Plasma derivatives and strategies for reaching self-sufficiency in Liguria: the role of the Transfusion Medicine Service of the Gaslini Institute

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Introduction

Since 2002, the Region of Liguria has been part of the Interregional Agreement on Plasma Derivatives (AIP) stipulated among some Regions of north Italy with the aim of contributing to self-sufficiency of the interregional system through exchanges between the facilities lacking products and those with an excess.

In Liguria, the management of plasma derivatives is entrusted to the Regional Centre for Co-ordination and Compensation (CRCC) which, with strategies of compensation, tries to guarantee that the needs for plasma derivatives are covered in the hospitals in its territory.

The Services of Immunohaematology and Transfusion Medicine (SIMT) have a goal of increasing the production of plasma in order to participate actively in achieving regional self-sufficiency.

Methods

The SIMT of the G. Gaslini Institute introduced some strategies aimed at reaching this goal. The increase in the number of donations made with a cell separator, the introduction of multicomponent donations of plasma and platelets and the collection of high concentration platelet concentrates led to a considerable increase category A plasma sent for fractioning. Finally, the implementation of shared guidelines on the use of blood components enabled the clinical use of the plasma collected to be kept under control.

Results and conclusions

The analysis of the trends of consumption of the most widely used plasma derivatives showed an increase in the overall demands, which can be attributed to the paediatric focus of our hospital and to its highly specialised wards.

On the basis of the industrial technical yield, it was possible to calculate the theoretical coverage of the requirements for plasma: this highlighted a better theoretical coverage for albumin but a shortfall of intravenous immunoglobulins. The amount of plasma necessary to meet the theoretical needs was calculated for each plasma derivative, revealing that the derivative requiring the greatest volume of plasma is intravenous immunoglobulins. This finding confirms the change in the “driving product”: it is now the consumption of intravenous immunoglobulins that determines the amount of plasma that is sent for industrial processing.

Key words: plasma production, blood derivatives.
Regions on the basis of the amount of plasma supplied by each one of them.

The primary purpose of the Agreement is to combine the efforts of the individual members, in a unanimous and synergistic way, in order to contribute to reaching the priority goal, established by law n. 219/05 and its subsequent modifications and integrations, that is, national self-sufficiency. Once internal self-sufficiency has been guaranteed, each participating region is committed to contributing to the self-sufficiency of the interregional system, through exchanges between the facilities lacking products and those with excesses.

Being part of the AIP carries economic and organizational advantages both in relations with the pharmaceutical industry and in interregional relations among the Regions adhering to the Agreement. The AIP:
- guarantees greater negotiating power and, therefore, better conditions, with respect to single Regions, with the pharmaceutical industry, that produces drugs derived from the industrial processing of plasma;
- encourages exchanges of blood derivatives between Regions with excesses and those with shortfalls of products at costs lower than market prices;
- guarantees, through the contribution of plasma conferred by each Region, the constant availability of blood derivatives also for Regions that are not able to confer sufficient volumes of plasma for autonomous formation of batches for industrial transformation, thereby limiting these Regions’ recourse to the commercial market;
- imposes the standardisation and use of the same production processes (selection of donors, stages of processing and storage, tracking procedures), contributing to the definition of the Plasma Master File (PMF), which is obligatory for safer and more reliable production of blood derivatives;
- may foster a more extensive sharing adoption of guidelines on the use of blood components and close monitoring of the requests from wards, to limit the clinical use of plasma.

Methods

Strategies for increasing the production of plasma to send for industrial fractionation

Until 2002, plasma in our SIMT was obtained exclusively from two sources: productive plasmapheresis (for category A plasma) and whole blood (for category B plasma and a minimal proportion of category C plasma). Three possible areas of intervention were identified:
- an increase in the plasmapheresis procedures;
- changing the collection of platelets into multicomponent donations of plasma and platelets and, subsequently, the introduction of procedures to collect high-concentration platelet concentrates to increase the volumes of plasma yielded in each procedure;
- the introduction of guidelines on the good use of blood components and close monitoring of the requests from wards, to limit the clinical use of plasma.

