The first data from the haemovigilance system in Italy

Adele Giampaolo, Vanessa Piccinini, Liviana Catalano, Francesca Abbonizio, Hamisa Jane Hassan

Reparto di Metodologie Transfusionali, Dipartimento di Ematologia, Oncologia e Medicina Molecolare, Istituto Superiore di Sanità, Roma, Italy

Introduction

The clinical risk of transfusions is perceived predominantly as the risk of acquiring infectious diseases. In reality, over the last 20 years, the incidence of transfusion-related transmission of diseases has decreased significantly, thanks to ever greater attention given to the stages of selecting donors and screening the units collected. The real transfusion process, mostly carried out in hospital wards and operating theatres, tends to be less considered, but now needs to be monitored to increase the safety of the whole process. Errors related to the identification of the patient, of the sample test-tube and of the blood component expose patients to risk and, in some cases, increase the risk of mortality.

From the monitoring of the adverse reactions due to transfusions, reported by countries in which a haemovigilance system has been active for some time,
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it can be deduced that immunological adverse events, transfusion-related acute lung injury (TRALI) and errors in the transfusion process are much more likely than infections transmitted by transfusion of blood components. The ultimate purpose of haemovigilance, defined as the surveillance of unexpected or adverse reactions in donors and recipients and as epidemiological surveillance in donors, is to prevent the repetition of adverse events and reactions\(^1\). In fact, the information obtained from haemovigilance systems can contribute to improving the safety of blood collection and transfusion by: a) supplying the medical community with a valid source of information about the risks related to transfusion; b) indicating corrective measures to prevent the repetition of some accidents or dysfunctions of the transfusion process, including particularly significant ones, such as samples taken from the wrong person, mistaken identification of the sample, errors in the request form, and blood transfused to the wrong person; c) alerting the hospital wards and Transfusion Structures (TS) about adverse events that could involve several patients, such as those related to the transmission of infectious diseases and to the collection and processing of the blood.

In Europe, the first haemovigilance systems were activated in France in 1994\(^2\) and in the United Kingdom in 1996\(^3\), although these two systems differ greatly. The former is obligatory and requires notification of adverse events of all degrees of severity; notification of near miss errors (that is, errors recognised before the transfusion) is voluntary. The latter system is voluntary and collects information on severe adverse reactions, transfusion errors and near miss errors. Since Directive 2002/98/EC came into force, the introduction of haemovigilance systems has become a priority for all countries in the European Community.

In Italy, the surveillance of adverse events in recipients was activated at the end of 2004 by the National Institute of Health (Istituto Superiore di Sanità - ISS)\(^4\). There were already systems for monitoring adverse reactions in some Regions\(^5\); at a national level, efforts were made to guarantee the homogeneity of the data collected by using the same forms. The proposed form for national surveillance was designed by Transfusion Medicine specialists and agreed upon through consultatory meetings with representatives of the Regional Centres of Co-ordination and Compensation (Centri Regionali di Coordinamento e Compensazione – CRCC). Subsequently, dedicated software was developed, based on the paper form. This software, called PETRA (Programma degli Errori Transfusionali e delle Reazioni Avverse – Programme for Transfusion Errors and Adverse Reactions), was distributed by the ISS to all TS. Participation in the haemovigilance system was not obligatory, but was strongly recommended by the institutions (ISS and CRCC).

The assimilation of Directive 2002/98/EC of the European Parliament and Council of Europe, during 2005, has made the notification of severe unwanted reactions and incidents obligatory: “Whatever severe incident, whether due to an accident or an error, related to the collection, control, processing, storage, distribution or assignation of blood or blood components, which could influence their quality and safety, as well as any severe unwanted reaction observed during or after a transfusion which could be related to the quality and safety of the blood and its components, or to human error, is notified to the region or autonomous province involved, which, in its turn, notifies the ISS” (article 13 in\(^6\)).

The Italian system of haemovigilance is substantially in line with the European Directive, although it lacks the surveillance of adverse or unexpected events in donors and registration at a national level of severe incidents related to the collection, processing and storage of blood and blood components, which could have effects on the quality and safety of the blood component. In the future, changes should be made to the current national haemovigilance system in order to render it conform with the new requisites. Epidemiological surveillance of donors was started at a national level in 1989 for HIV and in 1999 for HBV, HCV and Treponema pallidum. This monitoring enables estimations of regional and national prevalences and incidences of the major transfusion-transmissible infections and also enables evaluation of the residual risk of such infections\(^7\).

The collection and analysis of data on undesired effects of transfusion rely on a close collaboration between the TS, which supply the blood components, and the hospital wards. This collaboration is essential, in order to ensure complete investigations of every unfavourable event. The Committee for the Good Use of Blood, by involving all the professional figures

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dealing with blood", could represent the context in which to spread the culture of haemovigilance, making collaboration between TS and hospital wards more possible.

