Evidence-based clinical indications of plasma products and future prospects

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Abstract: Plasma derived medicinal products (PDMPs) or plasma products are medicines manufactured from human plasma from more than 1,000 plasma donations. Plasma is a rich biological substance and about 15–20 plasma proteins can be isolated from plasma into concentrated therapeutic plasma protein products. The therapeutic functions of PDMPs are diverse. Many patients with a variety of diseases and disorders benefit from treatment with PDMPs. Due to the fact that plasma proteins have an important function in the well-functioning and well-being of the human body, a therapy with PDMPs can be lifesaving and important in reducing morbidity and mortality.

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Introduction

Of the human blood that flows through arteries and veins, plasma is the liquid that is most abundantly present and in which the cellular components red cells, leucocytes and platelets are suspended. Fifty-five percent of whole blood is plasma of which 89% water, 2% salts, 3% lipids and 6% proteins. The plasma proteins (60 g/L) consist of 2,000–4,000 different proteins in a concentration ranging from ng/mL (hormones) to ±40 mg/mL (albumin). Each protein constituent has a specific function in the homeostasis of the human body and a lack or a deficiency of a plasma protein might be life-threatening. In a number of clinical pathological situations, plasma proteins are observed as not present or malfunctioning. In others where non-plasma protein laboratory parameters are indicative for the disorder, clinical evidence has shown that plasma protein therapy might be efficacious. Unfortunately, in a number of these diseases and disorders the underlying mechanisms of pathology and treatment are still unknown and the effect of plasma protein therapy can be found only clinically present without or with limited supportive evidence shown by plasma protein laboratory parameters.

Plasma is used in clinical care as plasma for transfusion or fresh frozen plasma (FFP). Plasma for transfusion is indicated for general clotting factor deficiencies, isolated clotting factor deficiencies in case a purified plasma derived or recombinant product is not available, correction of hyper-fibrinolysis in case of thrombolysis, and substitution of clotting factors or deficient factors during plasmapheresis therapy. In order to prevent transmission of blood borne transfusion transmitted infections, safety measures additionally to donor information, donor exclusion and donation screening, such as a quarantine period and/or pathogen inactivation are in use.

Plasma is a rich biological substance and about 15–20 plasma proteins can be isolated from plasma into concentrated therapeutic plasma protein products. The presence and concentration in plasma differ between the proteins. Albumin (64.3%) and immunoglobulin G (IgG) (20.3%) are present in a relatively high concentration. In a much lower concentration fibrinogen (5%), α2-macroglobulin (4.4%), α1-antitrypsin (2.5%), fibronecctin (0.5%), anti-thrombin (0.3%), plasminogen (0.3%), C1-esterase inhibitor (0.3%), and prothrombin (0.25%) are present. Between the other proteins (1.7%), von Willebrand...
factor (vWF), factor VII, factor XI, factor IX, protein C, and factor VIII are traceable. A relative lower concentration however is not necessarily an indication of less important functionality. Complete absence of factor VIII results in mortality at relatively young age due to the occurrence of fatal bleedings.

As a result of basic research and research and development (R&D) after the first publication regarding the plasma fractionation process by Cohn, a variety of plasma derived medicinal products (PDMPs) have become available (1). Prior to a manufacturing process, units of plasma recovered from whole blood donations (recovered plasma) or obtained by plasmapheresis (source plasma) are pooled and processed through manufacturing processes including cryoprecipitation, fractionation steps that employs differences in time, temperature, pH, and ethanol concentrations and chromatography columns with the objective to isolate and extract the specific proteins. The isolated proteins are subsequently subject to various purification methods followed by virus-inactivation and virus-removal processes to further ensure their safety and efficacy. Preparing for a therapeutic product often takes seven to twelve months between the plasma donation and the final product release. This sets the production of PDMPs apart from chemical pharmaceuticals and other biologics whose manufacturing processes are more condensed and whose direct manufacturing costs are a significantly smaller portion of the overall costs.