Analysis of the production and internal consumption of plasma

The data on the production of plasma in the SIMT of the Gaslini Institute in the period 2001-2005 were analysed (volume of each category of plasma), as well as the data relating to the proportion of plasma sent for industrial processing and the proportion retained for clinical use.

Analysis of the consumption of plasma derivatives and of the percentages of theoretical cover of the requirements

The data relating to the consumption of plasma derivatives most widely used in the wards in our hospital (albumin, intravenous IgG and antithrombin III) were analysed.
Plasma derivative self-sufficiency in Liguria

On the basis of the yields of each derivative produced per litre of plasma, defined by the pharmaceutical industry in agreement with the AIP (Table I), we calculated the amounts of plasma derivatives obtained from the volume of plasma sent for industrial processing. We, therefore, obtained the percentage theoretical coverage of requirements for each blood derivative guaranteed by the plasma production of the SIMT and identified the derivative whose requirements define the amount of plasma that must be sent to the industry to guarantee internal self-sufficiency.

Table I - Industrial technical yields of plasma derivatives

<table>
<thead>
<tr>
<th>Derivative</th>
<th>Albumin</th>
<th>I.V. IgG</th>
<th>Antithrombin III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma A</td>
<td>25 g</td>
<td>2.9 g</td>
<td>250 UI</td>
</tr>
<tr>
<td>Plasma B</td>
<td>25 g</td>
<td>2.9 g</td>
<td>-</td>
</tr>
<tr>
<td>Plasma C</td>
<td>25 g</td>
<td>2.9 g</td>
<td>-</td>
</tr>
</tbody>
</table>

Results

Strategies introduced

Starting from the second half of 2002, attempts were made to increase the number of plasmapheresis procedures through a reorganisation of the system in the blood donation room; after 6 months, this organisational model was suspended because of the negative repercussions observed in the management of the blood donations. Other strategies of this type are currently not possible.

However, thanks to new cell separators, since September 2003 it has been possible to replace the collection of platelets by apheresis by multicomponent donations of plasma and platelets, without this causing significant reductions in the yields of platelet collections.

In the two years 2004-2005, the mean volume of plasma from plasmapheresis was increased slightly, by modifying the programme of the cell separators. In September 2006, the collection of high-concentration platelet concentrates began, leading to a significant increase in the volume of plasma collected.

In December 2004, the Committee for the Good Use of Blood approved guidelines on the use of blood components. Thanks to these guidelines, a more rigorous control of the requests for plasma for clinical use was possible. In contrast, internal guidelines, approved by Committee for the Good Use of Blood, on the use of albumin, intravenous immunoglobulins and antithrombin III are still not available, although they have been the subject of discussion and debate for some time now.

Plasma production

The analysis of the data for the period 2001-2005 showed a considerable increase in the volume of plasma produced (Figure 1): the production increased from 1,560 litres in 2001 to 1,720 and 1,730 litres in 2002 and 2003, respectively; there were further increases in production in 2004 and 2005, reaching 1,830 and 1,890 litres of plasma, respectively. From the destination of the plasma that, after the validation process, enters the distribution circuit, it can be seen that during the 5 years considered, the volume of category B and C plasma did not vary significantly, ranging between 1,008 and 1,096 litres a year. In contrast, the increase in plasma from apheresis (plasma A) sent for industrial fractionation was constant and appreciable, passing from 267 litres in 2001 to 508 litres in 2005.

The observed increase was not, overall, related to the increase in the number of apheresis procedures which, particularly in the three years 2003-2005, was basically stable and lower than the values in the preceding two years (Table II), but rather, could be attributed to the optimisation of the collection procedures carried out using cell separators. Finally, it can be seen that during the period studied, the volume of plasma used for clinical purposes remained relatively steady (Table III and Figure 2).

