Global Immunoglobulin supply – steaming towards the iceberg?

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Abstract

Purpose of Review

This review describes how plasma is sourced for fractionation into Plasma Derived Medicinal Products (PDMPs) such as immunoglobulin (Ig) together with differences between plasma from whole blood (recovered plasma) and from plasmapheresis (source plasma) in terms of global plasma supply. Specific areas of growth in immunoglobulin use are identified alongside novel therapies which may reduce demand for some immunoglobulin indications.

Findings

There has been a 6-8% annual growth in immunoglobulin use. Secondary immunodeficiency alongside improved recognition and diagnosis primary immunodeficiency disorders are drivers while the novel neonatal Fc receptor inhibitors (FcRni) may reduce demand for some immunomodulatory indications.

Summary

There is a significant geographical imbalance in global supply of plasma with 65% collected in the US. This results in a dependency of other countries on US supply and argues for both more plasma supply and greater regionally balanced plasma collection. In addition, progress towards a transparent, regulated and safe framework for the coexistence of unpaid and compensated plasma donations is needed as unpaid donation will not be sufficient. These discussions should be informed by the needs of patients for this life-saving therapy, the care of donors and the safety of plasma and PDMPs.

Keywords – plasma, immunoglobulin, plasmapheresis, fractionation, convalescent plasma

Abbreviations

CIDP - Chronic Inflammatory Demyelinating Polyneuropathy

COVID-19 – Coronavirus Disease 2019

CPT – Convalescent Plasma Therapy

EDQM - European Directorate for the Quality of Medicines

ESID – European Society for Immunodeficiency Diseases

FcRn – Neonatal Fc Receptor

FcRni – Neonatal Fc Receptor inhibitors

Fc – Fraction crystallizable

FcR – Fc Receptor

FFP – Fresh Frozen Plasma

HdIVIg – high dose intravenous immunoglobulin

HIV – human immunodeficiency virus

HAV – human hepatitis A virus

HBV – human hepatitis B virus

HCV – human hepatitis C virus

Ig – Immunoglobulin

IgRT – Immunoglobulin replacement therapy

IPOPI – International Patient Organisation for Primary Immunodeficiencies

IUIS – International Union of Immunological Societies

IQPP - International Quality Plasma Program

ITP – Primary Immune Thrombocytopenia

MG - Myasthenia Gravis

MRB – Marketing Research Bureau

NAT - Nucleic Acid Testing

NMO – Neuromyelitis Optica

PDMPs – Plasma Derived Medicinal Products

PID – Primary Immunodeficiency

PPTA – Plasma Protein Therapeutics Association

SID – Secondary Immunodeficiency

vCJD – variant Creutzfeldt-Jakob Disease

WHO – World Health Organization

Introduction

Immunoglobulins, polyclonal/polyvalent (IgG) and hyperimmune (H-IgG) are plasma derived medicinal products (PDMPs) produced by fractionation. Immunoglobulin replacement therapy (IgRT) began in 1952[1] with subsequent developments in intramuscular immunoglobulin (IMIg), intravenous immunoglobulin (IVIg), subcutaneous immunoglobulin (SCIg) and most recently, facilitated SCIg (fSCIg) routes.[2]

Today Ig therapies are used in a wide range of indications with increasing demand and availability directly linked to supply of the raw material, human plasma. This paper reviews plasma sourcing and manufacture alongside a global perspective to challenges in supply and new therapies which may impact on some of the current indications for immunoglobulin therapy.

Plasma collection and Immunoglobulin manufacture

Ig therapies are manufactured from plasma collected from a large number of donors to ensure diverse specificities of antibodies against a broad spectrum of pathogens[3 4]. Manufacture is a complex, strictly regulated process to ensure safety, quality, purity and potency of therapies. [3,4, 5, 6, 7, 8, 9, 10, 11, 12]

Plasma is obtained either from whole blood donation by separating from cells (recovered plasma) or by direct plasma donation through plasmapheresis (source plasma) or co-collected during platelet apheresis. Plasmapheresis separates plasma by centrifugation while returning blood cells to the donor. Donor care is key both for the well-being of the donor and quality of the plasma.

A unit of recovered plasma ranges from 100-260 ml [WHO][13] and can be used as Fresh Frozen Plasma (FFP), Convalescent Plasma Therapy (CPT) as for COVID-19, or to manufacture PDMPs. Whole blood donors are usually only permitted to donate every 3 months to avoid anemia.

