with IG therapy. Although these surveys are not probability samples from which we can make population estimates within known limits of sampling error, they provide the most representative samples currently available of patients with a rare disease from which we can examine treatment experiences.

The Second and Third National Treatment Experiences and Preferences of Patients with Primary Immunodeficiency Diseases Surveys provide data on the treatment of patients with PIDD including the patients' needs, specific concerns and medical issues. The data from these surveys showed that the average time to diagnosis from symptom onset for this population is between 9–13.4 years [5,6]. This extended period of time without diagnosis, and thus without effective treatment, resulted in more complex treatment needs as additional medical issues increased for the PIDD patient population. Analysis from the *2007 IDF National Patient Survey* indicates that there is a positive correlation between time to diagnosis as primary immune deficient and the number of permanent functional impairments (Pearson's $r(1127) = 0.301, p < 0.001$).

As a result of late diagnosis, and repeated and severe infections prior to diagnosis, over one half of patients with PIDD reported at least some permanent impairment before their diagnosis as immune deficient. This complicates a number of systems and functions within the body. Nearly two out of five patients with PIDD reported permanent impairment of lung function (37%) prior to diagnosis. Additionally, 17% had permanent impairment to digestive function, 13% hearing loss or impairment, 8% neurological impairment, 7% loss of mobility, and 5% had either vision loss or impairment. Another 11% had some other permanent impairment or loss prior to diagnosis as immune deficient [6].

4. Efficacy of immunoglobulin replacement therapy in treating PIDD

The data cited in Boyle and Scalchunes' article in *Pharmaceuticals Policy and Law* based on past IDF surveys not only illustrates the specific medical issues of this population, but also highlights the use of IG therapy as an effective treatment for the majority of patients with PIDD, which greatly improves the health and quality of life of these patients. To best measure the efficacy of IG therapy among patients, a series of questions were asked to gauge the health of the patient in the twelve months prior to diagnosis and in the twelve months most recent to the survey. The comparison in health status provides the most compelling evidence of the efficacy of IG therapy to control PIDD and demonstrates the improvement in the health and well-being of the patient since treatment had begun. Prior to diagnosis, less than one-in-five patients with PIDD who used IG therapy described their health status as excellent (4%), very

good (4%) or good (11%). However, in the twelve months most recent to the survey, the same patients with PIDD described their health status in a much more positive way. Three-quarters of patients with PIDD using IVIG therapy described their health in the 12 months most recent to the survey as excellent (16%) very good (28%) or good (29%) [7].

One reason that most patients with PIDD described their health as good or better in the 12 months prior to the survey, compared to the 12 months prior to treatment, was a lower incidence of chronic and acute infections associated with PIDD. These patients reported a decrease in many chronic conditions, including a decrease in pneumonia (51% prior to diagnosis, 13% recent), bronchitis (56% prior, 34% recent), and ear infections (47% prior, 27% recent) [7]. IG therapy for patients with PIDD translates into improved quality of life and better health outcomes for these individuals. Fifty-seven percent of patients with PIDD reported being hospitalized during the year prior to their diagnosis. In contrast, only 25% reported a hospitalization in the year most recent to the survey. When diagnosed patients do go to the hospital, they spend less time there. Patients reported an average number of nights in the hospital of 9.2 in the year prior to diagnosis versus only 4.3 nights in the year most recent to the survey [7].

5. Underuse of immunoglobulin replacement therapy in treating PIDD

Despite the overwhelming evidence of the efficacy of IG therapy for patients with PIDD, IDF survey data has also shown that underuse of IG therapy for these conditions persists. In the two most recent IDF national surveys of patients known to the Foundation, *Primary Immune Deficiency Diseases In America*, IDF found that two-thirds of patients with a PIDD were using intravenous immunoglobulin for their condition [8,9]. Boyle and Buckley's article in the *Journal of Clinical Immunology* based on research conducted by IDF indicated that there might be a serious problem with underuse of IG therapy in the treatment of PIDD. Although 57% of the patients in this survey had a PIDD diagnosis for which IG therapy is the standard of care, only 22% of these patients from the national household telephone survey were currently being treated with immunoglobulin for their disease [2]. This estimate of 22% is based on a very small sample size. In order to examine the rates of immunoglobulin therapy in a large, national sample of patients diagnosed with PIDD, IDF conducted an Internet survey in 2010 using a national online general population panel that sent more than 850,000 invitations to participate. Based on this national survey, the data shows that less than half of patients with PIDD who have a diagnosis for which IG therapy is recommended (46%) are currently being treated with any form of immunoglobulin therapy [10].

