Macopharma Blood Safety Symposium

THERAFLEX Pathogen Reduction Technologies

Chairpersons: Pieter van der Meer, Axel Seltsam

Analysis of UK transfusion reactions to different FFP types
Helen New
SHOT (Serious Hazards of Transfusion) Working Expert Group, U.K.

A regional haemovigilance retrospective study of four types of therapeutic plasma in a ten-year survey period in France
Olivier Garraud
EFS Auvergne-Loire, France

THERAFLEX UV-Platelets, the next generation pathogen reduction systems for platelets: pre-clinical and clinical results
Axel Seltsam
Red Cross Blood Services NSTOB, Germany

THERAFLEX MB-Plasma & THERAFLEX UV-Platelets
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A regional haemovigilance retrospective study of four types of therapeutic plasma in a ten-year period survey in France (EFS Auvergne-Loire)

Prof. Olivier Garraud, MD PhD

Symposium: THERAFLEX Pathogen Reduction Pathologies

2013 Regional ISBT Satellite Symposium

AMSTERDAM

EFS

Université Jean Monnet
SAINT-ETIENNE
Conflicts of interest

• No stakeholder w/ any company in the transfusion business
• No stock share
• No honorarium accepted

• Occasional consultancy w/o retribution for: MacoPharma, Cerus, Fenwal, Haemonetics, Terumo-Caridian, Dometic.
Agenda

1. The therapeutic plasma in France
2. The 1\textsuperscript{st} Auvergne-Loire EFS experience, published
3. Perspectives
The therapeutic plasma in France

- Collection

- Since >10 years, 100% obtained from hemapheresis
- Until 2012: only plasmapheresis; since 2012, possible from combined platelet and plasma pheresis
- 0% from Whole Blood collection (yet)
- Various machines (3 main processes)
The therapeutic plasma in France

Preparation

- Leukoreduction, <10⁴/L!
- Deep Freezing ⇔ time frame depends on the process
  - Quarantine: < 24h
  - Source for SD: < 6h
  - Amotosalen: < 8h
- Methylene Blue: effectively stopped in 2012
- Quarantine: reintroduced, fall 2011
- Amotosalen, INTERCEPT: authorized (Afssaps, now ANSM: 2006); introduced 2009 @ EFS Auvergne-Loire
The therapeutic plasma in France
_Distribution as of 2012-2013_

- Theoretically:
  - Solvent-Detergent: 1/3
  - Quarantine: 1/3
  - Amotosalen: 1/3 (initially aimed at being limited to a maximum of 25%)

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**Solvent-Detergent:**
- EFS produced -
  Considered a Labile Blood product
  1 Production Platform

**Quarantine:**
- EFS produced -
  Every Regional setting apart from Overseas Departments

**Amotosalen:**
- EFS produced -
  6 Metropolitan Regional platforms; major producers or minor producers

_Nationwide_
The therapeutic plasma in France
_ Quality Control _

• Leukoreduction in process (collection) ≤ 10^4 / L in ≥ 95% of the production
• Clotting factors
  – FVIII ≥ 0.5 on ≥70% of the production
  – Fibrinogen ≥ 2g on ≥70% of the production (to be extended to all therapeutic plasma products)
  – [Leukocytes], Platelets ≤ 25^9L, RBCs < 6x10^9L, in ~ 95% of the production but not as-yet formally stated
  – (Amotosalen ≤ 2µM in ~ 95% of the production)
  – Pathogen chemicals: residues to be tested
• Preservation: < 1 year, -25°C
The therapeutic plasma in France _Surveillance_

- Countersigned by the Blood Establishment representative
- Transfusion
- Observation: AE
- Declaration
- E-reporting (report by the physician in charge of haemovigilance in the clinics)
- Countersigned by the Regulatory Body representative

Wrong Product, Wrong patient?

Quotation 1: Severity (ISBT scale)

Quotation 2: Accountability (ISBT scale)
The 1\textsuperscript{st} Auvergne-Loire EFS experience

A regional haemovigilance retrospective study of four types of therapeutic plasma in a ten-year survey period in France

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\textsuperscript{2}Faculty of Medicine, University of Lyon, Saint-Etienne, France
Background and objectives Our objective was to compare the frequency of adverse events (AEs) due to any of the 4 types of fresh-frozen plasma (FFP) prepared and delivered by the French Blood Establishment (EFS) over a 10-year period. Surveillance of AEs and vigilance was performed according to a homogeneous policy. The four types of FFP comprised of one type (methylene blue [MB] that was stopped since then and of another type [amotosalen (AI)] that was recently introduced, along with two conventional products [quarantine (Q) and solvent–detergent (SD)].

Materials and Methods This is a retrospective study based on the national AE reporting database and on the regional database system for deliveries. AEs recorded after the delivery of 1 of the 4 types of FFP were pairwise compared, with appropriate statistical corrections.

Results 105,964 FFP units were delivered (38.4% Q, 17.9% SD, 9.7% MB, and 34% AI).

