

The need to increase plasma collection is fact based: just listen to patients and physicians!

In the past months, there have been calls by Brand *et al.*ⁱ and Strengersⁱⁱ to reduce and narrow the clinical indications for immunoglobulin (Ig) replacement therapies, rather than to collect more plasma in order to meet the growing need for these medicines. They further argue for a restriction of plasma donations with a focus on limited regional (mainly European) solidarity which would exclude low- and medium-income countries and be detrimental to a global approach to sufficiency.

The International Patient Organisation for Primary Immunodeficiencies (IPOPI) and the SAFE Task Force finds the paper factually inaccurate, not up to date and disagrees with the proposed solutions which are geographically limited, likely to fail and dangerous. We strongly object to both suggestions, restricting clinical use of Ig therapies to achieve regional sufficiency in plasma and plasma derived medicinal products (PDMPs) as well as attempting limited regional sufficiency based on donation-centred arguments rather than on patient needs and patient-centred policies. Such arguments are not only flawed and dangerous but fundamentally fail to take into account the fact that, for years, many patients have lacked these lifesaving treatments altogether or experienced repeated tensions or shortages. In addition, the authors have failed to listen to the voice of patients, indeed threaten patient safety and propose solutions which are an abrogation of global public health responsibility.

Arguing that the legitimate demand for medicines should be reduced in order to meet current supply appears both callous and goes against the views of international organisations, such as the World Health Organisation (WHO), the Council of Europeⁱⁱⁱ, or regional representatives, such as the European Commissioner for Health Ms. Stella Kyriakides^{iv}. Patient-centredness should be the cornerstone of any public health and pharmaceutical policy or legislation and patients' needs should be put at the centre of healthcare decision making. In addition, regional efforts to collect more plasma should be undertaken with a view to contribute to global plasma sufficiency based on regionally balanced collection rather than the creation of a plasma apartheid of the haves and have nots suggested by Brand and Strengers references.

Arguments that deny the need for increased plasma collection in a given region in the context of increasing global demand tacitly imply that patients living outside that region are 'less important'. Patients depend on a stable supply of PDMPs and have long called for increased plasma collection and for PDMPs^v to be viewed as global life-saving medicinal products that should be accessible across regions. The COVID19 pandemic has demonstrated the value of plasma and PDMPs as global resources, where one world region can mitigate risk by supporting another to maintain access to supply.

The arguments developed in the paper neglect the health of patients and the need to access their medicines as prescribed by their treating physicians. It also includes inaccurate and outdated data. IPOPI and the SAFE Task Force are concerned that the paper was accepted within a peer-reviewed process given the flawed views and arguments contained therein.

The Brand *et al.* paper contains a series of **inaccuracies and lack of up to date references** in the section on primary immunodeficiencies (PIDs) and immunoglobulin for replacement (page 2 and 3, Section 4.1.1, 4.1.2.5.3 and table 1)). The paper, published in early 2021, states that “PIDs are caused by more than 250 different rare genetic mutations”, although the International Union of Immunological Societies (IUIS)^{vi} published in 2019 its latest classification of inborn errors of immunity with a total reference of 430 disorders. This quoted lower number of PIDs was described as far back as 2014^{vii} and the paper therefore misses the rapid growth in new PIDs and the increasing rate of diagnosis with improved screening.

Another inaccuracy that we fail to understand is the use of 1 in 25,000 as an incidence for PIDs. This figure lacks a source but recent data from the IUIS IEI Committee publication by Tangye *et al.* estimates that the collective prevalence of these conditions is more likely to be at least 1/1,000 – 1/5,000^{viii} a five to twenty-five-fold difference. Furthermore, around 70% of patients with PIDs are undiagnosed, even in countries with existing PID facilities^{ix}.

Further inaccuracies relate to the statement that subcutaneous Ig (SCIg) replacement was delivered to PID patients from 1952 to 1981 and was then replaced by IVIG in 1982 (page 3 of the publication). In fact, the intravenous route gradually replaced the intramuscular route that was proven suboptimal and painful. This occurred in the 1980s and by 2006, immunoglobulin preparations designed exclusively for subcutaneous administration became broadly available^x.

The profound **lack of patient-centredness** is another shortcoming of the paper. The authors approach demand of Ig as an equation simply resulting from increased doses of Ig in patients, failing to appreciate that the increasing number of diagnosed patients with PIDs alone would explain the increase in the demand of Ig, irrespective of all of the other indications. Data shows that the average potential usage of Ig for the treatment of CVID and XLA alone is 72g per 1,000 population, which is higher than the total Ig usage in most countries where these data are available^{xi}. Patient-centredness is the cornerstone of international and European policies regarding personalised/customised medicine and it is a concept that has been omitted by the authors when considering how to narrow the gap between supply and demand.

The authors neglect to see that the indications for immunoglobulin therapy in the varied clinical presentations of immunodeficiency are likely to broaden as more of the disorders are diagnosed, diagnosed earlier, better understood and as new disorders continue to be rapidly discovered. Earlier diagnosis and treatment mean patients live longer better lives^{xii}. An increase in the number of patients with PIDs should be celebrated, as it means that more persons with such debilitating conditions should have access both to the diagnosis of their disease and its treatment – which in many cases will be Ig therapies.

Patient safety is paramount, as patients with PIDs need Ig therapies as prescribed by their treating physician throughout their lives to keep the levels of antibodies at a protective threshold to fight life-impairing or life-threatening infections. No alternative treatments are available for these patients at present and are not expected in the coming decade. As the WHO recognises, the principle of patient centredness is crucial to ensure the optimal use of PDMPs^{xiii}.