This evaluation of the production of plasma in the Region of Liguria enabled a quantification of the role played by the SIMT of the Gaslini Institute within the Region: during 2005, our Institute collected 8% of the total regional collection (Figure 3) of plasma from ordinary donations and 16% (Figure 4) of the plasma collected by cell separators.
Table II - Productive apheresis procedures carried out in the SIMT

<table>
<thead>
<tr>
<th>N. of plasmapheresis procedures</th>
<th>N. of plateletpheresis procedures</th>
<th>N. of plasma-plateletpheresis procedures</th>
<th>Total n. of productive apheresis procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001 882</td>
<td>922</td>
<td>0</td>
<td>1,804</td>
</tr>
<tr>
<td>2002 1,041</td>
<td>874</td>
<td>0</td>
<td>1,915</td>
</tr>
<tr>
<td>2003 727</td>
<td>288</td>
<td>671</td>
<td>1,686</td>
</tr>
<tr>
<td>2004 808</td>
<td>0</td>
<td>975</td>
<td>1,783</td>
</tr>
<tr>
<td>2005 866</td>
<td>3</td>
<td>887</td>
<td>1,756</td>
</tr>
</tbody>
</table>

Table III - Distribution of plasma (in litres) in the period 2001-2005

<table>
<thead>
<tr>
<th>Total plasma distributed</th>
<th>Plasma for clinical use</th>
<th>Class A plasma sent for industrial fractionation</th>
<th>Class B+C plasma sent for industrial fractionation</th>
<th>Total plasma sent for industrial fractionation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001 1,520</td>
<td>245</td>
<td>287</td>
<td>1,008</td>
<td>1,275</td>
</tr>
<tr>
<td>2002 1,619</td>
<td>286</td>
<td>308</td>
<td>1,025</td>
<td>1,333</td>
</tr>
<tr>
<td>2003 1,621</td>
<td>250</td>
<td>360</td>
<td>1,011</td>
<td>1,371</td>
</tr>
<tr>
<td>2004 1,774</td>
<td>290</td>
<td>461</td>
<td>1,023</td>
<td>1,484</td>
</tr>
<tr>
<td>2005 1,864</td>
<td>260</td>
<td>508</td>
<td>1,096</td>
<td>1,604</td>
</tr>
</tbody>
</table>

The overall normalised needs, obtained by summing the specific needs, are also represented graphically.

As can be seen from this latter graph, the overall requirements are increasing constantly (with a mean annual increase of about 6%), even if the specific requirements for each plasma derivative are obviously dependent on the population of patients in the corresponding year.

In particular, it can be seen that in 2002, the maximum relative need for intravenous IgG (8,445 g) corresponded to the minimum requirements for both albumin (34,190 g) and antithrombin III (386,000 U.I.); similarly, in 2004, a minimum relative need for intravenous IgG (6,476 g) corresponded to maximum requirements for both albumin (44,000 g) and antithrombin III (550,000 U.I.).

Covering the needs

Starting from the industrial technical yields (Table I), it is clear that the increased production of plasma in our SIMT improved the theoretical coverage of the need for albumin, which increased from 82.6% in 2001 to 91.6% in 2005.

The data on intravenous IgG were less comforting: the theoretical coverage of needs, which in 2001 was 61.4%, decreased to 54.2% in 2005 (Table V).

As far as concerns antithrombin III, we calculated that 23.9% of the requirements were covered in 2005. It should be noted that this is a partial result in that...
Figure 3 - Pie chart of the production of plasma from ordinary blood donations in the Region of Liguria in 2005

Figure 4 - Pie chart of the production of class A plasma from apheresis in the Region of Liguria in 2005
Table IV - Consumption of plasma derivatives by the Gaslini Institute

<table>
<thead>
<tr>
<th>Year</th>
<th>Consumption of albumin (g)</th>
<th>Consumption of intravenous IgG (g)</th>
<th>Consumption of antithrombin III (UI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>36,580</td>
<td>6,024</td>
<td>405,000</td>
</tr>
<tr>
<td>2002</td>
<td>34,190</td>
<td>8,445</td>
<td>396,000</td>
</tr>
<tr>
<td>2003</td>
<td>43,290</td>
<td>7,830</td>
<td>388,000</td>
</tr>
<tr>
<td>2004</td>
<td>44,000</td>
<td>6,476</td>
<td>550,000</td>
</tr>
<tr>
<td>2005</td>
<td>43,762</td>
<td>8,579</td>
<td>530,500</td>
</tr>
</tbody>
</table>

