Editorial
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Ensuring access to immunoglobulin therapies for people with primary immunodeficiency: a need to improve individuals' quality of life and the sustainability of healthcare systems

Classified as "rare diseases", primary immunodeficiency diseases (PI) are hereditary and genetic disorders of the body's immune system, which is partly or totally missing, or does not function properly. These deficiencies lead to increased susceptibility to a wide range of infections affecting different parts of the body including the skin, ears, lungs, intestines, etc; and are often chronic, persistent, and debilitating. While antibody deficiencies are the most commonly diagnosed type of PI, over 300 forms exist[1], and because they often present themselves in the form of "common" infections, practitioners may just treat these infections while missing the underlying cause. This situation means infection can reoccur and leave the individual vulnerable to permanent organ damage, physical disability or even death. However, once recognized, these rare disorders are treatable and in some cases curable[2].

The seventh edition of the World Primary Immunodeficiency Week will take place from the 22nd to the 29th of April 2017 with the aim to raise awareness of PI and ensure that the need for access to immunoglobulin (Ig) therapies for people with PI is recognized worldwide. Action needs to be taken to ensure effective and universal access to currently available treatment options for people living with PI, and particularly to the best-suited immunoglobulin replacement therapy as prescribed.

Immunoglobulin replacement therapy is a universally accepted indication in PI and a life-saving treatment for a majority of people with PI[3] as it offers protection against infections and reduces autoimmune

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[1] Bousfiha A, Jeddane L, Al-Herz W, Ailal F, Casanova JL, Chatila T, Conley ME, Cunningham-Rundles C, Etzioni A, Franco JL, Gaspar HB, Holland SM, Klein C HD, Oksenhendler E, Picard C, Puck JM, Sullivan KE, Tang ML. The 2015 IUIS Phenotypic Classification for Primary Immunodeficiencies. J Clin Immunol. 2015 Oct 7.
[2] Chapel et al. Primary Immunodeficiencies – Principles of Care. Frontiers of Immunology. 2014 Dec 15. Doi: 103389/fimmu.2014.00627
[3] Farrugia A, Visentini M, Quinti I. Editorial: Immunoglobulin Therapy in the 21st Century – the Dark Side of the Moon. Front Immunol. 2015 Aug 26. Doi: 10.3389/fimmu.2015.00436
http://journal.frontiersin.org/researchtopic/2451/immunoglobulin-therapy-in-the-21st-century-the-dark-side-of-the-moon

symptoms[4]. It consists of the regular administration of immunoglobulin therapies derived from human plasma providing antibodies that protect individuals against infections. In this sense, Ig therapies are "biological" medicines. Ig therapies have significantly improved the quality of life of people with PI, many of which can now live normal lives, and this is particularly important as antibody defects represent approximately half of the well-known PIs requiring immunoglobulin replacement therapy[5]. They have similarly decreased the frequency of infections and improved the prognosis of individuals.

It has been extensively demonstrated that early diagnosis and adequate implementation of appropriate treatment including Ig therapies are not only life-changing, life-enhancing for individuals, but also cost-saving for the healthcare system, as they prevent the occurrence of unnecessary co-morbidities and infections and thus represent significant decreases in the long-term cost of healthcare.

The success of immunoglobulins in antibody deficiencies administrated either intravenously or subcutaneously relies mainly on maintaining an adequate protection against infections. International guidelines recommend an Ig monthly dosage of 300–600 mg/kg body weight to be administered intravenously every 3 or 4 weeks or subcutaneously once/twice a week[6]. Nevertheless, as the objective of Ig replacement therapy is to maintain one's effective antibody level, treatment strategies shall be individualised and a personalised regimen (dosage and treatment route) must be developed for each patient, and modified as necessary to achieve treatment goals and meet the needs of each person, taking into consideration possible disease-associated complications. The importance of personalised treatment is all the more relevant given that many different Ig therapies are available, differing in terms of their ingredients and production, and individuals can respond differently to each of them.

However, barriers to an effective supply of the therapies to people with PI exist, and availability and access greatly vary across regions of the world but also across countries of the same region. Depending on geographical situation, the availability of Ig therapies ranges from none at all, to 15 products. Not all people with antibody deficiencies therefore have the chance to benefit from regular Ig treatment: an estimated 80% of people with PI do not have access to adequate care.