**Clinical therapy with PDMPs**

The therapeutic functions of PDMPs are diverse. Many patients with a variety of diseases and disorders benefit from treatment with PDMPs. Due to the fact that plasma proteins have an important function in the well-functioning and well-being of the human body, a therapy with a PDMP can be lifesaving and important in reducing morbidity and mortality. In particular for patients with coagulation and bleeding disorders, immunological disorders, infectious diseases, metabolic diseases and trauma, PDMPs have a therapeutic effect both in prevention and treatment of the disease. The World Health Organization has underlined the importance of PDMPs for global clinical care by putting a number of PDMPs on the WHO Model List of Essential Medicines (2). Anti-D immunoglobulin, anti-rabies immunoglobulin, anti-tetanus immunoglobulin, normal immunoglobulin for intramuscular, for intravenous and subcutaneous use, coagulation factor VIII and coagulation factor IX are appointed as essential medicinal products and governments “should make sure that all people can get access to these medicines they need, when and where they need them, which is vital to countries’ progress towards universal health coverage”.

For a better understanding but with the risk of oversimplification, therapeutic treatments with PDMPs can be divided into four categories: replacement or substitution therapies, immune modulating therapies, therapies directed on plasma protein antagonist functions, and anti-inflammatory therapies. Finally, some plasma proteins are under study for drug delivery for example acting as a carrier of a chemotherapeutic medicine in cancer treatments.

**Replacement therapy**

Replacement or substitution therapy implies that a PDMP is administered in patients with primary (congenital) or secondary (acquired) plasma protein deficiencies in whom the concentration of the protein concerned in plasma is absent or has become relatively too low and an adjustment of the plasma level is required. Depending on the plasma protein, an absent or too low concentration might be not compatible with life or is seriously disabling resulting in increased morbidity and mortality. Replacement therapy with the required plasma protein product is needed in such situation.

In the field of haemostasis, some patients are born with a quantitative or qualitative deficiency of a coagulation factor and replacement therapy is a therapeutic solution for overcoming coagulation disorder. These disorders are mostly rare diseases, hereditary in origin, with a prevalence of less than 1:2,000 and they are chronic requiring lifelong treatment. Other patients have a factor deficiency acquired due to an auto-immune response or as a complication of cancer. The best-known diseases in this field are hemophilia A (congenital, in primarily male patients, and acquired factor VIII deficiency) and hemophilia B (congenital factor IX deficiency). Depending on the level of endogenous factor, patients have a risk on life-threatening bleedings primarily in joints and muscles if not prophylactically or on demand treated with factor VIII or factor IX concentrate, respectively (3). Another factor deficiency is von Willebrand disease, which is caused by a deficiency of vWF and affects both men and women. Plasma derived vWF concentrate is used as replacement therapy for patients with von Willebrand’s disease type III. Purified plasma-derived concentrates of vWF/factor VIII are also used for treatment of bleeds and for surgical prophylaxis, when DDAVP (the first treatment choice) is ineffective or contraindicated (4). Prothrombin complex concentrate (PCC) containing
factor II, factor VII, factor IX with factor X (4F) or without factor VII (3F) is indicated for replacement therapy of isolated or combined congenital deficiency of (one of) these coagulation factors. These factors may however also be offered in a concentrated form as a single factor concentrate. PCC is further substituted in liver diseases with a too low concentration of clotting factor II, VII, IX and X and when a correction is needed due to a (threatening) bleed or surgery. Factor VII and factor XI are used to treat bleed prophylactically and on demand in patients with congenital or acquired deficiency of the relevant clotting factor. Factor XIII concentrate is indicated for congenital deficiency of factor XIII which if untreated results in hemorrhagic diathesis, hemorrhages and disturbances in wound healing. Fibrinogen (factor I concentrate) is indicated as replacement therapy in hemorrhagic diathesis in case of congenital afibrinogenemia, dysfibrinogenemia and hypofibrinogenemia. Fibrinogen is also indicated in acquired hypofibrinogenemia due to diffuse intravasal coagulation (DIC) and hyperfibrinolysis in patients who do not respond on FFP and who do not react on other measures intended for correction of the fibrinogen consumption and the underlying cause. Fibrin sealant is indicated for creating a fibrin clot.

Some proteins have a role in the prevention of thrombosis and protein C is indicated as replacement therapy for severe congenital protein C deficiency. This product is also administered for the prevention and treatment of venous thrombosis, and purpura fulminans.

