Clinical Application of Plasma Derived Medicines: Current Situation and Future Trend

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Introduction

Blood plasma consists of a number of functional groups which have a major function in order to maintain or restore the physiological status of the human body. About 13% of the body weight consists of blood including the cellular components erythrocytes, leucocytes and platelets, and plasma. Plasma contains many different substances such as secreted proteins e.g. albumin, clotting factors, fibrinogen, and immunoglobulins (IgG, IgA, IgM, IgD, IgE); tissue leakage products e.g. cardiac myoglobin; "distant" receptor ligands e.g. insulin; "local" receptor ligands e.g. interleukin 8; aberrant secretions e.g. prostate specific antigen (PSA) in prostate cancer; temporary passengers e.g. lysomal enzymes; and foreign proteins e.g. virus. In general, the medicinal products that are isolated from plasma are divided into a number of functional groups: albumin solutions, clotting factor concentrates, immunoglobulins, serine protease inhibitors, and other products.

Current situation

Currently, the therapeutic products which are derived from plasma are albumin solutions, clotting factor concentrates such as fibrinogen, factor VIII concentrate, factor IX concentrate, prothrombin complex concentrate, factor VIIa concentrate, activated prothrombin complex concentrate, Von Willebrand factor concentrate and thrombin, polyvalent and hyper-immune (or specific) immunoglobulins, alpha-1-antitrypsin, protein C, and haptoglobin. Less common products are anti-thrombin for hereditary or acquired deficiency, C-1 esterase inhibitor concentrate for hereditary angioedema, a-1 antitrypsin for congenital deficiency and cystic fibrosis, activated protein C for congenital deficiency and sepsis, factor VII concentrate for congenital deficiency, factor XI concentrate for congenital deficiency, factor XIII concentrate for congenital deficiency, fibrin sealant as haemostatic agent and apo-transferrin as target protein for chemotherapy or for atransferrinemia. Novel products with therapeutic potential which were or are in development are factor V concentrate for con-

genital deficiency, factor X concentrate for congenital deficiency, haemoglobin solutions for oxygen transport, haptoglobin for burns therapy, mannose binding lectin for immune deficiency, a-acid glycoprotein as anti-infectious agent, butyrylcholine esterase for cocaine abuse reversal, C-reactive protein as antibacterial agent, and hemopexin for the treatment of haemolysis. Besides these developments, research is ongoing and continuous efforts are made to derive more proteins from plasma for the treatment of patients.

Albumin.

Albumin is quantitatively the most important plasma protein. The concentration is 4 - 5 g albumin/kg body weight, which equals 38-44 g albumin/l plasma. The distribution is in the intravascular part for 40 - 45 %, and in the extra vascular part for 55 - 60 %. Albumin has strong hydrophilic characteristics and 1 gram of albumin binds 18 ml of water. Due to its specific stereochemic structure, albumin crosses the capillary membranes and maintains the colloidal osmotic pressure and the three-dimensional structure helps in binding of physiologic and pharmacologic substances. The pharmacologic properties of human albumin are maintaining 60 - 80 % of the colloidal osmotic pressure, and play a significant role in the fluid transfer between the extra vascular and intravascular spaces, i.c. volume expansion. The transport and binding function of albumin includes endogenous substances, such as bilirubin, fatty acids, metals, and hormones. This is important for example for the prevention of the toxic effects of bilirubin and the solubility of free fatty acids in plasma. The transport and binding function for exogenous substances like drugs has an influence on their therapeutic activity on free active drugs or fixed inactive drugs. The scavenger effect of albumin plays a role for example by removing radicals and the prevention of lipid peroxidation. Finally, albumin is important for the prevention of changes in the cellular membranes. Because of its properties, the beneficial effects of albumin are apparent in a wide array of clinical settings. Albumin as plasma derived medicinal product is a pasteurised solution of plasma albumin prepared from human blood. Transmission of blood borne infections has not been reported, but might be possible theoretically. Unfavourable effects attributable to albumin have rarely been reported.

