Making Plasma Derived Medicines Available

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Abstract
Recent progress in past two decades in recombinant technology has created the opportunity of production of some of the plasma proteins including coagulation factors using mammalian cell cultures. However, some limitations including productivity, costs and immunogenic risks have limited worldwide availability of these products. Therefore, fractionation of human plasma still remains as the main source of producing wide range of the therapeutic proteins.
Plasma contains several therapeutically important proteins. Currently more than 25 of them are commercially available to treat life-threatening diseases. However, unfortunately due to very high cost of treatment with plasma-derived medicines, theses are not affordable for the patients living in developing countries. Local production, importation and /or contract fractionation of locally produced plasma are among the available options for providing plasma derived medicines.
Key words: Plasma fractionation, plasma derived medicines, availability

Introduction

Development of fractionation method in 1940s has been of the major milestone in modern health services. Plasma derived medicines are invaluable medicines in management of numerous disease such as bleeding, immunological and metabolic disorders. These medicines have greatly contributed to overall survival of patients. Plasma, the clear protein-rich fluid which is left behind when platelets, red blood cells, and white blood cells are removed from blood, contains therapeutically precious proteins. Plasma proteins constitute around 7% of the blood volume. Although there are more than 300 different proteins in plasma currently only 25 have been recognized for therapeutic purposes and are commercially available and used for

treating the life-threatening diseases or injuries such as bleeding and thrombotic disorders, immunological diseases, infectious conditions as well as tissue degenerating diseases. The most important plasma derived products are coagulation factors, albumin, immunoglobulins, sealants and protease inhibitors.

Plasma protein therapies are still very expensive and considerably inaccessible to the patients living in countries with limited resources available to their health sector. Therefore, today economic status of the nations and not needs of the patients, influence the distribution and usage of these therapeutic products. Although there are some biotechnology-derived coagulation factors available in the market, financial constraints have impeded the access to these products in developing countries.

Coagulating factors including factor VIII (FVIII), factor IX (FIX), von Willebrand's factor, fibrinogen, fibrin sealants (comprising of fibrinogen-rich and purified thrombin concentrates), prothrombin complex concentrate (PCC; mixture of vitamin K dependent coagulation factors including factors IX, II, X, protein C, protein S and sometimes FVII), factor XIII, factor XI concentrate and specific concentrates rich in factor VII with reduced amount of other vitamin K dependent clotting factors are among the most used plasma derived medicines (PDM) around the world [1].

The global market for PDM is a dynamic market growing about 10% each year.

However, it should be noted that North America and Europe with less than 20% of world's population consume more than 75% of the total PDM [2]. Introduction of recombinant coagulation factors in recent decades has created a substantial shift toward use of these products in wealthy nations. It is obvious that successful treatment of patients in need of PDM requires strong support of governments, insurance companies and patient advocacy groups.

Although per capita usage of FVIII worldwide is increasing, the trend is more pronounced in emerging economies. This might indicate improving care for hemophilia patients living in these countries. Between 2002-2007 there was a 35% increase in the number of identified patients and a 63% increase in factor use from 0.80 IU per capita in 2002 to 1.32 IU per capita in 2007. Despite this, it is reported that about 70% of patients with bleeding disorders have not been diagnosed worldwide and only 25% of diagnosed patients receive proper treatment [3].

The past two decades have seen dramatic changes within the global plasma industry. Mergers and acqui-

sitions, the development of recombinant alternatives for existing plasma products, and increasing levels of regulation with respect to product safety are among the most important developments of the field. Arrangements for the collection of plasma, and for its subsequent fractionation, reflect domestic demand together with various economic, demographic and historical factors of countries.

Although, it is reported that over 23-28 million liters of plasma are fractionated each year in the world and about 35% of these amounts of plasma are collected from recovered plasma, it is estimated that at least 5.8 million liters of recovered plasma are destroyed, mainly in developing countries [4]. Global production of plasma for fractionation in 2007 increased by 20% compared to 2005 [5]. However compared to recovered plasma, the role of source plasma in this increase is more pronounced. Although in recent years mainly due to mergers among fractionators, the number of fractionators has decreased while the capacity to process plasma has increased to about 37 million liters per year [3].

In contrary to the conventional pharmaceuticals, production cost of PDM is much higher and estimated to be about 65% of the product price. This is mainly due to the high cost of the raw material. Price of plasma as the main starting material for production of PDM is a major contributor to the final price of PDM. Therefore any attempt to improve quality and safety of the plasma produced in developing countries to be used for fractionation would be considered a substantial step toward improving availability of the PDM in these countries. Production of sufficient quantity of qualified plasma for fractionation is the key element in availability of PDM. Therefore, the main goal should be to use all recovered plasma available in the country, which is very cost effective and can contribute to improve the overall quality of health care services.