Plasma proteins have many functions in the homeostasis of the body. Due to the physiological properties of albumin such as maintaining the oncotic pressure, its transport and binding function and its scavenger effect by remove radicals, albumin is indicated for restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated. Albumin is presented in two concentrations: albumin with 40 or 50 g/L and albumin with 200 or 250 g/L, and each concentration has its own specific indications. Albumin 4% and 5% is indicated for the treatment of existing or threatening shock for example in case of serious bleed or burns, for extracorporeal circulation, sepsis or serious infections accompanied with serious protein loss (peritonitis, mediastinitis), transient arterial hypotension during hemodialysis and plasmapheresis or plasma exchange. Albumin 20% and 25% is indicated for ascites in combination with paracentesis, the treatment of hyperbilirubinemia in neonates as adjuvant, nephrotic syndrome in case diuretics do not have sufficient effect, acute liver insufficiency, serious postoperative hypo-albuminemia and serious hypo-albuminemia in neonates. Between 1998 and 2013, based on a number of studies, scientific discussions have taken place on the safety of albumin compared to alternative treatments such as artificial colloids and crystalloids and whether albumin is associated with increased rate of death. The latest outcome was that although albumin has been determined to be safe for use as a resuscitation fluid in most critically ill patients and may have a role in early sepsis, its use is associated with increased mortality among patients with traumatic brain injury. From the alternative treatments, the use of hydroxyethyl starch (HES) solutions is associated with increased rates of renal-replacement therapy and adverse events among patients in the intensive care unit (ICU). There is no evidence to recommend the use of other semisynthetic colloid solutions (5).

α1-proteinase inhibitor is used as replacement therapy for α1-antitrypsin deficiency, a genetic disorder that causes defective production of α1-antitrypsin leading to decreased α1-antitrypsin activity in the blood and lungs and deposition of excessive abnormal α1-antitrypsin protein in liver cells. Severe α1-antitrypsin deficiency causes panacinar emphysema or chronic obstructive pulmonary disease (COPD) in adult life in many people with this condition, especially if they are exposed to cigarette smoke. Unfortunately, the expansion of the α1-antitrypsin market is hampered by the absence of regulatory approval in many countries, lack of clinical trials demonstrating evidence-based therapeutic efficacy, inadequate diagnosis, limited awareness in the medical community and in the general public, and high cost of therapy (6).

For a rare under-recognized medical condition that is associated with inadequate endogenous anticoagulation thought to result from impaired inhibition of serine protease coagulation factors, anti-thrombin III concentrate is indicated for prophylaxis and treatment of thromboembolic complications in congenital or acquired anti-thrombin III deficiency (7). C1-esterase inhibitor concentrate is indicated as substitution therapy for the prevention and acute treatment of attacks of edema in primarily the throat area, in extremities and abdomen caused by hereditary angioedema, a congenital or acquired C1-esterase inhibitor deficiency (8). In case of an attack of edema in the larynx area, the edema can block the trachea and, if untreated with lifesaving C1-esterase inhibitor concentrate, the patient may suffocate.

In 1952, Bruton published his classical description of congenital agammaglobulinemia and following this publication
the intramuscular administration of immunoglobulin concentrations became regular practice (9). Patient groups with primary and secondary immune deficiency are dependent on IgG concentrate which prevents them against life-threatening infections, and polyvalent intravenous immunoglobulin (IVIG), intramuscular immunoglobulin (IMIG) and subcutaneous immunoglobulin concentrate (SubIG) are indicated to substitute the missing protein. IgG products are indicated for primary immune deficiency syndromes and/or disorders in the specific antibody formation due to congenital a-gammaglobulinemia and hypogammaglobulinemia, common variable immune deficiency (CVID), serious combined immune deficiency (SCID), syndrome of Wiskott-Aldrich, syndrome of DiGeorge, ataxia-teleangiectasia, and IgG-subclass deficiency. In secondary immune deficiency syndromes, IgG products are indicated for chronic lymphatic leukemia, children with AIDS, allogeneic bone-marrow and other forms of transplantation, and premature with a body weight at birth of less than 1,500 g. Hyper-immune globulins or specific globulins, mostly administered intramuscularly, are immunoglobulin concentrates manufactured from plasma from donors with a high titer of specific antibodies. Hyper-immune plasma is collected from donors who have been actively immunized with specific antigens such as anti-D, rabies, tetanus, hepatitis B, anthrax and smallpox. Hyper-immune plasma can also be obtained from donors with naturally occurring antibodies such as cytomegalovirus (CMV), varicella (VZV), hepatitis A or respiratory syncytial virus (RSV). Hyper-immune globulin preparations are of outmost importance for the prevention and mitigating of life-threatening infections with the pathogens concerned if the persons are not vaccinated, if vaccination is not possible, or in whom the vaccination has not resulted in a sufficient protective antibody plasma level. IMIG is indicated for passive immunization against hepatitis A, as well.