Statistical comparisons of AEs identified only a difference in AE rates between quarantine and solvent–detergent plasma.
Fig. 1 Plotted are the numbers of reported adverse events (EAs) in the Auvergne–Loire regional setting of the French Blood Service EFS, during years 2000–2010, with respect to all types of labile blood products [packed red blood cells (pRBC), fresh-frozen plasma (FFP) and platelet components (PC); grey line] and to pRBC alone (grey line). This illustration aims at showing the consistency of surveillance of declaration (haemovigilance) in this unique setting, as pRBC content and preparation did not vary over time, while FFP and PCs varied.
Data:
• Total number of plasma components transfused for each type of plasma.
• Counts of allergic reactions which were experienced by the patients receiving each type of plasma component.

Statistics:
• The unit of measure for the statistical analysis is the plasma component.
• The statistical analysis assumes that the plasma components transfused are completely independent and that the allergic reaction is a consequence of the plasma component transfused immediately prior to the reaction.
• The statistical analysis addresses the question, "Is there a difference in the proportion of allergic reactions for the various plasma products transfused?"
• Statistical significance is defined as a p-value of less than 0.05.
Possible, Probable or Certain Allergic Reactions

Data Table 1. Possible, probable or certain allergic reactions

<table>
<thead>
<tr>
<th>Type of Plasma Component</th>
<th>Total Plasma Components Transfused (Jan. 2000 – Oct. 2011)</th>
<th>Number of Plasma Components Eliciting an Allergic Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarantine</td>
<td>40631</td>
<td>29</td>
</tr>
<tr>
<td>Solvent Detergent</td>
<td>19015</td>
<td>2</td>
</tr>
<tr>
<td>Methylene Blue</td>
<td>10283</td>
<td>5</td>
</tr>
<tr>
<td>INTERCEPT</td>
<td>36035</td>
<td>15</td>
</tr>
</tbody>
</table>

Initially, the Fisher-Freeman-Halton exact test was used to determine whether there were differences in the proportion of possible, probable or certain allergic reactions amongst the plasma components listed in Data Table 1. This exact test resulted in a p-value of 8.161e-3 indicating statistically significant differences in the proportion of allergic reactions amongst the plasma components. The Benjamini-Hochberg false discovery rate (FDR) control method was used in multiple hypothesis testing to correct for multiple comparisons (6 total pairwise comparisons). It is a less conservative procedure for comparison, with greater power than family-wise error rate control, e.g. Bonferroni methods, at a cost of increasing the likelihood of obtaining Type I errors (false positives). The results are displayed in Results Table 1:
Results Table 1. Pairwise comparisons and their associated p-values using FDR control methods

<table>
<thead>
<tr>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarantine plasma vs. Solvent detergent plasma</td>
<td>9.018e-3</td>
</tr>
<tr>
<td>Solvent detergent plasma vs. INTERCEPT plasma</td>
<td>0.1411</td>
</tr>
<tr>
<td>Solvent detergent plasma vs. Methylene blue plasma</td>
<td>0.1411</td>
</tr>
<tr>
<td>Quarantine plasma vs. INTERCEPT plasma</td>
<td>0.1455</td>
</tr>
<tr>
<td>Quarantine plasma vs. Methylene blue plasma</td>
<td>0.6308</td>
</tr>
<tr>
<td>Methylene blue plasma vs. INTERCEPT plasma</td>
<td>0.7879</td>
</tr>
</tbody>
</table>

Given that statistical significance is defined as a p-value of less than 0.05, there was a significant difference in the proportion of possible, probable or certain allergic reactions between quarantine plasma and solvent detergent plasma (p=0.009018).
Probable or Certain Allergic Reactions

Data Table 2. Probable or certain allergic reactions

<table>
<thead>
<tr>
<th>Type of Plasma Component</th>
<th>Total Plasma Components Transfused (Jan. 2000 – Oct. 2011)</th>
<th>Number of Plasma Components Eliciting an Allergic Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarantine</td>
<td>40631</td>
<td>23</td>
</tr>
<tr>
<td>Solvent Detergent</td>
<td>19015</td>
<td>1</td>
</tr>
<tr>
<td>Methylene Blue</td>
<td>10283</td>
<td>3</td>
</tr>
<tr>
<td>INTERCEPT</td>
<td>36035</td>
<td>8</td>
</tr>
</tbody>
</table>

As in the previous analysis, the Fisher-Freeman-Halton exact test was used to determine whether there were differences in the proportion of probable or certain allergic reactions amongst the plasma components listed in Data Table 2. This exact test resulted in a p-value of 4.461e-3 indicating statistically significant differences in the proportion of allergic reactions amongst the plasma components.

