Plasma-derived medicinal products self-sufficiency from national plasma: to what extent?

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Introduction

Achievement of self-sufficiency in blood and plasma products from voluntary non remunerated healthy donors has been advocated by WHO in a resolution dating back nearly 40 years[1,2] and it is the current basis for the collection of blood in almost all European countries; in Italy, self-sufficiency obtained through donations from volunteer donors, not only in labile components but also in plasma products, is an aim stated by the legislation[3]. Is self-sufficiency from national plasma a practice goal for Italy and, if so, to what extent is it feasible? In this paper we will try to analyse some factors that can contribute to answer the question: the origin of plasma for fractionation and the rate of collection, the influence of production processes, the products for which self-sufficiency would be advisable and the policies for an appropriate utilisation of plasma products.

Present situation and future trends in Italy

The topic has been extensively covered elsewhere[4] but some data need to be summarised here, because they represent the consequence of the concept of "self-sufficiency" *tout-court*. With 768,435 litres of plasma collected in 2012, Italy is the third European country for volume of plasma fractionated (following Germany and France) and the fractionation rate is 12.3 L/1,000 population; there is a pronounced difference across the country between regions collecting up to 22 L/1,000 population plasma for fractionation (mainly in the North) and others collecting less than 4 L/1,000 population (mainly in the South). The Italian blood supply system relies on contract manufacturing for the fractionation of plasma collected in the blood transfusion centres. Altogether, the fractionation of Italian plasma covers around 60% of the internal demand for albumin and around 80% of that for intravenous immunoglobulin (IvIg), the remaining part relying on the market.

Italy registers the highest consumption of albumin in the world (600 g/1,000 population), two-three fold (but up to seven-eight fold for some regions) higher than European countries of the same socio-economic level. On the contrary, the present use of IvIg is consistent with the European average (60 g/1,000 population), but significantly lower than the United States and Canada (140 g/1,000 population) and France (100 g/1,000 population). As for coagulation Factor VIII (FVIII) utilisation, the value of 7 I.U. *per capita* is similar to that of Australia, United Kingdom and Germany, but, in contrast with Germany where plasma derived product is around 50% of total consumption, in Italy recombinant products represent the large majority (80% of total consumption). As to Antithrombin III (ATIII), with 2 I.U. *per capita* Italy is the second highest consumer in the world after Japan (3 I.U. *per capita*), two and six-fold higher than Germany and France, respectively.

It must be underlined that, due to the ethical principle stated by the Italian blood legislation ("self-sufficiency from national voluntary non remunerated blood donors in blood components and plasma products") plasma collection in Italy tends ideally to cover the production of the driving biological product, thus leading to a significant excess of production of other proteins. At present, FVIII, and other coagulation factors are extracted in excess, but since the Italian legislation prohibits selling on the market products coming from voluntary non-remunerated blood donation, added to the fact that the adhesion of Italian blood centres to European Medicines Agency guidelines regarding the regulation of blood and plasma collection is still partial, it is not clear now what will be the destiny of these products.

Assuming for the country a positive trend of 3% yearly increase in plasma collection (the value reported during the last 5 years), a decrease in the inappropriate use of albumin and AT III (due to educational programmes enforced by the National Blood Centre) and an increase in the use of IvIg, following the international trend but at a prudential value of 110 g/1,000 inhabitants, we can speculate that the fractionation of national plasma in 2023 will reach approximately 1 million Kg (around 17 L/1,000 inhabitants, assuming the stability of Italian population). This will still be insufficient for IvIg self-sufficiency but will generate a substantial excess of all the remaining plasma products currently covered by the national plasma programme, i.e. Albumin, FVIII, FIX, Prothrombin Complex Concentrate (PCC), and AT III (Table I). The prospect is even worse if a higher IvIg use is anticipated, due to the approval of the product for Alzheimer's disease treatment[5].