There are several reasons for this situation, including the cost of the Ig therapies. In this context, the healthcare system is a major determinant of patients' health outcomes. Reimbursement on the national healthcare system plays a key role in ensuring access to the therapies, but these are not always equally reimbursed in the different countries. As an example, treatment with intravenous or subcutaneous immunoglobulin G (IgG) is covered by the national health system in most European countries, but it is not consistently available in lower- or mid-income regions of the world. Reimbursement policies also vary between different Ig therapies and in some countries only one Ig product is reimbursed. In some cases, reimbursement is based on the type of PI, meaning that in the case of less severe PI, patients have to

[4] IPOPI. Position statement - Access to Immunoglobulin Therapies for patients living with a Primary Immunodeficiency. 2012 May 8.
http://www.ipopi.org/uploads/IPOPI Position Statement Access to IG Therapies_FINAL.pdf
[5] Azizi G, Abolhassani H, Hosein Asgardoon M, Rahnavard I, Zaki dizaji M, Yazdani R, Mohammadi I, Aghamohammadi A. The use of Immunoglobulin Therapy in Primary Immunodeficiency Diseases. Endocrine, Metabolic & Immune Disorders-Drug Targets Vol 16, Number 2. 2016 June; pp. 80-88(9)
http://www.ingentaconnect.com/contentone/ben/emiddt/2016/00000016/00000002/art00004
[6] Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. Br J Haematol. 2009 Jun; 145(6):709-27.

bear the cost of treatment on their own. Significant disparities in terms of reimbursement are also noticeable according to insurance plan options. Furthermore, in the light of a recent rise in the demand for plasma and the related need for increased numbers of donors, risks of global shortages have pressured access to the therapies, although the availability of immunoglobulins is an essential factor of successful treatment[7]. The increasing demand for immunoglobulin has been driven by vehicles such as better recognition and diagnosis of antibody deficiencies, an ageing population, the introduction of new therapeutic indications and an undefined period of treatment in some indications, for instance for some neurological illnesses, in addition to immune deficiencies[8]. As scientific experts acknowledge that supply for people with PI must be given primary consideration as Ig treatments remain the main and only treatment option for most of them, this should be widely reflected in national clinical guidelines.

Addressing these inequalities would mean that in the future people with PI may have continuous, equal and optimised access to the widest range of safe and effective Ig therapies available, as supported by the Council of Europe's resolution "on principles concerning human normal immunoglobulin therapies for immunodeficiency and other diseases"[9]; and physicians may have the flexibility to choose the therapy tailored to the needs of each patient.

Stakeholders ranging from healthcare professionals, patient organisations, industry stakeholders to decision-makers and Governments need to work jointly to direct efforts towards this goal. While immunoglobulins are included in the World Health Organisation List of Essential Medicines for both adults and children with PI, there are several areas for consideration by governments and regulatory authorities which include: appropriate supply of immunoglobulins on the national healthcare systems to ensure equal access for all individuals and also guarantee (appropriate) reimbursement of the therapies; introduction of alternative funding mechanisms to ensure the availability of several Ig products; evidence-based clinical guidelines for immunoglobulin use which recommend administration to people with PI and prioritize indications giving primary consideration to PI; and incentivise awareness-raising campaigns addressed to the general public for voluntary plasma and/or blood donations, as Ig supply is dependent upon plasma availability.

It is essential that steps are taken at all levels to fully support Ig treatment in PI and to consider such treatment a priority in maintaining optimal quality of care for people with PI.

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[7] *Idem source 3*

[8] NHS Scotland, Dpt of Health. Clinical Guidelines for Immunoglobulin Use. 2nd Edition update. 2012 March. http://www.nsd.scot.nhs.uk/Documents/clinimmumoMarch12.pdf

[9] Resolution CM/Res(2015)2 on principles concerning human normal immunoglobulin therapies for immunodeficiency and other diseases. Council of Europe, Committee of Ministers. 2015 Apr 15. https://search.coe.int/cm/Pages/result_details.aspx?ObjectID=09000016805c40ae

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Access to Ig therapies : a snapshot of the reality in some countries

The attainment of immunoglobulin replacement therapy for long-term use represents such a herculean effort in some areas of the developing world that highly morbid alternatives such as bone marrow transplant have to be used. For example, in India, access to long term Ig supplementation is so challenging that patients with X-linked agammaglobulinemia often undergo bone marrow transplantation to avoid periods of untreated disease[10]. Even in well-developed countries, access to long term Ig supplementation can be a real challenge. In the United States, health insurance coverage is connected to employment status. Therefore, the adult PI population can often suffer from prolonged periods of untreated disease due to inability to self-pay for costly Ig supplementation during periods of unemployment[11]. This same challenge is present in the US population that is transitioning from paediatric to adult care, in which patients have "outgrown" parental health insurance coverage and have not attained financial stability. The health of these patients can often deteriorate in these transitional years due to lack of Ig therapy, leading to hospitalizations that incur cost, further worsening their ability to obtain proper medical care and treatment. In summary, initiation and maintenance of Ig therapy represents a challenge in developing and developed areas of the world. Global efforts should be made toward the ability to provide an often lifesaving/changing therapy and provide optimal quality of care for people with PI.

[10] Kapoor N, Raj R. Hematopoietic Stem Cell Transplantation for Primary Immunodeficiency Disorders. Indian J Pediatr. 2016 Mau;83(5):450-4

[11] Modell V, Gee B, Lewis D, Orange J, Roifman C, Routes JM, Sorensen RU, Notarangelo L, Modell J. Global study of primary immunodeficiency diseases (PI)—diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation. Immunol Res. 2011 Oct;51(1):61-70. doi: 10.1007/s12026-011-8241-y.