

# Accessibility to plasma-derived medicinal products in Malaysia: The challenges faced by patients with inborn errors of immunity

Bruce Wee Diong Lim<sup>1,2</sup>, and Amir Hamzah Abdul Latiff<sup>2,3,4,\*</sup> 

## ABSTRACT

Inborn errors of immunity (IEI) (also known as primary immunodeficiencies) is an umbrella term for a growing group of over 450 different disorders that are characterized by defects in some of the components of the immune system. IEI are chronic diseases of genetic origin that render individuals suffering from them susceptible to infections. The mainstay of treatments for most patients with IEI, that is, predominantly antibody deficiencies is immunoglobulin replacement therapy (IRT), which is commonly delivered intravenously. Immunoglobulin (IG) therapy contains antibodies to compensate for the defective immune system's inability to produce them. Individuals with IEI need IRT regularly throughout their lives to help combat infections and prevent organ damage. Without IRT, they are in danger of suffering from morbidity, poor quality of life, and reduced life expectancy. In the last 20 years, the use of IG preparation has tripled and this is partly attributed to the growing awareness and improved diagnoses of IEI cases. IG preparations are also used for the treatment of other medical conditions including secondary immunodeficiencies and autoimmune diseases. As IG is derived from human plasma, there are concerns about the availability of supply, particularly to treat life-threatening conditions that cannot be improved with other medications. It is estimated that 75% to 80% of IEI patients do not have access to adequate IG therapy throughout the world. This concern of supply and other challenges faced by patients with IEI in Malaysia are described from the patients' perspective.

**Keywords:** Immunoglobulin; immunoglobulin replacement therapy; inborn errors of immunity; Malaysia; plasma-derived plasma products; primary immunodeficiencies

Inborn errors of immunity (IEI) (also known as primary immunodeficiencies) is an umbrella term for a growing group of over 450 different disorders that are characterized by defects in some of the components of the immune system. IEI are chronic diseases of genetic origin that render individuals suffering from them susceptible to infections. IEI vary in severity but without proper treatment and care, every individual suffering from IEI will face a lifetime of compromised health, which could lead to permanent functional impairments, physical incapacitation, and even death. This will have a profound impact on their quality of life, hampering their ability to function normally and pursue education, career, and social lives.

IEI affect at least 10 million people worldwide where its prevalence is estimated at approximately 1 in 8,000 to 10,000 people [1]. While each of the 450 disorders categorized as IEI may be rare, collectively they occur more commonly than childhood leukemia and lymphoma combined. Despite their higher rate of prevalence than other genetic disorders such as hemophilia (less than 15,000), cystic fibrosis (30,000), and Huntington disease (30,000) [2], IEI has a much lower profile and are less known to the general public [3]. Hence, the status of IEI as a rare disease is increasingly being called into question as new knowledge and understanding about it continue to emerge.

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<sup>1</sup>International Patients Organization for Primary Immunodeficiencies (IPOPI), Brussels, Belgium <sup>2</sup>Malaysian Patients Organization for Primary Immunodeficiencies (MyPOPI), Shah Alam, Selangor, Malaysia <sup>3</sup>Allergy & Immunology Centre, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia <sup>4</sup>Sunway Centre for Planetary Health, Sunway University, Petaling Jaya, Malaysia

\*Correspondence to Amir Hamzah Abdul Latiff, Allergy & Immunology Centre, Pantai Hospital Kuala Lumpur, 8 Jalan Bukit Pantai, 59100 Kuala Lumpur, Malaysia  
Tel: +60123050022

Email: amirlatiff@sunway.edu.my

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The concerns on availability of IG supply are mirrored in Malaysia and other challenges have been faced over the years pre-COVID-19 pandemic and accentuated during the pandemic itself, leading to decreased quality of life. While accessibility may not always be an encumbrance, patients have voiced concerns about their inability to get a sufficient amount of dosage and have suffered recurring infections as a result. While the cost of the treatment is cited as an obstacle in obtaining the appropriate amount of IG preparation, studies have shown that IRT is actually cost effective as it prevents hospitalizations, reduces visits to physicians, limits the need for expensive antibiotics, and helps avoid missed days of school and work. Many of such cases occur in public hospitals where IIEI patients are not under the care of clinical immunologists. IRT is provided for 40% of IIEI patients in Malaysia [5] but commercial IG is expensive and the treatment is lifelong. Without it, patients will suffer from medical complications and the resulting financial strain so it needs to continue to be subsidized in the country.