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Table I - Self-sufficiency in albumin, intravenous immunoglobulin, coagulation factor VIII and factor IX + prothrombin complex concentrates and Antithrombin III in Italy from national plasma: provisional data 2013 and trend in 2018 and 2023 (*see text*).

	2013		2018		2023	
	Production	**Use**	**Production**	**Use**	**Production**	**Use**
Plasma (kg)	791,000		917,000		1,063,000	
Albumin (tons)	19.5	33 (550 g/1,000)	22.3	24,5 (400 g/1,000)	25.4	22 (350 g/1,000)
IgIv (tons)	2.86	3.9 (65 g/1,000)	3.76	5.2 (85 g/1,000)	4.36	6.8 (110 g/1,000)
FVIII (IU)	108,000,000	100,000,000	123,000,000	110,000,000	140,000,000	120,000,000
FIX+PCC (IU)	37,000,000	35,000,000	42,000,000	40,000,000	48,000,000	45,000,000
AT III (IU)	118,000,000	120,000,000	135,000,000	95,000,000	154,000,000	80,000,000
	Difference (2013)		**Difference (2018)**		**Difference (2023)**	
Albumin (tons)	–13.5		–2.2		3.4	
IgIv (tons)	–1.0		–1.4		–2.4	
FVIII (IU)	8,000,000		13,000,000		20,000,000	
FIX+PCC (IU)	2,000,000		2,000,000		3,000,000	
AT III (IU)	–2,000,000		40,000,000		74,000,000	

Legend IgIv: immunoglobulin for intravenous administration; FVIII: factor VIII; I.U.: international units; FIX: factor IX; PCC: prothrombin; AT III: antithrombin III.

This scenario will be realised while increasing the plasma collection (whatever the driving product) unless there is the adoption of corrective measures represented by the use of market derived product for a variable part of the driver, a better technology for fractionation, a global strategy for utilisation of excess products abroad, a strict clinical control of the use, or a combination of all these.

The origin of human plasma

Worldwide, the collection of the raw material (human plasma) is managed both by public and private organisations. In the case of public blood establishments, plasma is generally obtained from whole blood collected by transfusion services for the preparation of labile blood components; in this case, plasma is regarded as a by-product and, provided that a good quality system is in place in the blood establishments, then plasma can be fractionated by pharmaceutical industries. However, the amount of plasma separated from whole blood exhibits huge variations in Europe. In the 2008 (final version) report of the Council of Europe on blood collection and use in the reporting Member States (MS) of Europe[6], an average yield of 8.5 L (range 0-56 L) per 1,000 inhabitants is reported of plasma for fractionation into medicinal products and 5 of 31 responding MS (16%) deliver 15 L or more plasma for fractionation per 1000 population.

A recent report[7] emphasises that only countries with both unremunerated and remunerated plasma collection collect more than 30 L per 1,000 population (Austria 56, Czech Republic 33, Germany 31 L/1,000 population), consistent with the production of the IvIg amount required to meet the actual demand in the majority of western countries[8]. Thus, as to the origin of plasma for fractionation, it appears that plasma derived medicinal products made from both non-remunerated and remunerated donations are currently essential to meet global health requirements and in this respect, cooperation between blood establishments and the plasma industry is important to ensure that the best community outcomes are achieved including sufficiency of supply for patients[9]. However, since remuneration of donors is forbidden by the Italian legislation, this part of supply can only come from imported plasma, to be further fractionated in Italy, or imported medicinal products.

Whenever the need for whole blood derived labile components decreases, as a consequence of policies strongly advocating their optimal use[10,11] also the amount of recovered plasma decreases, thus jeopardizing the achievement of self-sufficiency in plasma products. This happened in recent years in Denmark, where the implementation of policies for the rational use of red cell transfusion reduced the use of red cell concentrates from more than 70 to less than 50 units/1,000 population[12], at the same time reducing the amount of recovered plasma to be fractionated under contract manufacturing by CSL Behring (Bern, Switzerland).