**Immune modulating therapy**

In the beginning of its clinical use in the 1950’s, immunoglobulins were administered only intramuscularly because after an intravenous injection, serious adverse events occurred caused by activation of the complement system due to aggregation of IgG. It took almost 20 years after the discovery of Barandun in 1962 of the development of an intravenous preparation of IgG before the administration of IVIG became common practice (10). The observation of Imbach that the therapeutic value of IVIG could be associated with other effects than the passive transfer of antibodies alone changed the IVIG treatment options completely (11).

In the treatment of two immune deficient children suffering simultaneously from serious immune thrombocytopenia, he noticed that the platelet count increased after administration of a high dose of IVIG. This observation could be confirmed by others and following the results with idiopathic thrombocytopenia (ITP), high dosages of IVIG have been administered in patients suffering from many other immune-hematological disorders, autoimmune diseases, neurological syndromes and other disease of the immune system. Some of these reports are only case reports, others are the result from randomized clinical trials. The results are sometimes not in concordance with other studies, which can be explained by the fact that the pathophysiology of the disease and the mechanisms of action which could explain the therapeutic effect of IVIG, have not been elucidated.

Currently high dose IVIG is indicated for ITP, Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP) and Kawasaki’s disease. For some IVIG products multifocal motor neuropathy (MMN), dermatomyositis, autoimmune uveitis and myasthenia gravis are also indicated. Since the introduction of high dose IVIG, the need for polyvalent IVIG has grown significantly for the treatment of an increasing number of hematological, neurological and dermatological auto-immune diseases such as auto-immune limbic encephalitis, stiff person syndrome, autoimmune haemolytic anaemia, post bone marrow transplantation, parvovirus B19-associated aplasia, toxic epidermal necrolysis, Stevens-Johnson syndrome, and immune bullous disease. Both in Cochrane meta-analyses for isolated indications and national and international consensus meetings on multiple indications, efforts are made to classify the indications for immune modulating therapy of IVIG in order to establish evidence-based usage and to minimize off-label use (12-15).

**Antagonist functions**

PCC containing factor II, factor VII, factor IX and with factor X (4F) or without VII (3F) is indicated for reversal of vitamin K antagonist treatment. The vitamin K-antagonist function of PCC is stronger than FFP and also lifesaving (16). Activated PCC (anti-inhibitor coagulant complex or factor eight bypassing agent-FEIBA) is a factor VIII inhibitor bypassing agent to control of spontaneous bleeding episodes and use in surgery in hemophilia A patients with inhibitors (17). This function is quite important given the fact that inhibitor formation is currently the major adverse effect of hemophilia treatment (18).
Anti-inflammatory functions

The anti-inflammatory actions of IVIG are mainly based on the hypothesized working mechanisms of immune modulation in which IVIG in a high dose has shown to be efficacious. IVIG is manufactured from more than 1,000 donations and contains more than two mill antibodies. For that reason, it is hypothesized that IVIG may have its immune modulating effect i.e., due to an anti-inflammatory function. A number of the approved indications are correlated with a pre-existing infection. For example, in 25% of the cases of Guillain-Barré syndrome a correlation with infection with *Campylobacter Jejuni* has been shown (19). A survival benefit was observed for patients with sepsis who received polyclonal IVIG therapy compared with those who received placebo or no intervention (20). More importantly, in the search into the immune modulating working mechanisms of high dose IVIG the anti-inflammatory properties in particular regarding its role in the innate immunity are becoming more prominent (21,22).

Future prospects

Based on epidemiological data, many patients worldwide lack essential plasma product treatment taking into account data on the percentages of diagnosed and treated patients. According to the World Federation of Hemophilia, only 30% of the patients with hemophilia A or B have been diagnosed and only 25% receive treatment. Other patient’s organizations present similar or even worse data: of patients with primary immune deficiency, worldwide, less than 10% is diagnosed and only 6% receives treatment with immunoglobulin (23). Due to the increasing number of patients who are suffering from diseases and disorders that can effectively be treated with plasma products, the need for these products will continue to grow and the demand for plasma, the source material for the production of these products, will increase equally. The cost of care in the emerging markets however will remain the main obstacle to demand increase and access to care.