This suggests that a substantial segment of patients with PIDD are being under-treated for their condition compared to clinical guidelines and thus put at increased risk for more health concerns. As expected, the patients with PIDD in this national sample also reported generally lower health status than those found in previous IDF

patient surveys based on patients in the IDF database where the percentage of those using IG therapy was higher. These poorer health outcomes of patients in the Internet survey, compared to surveys of patients in the IDF's databases, may be related to the lower rates of IG therapy for patients with PIDD in the general population [9,10].

Among the patients with PIDD in the *National Internet Treatment Survey of Primary Immunodeficiency Diseases in the United States*, who had previously been treated with IG therapy but were no longer receiving these treatments, the most common reasons for cessation of treatment were that the product was too expensive (43%), lack of insurance (29%), or difficulty in obtaining the product (29%) [10]. In the case of access to appropriate treatment for patients with PIDD, this data shows that in some cases cost supersedes quality of care. In order to better understand how primary care physicians are diagnosing, managing and treating patients with primary immunodeficiencies, IDF conducted national mail surveys of pediatricians and family practitioners. Results from these surveys indicate a lack of understanding by many of these physicians as to the efficacy and safety of IG therapy as treatment for patients with antibody deficiencies (unpublished results, manuscript in preparation). It is likely that in many instances, this leads to less than optimal health outcomes for patients with PIDD under the care of these physicians.

6. Patients tolerate immunoglobulin replacement therapies differently

IDF data also confirms the research done by others in the field showing the importance of individualized medicine and differences in treatment responses for patients with PIDD who are treated with immunoglobulin replacement therapy. While all immunoglobulin therapies available on the US market are approved by the Food and Drug Administration (FDA) and clinically effective in treating patients with PIDD for which IG therapy is indicated, there are currently no generic or equivalent versions of IG. Rather, a number of factors impact how an individual patient will tolerate and respond to a particular brand of immunoglobulin, including the patient's medical history and the product's characteristics such as the volume delivered, sugar content, IgA content, pH, route of administration and osmolality. The FDA requires that an individual clinical trial protocol is completed for each immunoglobulin product to receive licensure, even if it is from the same manufacturer, effectively recognizing that each product is unique and not interchangeable [11]. Manufacturing differences can, and do, affect individuals' tolerability, risk of adverse events, infusion rate, and potential efficacy [12].

The Third National Treatment Experiences and Preferences of Patients with Primary Immunodeficiency Diseases Survey found that 41% of the patients surveyed reported tolerating some IG therapy products better than others. Of those who reported having a serious side effect or reaction to their IG therapy, 28% reported having a serious side-effect or reaction when they tried a new IG product for the first time and 13% had a serious side effect or reaction when they switched products [6].

Adverse reactions can range in severity from redness at the infusion site and severe headaches to anaphylaxis, kidney failure – and even death. As a result of the data and the clinical experience of some of the nation’s leading immunologists, the leading body of specialists in immunology, the American Academy of Allergy, Asthma and Immunology (AAAAI), included a principle in the *AAAAI Eight Guiding Principles for Appropriate Use of IVIG for Primary Immunodeficiency Diseases* stating that IVIG is not a generic drug and IVIG products are not interchangeable [13].

The data reported by IDF showing the difference in treatment responses to IG therapy is supported by Feldmeyer et al who report that 35% of patients in their study experience mild or moderate adverse reactions during or within 48 hours of the administration of a standard IVIG preparation which did not recur after switching to an alternative preparation [14]. Similarly, Dashti-Khavidaki et al found in their study of patients with primary immunodeficiency disease over a 13 year period that “34 out of 216 [roughly 15%] of adverse reactions were caused by a change in the IVIG product” [15]. Amertunga, Sinclair, & Kolbe also report in their study that a change in IVIG formulation of a specific product resulted in adverse reactions by seven of the 49 (roughly 14.2%) patients involved in the study [16]. This body of research speaks to the need for personalized medicine with regard to the complex health care needs of patients with PIDD.

While the inclination of some insurers may be to treat IG therapies as generic and interchangeable with the goal of instituting cost cutting formularies, this is not a viable option for patient safety. Not only may the health of patients be negatively impacted if these individuals are switched with no medical justification, but instituting a policy that treats IG therapies as generic is also an unwise cost option. There is no way to predict which patients will have an adverse event or how serious the adverse event will be when switching a patient to a product that they have never before used. There is no question that instituting such a policy will result in increased cost in some patients due to additional medical treatment for patients who experience adverse events.