In order to obtain more source material, some MS have promoted the collection of plasma by apheresis, with different yields (in Europe, on average 55% of the plasma for fractionation is from recovered whole blood, with a wide variability, while it is calculated that in the world this percentage lowers to 30-40%[13]). However, due to the costs, many countries are reluctant to increase the collection of apheresis plasma and even France, a country in which for many years the blood establishments increased the number of plasmapheresis collections to

ensure self-sufficiency in plasma products[14], has recently questioned the feasibility of this policy, leading to a decrease in plasmapheresis procedures[15].

In Italy, according to the Italian National Blood Centre report[4], total plasma from apheresis (plasma and multi-component apheresis) represents around 25% of all raw material. Red cells are transfused in the country at a rate of 41.4 units/1,000 inhabitants and the country is self-sufficient for red cell transfusion; thus, no increase in the amount recovered plasma can be expected, because there is no need to increase whole blood collection and this implies that any further increase in plasma collection must come from apheresis. This, however, presents problems related to the fragmentation of plasma collection in Italy in a great number of collection units and to the costs of apheresis plasma. In a comprehensive report by the Italian Society of Apheresis and Cell Manipulation (SidEM) and the Italian Society of Transfusion Medicine and Immunohematology (SIMTI), the two Italian scientific societies acting in the field of blood transfusion and apheresis[16], the number of plasma collections by apheresis recorded in Italy in 2009 was on average 7.9/1,000 population. The number of plasmapheresis procedures/cell separator/year (productivity index) was 319 at national level, with decreasing indexes from Northern to Southern Italy (North 417, Centre 255, South 123), corresponding to around one procedure/separator/day, which is clearly not cost-effective. This is the reason why in Italy plasma by apheresis holds a very high cost; indeed, in a survey performed on 12 Italian blood establishments by the National Blood Centre, this cost has been calculated to be on average € 302/kg[4], while, according to an evaluation performed in Veneto Region in 2011 (using a different methodology published elsewhere[17]) this cost accounts for € 423/L (Breda A, personal communication, presented at "*Il sistema sangue in Italia: criticità e risorse nella cura dell'emofilia - The Italian Blood System: criticalities and resources for the haemophilia care*" Vicenza, 5 June 2013). Both values are clearly higher than the average cost of apheresis plasma, which is calculated at around € 130/L (personal communication from commercial sources). A profound re-organisation of plasma collection in blood establishments would be required, leading to a more rational utilisation of equipment and staff, in order to decrease the cost of collection, making it cost-effective and, to some extent, closer to the commercial value.

Whole blood collection aimed at an evidence-based target for red cell requirements cannot lead to a sufficient production of plasma for the actual use of plasma products but no programme of increasing plasmapheresis can be realised without a re-organisation of plasma collection in Italy.

Characteristics of products and technology

Factors related to the products can greatly influence self-sufficiency achievement. Firstly, the number of plasma proteins is incomparably larger than that of labile blood components; the most widely used of those products (such as albumin and IvIg) are produced by all the manufacturers, while others (mainly low-volume products or special products), due to intellectual property rights issues and the economies of scale, are manufactured by only one or few producers. Hence, for the large majority of countries, self-sufficiency cannot be guaranteed for all products either because of lack of technology or lack of raw material. For instance, in the majority of European countries, where immunisation of D negative healthy donors against D antigen is not practiced, anti-D immunoglobulin can only be imported or must be produced from imported plasma.

Secondly, the yield of proteins is largely dependent on industrial technology. So, from one litre of plasma, whether source or recovered, a fractionation plant can produce, according to generally agreed production yields, 25 to 28 grams of albumin, 150 to 200 international units of factor VIII (or more, if the source plasma is frozen immediately after collection), 250 to 300 international units of factor IX, 3 to 5 grams of intravenous immunoglobulin, 250 international units of antithrombin, 0.20 grams of alpha-1 anti-trypsin, and, if a sufficient antibody titre is provided, various amounts of hyper-immune globulin products. It is easy to see that there are differences in the yield of products and, for some of them (notably IvIg and FVIII), this difference can be very important (also two-fold) depending on the producer's technology[18]. Thus, in order to meet the same demand for IvIg, the amount of raw plasma required can double, depending on a process yield of 5 g/L or 2.5 g/L.