The superiority of therapy with albumin is clearly demonstrated in following indications:

- Cirrhosis and spontaneous bacterial peritonitis
- Cardiopulmonary bypass surgery:
- Hypovolaemia

- Septic shock
- Gastrointestinal surgery
- Hypoalbuminaemia

Additional protective properties of albumin such as antioxidant activity, binding affinity, inhibition of apoptosis, and modulation of inflammatory response are important. There are two major forms of albumin solutions: albumin 4-5% and albumin 20-25%. Albumin 4-5% have bee used safely for decades as volume expander. The usage of albumin as plasma-expander was questioned by a systematic review of the Cochrane-group of randomised trials regarding the administration of albumin to seriously ill patients in a wide scale of indications and patient categories. This meta-analysis showed no decrease of mortality, but suggested a relatively higher mortality in the treated groups (1). A critical analysis on the set-up of the CIGAR-study however resulted in serious criticism on the set up of the meta-analysis. In the meta-analysis, studies had been included in which the primary outcome was not equal to the outcome of the meta-analysis. A wide variety of albumin products had been analysed, and the selection of the patient groups covered a wide range (2). A subsequent meta-analysis of controlled randomised trials where the resuscitation of albumin had been compared with crystalloids showed no effect of albumin on mortality (3). This outcome was confirmed by a big prospective, randomised, double-blind, multi-centre trial comparing 4% albumin with normal saline in the primary resuscitation of patients in Intensive Care Units (4). The overall conclusion of this study was that, in a heterogeneous group of critically ill patients, albumin given as primary resuscitation fluid is as safe as normal saline. Safety had not been established in patients with brain trauma, but in patients with severe sepsis, albumin may have a benefit. The SAFE study showed clearly that the conclusion of the CIGAR-study could not be confirmed.

Immunoglobulines.

Immunoglobulins are normal constituents of the human body. Intact IgG plays a central role in the immune defence system, predominantly during a secondary antibody response. The antibody spectrum in plasma reflects the immunity status at a given moment, as a result of natural infections and effects of vaccinations. IgG1 and IgG2 are the most common of the four IgG subclasses. The most important biological activities of antibodies are related to their effector functions, aimed at inactivation or removal of infectious agents and their products, e.g. bacteria, viruses and toxins. IgG antibodies exert two ma-

jor effector functions: activation of complement and opsonisation which leads to the induction of phagocytosis. The effector functions, mediated via the constant Fc part, are induced as a result of binding of the variable Fab parts of IgG to the antigen.

The current IVIG products are concentrations of intact IgG molecules with a distribution of IgG subclasses corresponding to that in normal human serum. Some preparations contain a relatively low amount of Ig3, with has no clinical relevance since mainly low IgG2 and IgG4 plasma levels are associated with recurrent upper respiratory infections. Most products contain traces of IgA and IgM. Although IgA may induce severe anaphylactic reactions in patients with anti-IgA antibodies, the number of published cases of this adverse event, which may also occur after treatment with other blood products, is extremely small. The amount of IgA in the product is only of relatively significance, because being an immunological reaction, even a very small trace of IgA may induce this anaphylactic reaction in patients having IgA antibodies. In preventing this adverse event, before each treatment with IVIG the IgA status of the patient should be determined. IVIG also contains trace amounts of soluble CD4, CD8 and HLA molecules and certain cytokines. The half-life of infused IVIG in immune competent persons is 21 days, with inter-individual variations, but in immune compromised patients, the half-life may be shortened because of IgG consumption. The Fc region in IgG allows it to interact with and signal through Fcg receptors on phagocytes, B cells, and other cells as well as with Fc-binding plasma proteins, such as components of the complement system. IVIG is prepared from pooled plasma from 1000-10,000 donations of healthy blood donors. It can thus be assumed to contain the entire array of variable, antigen-binding regions of antibodies of normal serum. The passive immunisation by treatment with immunoglubulin products takes place with immunoglobulin products for intramuscular and/or subcutaneous administration and intravenous immunoglobulin. Some intravenous immunoglobulin products are presented in a lyophilised form, others in liquid form, which is more user and patient friendly. Both presentations have in general the same properties and studies showing a difference in clinical effect between these two presentations have not been published.