**Methods**

The collection of haemovigilance data is the responsibility of the 326 Italian TS distributed throughout the country and located within hospitals.

Inside the TS, blood is donated, tested and processed to produce the blood components, that are then sent to the wards; the TS must then receive, from the doctor who uses the transfusion therapy, documentation on every transfusion and any adverse reactions (article 15, paragraph 3). The TS store and manage the information, filling in the computerised PETRA form for every case identified. The records are periodically sent to the CRCC, which then transmit the regional data to the ISS. The data collected can be used at local, regional, national and international levels.

The haemovigilance system calls for the registration of immediate transfusion reactions (haemolysis, TRALI, bacterial contamination, anaphylactic shock, etc.), late effects (haemolysis, graft-versus-host disease (GvHD), post-transfusional purpura, etc.) and transfusion of wrong blood components.

The system is also designed to collect information on near miss errors, that is, mistakes recognised before the transfusion, which could have led to the transfusion of a mistaken blood group or the registration, collection or management of a wrong, inappropriate or unusable blood component.

The information required by the PETRA notification form are those considered minimum by Recommendation R(95)151, that is: (a) date of birth, sex and identification code of the patient transfused; (b) number of the units and identification codes of the blood components involved in the adverse event; (c) description of the type of blood component, its method of preparation and the conditions and duration of storage of the blood component prior to its transfusion; (d) severity of the event, reported according to a graded scale (mild symptoms, long-term morbidity, immediate threat to life, death); (e) imputability, that is, the relation between the unfavourable effects observed and the blood component transfused, using a graded scale.

The PETRA forms sent by the Region of Piemonte are filled in electronically, interfacing the PETRA software with that of the "Form for recording adverse events of transfusion therapy", used by the Region.

The incidence of adverse events was calculated based on the number of units of blood components distributed, which is monitored by the National and Regional Register of Blood and Plasma.

**Results**

**Survey of adverse events in 2005**

In 2005, the percentage of the 326 Italian TS that participated in the haemovigilance survey was 38.4%, which was almost double that in 2004 (21.0%). This percentage also includes the TS that did not use PETRA and those that stated the absence of adverse reactions.

Table I reports the percentage participation in 2004-2005. The regions in which all the TS participated in 2005 survey were Friuli-Venezia Giulia, Liguria, Lombardia, the Marche, Piemonte, the Autonomous Province of Bolzano and Valle d’Aosta; the coverage in military TS was 100%. The rate of responses was high in Lazio and Veneto.

Considering the number of units of blood components distributed in 2005 by the TS, which were included in survey (1,834,474), the system monitored 49.6% of the units distributed in Italy (3,701,724) (Figure 1).

In 2005, there were reports of 1,495 adverse reactions, 823 of which were reported using a summary data sheet other than PETRA, such that, in most cases of events notified, a description of the causative role of the transfusion in the adverse reaction was not given.

Overall, 0.8 reactions were reported every 1,000 units of blood components distributed.

Almost all the adverse events reported were acute: 46.9% of the reactions were febrile type reactions and 38.7% were of an allergic nature (urticaria and anaphylactic reactions). Only six delayed type adverse reactions were reported: four late haemolytic reactions, one case of GvHD and one HIV infection (Figure 2).

The collection of data carried out with different methods by the structures that participated in the haemovigilance system in 2005 was not homogenous and did not enable further analysis.

Table I - Participating Transfusion Structures

<table>
<thead>
<tr>
<th>Region</th>
<th>2004 (%)</th>
<th>2005 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abruzzo</td>
<td>7.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Basilicata</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Calabria</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Campania</td>
<td>0.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Emilia Romagna</td>
<td>0.0</td>
<td>25.1</td>
</tr>
<tr>
<td>Friuli Venezia Giulia</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Lazio</td>
<td>14.7</td>
<td>58.3</td>
</tr>
<tr>
<td>Liguria</td>
<td>90.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Lombardia</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Marche</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Molise</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Passone</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Puglia</td>
<td>8.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Sardegna</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Sicilia</td>
<td>36.4</td>
<td>33.3</td>
</tr>
<tr>
<td>Toscana</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Autonomous Province of Bolzano</td>
<td>25.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Autonomous Province of Trento</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Umbria</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Valle d’Aosta</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Veneto</td>
<td>31.6</td>
<td>63.2</td>
</tr>
<tr>
<td>Military structures</td>
<td>0.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Figure 1 - Monitoring of the blood components distributed –2005
Overall, 986 forms were returned (Table II), of which 871 reported adverse reactions and 63 reported near miss errors or errors; 52 forms could not be evaluated (Figure 3A).