Subcutaneous infusion of immunoglobulin (IGSC), which was first used back in 1952, experienced a revival in the 1990s with better fractionation methods that enabled large-scale extraction of concentrated IG. It is now increasingly used in Europe where it is standard practice in countries like Norway and Sweden. Through this method, IG is delivered into the fatty tissues under the skin, where it enters the circulation slowly over a period of days. While IGIV requires hospital visits and sometimes even admission to undergo the treatment, IGSC can be self-administered or administered by a caregiver at home after undergoing the necessary training [6].

In Argentina, 30 patients who had previously been treated with IGIV were given IGSC treatment as part of a study for a period of 10 months from July 2011 to May 2012 [7]. After the study, all patients said that they preferred to continue with IGSC, choosing to follow a home therapy regimen. A comparison of the IgG levels between IGIV and IGSC treatments in the same study revealed that the median ratio of serum IgG levels during IGSC therapy was higher and remained constant throughout the evaluation period. The study determined that the benefits of IGSC include elimination of venous access, improvement and stabilization of serum IgG levels, reduction in the frequency and severity of infections, and decreased systemic adverse reactions.

Subcutaneous IG is also associated with cost savings in various countries in Europe, which reported 25% to 75% lesser cost when patients are on home-based IGSC compared to hospital-based IGIV [8]. A study in Japan concluded that there was a significant reduction in productivity loss and hospital-related absenteeism following a change from IGIV to IGSC [9]. Malaysia is the first country in Southeast Asia to implement a pilot program on IGSC (in Hospital Universiti Kebangsaan Malaysia) in 2014. However, since then it took another 6 years before a second patient had IGSC in 2020 and another 3 years thereafter before 4 more patients were on the IGSC program, including the first adult patient. Hence, while only 6 patients had their IRT via IGSC in almost a decade of starting this program, we envisage more would be expected to switch to IGSC from IGIV treatment in the near future, including 2 pediatric patients ready for 2024.

IRT is recognized as 'essential medicine' for adult and pediatric IIEI patients by World Health Organization (WHO) because it has been proven to be efficient in treating the disease and there are no alternative treatments available. As such, IG therapy should be prioritized for patients with IIEI. In times of IG shortage, all IIEI patients who require the treatment should have sufficient access to ensure clinical efficiency to avoid the increase

of recurrent infections, as had been anecdotally reported by patients from Malaysian Patient Organization for Primary Immunodeficiencies (MyPOPI), when their IGIV infusion were given every 6 weeks, instead of every 3 to 4 weeks, even before the COVID-19 pandemic, what more during it [10]. Hence, in 2022, a joint letter by MyPOPI and the Malaysian Society of Allergy and Immunology was issued to the Minister of Health raising the concern of insufficient stock for IGIV in several public hospital across Malaysia and thus affecting IIEI patients. IIEI patients' IGIV treatment frequency was extended from 3 to 4 weekly to 4 to 5 weekly and some even reduced the amount of dosage. Evidently, medical practitioners in the public hospitals across Malaysia who are treating IIEI patients are now aware of the serious implications that might cause serious health risk for IIEI patients when their IGIV treatment frequency and amount of dosage reduced and compromised.

The choice of IG therapy should depend on the patient in consultation with a clinical immunologist as there are several factors to consider including the patient's medical background, frequency and efficacy of treatment, and especially venous access, among others. Therefore, a wide range of IG therapy options should be made available to ensure optimal treatment for all IIEI patients. This will also allow for more effective management of health care budgets.

Clinical immunologists play a pivotal role in ensuring that IIEI patients get the proper care they need in order to reduce personal suffering and avoid morbidity, which would result in financial burden not just for the patients and their families but also the country's health care system. In the case of IIEI, the role of a clinical immunologist is paramount as lack of awareness about the disease often results in delayed diagnoses, which means the treatment and care of the patient are jeopardized as the disease is left untreated and its symptoms and effects worsen. A study in the US surveyed family practice physicians, who are considered the frontliners in health care delivery, to compare their responses on IIEI to responses from a previous survey conducted with subspecialist immunologists [11]. The majority (77%) of family practice physicians responded that they were not at all comfortable with recognizing and diagnosing IIEI, and none indicated complete comfort in recognizing and diagnosing among the group of disorders. However, 22% reported that they were 'somewhat' comfortable. Forty percent of family practice physicians maintained that they would refer the patient to a specialist (such as immunology, allergy, and hematology) if they suspected that the patient might have IIEI.