Plasmapheresis (source plasma) yields more plasma (450-880 ml)[WHO][13] depending on regulations in the country of collection[14 15,16]. In the U.S. donation frequency is twice weekly with 2 days between and maximally 104 donations annually[9] but only 0.3% donate >100 times, 14% >50 times, while 49% donated 10 times or fewer annually [17]. In Europe maximum annual donations range from 24-60. The European Directorate for the Quality of Medicines (EDQM) non-binding recommendations advise a maximum of 33 plasma donations per year with at least 96 hours between[18]. Compared to recovered plasma, plasmapheresis allows collection

of much larger annual plasma volumes available for fractionation due a combination of higher donation frequency and a larger volumes per donation.

Manufacture by fractionation of Ig from up to tens of thousands of units of pooled plasma takes from 7-12 months and is based on cold ethanol precipitation of proteins developed by Cohn and collaborators in the 1940's[19,20,21] with additional dedicated steps to increase purity, yield, improve quality and enhance safety margins to prevent potential transmission of pathogens. These steps vary between brands and include plasma protein separation by precipitation and/or chromatography, protein purification using ion-exchange or affinity chromatography, and steps (one or more) for the inactivation or removal of potential infectious agents such as blood-borne viruses and prions [22,23] [24,25] [26,27].

Indications and uses of Ig Therapies

Ig therapies for PID and Kawasaki diseases are on the WHO List of Essential Medicines[28,29] and are unique biological products with no single product or method of administration suitable for all patients[30]. It is well established that the differences in manufacturing processes can affect individual tolerability, risk of adverse events, infusion rate, and potentially efficacy[31] making access to a range of different Ig therapies vital.

Indications for Ig therapy vary depending on the region/country (Table 1) as does use in a wide range of other off-license indications.[32, 33, 34] [35].

Currently PID and SID are the major indications as exemplified from Australian National Blood Authority data [36] (Figure 1) and the UK Database [37] with PID (1,514,760g), CIDP (1,239,547g) and SID (991,511g). In the US, PID represents roughly 30% (including some SID), CIDP 20%, myasthenia gravis (MG) 10%, ITP 9%, others 31%, (Hotchko, M., MRB Personal communication 01/07/20).

Overall global Ig demand has increased annually by 6-8% (Figure 2), with a higher rate in emerging markets because of lower starting consumption levels [38].

Factors influencing annual growth in consumption are complex and include increasing use in SID and neurological conditions, but also improved diagnosis for PID particularly in developed countries linked to increasing use of newborn and calculated globulin screening [39] [40] [41] [42]. However, the reality of massive worldwide underdiagnosis for around 70-90% of PID patients persists[43]. Encouragingly, disease-specific diagnostic tests for PIDs are now on the WHO List of Essential In-Vitro Diagnostics Tests[44] with 430 different PIDs identified in the latest IUIS classification[45].

Supply-dynamics of PDMPs have historically been characterized by intermittent shortages with Ig therapies recently ranked third most frequent medicinal product facing shortages in the EU pharmacists report of medicinal products[46].

New therapies which may reduce Ig use

Set against this growth are some potential areas of reduction for immunomodulatory indications because of new therapies.

Three evolving therapeutic approaches overlap with immunomodulatory mechanisms of action of Ig including – blockade of the neonatal Fc receptor (FcRn) and other Fc receptors (FcR), reducing autoantibody production, and complement inhibition [32 47 48 49 50 51 52] .

The FcRn functions as a recycling mechanism to prevent degradation and extend the half-life of IgG and albumin in the circulation. Maintenance of serum IgG levels is proportionally more dependent on recycling than production [49 50]. One mechanism by which hdIVIg reduces pathogenic autoantibodies is by saturation of FcRn receptors[53].

Several FcRn inhibitors (FcRni) rozanolixizumab, efgartigimod, orilanolimab, and nipocalimab selectively targeting IgG recycling are in clinical trials for CIDP, MG and ITP. These can reduce serum IgG by 45-80%, [54 55 56 57] levels returning to baseline after 28 and 57 days depending on the FcRni [54 55 58]. FcRni have potential for future use in a much wider variety of antibody-mediated autoimmune diseases which may reduce pressure for Ig on repertoire dependent indications such as PID and SID.

Further strategies targeting FcR in autoimmune disease are multimerization of recombinant Fc portion of antibodies and modification of Fc by hyper-sialylation[59] (M254). Recombinant fragment crystallisable (rFc) multimers primarily target Fcγ receptors (FcγRs) but may also affect the complement system[60 61].

Significant advances have also been made in terms of targeting B cells predominantly for hematological malignancies such as CD19 (Ineblizumab), CD22 (Epratuzumab), CD38 (Daratumumab, Isatuximab) as well as proteasome inhibitors. Future indications in autoimmune and inflammatory disease as with rituximab are likely, impacting indications for hdIVIg eg neuromyelitis optica (NMO).[58]

There is also increasing interest in complement inhibition in autoimmune and inflammatory diseases with novel inhibitors (eclulizumab, tesidolumab and ravulizumab targeting C5 and the C5a blocking antibody (IFX-1) noting that complement inhibition is another mechanism of action of hdIVIg[62].

