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Self-sufficiency in Italy**

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sufficiency in Italy**

ABSTRACT

Until 2014, in Italy domestic plasma toll fractionation, done only by one company, have been limited in accessing different technologies and products and in cost competition; now four companies have been identified as competitive fractionators: CSL Behring, Kedrion, Grifols, Octapharma and Shire. Following the tenders, in 2017, four companies acted as competitive toll fractionators of a total of 821.437 Kg of plasma collected in four partnerships of Italian regions. The higher yield granted by fractionators increased IgG production (from 11 % up to 41 %) significantly contributing to decrease market dependence, although the continuous rise in demand will still require market compensation. The decrease of albumin use (-2,6 % 2015 vs. 2014) is probably due to a better control on an impressively high (and inappropriate) demand (35,4 tons and 582 g/1000 population in 2015, highest in the world) but more must be done in this direction through clinical audits. Plasma derived Factor VIII demand is still higher than potential production (137.994.500 IU vs 1.061.496 IU) but, since all therapeutic options must be guaranteed to patients, domestic plasma cannot serve as the unique source of FVIII. The new tenders also allowed the enlargement of the basket of products; at present, the amount of domestic plasma collection is in large excess than that required for the national self-sufficiency of Factor IX, Prothrombin complex concentrates, Antithrombin, Fibrinogen and a-1-antithrypsin. In conclusion, competition resulted in better yields of Albumin and Ig, decreasing level of market dependence, an increase in the basket of plasma derived products, and a decrease in cost for fractionation (20 to 30 %), thus significantly contributing to national self-sufficiency.

Keywords: plasma, plasma-products, self-sufficiency, toll manufacturing, competition

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Introduction

More than 40 million litres of human plasma are needed every year in the world for all PDMPs, which are not more than 20 families of bioactive molecules.

In Italy, toll manufacturing is, by law, the only possibility to fractionate into medicinal products plasma collected and tested by the blood establishments from voluntary non remunerated donors (VNRDs) (Legge 21 ottobre 2005, n. 219); the reasons for this are different: supply of medicinals can be maintained during shortages or for security reasons, the source of plasma is known, leftover plasma from blood transfusions is not wasted, there is an improvement of the blood collection system due to the stringent quality system of pharmaceutical production and the use of national products is privileged; in the contract, all products are delivered back to the Country and a long-term partnership is established with the company.

In this paper we try to evaluate the effective contribution of medicinal products from toll manufacturing of domestic plasma to their national self-sufficiency and to explore some scenarios expected in Italy in the next years.

Materials and Methods

With 830.257 kilograms (kg) of plasma collected in 2017, Italy is the second European country for volume of plasma fractionated (following Germany and together with France) and the fractionation rate is 13,7 kg/1000 inhabitants (Italian National Blood Center, unpublished data). However, there is a pronounced difference in the country between regions collecting up to 22 kg of plasma per 1000 inhabitants and others as low as 4 kg/1000 inhabitants. This discrepancy is at the origin of a Ministerial Decree (Ministero della Salute Decreto 02 dicembre 2016) planning the improvement of plasma collection, through the maintenance of a good performance in high productivity regions while increasing production in the low performance areas, as to reach a rate of plasma collection of 16-17 kg/1000 inhabitants within 2020.

As to the origin of plasma, around one fourth comes from plasmapheresis but the majority comes from the processing of whole blood donations; this amount is expected to decrease in the next years, as the clinical use of red cells as well as whole blood donations, are decreasing.

The main feature of the Italian toll manufacturing is that plasma from blood establishments is sent to a pharmaceutical company which is paid for fractionation in a separate cycle and for distribution to the Regions of all medicines derived from the process. There is not a unique national tender but one region runs the contract on behalf of many others, a partnership needed to reach adequate volumes of plasma to be fractionated, estimated between 150.000 and 250.000 kg of plasma per year, in order to guarantee a continuous production and distribution of PDMPs; smaller volumes may give technical and economical drawbacks, as small batch sizes may have to be processed and

the regular supply of products can be compromised. On the other hand, larger volumes restrict the number of companies with sufficient capacity and require contingency plans to reduce risks of product shortage in case of problems at the fractionation plant (The World Federation of Hemophilia, 2008).

The characteristics (population, state of the tender, cost and present fractionator) and data on plasma collection in the 4 groups of Regions (kg total and standardized /1000 inhabitants) for 2017 are presented in table 1 and table 2.

While in the past only one pharmaceutical company was allowed to fractionate Italian plasma, now, after modifications of Italian regulations (Ministero della salute Decreto 12 aprile 2012 and Ministero della salute Decreto 5 dicembre 2014) agreements are in place involving four partnerships among different Italian regions and different fractionators: ACCORDO group, the NAIP (Nuovo Accordo Interregionale Plasma) group, the PLANET (PLASma NETwork) group and the RIPP (Raggruppamento Interregionale Plasma Produzione) group.