It is believed that the new market driver in rich countries is recombinant factors that will diminish economic interest of commercial fractionators to manufacture PD coagulation factors which remain mainstream therapy for patients in developing countries. Therefore these patients might face a decreased supply of factor concentrates and ultimately an increase in price of these products. It is believed that the assumption that decreased use of plasma derived FVIII or FIX in developed countries would increase the supply of products to developing countries may not be economically viable [1]. In fact in this scenario as fractionators will determine price of plasma based on fewer products,

other PDM e.g. IVIG will experience higher prices and hence developing countries will possibly face lower availability of PDM.

Current situation

It is clear that the economic status of nations directly influences quality of the care of patients in need of PDM including those with blood disorders. According to WFH in 2007 more than 5.2 billion IU of FVIII and about 475 Million IU FIX have been used worldwide. However there is a considerable diversity in amounts of coagulating factors used in different countries. Per capita consumption of FVIII is directly influenced by the wealth of the nation. Although usage of 1 IU per capita coagulation factor could provide survival for hemophilia patients it is estimated that to live a normal life, these patients might require much higher factor usage, up to 5-7 IU per capita [5]. In 2007 global per capita FVIII usage in countries with per capita GDP more than 10,000 USD was 3.47 IU which is 11 times more compared to countries with per capita GDP between 2000-10,000 USD and at least 173 times more than in countries with per capita GDP below 2000 USD [6]. However there is a substantial increase in usage of FVIII both in developed and emerging economies. For example only in Russia since 2004 the total consumption of FVIII increased from 32 million IU to more than 463 million IU in 2008. Due to increased usage of recombinant FVIII (rFVIII), especially in developed economics, the share of rFVIII in the global market is increasing. Usage of rFVIII in the world shows a 163% increase while the increase for plasma-derived FVIII in only 15% [3].

Although until the mid 1990s plasma derived FVIII was the driving product for plasma fractionators, the demand for recombinant coagulation factors VIII and IX especially in developed economies and increasing global demand for IVIG has now placed this product as the most important plasma-derived medicines. In 2007 about 82 tons of polyvalent IVIG was consumed worldwide [2]. Providing that prescription of IVIG remains limited to its current medical indications, it has been forecasted that IVIG usage would increase to about 120 tons in year 2012. However, there are some new indications for prescription of IVIG which obviously would dramatically increase the demand for this PDM in the coming years at least in developed economies.

Due to limited resources available for health care services in developing countries, patients in need of PDM should compete with much greater public health priorities such as primary health care, communica-

ble and non communicable disease and child care. Most governments in these countries spend less than 2% of their GDP on health care services. Spending on disease such as hemophilia or other "rare" disease in these countries is unlikely to become first priority. Therefore, patients with "rare" disease living in these countries might be totally ignored by their government. Due to high cost of PDM most patients, especially those who need chronic use of these medicines, would not be able to finance their needs. Therefore several countries both in developed and developing economies with established successful hemophilia care programs have implemented some sort of financial commitment from the government.

Available Options

Currently there are four options available responding to the needs of national health care systems for the PDM. These options will briefly be discussed here.

Local production of PDMs.

Local production of plasma either through blood banks (recovered plasma) and/or plasmapheresis (source plasma) creates the opportunity for local production of PDM. Although this seems lucrative, there are serious considerations surrounding this approach. In past decades several countries both in developed and developing economies, in an attempt to reach self sufficiency in PDM, have established local facilities for plasma fractionation. These facilities are mostly funded by governments. However, later due to concerns regarding cost-effectiveness of such facilities and more importantly, safety of products prepared, these facilities discontinued their activities. Later, developments in the field of transfusion have emphasized that the presence of an accountable national transfusion service is an essential component of any plasma collection and fractionation activities either as local production or contract fractionation activity. Therefore, self-sufficiency in plasma production depends heavily on the presence of an accountable blood transfusion service.

Local production of PDM could create the highest level of security for availability of PDM. However, this approach needs both a substantial investment and access to the know how for preparation of these medicines. Therefore only few countries, mostly developed countries, have pursued this option. Recently some countries in developing world have also implemented long term policies in plasma handling which may conclude in establishing a national facility for plasma fractionation. It is obvious that a viable local plasma fractionation facility could not only

create the greatest degree of security for availability of PDM for the national market but may also be taken as a sign of national pride in these countries.

Although lower cost of production of locally manufactured PDM is one major reason for promoting this option, it should be noted that mass production of some PDM especially factor concentrate by multi national fractionators has substantially reduced price of commercially available factor concentrates. This may reduce economic feasibility of establishing local fractionation facility.

Importation of PDM

Decision makers of national heath care system should decide whether to use the available resources for importation of PDM or investing on developing infrastructure for local production of such medicines. Importation of PDM and especially plasma derived coagulating factors which are now available commercially at about 0.15-0.25 USD per IU could provide prompt access to these medicines. However, even with minimum factor use, treating one hemophilia patient will cost at least several thousands USD per year. Much higher costs attributed to treatment of patients in need of IVIG with current price of about 40-60 USD per gram, will impose significantly higher burden on both patient and national health care system.