Administration of immunoglobulin products in order to reconstitute immunglobulin G (IgG) levels in the plasma of patients with primary and secondary immune deficiencies to normal is an accepted treatment for

several decades. Immunodeficiency can be congenital (genetic) as well as acquired or secondary e.g. as a result of leukaemia or AIDS. Patients with immunodeficiency are unable to produce (sufficient) antibodies, and as a consequence have a weak defence against common pathogens (e.g. bacteria). In these patients, substitution therapy with immunoglobulins reduces the number, the duration and the severity of infections.

In the EU, the following indications of intravenous immunoglobulin are granted:

Substitution therapy:

- Primary immune deficiencies such as a-gammaglobulinemia / hypogammaglobulinemia, common variable immune-deficiency, Wiskott Aldrich Syndrome;
- Secondary immune deficiencies for the treatment of infections based on hypo-gammaglobulinemia by myeloma or chronic lymphatic leukaemia, or for infections in children with AIDS

Immune modulation

- Idiopathic Thrombocytopenia (ITP)
- Guillain-Barré Syndrome
- Kawasaki Disease
- Allogeneic bone marrow transplantation

An important finding was the observation of Paul Imbach, showing that the therapeutic value of IVIG could also be associated with other effects than passive transfer of antibodies alone (5). In the treatment of two immune deficient children suffering simultaneously from serious immune thrombocytopenia (ITP), he noticed that after infusion with IVIG the platelet count increased. This observation could be confirmed by others and following the results with ITP, high dosages of IVIG have been administered in patients suffering from many other immune-haematological disorders, in auto-immune diseases, neurological syndromes and other diseases of the immune system (see table 1). Some of these reports are only case reports; others are the result of randomised-controlled trials (RCT). 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 mechanism, which could explain the therapeutic effect of IVIG, have not been elucidated.

It must be emphasised that the efficacy of intravenous immunoglobulin in a great number of these indications lack sufficient evidence due to the low number of patients with the disease, and the small number of good trials performed. Further some of these diseases are self-limiting and intravenous immunoglobulin might only effective in a certain stage of disease develop-

ment.

IVIG involved no risk of transmitting infectious agents. In 20 years hardly any reports were published about possible disease transmission related to the use of IVIG. All brands of immunoglobulin for intravenous use undergo extensive purification and quality control to eliminate as far as possible the risk of transmission of viral infection. There have been no reported transmissions of hepatitis B virus or HIV infection with IVIG products.

The immediate side effects of intravenous immunoglobulins in humans, like fever, chills, nausea or decrease in blood pressure, are regarded to be mainly caused by IgG polymers, IgA or prekallikrein activator (PKA) in the infused preparation. The reactions include headache, dyspnoea, flushing, myalgia, fever, chills, (low) backache, nausea and vomiting, chest tightness, wheezing, changes in blood pressure and tachycardia.

Severe, but rare side effects after the use of an IVIg product like aseptic meningitis, cerebral vasospasm, thrombosis causing myocardial infarction or pulmonary embolism have been described. Recently three products were involved in an increase of thrombosis events, but at the time of drafting this paper the rout causes were not known yet (6,7). According to the literature, most side effects are related to high infusion rates and dosages administered

For specific virus infections, hyper-immuun immunoglobulin products are indicated such as anti-CMV, anti-hepatitis B, anti-tetanus, anti-varicella zoster, anti-pneumococcus, anti-vaccinia, anti-hepatitis A, anti-rabies, anti-measles, anti-pertussis, anti-respiratory syncytium virus, etc. Rhesus (D) immunoglobulin is the treatment of choice for the prevention of the haemolytic disease of the newborn due to Rhesus (D) antagonism. The hyper-immunoglobulins are produced from plasma with a high titre of a specific antibody and are indicated for the treatment, mitigation or prevention of a specific disease. The plasma for these products is obtained from donors who have a high concentration of these specific antibodies either by natural infection and/or by inducing the endogenous production of these antibodies by immunisation with a specific antigen.