7. Conclusion

With the continued emphasis on reducing healthcare costs in the United States, there is concern that comparative effectiveness research could be used as justification for instituting health care protocols that focus on cost containment rather than quality of care. This is of particular concern for patients who, like those with primary immunodeficiency diseases, have rare and chronic conditions. IDF research illustrates the efficacy of treatment with immunoglobulin replacement therapy (IG therapy) for many patients with primary immunodeficiency diseases. The research also shows that IG therapy is underused in the primary immunodeficient community as a result of cost and lack of insurance coverage, as well as physician and patient lack of awareness. It is important to note that immunoglobulin replacement therapy

products are unique and tolerated differently by different patients. Attempts to treat these therapies as generic, with the hope of containing costs, will be detrimental to patient safety.

IDF will continue to monitor the activities of the Patient-Centered Outcomes Research Institute as well as efforts, such as formularies, by insurance companies to contain costs. At the same time, IDF will use its research to advocate for the needs of patients with primary immunodeficiency diseases and ensure that their unique medical concerns are integrated within an overall health care emphasis on personalized medicine.

References

- [1] L. Notarangelo, J. Casanova, M. Conley, M. Chapel, A. Fischer, J. Puck et al., Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005, *J Allergy Clin Immunol* **117** (2006), 883–896.
- [2] J.M. Boyle and R.H. Buckley, Population Prevalence of Diagnosed Primary Immunodeficiency Diseases in the United States, *J Clin Immunol* **27** (2007), 497–502.
- [3] Patient Protection and Affordable Care Act, Pub. L. 111-148 (2010).
- [4] Preserving Access to Targeted, Individualized, and Effective New Treatments and Services (PATIENTS) Act of 2011, S. 660, 112th Cong. (2011).
- [5] IDF (Immune Deficiency Foundation). Treatment Experiences and Preferences of Patients with Primary Immune Deficiency Diseases: 2002 – The Second National Treatment Survey of Patients. Prepared by Schulman, Ronca & Bucuvalas, Inc. June 2003.
- [6] IDF (Immune Deficiency Foundation). Treatment Experiences and Preferences among Patients with Primary Immunodeficiency Diseases: 2008 – The Third National Treatment Survey of Patients. Prepared by Abt SRBI, Inc. May 2009.
- [7] M. Boyle and C. Scalchunes, Impact of Intravenous Immunoglobulin (IVIG) treatment among patients with Primary Immunodeficiency diseases, *Pharmaceuticals Policy and Law* **10** (2008), 133–146.
- [8] IDF (Immune Deficiency Foundation). Primary Immune Deficiency Diseases in America: 2002 – The Second National Survey of Patients. Prepared by Schulman, Ronca & Bucuvalas, Inc. April 2003.
- [9] IDF (Immune Deficiency Foundation). Primary Immunodeficiency Diseases in America: 2007 – The Third National Survey of Patients. Prepared by Abt SRBI, Inc. May 2009.
- [10] IDF (Immune Deficiency Foundation). National Internet Treatment Survey of Primary Immunodeficiency Diseases in the United States. Prepared by Abt SRBI, Inc. July 2010.
- [11] U.S. Food and Drug Administration: *Immunoglobulin intravenous (IGIV) indications, 2007*. Retrieved June 30, 2011 from <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm>.
- [12] J. Siegel, The Product: All intravenous immunoglobulins are not equivalent, *Pharmacotherapy* **25**(11 pt2) (2005), 785–845.
- [13] American Academy of Allergy Asthma and Immunology eight guiding principles for the safe, effective and appropriate use of IVIG for PI. Retrieved June 30, 2011 from http://www.aaaai.org/members/resources/initiatives/ivig_toolkit/ivig_coverage.pdf.
- [14] L. Feldmeyer, C. Benden, S. Haile, A. Boehler, R. Speich, L. French and G. Hofmauer, Not all intravenous immunoglobulin preparations are equally well tolerated, *Acta Derm Venereol* **90** (2010), 494–497.
- [15] S. Dashti-Khavidak, A. Aghamohammadi, F. Farshadi, M. Movahedi, N. Parvaneh, N. Pouladi, K. Moazzami, T. Cheraghi, S. Mahdaviyani, S. Saghafi, G. Heydari, A. Abdollahzade and N. Rezaei,

Adverse reactions of prophylactic intravenous immunoglobulin; A 13 year experience with 3004 infusions in Iranian patients with primary immunodeficiency diseases, *J investing Allergol Clin Immunol* **19**(2) (2009), 139–145.

- [16] R. Amertunga, J. Sinclair and J. Kolbe, Increased risk of adverse events when changing intravenous immunoglobulin preparations, *Clin Exp Immunol* **136** (2004), 111–113