Data presented in table 2 demonstrate that the four agreements have contracts in place with different yields and different costs. In general (and as expected) the new tenders gave more favorable results, granting more product with a lower cost of the service. This is an intended result, because of the present heavy dependence on the market of Italian use in driving products (albumin and immunoglobulins).

Albumin

Actual production of albumin in Italy is not in line with the average use of the product in the European Union: in 2015, the standardized demand per thousand inhabitants was 582 grams (Candura F. et al., 2015), confirming that Italy is the first consumer in the world of this protein and its domestic production covers only 60 % of the demand. The national plan for self-sufficiency states that “a use of albumin exceeding 400 kg/million inhabitants must be considered inappropriate” (Ministero della Salute Decreto 02 dicembre 2016) and actions are required from the health authorities to set the use below this limit. To ensure this result, clinical audit on plasma product utilization must become common practice, as to promote an appropriate demand. In regions where projects aiming at monitoring albumin demand have been implemented, use of albumin fell from more than 400 to less than 300 kg/million inhabitants, thus allowing albumin self-sufficiency (De Angelis V, Tillati S, 2012).

Intravenous (Iv) and subcutaneous (Sc) Immunoglobulins (Ig)

Although rapidly increasing also in Italy, their use is consistent with the European average but significantly lower than in the United States and Canada (from 150 up to 200 g/1000 inhabitants) (Robert P, 2016). At the yield of 3,7 g Ig per kg of plasma the production was insufficient to cover use in 2015 and only 71 % of Ig used in Italy came from domestic source. New tenders resulted in a relevant increase in the yield of Ig in plasma fractionation: it rose from 3,7

to 4,1 (RIPP) and 4,9 (NAIP) g/kg granted at minimum by the contract, Therefore, the increased yield allowed the NAIP consortium to reach self-sufficiency for Ig and an 80 % rely on domestic plasma in the RIPP consortium.

It's our opinion that the combination of an increased plasma collection and strict control on appropriate use could provide self-sufficiency for albumin in Italy and, at present, this result has been reached at least in one group of Italian regions.

However, as to the Immunoglobulins, assuming an increase in their demand in line with the international trend, we can speculate that also a production of national plasma for fractionation of approximately 1 million kg will still be insufficient for Ig self-sufficiency in Italy.

Antithrombin III

With 2 I.U. per capita, Italy is the second highest consumer in the world (Candura F et al, 2015) after Japan (3 I.U. p.c.). Nevertheless, plasma for labile proteins production collected just in one partnership of regions would have the potential - at the yield of 360 IU/kg - to meet all the national need of AT, even in the presence of this very high demand.

Plasma-derived Factor VIII and Factor IX

The use of 7 I.U. of Factor VIII per capita is similar to that of Australia, UK and Germany, but in Italy recombinant products represent 80% of total consumption (Candura F et al 2015, Abbonizio F et al, 2015). The extended half-life products, a bispecific antibody mimicking the coagulation function of FVIII and inhibition of anticoagulation proteins with antibodies, aptamers or RNA interference technology, are likely to change in the next years hemophilia A treatment and pd-FVIII is not a first choice therapy in Italy (Balkaransingh P et al, 2018, Franchini M, Mannucci PM 2018, Pasca S et al, 2018). The need of plasma derived Factor IX (pd-FIX) is rather low (Candura F et al, 2015) and, at a yield of 256 IU/kg (as granted by Kedrion), few lots of production are needed to satisfy the national demand of 12.367.700 IU pd-FIX, corresponding to 0,2 IU per capita, registered in 2015.

Other Products

Demand for prothrombin complex concentrates, corresponds to 0.6 IU per capita and the use of Fibrinogen and a-1-antithrypsin is rather low (Candura F et al, 2015); for all these products, national self-sufciency can be ensured from the volume of plasma collected in any of the four partnerships of Regions taking over the duty of fractionating these products for all the Country (Grifols Investors Meeting 2018, Godier A 2018).

Data on plasma (Kg) needed to meet the actual demand for accessories products supplied by companies fractionating Italian Plasma are presented in Table 3.

Discussion

At present, contract manufacturing in Italy is facing a promising development. Before the possibility of a competition among companies, many limits affected the vitality of toll manufacturing: there was no possibility to access different technologies for improving yield of some products, there was an unique basket of products, the exchange among Regions was limited to few surplus products and there was no cost competition for the service, thus limiting the exploitation of the therapeutic potential of plasma from Italian VNRDs. With the opening to competition, an improvement in the national self-sufficiency program took place.

The National Health Service has now access to a wider basket of PDMPs manufactured from plasma of Italian donors and the use of domestic plasma in several industrial processes offers to the patients the right of accessing many products which would need otherwise a regular supply from the market.

Probably the most important result of the new tenders is the increased yield in driving proteins (mainly immunoglobulins). It has to be remembered that globally, Ig represent over 50% of total expenditure for PDMPs and their demand is constantly increasing (EU Commission 2017, Perez EE 217).