Nearly all subspecialist immunologists in the survey who treat patients with IIEI commonly recommend IGIV therapy for their patients with Bruton agammaglobulinemia, common variable immunodeficiency, hyper IgM syndrome (hyper IgM), and severe combined immunodeficiency disease, but substantially fewer family practice physicians recommended IGIV therapy for these same diagnoses. Furthermore, 65% of prescribing family practice physicians believed that IGIV therapy was only a somewhat effective treatment approach for patients with antibody deficiency disorders. The study concluded that perhaps its most significant takeaway is that clinical immunologists should be consulted when the potential of an IIEI case emerges as this will help ensure treatment guidelines and best practices are adhered to in the diagnosis, treatment, and care of the patient to ensure a favorable outcome.

In Malaysia, the average interval from the onset of first symptoms to the age a diagnosis is made (diagnostic delay) is 3.87 years. Prior to 2007, basic immunological tests were not performed on a regular basis, while molecular tests were

sent overseas because the country did not have specialist laboratories and facilities. Through the initiatives of the Clinical Immunology Unit at Universiti Putra Malaysia and Cluster of Immunological Science at Universiti Sains Malaysia, these units provided advanced specialist care in clinical service and diagnostic immunology tests for children and adults with IEI. Additionally, the Institute for Medical Research, Malaysia has begun providing specialized immunological tests, including limited molecular genetic tests, which are being further expanded. These collaborative efforts are necessary to ensure that cases are being accurately diagnosed and managed [5, 12].

Malaysia's clinical immunologists have personally championed the cause of patients suffering from a disease considered rare and therefore receive minimal attention, by striving to get them access to the appropriate and latest treatment to help minimize the physical, psychological, mental, and financial burdens of the disease, as well as save patients' lives.

Several pediatric patients' parents have expressed concerns about whether their children will continue to have access to appropriate treatment and care once they become adults as there are currently no practicing adult clinical immunologists within the public health care sector in Malaysia. Without a system for transitioning them from adolescent care to adult care, patients may fall through the cracks, resulting in loss of access to or poor compliance with treatment. This will put their health in jeopardy with the consequences being possible organ damage, compromised quality of life, and reduced life expectancy. The need for adult clinical immunologists is not meant for these circumstances only, but also in diagnosing and managing patients who first present with IEI in adulthood [13], rather than during childhood.

The extremely small number of clinical immunologists in the country is mainly attributed to its lack of recognition as a subspecialty. Without recognition, the discipline is unlikely to attract young doctors who are more familiar with higher profile specialties such as neurology and cardiology. Recognizing clinical immunology as a subspecialty will allow for training program to produce more clinical immunologists for both adult and pediatric patients. This will pave the way to increasing the number of clinical immunologists in the country, hopefully to at least one for every regional hospital [14].

With all these challenges, recommended solutions were laid out in a white paper for managing patients with IEI [14] and these include:

- (1) IG therapies should be made available with adequate and proper amount of dosage of IGIV to all IEI patients in Malaysia
- (2) Make IGSC therapy available in the country, especially for patients with poor venous access, so that patients have the option of self-administration at home
- (3) IG therapy should be prioritized for IEI patients since it is considered 'essential medicine' for the disease by WHO because its efficacy has been proven and there are no alternative treatments available
- (4) Provide access to a wide spectrum of IG products, to provide optimal treatment for all IEI patients
- (5) Implement training program to produce more clinical immunologists for both pediatric and adult patients
- (6) Create a transitional plan for adolescent patients to continue receiving treatment and care upon reaching adulthood

It is envisaged with the above solutions, there will be desirable expected outcomes:

- (1) Long-term survival and well-being of patients are more ensured as access to appropriate and wide range of treatments is available
- (2) More hospital beds and facilities are made available for non-IEI patients due to the option to self-administer at home through IGSC replacement therapy (IRT)
- (3) Patients and their caregivers do not have to take up time and deal with the stress of having to maintain regular appointments at the hospital
- (4) Patients can decide with their physicians the most suitable treatment options, which will result in improved quality of life for them and their families
- (5) Patients are able to receive appropriate treatment in a timely manner
- (6) Adult patients do not get lost in the system and are able to receive the treatment and care they need
- (7) Easy access to specialists for patients throughout the country

It is with the greatest hope that MyPOPI, as the national patient organization advocating for optimal diagnostics and treatment for IEI patients, sees the policymakers and relevant stakeholders accepting their recommendations for a just cause.

### Conflicts of interest

The authors have no financial conflicts of interest.

### Author contributions

BWDL and AHAL were involved in the formulation of the content and review of the manuscript.

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