Although importation of PDM, whenever resources are available, might look the easiest approach for availability of these medicines it could also create some serious problems. Worldwide shortage of these medicines and limited resources available in countries' health care system makes this approach far from ideal. In case of global shortage most of the national authorities give priority to their own market and will put some restrictions on exportation of the medicine. Therefore, importing countries have to struggle to sustain availability of such products for their patients. On the other hand brand switching of imported PDM could also result in undesirable effects on patients and clinicians.

Contract Fractionation

Another successful approach adopted by many countries both in developed and developing economies for provision of PDM is contract fractionation of plasma produced in their national transfusion services. Plasma contract fractionation is a program in which local plasma is sent to the fractionator and end products are returned to the country of the plasma supplier.

Although plasma recovered from blood donations could be a main source for production of PDM, not meeting the standards imposed by the regulators is a major cause for discarding recovered plasma produced in transfusion services. Therefore any investment on national blood service quality assurance system for improving standards of the plasma recovered in blood centers could be considered as a significant mean to improve national availability of PDM. Before implementation of a plasma fractionation program some operational changes in the national transfusion systems are necessary. Epidemiological surveillance of the donor selection, implementation of an information system, donor screening and traceability, blood/plasma collection procedures, screening tests and plasma freezing and storage and preparing plasma mater file are among the most important aspects of a national program intending to meet the international standards. Obviously such operational improvements will have positive impacts on the quality and safety of blood components [7-8].

Before starting any contract fractionation activity the economic balance of the whole program and its cost-effectiveness should be carefully evaluated. In order to do so, the main elements of cost contributing to such program should be taken into account. Some of the main elements include cost of plasma collection including donor recruitment, serology and NAT testing of donations, costs attributed to plasma storage, fractionation charge per unit of product made, shipment of the products back to the country of origin, plasma product registration, marketing/ sales expenses and administration and overhead charges.

Following are the main advantages of a contract fractionation program:

- improving national blood and/or plasma collection system through enforcement of standards required for plasma production to be suitable for fractionation
- the source of the plasma and its level of quality is known
- surplus of the recovered plasma produced in national transfusion system will not be wasted
- provides a fairly rapid access to the PDM
- provides a relatively secure approach for access to PDM even during global shortage of PDM
- does not need capital investment
- flexibility for selection of the fractionator

However before putting plasma contract fractionation on the table of a national health system it should be

kept in mind that a reliable and well organized national transfusion, preferably centralized, system should be in place and a real cost estimation should be considered. While negotiating with the fractionators to finalize the agreement a range of topics including source of plasma supply, plasma volume, duration of the agreement, product profile and characteristics should be considered. Yield, particularly for IVIG is an important parameter and should be given close consideration while negotiating contract fractionation agreement.

A plan for picking up and transferring of plasma produced in collection points across the country to the central warehouse should be arranged. A reliable cold chain for transferring plasma from collection centers throughout the country and its shipment to the fractionator site is mandatory for any contract fractionation plan.

From both economic and logistic aspects, most likely transfer of large volume of the plasma for contract fractionation by airfreight to the fractionator site is not feasible. Therefore land and/or sea shipment are the most practical options. However, the fact that it may take several weeks to ship plasma consignments to the fractionator site, advanced planning is necessary in order to avoid any delay for receiving back produced PDM. However, the return of produced PDM from fractionator site by airfreight should always be considered as the first option. This will significantly reduce the turnaround period between plasma shipment and availability of PDM produced from national plasma.

Contract fractionation could also create some difficulties. Any technical problems in the fractionator site might seriously impair national availability of PDM, if a contingency option is not in place. The activity may also create hostility from PDM importers and they may cause resistance toward prescription and use of produced medicines through complaints of some physicians and patient groups.

Any contract fractionation activity should be evaluated periodically and its impact on affordability of PDM in national market assessed. Although several countries, both in developed and developing economies, are using the plasma contract fractionation approach to meet their national needs for the PDM, only few have reported its economical impacts on their health care system [7, 9-10].

Combined approach

Availability of the PDM in the national market should be influenced by the clinical needs of the patient and not by the capacity of the contract

or local fractionation project. Therefore many countries have adopted a combined approach to supply their national market with PDM. There are very few countries worldwide which are self sufficient in plasma production and PDM. Therefore, combined approach including importation, local production and/or contract fractionation would be the most practical way for accessibility to PDM.

Although PDM market is currently dominated by multi-national fractionators based in developed economies there are still a few countries in the developing world which still have a national plasma fractionation plant. However, these countries are still not self sufficient and they either have to import some PDM or do not fully respond to the patient needs to PDM.

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