The clotting factors

Haemostatic disorders secondary to plasma factor deficiencies may be congenital as in haemophilia or von Willebrand disease with a lifelong and often family history of bleeding. Specific diagnosis of a single factor deficiency is desirable to permit selection of the most appropriate product such as cryoprecipitate or a concentrate for factor VIII deficiency. The clotting fac-

tors Factor VIII concentrate and Factor IX concentrate which are being manufactured with different purity are indicated as replacement therapy for the treatment of haemophilia A and B, respectively. Several factors determine the choice of concentrate from the many different products available. One of the most important is costs, which varies in different countries as do facilities and arrangements on reimbursement. Therefore cost has a variable impact on haemophilia care. Such variability makes it difficult to analyse fully the effects of concentrate cost on the choice of therapeutic products for haemophilia. The other major factors influencing the clinician's choice are purity and safety.

Very recently, a meta-analysis based on a systematic review examined the incidence rates of inhibitor development in previously untreated patients with haemophilia A treated with either plasma-derived FVIII concentrates or with recombinant FVIII concentrates and explored the influence of both study and patient characteristics (8). Meta-regression and analysis-of-variance (ANOVA) were applied to data from 1,167 patients treated with plasma-derived FVIII and 927 patients treated with recombinant FVIII in 24 studies. The pooled incidence rate of inhibitor development was 14.3% (C.I. 10.4-19.4) for plasma-derived FVIII and 27.4% (C.I. 23.6-31.5) for recombinant FVIII; the incidence rate of high responding inhibitor was 9.3% (6.2-13.7) for plasma-derived FVIII and 17.4% (14.2-21.2) for recombinant FVIII. Using the multi-way ANOVA study design, study period, testing frequency and median follow-up were found to explain most of the variability, while the source of FVIII concentrate lost statistical significance. Thus, it is still unclear whether the plasma-derived concentrate is better than the recombinant concentrate.

Prothrombin Complex Concentrate (PCC which contains factor II, factor VII, factor IX and factor X) is used for the treatment of haemophilia B, if a purified product is not available. However the real indication of PCC is the reversal of vitamin K antagonist in case the International Normalised Ratio (INR) is too high and bleeding or emerging surgery need to be treated. Other single factor concentrates are indicated for the treatment of patients with congenital single factor deficiencies..

Other products

With albumin, imunoglobulins and clotting factor concentrates, the three main products that are manufactured from blood plasma are described. However plasma harbours many more proteins which in a concentrated form could act as therapeutic medicinal product. Alpha 1 antitrypsin for the treatment of patients with alpha 1

antitrypsin deficiency, C1-esterase inhibitor concentrate for patients with hereditary angio edema (HAE), specific clotting factor concentrates (Factor VII-, Factor XIII-concentrate) are as much important. However, due to the limited number of patients worldwide these products deserve the status of orphan drugs and they are not available in most countries.

Future trends

Prophylactic use and home treatment For patients is one of the major trends, the prophylactic use of plasma products which is increasing in the treatment with factor VIII, factor IX, Von Willebrand Factor concentrate, and subcutaneous immunoglobulin, in particular. Home treatment with these products which enables the patient to be more independent and improves the quality of life is increasing. Studies have shown that home treatment has a positive effect on less hospital stay, less absence in school and work, and less invalidation due to the more effective.

New formulations

In order to make the plasma products more easy to use, many research projects are ongoing in this field. Increase of the concentration of intravenous immunoglobulin products from 5% to 10 % and the change from the lyophilised form to a liquid formulation have improved the product significantly. The benefits of a lyophilised product are the long term room temperature stability and the flexibility of the product concentration after reconstitution. The benefit of the liquid products is ease of use. The same improvements apply to intramuscular or subcutaneous immunoglobulin in which developments are ongoing on the increase of the concentration from 16% to 20-25% immunoglobulin. In particular for subcutaneous administration the highest concentration is preferable in order to minimise the pain at the administration site. However it is not clear yet whether and how these changes affect the risk benefit profile of the product in particular regarding the incidence of serious adverse events or long term adverse effects.