In 848 of the forms, the adverse reaction was attributed to the transfusion; in 65% of these (n=555) the association with the transfusion was stated to be strong (certain or probable cause); only these were taken into consideration for the analysis (Figure 3B).

As far as regards the severity of the reactions, these caused mild symptoms in 65.8% of the reported cases and long-term morbidity in 31.9%, were life-threatening in 2.1%, and led to death in 0.2%. Figure 4 shows the severity of the reactions in the events in which the transfusion was probably or certainly the cause of the reaction. The only death was due to an acute haemolytic reaction caused by ABO incompatibility. Life-threatening events were anaphylactic reactions (n=5), volume overload syndrome (n=2), TRALI (n=1), febrile reaction (n=1), urticarial reaction (n=1) and reactions defined as "other" (n=2).

Almost all the adverse reactions reported were acute; only three were delayed (late haemolysis). As regards the type of reaction, 46.4% were of an allergic nature (urticaria and anaphylactic reactions) and 33.9% of a febrile type (Figure 5).

The type of blood component involved in the adverse reactions was reported in 92.9% of the cases of which 72.1% were whole blood products, 15.2% were red cells, 12.7% were platelets, 0.1% were plasma, 0.01% were cryoprecipitate and 0.01% were leukocytes.

**PETRA 2004-2005**

**Adverse reactions**

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(n=516), in which the transfusion was stated to be probably or certainly the cause of the reaction: red blood cells in 374 reactions, platelets in 73, fresh-frozen plasma in 53, whole blood in 5 and stem cells in 11.

Errors

There were 16 notifications of errors, concerning transfusions given to the wrong patient: the transfusions were ABO incompatible in 56% of the cases, Rh incompatible in 6% and not specified in the other 38% of the cases. The cases notified were errors of identification of the patient and/or sample test-tube: in one case, the sample used for the request was taken from a different patient; in another case, the error was caused by the patient having the same name as another patient, already registered in the TS archives; in one other case, the transfusion request, related to another patient, was not checked; in the other cases, the error was caused by not correctly identifying the patient in
the ward at the time of the transfusion. In the six reports in which the patients’ outcome was described, one patient died, three had no consequences and two had mild symptoms.

Near miss errors

There were 47 reports of near miss errors, that is, errors recognised before the transfusion. Six of the forms did not report the type of error that had occurred, the other forms described, for the most part (75%), errors occurring in the wards at the time of taking the samples, errors in filling in the identifying data on the test-tube, and errors in completing the request form.

The other 25% of the reports concerned errors occurring in the TS at the time of accepting the request and the samples, when issuing the units, and when conducting serological tests in the laboratory. Table III presents the various types of near miss errors in detail.

Discussion and conclusions

This study, the first Italian report on the notification of adverse reactions to transfusions, refers to years 2004 and 2005 and concerns about 50% of all blood components distributed in the nation.

In this first analysis of national haemovigilance data it was considered useful to analyse both the PETRA forms that were received and the summary data-sheets (concerning only the type of adverse reaction) supplied by those regions, which, in compliance with Italian legislation, had already set up a system for recording transfusions and notifying adverse reactions. These different systems of reporting did, however, lead to a lack of homogeneity in the notifications, thus enabling only a partial analysis of the events notified. A more detailed analysis was possible only of the PETRA forms.

The notification form was designed by transfusion medicine specialist and agreed upon consultatory meetings with representatives of CRCC and other components of the transfusion system. Health care managers were informed of the new haemovigilance system by the ISS and invited, as presidents of the Committees on the Good Use of Blood, to spread the culture of haemovigilance and to encourage wards, in which blood products are used, to notify an adverse events occurring after a transfusion.

In 2005, 1,495 adverse reactions were notified, including those reported by TS not using PETRA. The TS participating, including those which declared no transfusion reactions, had distributed 1,834,474 units of blood components. Therefore, the reported rate of reactions was 0.8/1,000 units. This is undoubtedly an underestimate, given that the French system has consistently recorded about 3 adverse reactions/1,000 units of blood components since 1998.

The percentage of notifications varied greatly from region to region. The scarcity of notifications (under-reporting) is a problem in all haemovigilance systems and can have various causes: the adverse reaction and/or its relation with the transfusion is not always recognised; when it is recognised, the importance of notifying it is not accepted as a tool to improve transfusion safety; staff may be afraid of disciplinary action in the case of notified errors.