For the less used products, any of the four partnerships of Regions can take over the task of the production of one protein to meet the demand of all the Country: a critical mass of plasma between 150.000 and 250.000 kilograms per year is in line with the availability of accessory products in the amount yearly required in clinics for pd-FVIII/vWF, pd-FIX, PCC, AT, Fibrinogen and a-1-antithrypsin. At present, at least two mechanisms are in place to favor national exchange of products:

- 1) “Pay the products”. The possibility of exchanging products coming from contract manufacturing among Regions is laid down in an “ad hoc” national regulation (Accordo Stato-Regioni 2015) and the process for this is simple: Regions needing PDMPs from toll manufacturing can access the warehouse of other Regions with surplus products and buy them. Fees of the products are as follows: albumin 1,9 €/g, Ig 35 €/g, pd-FVIII € 0,23/IU, pd-FIX 0,23 €/IU, PCC (3 factors) 0,24 €/IU, AT 0,225 €/IU.
- 2) “Pay the process”. In this case, an agreement is made among Regions with a surplus of intermediates and other lacking a product: the intermediate of the process is gifted by the surplus Regions, while the Regions with inadequate supply pay the pharmaceutical Company only for the production process, thus accessing, at a low cost, the final product although lacking the raw material.

Beside these advantages, we must also underline the improvement of quality system in blood establishments and monitoring product utilization in clinical settings which is now a promising development of the national blood program.

Table 1. Main Characteristics of the 4 Groups of Regions

Partnership	Population (total, % Italy)	Tender	Fractionator	Plasma for fractionation 2017 (kg)	% Italian production	kg/1000 inhabitants 2017
NAIP (Abruzzo, Basilicata, Friuli V.G., Liguria, Trentino -Alto Adige, Umbria, Valle d'Aosta, Veneto)	11.661.971 (19 %)	concluded	CSL BEHRING	194.993	23%	16,7
RIPP (Emilia-Romagna, Calabria, Puglia, Sicilia)	15.534.498 (26 %)	concluded	KEDRION & GRIFOLS	207.879	25%	13,3
PLANET (Toscana, Campania, Lazio Marche, Molise)	17.328.149 (29 %)	in progress	KEDRION (previous contract)	182.019	22%	10,3
ACCORDO (Lombardia, Piemonte, Sardegna)	16.064.827 (26%)	in progress	KEDRION (previous contract)	245.366	29%	15,3
ITALY	60.589.445			830.257		13,7

Table 2. Plasma Production, Protein Yield (Ig and albumin), Products Demand and Rate of Self-sufficiency in the Four Partnerships of Regions

Partnership of Regions and Fractionator	Price for fractionation /Kg	Yield (g/Kg)		Demand 2015 (g)		Plasma for fractionation 2017 (Kg)	Plasma needed for self-sufficiency Kg		Present % Self Sufficiency	
		albumin	Ig	albumin	Ig		albumin	Ig	albumin	Ig
NAIP (CSL Behring)	€ 96,04	25,0	4,9	5.105.358	931.743	194.933	204.214	190.152	95%	103%
RIPP (Kedrion/ Grifols)	€ 118,00	26,0	4,1	8.880.723	1.093.923	206.067	341.435	266.810	60%	77%
PLANET (Kedrion old contract)	€ 144,00	25,7	3,7	11.984.644	1.416.880	181.135	466.329	382.941	39%	47%
ACCORDO (Kedrion old contract)	€ 144,00	25,7	3,7	9.404.018	1.191.762	245.126	365.915	322.098	67%	76%
ITALY				35.374.743	4.634.308	827.321	1.377.893	1.162.000	60%	71%

Table 3. Plasma (Kg) needed to meet the Actual Demand for Accessories Products supplied by Companies Fractionating Italian Plasma

Products	Theoretical Yield/Kg	Demand 2015	Plasma needed to meet the demand (Kg)
* FVIII and FVIII-vWF(IU)	130	137.994.500	1.061.496
\$ Pd-FIX (IU)	256	12.367.700	48.311
\$ PCC (3 factors) (IU)	336	36.562.200	108.816
\$ AT (IU)	360	128.888.000	358.022
# Fibrinogen (g)	0,9	24.248	26.942
# a-1-antithrypsin (IU)	0,152	23.335	153.520

* depending from the origin of plasma (apheresis or recovered) and resulting from an average yield from both

\$ Best yield (Kedrion)

Grifols Investors Meeting 2015

Conclusion

The ethical principle on self-sufficiency based on VNRBDs stated by the Italian legislation, requires a proper utilization of national plasma, an ethical use of the donations, an appropriate clinical use of plasma products, an adequate provision of medicines to patients and, finally, a cost-effectiveness of the national plasma program (De Angelis V, Breda A, 2013, O'Mahoney 2012) Importantly, opening the competition among different companies for domestic plasma toll fractionation has shown the potential to give a significant progress toward self-sufficiency of PDMPs from VNRDs in Italy.

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