New treatment options for PDMPs

The future developments of PDMPs are expected to grow within the foreseeable future due to the aging population, and better healthcare leading to better diagnosis and treatment. New therapeutic indications and the diagnosis of conditions for which PDMPs can be prescribed will play an important role. In particular for IVIG for which there seem to be no alternative at the horizon, potential new indications of IVIG in neurological diseases such as neuropathic pain, chronic fatigue syndrome, post-polio syndrome and others will expand the clinical use of IVIG. Also for albumin new indications are under study such as stroke, cirrhosis, Alzheimer disease, malaria and sepsis. PCC might be indicated for reducing bleed in liver transplantation and massive transfusion although a robust laboratory control parameter does not seem to be available yet. Inhibitor formation is the major adverse effect of hemophilia treatment. For hemophilia A treatment, plasma derived factor VIII seems to be the best option following landmark studies which showed that the incidence of inhibitor formation following treatment with plasma derived factor VIII is lower than with recombinant factor VIII (18,24).

New products

Currently a number of new PDMPs are under development and in clinical trials. An example is apotransferrin for iron binding therapies such as congenital deficiency, beta thalassemia and sickle cell anemia (25). Interest has been shown in ceruloplasmin an iron-export ferroxidase that is abundant in plasma and also expressed in glia, which could be indicated for congenital deficiency, Wilson disease, Parkinsons’ disease, acute stroke, or Menke disease. Factor H might be a candidate for atypical hemolytic uremic syndrome, dry age macular degeneration and wet age-related macular syndrome. And protein S for congenital and acquired protein S deficiency. The main challenge for the development of the potential new PDMPs does not seem to be the medical scientific background, the seriousness of the pathology that could be prevented or treated and the scientific interest in basic research and R&D. In the development process for new PDMPs it is becoming harder to comply with the formal regulatory requirements on efficacy and safety of the products. The costs of development, the clinical evidence and safety to be shown in randomized controlled clinical trials with sufficient number of subjects in a rare disease and the registration process are limiting the progress that could be made. Challenges and issues such as the high costs of treatments with PDMPs, high R&D costs, and the unclear and lengthy process of opening of new plasma collection centers might hamper the use of PDMPs and force to look for alternatives. These alternatives have already been found in the development of biotechnological products.
Alternative treatments for PDMPs

Triggered by the high costs of treatments with PDMPs the search for alternative treatments is present for years. Artificial colloids such as hydroxyl ethyl starch (HES) and the crystalloids are in use as alternatives for albumin suppletion but their use is becoming limited due to the occurrence of renal adverse events. Corticosteroids may act for some patients as alternative medication for the modulating effect of IVIG in ITP with a beneficial effect on the costs of care.

Several recombinant plasma protein products have become available since 1996 and new generation products with a prolonged half-life will certainly be an alternative. Recombinant products for plasma proteins factor VIII, factor IX, and C1-esterase inhibitor are on the market. Biotechnological products derived from milk of transgenic animals (C1-esterase concentrate and antithrombin III) have been licensed or are under study for the same indications as their plasma derived products.

However more challenging are new approaches for future treatments of patients currently dependent on PDMPs. Treatments intended to address the genetic cause of the disease. Gene therapy has been developed for primary immune deficiency, hemophilia B, and hemophilia A. Umbilical cord stem cell, hematopoietic stem cell and lentiviral stem cell transplantation are in phase I, II and III studies in a number of primary immune deficiencies. The results of clinical trials look quite promising and in some countries these treatments are reimbursed already.

Conclusions

Plasma derived medical products have a history of more than 75 years and have still an important function in clinical therapy of many diseases. Since a number of these diseases are hereditary and chronic, the treatment with a PDMP can be life-long. Because of the strict regulations on donor and patient safety, the serological and nucleic acid test (NAT) screening of blood and plasma donations on blood-borne transfusion transmitted infections and the pathogen inactivation and removal techniques during manufacturing, the treatments are since 1996 safe regarding the transmission of blood-borne agents. However, administration of a PDMP which is a transfusion of homologous proteins of donors may imply an immunological reaction at patient’ side. Encouraging is the fact that in general the incidence of these adverse reactions is low. In general, the incidence of adverse events of PDMPs is lower than adverse events rates following treatment with synthetically manufactured medicines. The future demand of PDMPs will be affected by demographics and health services, by improvements of health care in emerging countries, awareness and funding. It should be prevented that not enough availability of supply may limit the optimal usage of plasma products.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References


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