Almost all the adverse events notified were acute reactions, since only five delayed reactions were notified. An almost complete lack of recording of late reactions (delayed haemolytic reactions, GvHD, post-transfusional purpura, viral, bacterial and parasitic

Table III - Description of near miss errors

<table>
<thead>
<tr>
<th>In the ward</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample taken from wrong person</td>
<td>36%</td>
</tr>
<tr>
<td>Errors in data identifying the test-tube</td>
<td>12%</td>
</tr>
<tr>
<td>Incomparability between data on request form and on test-tube</td>
<td>17%</td>
</tr>
<tr>
<td>In the Transfusion Structure</td>
<td></td>
</tr>
<tr>
<td>Exchange of samples</td>
<td>10%</td>
</tr>
<tr>
<td>Error during the stage of accepting the request in the management system</td>
<td>2.5%</td>
</tr>
<tr>
<td>Mistaking one patient for another</td>
<td>2.5%</td>
</tr>
<tr>
<td>Error in serological test in the laboratory</td>
<td>2.5%</td>
</tr>
<tr>
<td>Issue of wrong units</td>
<td>2.5%</td>
</tr>
<tr>
<td>Preprinted unit belonging to another patient sent to another TS</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

infections, haemochromatosis) was reported. In France, these reactions represent 35% of all the adverse events reported.

The lack of agreed definitions negatively affects data collection. For example, it would be useful to have shared diagnostic criteria for TRALI, which is a transfusion reaction that is difficult to diagnose, because the symptoms can be very different and there is not a specific diagnostic test. TRALI is included as an adverse reaction in the United Kingdom haemovigilance system [Serious Hazards of Transfusion (SHOT)] which, between 1996 and 2004, reported 162 cases, of which 36 were fatal; of these, 13 were considered probably or certainly due to the transfusion. In France, this adverse reaction was not diagnosed until 2002 (although it was, perhaps, sometimes reported as volume overload). After an effort of the haemovigilance system to improve the diagnosis of this reaction, TRALI is now better identified and studied. In 2003, 15 cases probably or certainly due to transfusions were identified, of which three were fatal. Only one case of TRALI was reported in the Italian system, leading to the suspicion that there is underreporting of this reaction, perhaps due in part to the difficulty in its diagnosis.

The types of transfusion reactions were febrile in 46.9% of the cases and allergic (urticaria and anaphylactic reactions) in 38.7%. The analysis of only those cases, in which the transfusion was certainly or probably causal, notified with the PETRA system, showed opposite proportions of these two pathologies: 46.5% of the reactions were of an allergic nature and about 34% were febrile-type reactions. These percentages are in line with data reported by other haemovigilance systems.

The promotion of a different culture, in which notifying errors is in some way fostered, is a fundamental step in any attempt to identify and tackle system defects in the transfusion chain. Errors and near miss errors (the latter being more frequent) represent failures in the system and by analysing them, critical points to be kept under control can be identified.

It has emerged from the reports on haemovigilance in France and the United Kingdom that transfusional errors leading to ABO-incompatible transfusions require great attention. Up to 2002, the French haemovigilance system only recorded ABO incompatibilities that had a clinical effect; the notification of clinical grade 0 errors was introduced only subsequently, as an instrument to achieve improvements, even in the absence of adverse reactions.

In Italy, as in other countries, a transfusion reaction due to ABO incompatibility is considered a sentinel event, which can and must be prevented. “Recommendations for the prevention of transfusion reactions due to ABO incompatibility” has been issued by the Ministry of Health (Office III – Quality of activities and services – General Management of Health Care Planning, levels of care and system ethical principles).

The regions of Veneto and Emilia Romagna were particularly active in notifying errors and near miss errors. Previous implementation of systems for clinical risk management and a culture of reporting adverse events, with the aim of improving patient safety, increased participation to haemovigilance and enable better and greater integration of monitoring systems. Overall, there were nine reported cases of ABO incompatibility, of which one was fatal; all these cases were due to an error in one of the critical steps of identifying the patient. These nine cases account for 0.6% of the events notified.

SHOT found that the overall number of errors was equivalent to 70% of the events notified and that cases of ABO incompatibility accounted for 10% of the events notified. The need to educate and train staff is considered fundamental for the function of a haemovigilance system. The data on errors should be monitored for longer, in order that awareness of the importance of notifying errors, by staff, can make the haemovigilance system fully effective.

Estimating the incidence of errors is essential to monitor blood safety and to help health care managers to make informed decisions on systematically introducing instruments for the identification of patients/units of blood components. These instruments are commercially available and already used in some hospitals.

Compared to the organization of the transfusion system in other countries, in which blood banks are completely separate from hospitals, Italian TS are located within hospitals leading to a different management of blood units, presumably with a more effective traceability.

Having overcome the problem of under-reporting, given that the incidence of errors is lower than that
reported by other countries, it could be concluded that the organisation of the Italian transfusion system is better able to guarantee the correct identification of patients/units of blood components.

Acknowledgements

We thank the CRCC that participated in the national haemovigilance system and, in particular, all the Transfusion Structures that used the PETRA software.

We also thank Dr. Roberto Baroni for his precious contribution in standardising and analysing the clinical data.

References