Finally, sources of products other than plasma may have a profound influence on plasma need. The demand for intravenous/subcutaneous immunoglobulin has multiplied by 2.5 between 1996 and 2011 in Europe and that of FVIII has multiplied by 3.1. However, unlike FVIII, supplied by recombinant products, the increase in IvIg demand required an increase in plasma collection. Recombinant therapy has largely reduced the demand for anti-haemophilia coagulation factors, particularly FVIII, from the plasma supply, and it is expected that recombinant products will continue to substitute the plasma-derived product[5]. Plasma-derived coagulation proteins (particularly FVIII) will continue to be extracted in very significant amounts from the plasma necessary for immunoglobulin needs, putting them at risk of "wastage" (such as Australia's systematic discard of approximately 80×10^6 I.U. yearly[8]) unless a global strategy is designed for their utilisation in countries lacking the resource for treatment of patients. In fact, despite an impressive progress in closing the global

gap, still too few haemophilia patients receive adequate treatment throughout the world[19].

However, when considering coagulation replacement therapy, there are no reasons justified by evidence to consider recombinant products safer and more effective than plasma-derived medicinal products. As to efficacy, all products should be considered interchangeable, provided that appropriate therapeutic dosages and regimens are issued to patients[20]. With regards to safety, no case of blood-borne viral transmission has been documented in haemophilia patients since the late 1980s to early 1990s[21]. In recent years, a more frequent occurrence of inhibitors to FVIII has been often reported when using recombinant products in haemophilia care, although a recent meta-analysis[22] failed to confirm the statistical significance of this increased incidence. Also with respect to inhibitor development, plasma-derived FVIII must be considered at least equivalent (if not safer) than recombinant products[23]. A definite answer on this topic will come from the ongoing "survey of inhibitors in plasma-product exposed toddlers" (SIPPET) study[24].

In summary, advanced pharmaceutical technologies leading to an optimal yield in the fractionation process, together with a "global" perspective for utilisation of excess product and an evidence-based choice of products in clinical care, can help the "national self-sufficiency" programme.

Policies for an appropriate use of plasma products

Plasma-derived pharmaceutical products are used to treat a variety of life-threatening diseases and serious medical conditions and therefore plasma products contribute in major ways to life and health. Nevertheless, lessons learned by the blood borne spread of HIV and hepatitis viruses in the past have enforced the concept that a competent blood regulatory authority assures that appropriate standards are met for production of blood products and monitoring of blood safety[25]. This is not sufficient, of course, because quality of transfusion is the cumulative result of different activities along the transfusion process going "from vein to vein". In this chain, monitoring of the appropriateness of the use of products is a point of paramount importance and must be implemented by continuous education of the professionals[26].

Based upon WHO expert group definition[27], self-sufficiency in safe blood and blood products means that the national needs of patients for safe blood and blood products, as assessed within the framework of the national health system, are met in a timely manner, that patients have equitable access to transfusion services and blood products derived from voluntary non-remunerated blood donors. However, in common practice the term "need" is often used as equivalent to "demand", which is frequently also confused with the actual "use" of a certain product. Thus the terms "need", "demand" and "use" must be clearly defined, since the extent of self-sufficiency of plasma products would ideally depend only on the "appropriate demand" of plasma protein therapies. Based upon WHO definitions agreed in an expert's draft report on estimation of blood requirements in May 2010[28] and adapted to the plasma products, the "Use" can be defined as the actual amount of a product currently transfused by a defined number of facilities over a defined period of time and the use may be appropriate or inappropriate; thus, we have to avoid considering it as the driver for plasma collection. The "Demand" is the amount of a product required to meet all confirmed requests for that product at a defined number of facilities over a defined period of time. The "Need" is the amount of product required to transfuse all individuals who require that product in a defined population over a defined period of time.