Ensuring sufficient future global supply

Ensuring sufficient global supply and stability requires both increased plasma supply and improved fractionation technology to optimise yield from each litre of plasma alongside a vibrant R&D platform for novel PDMPs.

There are significant regional differences in collected volumes of recovered and source plasma. In 2017 the US supplied 65% of world plasma for fractionation (Figure 3), and 71% of all source plasma, while Europe was the largest supplier of recovered plasma with only 10% of source plasma.[63] Latin America and Africa currently account for a very small proportion of global plasma supply and have a rapidly growing demand. The US has the highest global Ig sales at 46% (Figure 4) but is in fact a net exporter with 65% of the world plasma collection.

Strategies to attract and retain more blood and plasma donors, especially source plasma donors given that in 2015 recovered plasma accounted for only 13% of fractionated plasma worldwide [64], are key alongside harmonisation of best practice in donation frequency and volume limits to ensure the safety of donors and quality of final products.

In the US and some EU countries such as Germany, Austria, the Czech Republic and Hungary, source plasma donors are compensated for their donations. However, in most other EU countries plasma donor compensation is currently not authorized with reliance on unpaid donations. Germany, Austria, the Czech Republic and Hungary collect proportionally a much higher plasma volume than any other European country (3 times higher). In 2017, whilst the non-profit public sector collected 55% of European plasma used for fractionation, the commercial sector collected 45%, but from just 4 countries with a population of 112 million (European population 743 million) (Hotchko, M., MRB. Personal communication. July 1st 2020).

Could both compensated and unpaid co-exist and contribute together towards increased plasma collection? From a viral safety perspective, it is well established that PDMPs made from compensated plasma donations are just as safe as those made from unpaid donations[65]. There is the need for a re-evaluation[66] of this growing disparity in collections across Europe to ensure future global supply based on more regionally balanced plasma collection.

Today's reality is that the US contributes the large majority of the world's plasma supply (Figure 3), making other regions such as Europe highly dependent on American (largely compensated) plasma donors, creating an imbalance which could jeopardize access to life saving Ig therapies. The past has shown us that national sources of plasma can become

unusable from one day to the next, such as with the variant Creutzfeldt-Jakob disease (vCJD) crisis in the UK in the 1990s. There has been significant inertia in evidence-based decisions concerning the ability to fractionate UK plasma again despite growing national and global need. The costs have been high in terms of opportunity, loss of sovereign fractionation capacity, supply shortages and the exposure to rising global price. Additionally, the COVID-19 pandemic is likely to lead to further strains on immunoglobulin supply as plasma donations have declined in 2020[67]. Stay at home and social distancing measures have led to reductions in regular attendances at donor centres whilst the urgent need for SARSCoV2 antibody positive plasma for CPT and H-IgG has been an ongoing priority. This highlights the need for universal and international access to PDMPs (including CPT and H-IgG) and for collecting more plasma. In the UK and other countries, response times to the pandemic for CPT would have been markedly quicker had an existing national network for plasma donation at scale already been in place.

Conclusions

There has been significant and year on year growth of around 6-8% in the requirement for immunoglobulin for predominantly Immunology, Neurology and Hematology indications. Major drivers include increases in secondary immunodeficiency, better recognition and diagnosis of primary immunodeficiency albeit on a background of massive underdiagnosis globally.

Novel therapies such as FcRn inhibitors may reduce demand in some of the current immunomodulatory indications for Ig. However, to meet demand there needs to be an increase in plasma collection with reduction in the current imbalance of 65% of plasma coming from the US towards a much more regionally balanced collection and with a view to attain global sufficiency in PDMPs. In addition, transparent and collaborative discussions concerning the regulatory framework to allow the coexistence of both unpaid and compensated plasma donation need to progress and should be patient-centered. The underpinning rationale should be the needs of patients for these life-saving therapies, the care of donors and the safety of plasma and PDMPs.

Summary

- The demand for Ig therapies is growing annually at 6-8% across a broad range of indications with particular growth in secondary immunodeficiency
- There is a significant imbalance in global plasma collection with 65% of this being from the US with a need for more regionally balanced collection
- FcRn inhibitors may mitigate future demand in some immunomodulatory indications
- To meet the demand more donors are needed alongside the development of a regulatory framework for the coexistence of both unpaid and compensated plasma collection is needed
- Progress towards global sufficiency will require collaboration guided by patients needs, donor care and safety of PDMPs

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Conflict of Interest.

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