Increase half-life in the circulation

With the clotting factor products interesting new developments are the studies on the increase of the residence time of the molecule in the body of the patient which enables the patient to decrease the number of administrations per week. A major challenge is to increase factor VIII half-life in the circulation. For a person with haemophilia, this could imply that the number of prophylactic infusions goes down from three to two or even once a week. One approach is to modify factor VIII protein in its binding sites for the cellular receptors that usually remove factor VIII from the circu-

lation. Studies are ongoing on which receptors are involved in this process and how such improved factor VIII molecules should be designed. Another strategy is based on the use of PEGylated liposome technology to obtain a prolonged survival time of the factor VIII protein (9). The first clinical trials are ongoing and if successful, it would mean a major improvement for patients and family as their lives will be interrupted less frequently. It is not clear yet whether on the increase of the residence the half life of the product is prolonged or whether other mechanisms are playing a role.

Another area of research aims at achieving a higher activity of factor VIII protein. This results in a more potent factor VIII protein that may be used in a lower therapeutical dose and thus may be cost saving.

Potential indications for licensed products

In particular regarding intravenous imunoglobulins, repeatedly new papers are published on new indications for these products on the indications are shown in Table 1.

For fibrin glue / tissue sealant, studies are ongoing on bandages, wound healing, drug delivery (growth factors, cytostatics, antibiotics), cell culturing; for alpha-1-antitrypsin: atopic dermatitis, psoriasis, cystic fibrosis, COPD, asthma; for antithrombin: septic shock; for prothrombin complex: single factor deficiencies, and liver disease

New products

Niche products or service products for specific patients groups are continuously being developed at research laboratories. Some of these products have real potential for up scaling because a market has been found. Others aim for the orphan drug application because the relative rarity of the disease.

Summary

In general, plasma derived medicinal products are important medicines which have a great impact in reducing morbidity and mortality in a great number of diseases. The current products are safer than ever regarding the potential transmission of blood borne diseases. Adverse events reporting show that the products have a great safety profile in particular in comparison with alternatives to blood or plasma products (10). The developments are focussing on increasing diagnosis and treatment, new to the world products, discovering and proving new clinical indications (modulation rather than substitution), treatment of rare diseases, and access to treatment globally. This is an expensive exercise due to the high costs of development, the high costs of clinical trials, and the non harmonised regulating environment which makes the process to marketing authorization complex and sometimes unpredictable. However as

long as the patients continue to raise their voices in order to influence the supply of these products the more efforts will be put in the developments in order to respond positively on these demands.

Abortus (spontaneous)	Multifocal Motor Neuropathy (MMN)
Advanced heart failure	Myasthenia Gravis
Alloimmunisation after transfusion with platelets	Neonatal immune thrombocytopenia
Antiphospholipid antibody syndrome	Parvo-B19 associated anaemia
Autoimmune neutropenia	Post-transfusion Purpura
Alzheimer's Disease	Polymyositis
Asthma	Prevention of graft-versus-host disease
Autism	Pure white cell aplasia
Bullus pemphigus	Recurrent miscarriage
Chronic Inflammatory Demyelinating Poly-neuropathy (CIDP)	Red cell aplesia
Critical Illness polyneuropathy (CIP)	Rheumatoid arthritis
M. Crohn	Rhesus immunisation
Chronic Fatigue Syndrome	Schizophrenia
CMV infection	Sepsis
Dermatomyositis / polymyositis	Stiff Person Syndrome
Diabetes mellitus	SLE
Gold induced thrombocytopenia	Syndrome of Felthy
Graves' Disease	Syndrome of Sjörgen
Hematological coagulation disorders	Systemic lupus erythematodes
Hematological, immunological cellular disorders	Thrombocytopenia after pregnancy
Infections in neonates	Thrombocytopenia in haemolytic uremic syndrome
Inhibitors to factor VIII	Therapy resistant epilepsia in children

Table 1- The list of deseases with reduced mortality and morbidity by using plasma product

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