In this context, it is our opinion that self sufficiency of plasma products from national plasma should be expected only in relation to the appropriate demand for products, under guidelines accepted by professionals and scientific societies. To ensure this result, clinical audit of plasma product utilisation must become common practice in healthcare institutions. Clinical audit is the most widely used tool for evaluation of proper use of scarce resources, as blood products certainly are. Clinical audit is a process that can be defined as "a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change"[29]. The key component of clinical audit is that performance is reviewed (or audited) to ensure that what should be done is being done, and, if not, it provides a framework to enable improvements to be made. It has been formally incorporated in the healthcare systems of a number of countries and there are many available resources to support the successful implementation of clinical audits[30,31].

In the field of plasma products, efforts have to be made in the future in order:

- to monitor product utilisation in clinical settings and to identify evidence which supports the use of blood products in different clinical situations, with the aim of establishing or reinforcing guidance for their appropriate use;
- to identify key performance indicators useful to document and to evaluate the appropriateness of use of products and to build up indicators capable of correlating the observed-to-expected ratio of use with the case-mix of the healthcare institutions, with the aim of continuous improvement of the prescriber practice;

- to identify factors capable of predicting the trends in utilisation, in relation to data on healthcare activity, in order to predict the need for transfusion resources and to lead to a better planning of plasma collection and to the ability to prevent both shortage of products and their unnecessary use[32].

Conclusions

From the considerations described here, it is clear that the number of countries having real potential to be totally self-sufficient for all products from national plasma is very limited and might be equal to zero. A more useful approach is that of a "global" provision of plasma proteins, to avoid limitations on the treatment of patients, both in terms of choice and in terms of supply, since availability of plasma products in the national market should be determined by the clinical needs of the patient and not by the capacity of the local fractionation project[33]. Therefore, a combined approach including national production by contract fractionation and importation (either plasma source or manufactured proteins) would be the most practical strategy for accessibility to plasma derived medicinal products[34]. As a consequence, the concept of "self-sufficiency" must be more precisely specified to guarantee a proper utilisation of nationally collected plasma, an ethical use of the donations, an appropriate clinical use of plasma products, an adequate provision of medicinal products to patients and, finally, a cost-effectiveness of the national plasma programme.

Contract manufacture programmes must, of course, endorse the technology with the most favourable yield, mainly in the driving product, in order to obtain the maximum allowed amount of driver product with the minimum required volume of plasma. Whenever products from origins other than human plasma become favourable in risk-benefit, cost-effectiveness and/or health technology analysis, they must be used instead of the plasma derived ones. Provided that the collection of plasma for any driving product will inevitably generate significant amounts of other products (e.g. coagulation proteins), programmes must be in place to guarantee the availability of these latter to countries where insufficient therapeutic products are delivered to patients, while recovering manufacturing costs, as allowed by the Italian legislation.

Optimal use of blood products is of paramount importance in the field of transfusion. Hence, the clinical use of the products must be controlled (either by regulatory agencies or by scientific societies) by means of programmes of appropriate use, attaining self-sufficiency from national plasma for the approved indications of use and possibly leaving to the market supply the fluctuation in the use due to indications still under investigation. However, as soon as the new indications have been incorporated into accepted clinical practice, product availability must be guaranteed to patients and the national programme for plasma collection must be modified accordingly.

In summary, technological and scientific advancements in the field of plasma biologicals use and their real or hypothetical benefit in clinical practice provide a pressure to increase collection of plasma, but ethical (the unique origin of plasma) and economical (the costs of collection) reasons require us to reach a compromise. It is the role of the transfusion medicine specialist to act giving the best possible advice to both donor associations, clinical doctors, regulators and companies to balance these sometime cooperating and sometime conflicting tendencies[35].

Keywords: plasma, plasma-products, self-sufficiency, clinical governance.

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