The paper states that “appropriate use should be determined by healthcare professionals and experts from blood establishments” (page 21) but we fail to see in what capacity experts from blood establishments enter into the field of prescribing medicines to PID patients in need. These decisions require joint decisions between experts in the conditions being treated (in this case the 430 and rising number of PID disorders) and patients themselves – both for the individualisation of care and to shape wider policy.

We also note with concern that the approach taken in the **publication is only centred on the situation of the most developed regions** like Europe and North America and fails to discuss European plasma collection in the context of global healthcare needs. It also ignores the differences between the national self-sufficiency concept of labile blood products for local use and the concept of global sufficiency in plasma products; by doing so, it misstates the factual realities of how these different medicines are collected, manufactured and distributed.

As each country collects more, it should be part of the goal to contribute to the plasma collection of its world region and ultimately contribute to the global plasma supply.

For all the reasons stated it is no longer possible to argue for national self-sufficiency – this also denies the vital current global movement of PDMPs. It also cannot be said that the Ig required to treat indications for which there is no reasonable alternative should be safeguarded by self-sufficiency (pages 20 and 21 of Brand *et al.*), as in many countries there is an insufficient domestic supply of plasma of a quality suitable for non-domestic fractionation along international gold standards and a lack of technical and financial capacity to implement a domestic plasma fractionation programme. What would happen to the patients in those countries with no fractionation capacity if we were to rely solely on self-sufficiency in PDMPs? Should they not be treated because their country does not have sufficient quality plasma or the capacity of plasma fractionation?

Even in countries with well-established blood and plasma collection and fractionation structures and companies developing PDMPs, patients with PIDs are faced with recurrent shortages which endanger not only patients’ quality of life but also their physical health. This has been even more evident during the last 15 months of the COVID-19 pandemic.

It is therefore essential to continue with efforts aimed at increasing plasma collection and therefore Ig supply for those patients in need of these live-saving treatments, not by restricting the access to PDMPs or limiting the collection of plasma and production of these therapies, but by strengthening plasma collection in all world regions and the development, where appropriate, of fractionation programmes, in line with WHO recommendations^{xiv}.

Patients with PIDs are very thankful to donors for their gesture and for their gift of life. Patient organisations have developed awareness raising campaigns on the importance of blood and plasma donations and recognise the dedication of donors to help those persons whose health and lives rely on their donation. After all, donors and patients agree that what matters most is saving lives. All ethical debates should evolve around this essential principle of allowing people in need to access their life saving treatments.

This statement was prepared by the IPOPI SAFE Task Force

About the SAFE Task Force: The Supply and Access for Everyone (SAFE) Task Force has been created by the International Patient Organisation for Primary Immunodeficiencies (IPOPI) to monitor plasma collection and the availability of immunoglobulin replacement therapies for patients with PIDs worldwide. The taskforce is composed of experts from different parts of the world and IPOPI staff (in alphabetical order): Ms Roberta Anido de Pena, Ms Jose Drabwell, Dr Nahla Ewra, Prof Stephen Jolles, Dr Nizar Mahlaoui, Ms Martine Pergent, Mr Johan Prevot, Prof John Seymour, Prof Surjit Singh, Ms Leire Solis.

ⁱ Brand A et al. Review of indications for immunoglobulin (IG) use: Narrowing the gap between supply and demand. (2021). *Transfusion Clinique et Biologique*, <https://doi.org/10.1016/j.tracli.2020.12.005>

ⁱⁱ Strengers P., Editorial. (2021). *Transfusion Clinique et Biologique*, <https://doi.org/10.1016/j.tracli.2020.12.003>

ⁱⁱⁱ Resolution CM/Res(2015)2 on Principles Concerning Human Normal Immunoglobulin Therapies for Immunodeficiency and Other Diseases. Council of Europe, Committee of Ministers (2015). Available from: https://search.coe.int/cm/Pages/result_details.aspx?ObjectID=09000016805c40ae

^{iv} Kyriakides S. World Blood Donor day: Statement by Commissioner Kyriakides. 2020. https://ec.europa.eu/commission/presscorner/detail/es/STATEMENT_20_1062

^v PLUS Consensus Principles on Strategies to encourage Blood and Plasma Donations in Europe (2019). https://plasmausers.org/wp-content/uploads/2021/04/PLUS-consensus-principles-on-strategies-to-encourage-donations_web.pdf

^{vi} Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* (2020). <https://doi.org/10.1007/s10875-019-00737-x>

^{vii} Chapel H et al. Primary immune deficiencies – principles of care. *Front. Immunol.* 2014. <https://doi.org/10.3389/fimmu.2014.00627>

^{viii} Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol* (2020). <https://doi.org/10.1007/s10875-019-00737-x>

^{ix} Chapel H et al. Primary immune deficiencies – principles of care. *Front. Immunol.* 2014. <https://doi.org/10.3389/fimmu.2014.00627>

^x Skoda-Smith, Suzanne et al. "Subcutaneous immunoglobulin replacement therapy in the treatment of patients with primary immunodeficiency disease." *Therapeutics and clinical risk management* vol. 6 1-10. 2 Feb. 2010, doi:10.1057/rm.2009.17

^{xi} Stonebraker JS et al. Modelling Primary Immunodeficiency Disease Epidemiology and Its Treatment to Estimate Latent Therapeutic Demand for Immunoglobulin. *J Clin Immunol* (2014) 34:233-244. Doi: 10.1007/s10875-013-9975-1

^{xii} Perez E et al. Update on the use of immunoglobulin in human disease: A review of evidence. *J Allergy Clin Immunol* 2017;139:S1-46.

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- ^{xiii} Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma. Geneva: World Health Organization; 2021. Pag 6.
- ^{xiv} Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma. Geneva: World Health Organization; 2021.