Table V - Theoretical coverage of the requirements of plasma derivatives

<table>
<thead>
<tr>
<th>Year</th>
<th>Albumin</th>
<th>Intravenous IgG</th>
<th>Antithrombin III</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>82.62%</td>
<td>61.38%</td>
<td>23.94%</td>
</tr>
<tr>
<td>2002</td>
<td>97.47%</td>
<td>45.78%</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>79.18%</td>
<td>50.78%</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>84.32%</td>
<td>66.45%</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>91.63%</td>
<td>54.22%</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5 - Requirements for albumin, intravenous IgG and antithrombin III, normalised to 2001 levels. The virtual overall requirements, calculated as the sum of the three products, is also reported, again normalised to 2001 levels.

Discussion

In line with the national plan for reaching self-sufficiency in plasma derivatives, the SIMT of the Gaslini Institute for children defined a plan to increase the volume of plasma to send for industrial fractionation as an objective of its Quality System. This led to the definition of new procedures for both production and clinical use of plasma. The increase in plasma production was obtained without compromising the primary objective of the SIMT.
Fig. 6 - The number of litres of plasma necessary to meet the demands for albumin, intravenous IgG and antithrombin III over the years studied.
that it is mainly the consumption of intravenous IgG that determines the amount of plasma to be sent for industrial processing.

Precisely because of its widespread clinical use, the goal of meeting demands for intravenous IgG is difficult to achieve, since it would require an annual increase of about 1,350 litres in the production of plasma, which is equivalent to about 84% of the current production. If such an aim were to be reached, it would be of great financial importance, given that the cost of intravenous IgG is much higher than that of albumin. It should be remembered that the greater productive efficiency, achieved in 2005-2006, by the company that processes the plasma, with the current yield of intravenous IgG being 3.1 g/L, could contribute to greater availability of the product, without lowering the level of purity of the drug.

As far as concerns antithrombin III, the problem of the low theoretical coverage of requirements (23.94%) derives from the fact that this drug is produced only from class A plasma. At a regional level, this makes Liguria dependent on the production in other regions belonging to the AIP, which collect a larger number of donations with cell separators.

In order to contribute to self-sufficiency in plasma derivatives, it is essential to implement regionally-based strategies and, in some circumstances, interregional ones. These strategies must take into account factors related to the type of population of the donors, logistical aspects and agreements between the Associations that promote the donation of blood. For this reason the role of the intra and extra-regional co-ordination, defined by law (Legislative Decree. 219/05), is fundamental.

Conclusions
The analysis of the data collected leads to the conclusion that, although the production of plasma in the last four years has increased and the consumption for clinical use has remained roughly stable, the volume of plasma sent for industrial processing is insufficient to meet the requirements for plasma derivatives: this is particularly obvious for intravenous IgG, which are heavily requested.

The optimisation of plasma production will never be sufficient to cover the notable increase in the consumption of intravenous IgG in our Institute: it is, therefore, extremely important to evaluate whether the increased requests are due to an increase or improvement in health care services delivered, or whether they are due to inappropriate consumption of these plasma derivatives. In the light of the most authoritative international recommendations, collaboration with clinicians is essential in order to optimise the use of plasma products and must have the concrete outcome of the production of guidelines and the control of the appropriateness of the requests.

In fact, the good use of plasma derivatives, achieved by following appropriate guidelines, has obvious implications for the safety of transfusions, but also has clear financial consequences.

The SIMT of the Gaslini Institute, thanks to its rationalisation of plasma production and optimisation of the consumption of plasma derivatives and plasma for clinical use, is participating actively in the attempt to reach regional self-sufficiency. Nevertheless, the CRCC is essential in order to evaluate the various realities in the regional context.

References