The Benjamini-Hochberg false discovery rate (FDR) control method was used to adjust the p-values for the 6 pairwise comparisons amongst the 4 plasma components displayed in Data Table 2. The results are displayed in Results Table 2:
Results Table 2. Pairwise comparisons and their associated p-values using FDR control methods

<table>
<thead>
<tr>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quarantine plasma vs. Solvent detergent plasma</td>
<td>0.0102</td>
</tr>
<tr>
<td>Quarantine plasma vs. INTERCEPT plasma</td>
<td>0.0573</td>
</tr>
<tr>
<td>Solvent detergent plasma vs. Methylene blue plasma</td>
<td>0.2548</td>
</tr>
<tr>
<td>Solvent detergent plasma vs. INTERCEPT plasma</td>
<td>0.2657</td>
</tr>
<tr>
<td>Quarantine plasma vs. Methylene blue plasma</td>
<td>0.4043</td>
</tr>
<tr>
<td>Methylene blue plasma vs. INTERCEPT plasma</td>
<td>0.7169</td>
</tr>
</tbody>
</table>

Given that statistical significance is defined as a p-value of less than 0.05, there was a significant difference in the proportion of probable or certain allergic reactions between quarantine plasma and solvent detergent plasma (p=0.0102). Borderline statistical significance was demonstrated for the difference in the proportion of probable or certain allergic reactions between quarantine plasma and INTERCEPT plasma (p=0.0573).
Table 1 Distribution of Fresh-Frozen Plasma types in the Auvergne-Loire Region (France) from 2000 to 2011, Adverse Event record and pairwise comparison of adverse event by plasma type

<table>
<thead>
<tr>
<th>Type of plasma component (FFP)</th>
<th>Total FFP transfused (January 2000–October 2011)</th>
<th>Number of FFP units eliciting an AE (Minor + Mild + Severe + Lethal = Total)</th>
<th>Pairwise comparison of FFP units and their P values using the FDR control methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Possible, probable and certain adverse events (AE)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Quarantine (Q) | 40 631 | $17 + 11 + 1 + 0 = 29 \ (7/10\cdot000)$ | Q vs. SD: $P = 0.0009$, S  
Q vs. BM: $P = 0.6308$, NS  
Q vs. Al: $P = 0.1455$, NS |
| Solvent–Detergent (SD) | 19 015 | $1 + 1 + 0 + 0 = 2 \ (1/10\cdot000)$ | SD vs. MB: $P = 0.1411$, NS  
SD vs. Al: $P = 0.1411$, NS |
| Methylene Blue (MB) | 10 283 | $4 + 0 + 1 + 0 = 5 \ (4.8/10\cdot000)$ | MB vs. IA, $P = 0.7879$, NS |
| Amotosalen (Al) | 36 035 | $11 + 2 + 2 + 0 = 15 \ (4.1/10\cdot000)$ | |
| Total | 105 964 | Total $= 48 \ (4.5/10\cdot000)$ | |
| (b) Probable and certain adverse events (AE) | | | |
| Quarantine (Q) | 40 631 | $12 + 10 + 1 + 0 = 23 \ (5.7/10\cdot000)$ | Q vs. SD: $P = 0.0102$, S  
Q vs. BM: $P = 0.4043$, NS  
Q vs. Al: $P = 0.0573$, NS |
| Solvent–Detergent (SD) | 19 015 | $1 + 0 + 0 + 0 = 1 \ (0.5/10\cdot000)$ | SD vs. MB: $P = 0.2548$, NS  
SD vs. Al: $P = 0.2657$, NS |
| Methylene Blue (MB) | 10 283 | $2 + 0 + 1 + 0 = 3 \ (2.9/10\cdot000)$ | MB vs. Al, $P = 0.7169$, NS |
| Amotosalen (Al) | 36 035 | $6 + 1 + 1 + 0 = 8 \ (2.2/10\cdot000)$ | |
| Total | 105 964 | Total $= 35 \ (3.3/10\cdot000)$ | |

FCR, false discovery rate; FFP, fresh-frozen plasma.

Bold stands for significant (S) and italics stand for non significant (NS).
Conclusions

• FFP was confirmed to be extremely safe in general, especially if one considers "severe" AEs.

• All types of FFP were associated with extremely low occurrence of AEs.

• Q, MB, SD and IA led, respectively, to 7.14, 4.86, 1.05 and 4.16 AEs per 10,000 deliveries.
Perspectives

• France forecasts to be back to Whole Blood Plasma
  – Quarantine
  – PI/PR?
  – When and how?
• Extension of PI/PR plasma to more settings in France?
• PI/PR processes – along with Amotosalen – move forward
(Of note...)

- FFP is no “universal therapeutic plasma”
  - Some plasma is delivered unfrost (kept at 4°C after whole blood or occasionally – aphaeresis collection) => far from being negligible worldwide in economically wealthy countries

- Quarantine “plasma is no universal procedure”
  - Some plasma is delivered “fresh” after routine safety (infectious) qualification
    - Routine/safety (infectious) qualification does not always comprise of NAT!

- Inactivated therapeutic plasma is disputed: the SD Octapharma (comprising of the Octaplas) process “against” the rest of the processes

- Cost Benefit issues? Safety (haemostatic) issues? Infectious issues (the prion nvCJD issue?); non enveloped viruses?
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- **Collaborators at EFS Auvergne-Loire**: Vincent Bost, MD; Patricia Chavarin, MD; Patrick Fabrigli, MD; Halim Benamara, MD; Hélène Odent-Malaure, MD; Sophie Acquart, PhD; Françoise Boussoulade, LSc, etc.
- **Physicians in Clinics**
- **Donors**, still generous, altruistic, volunteer and non remunerated in France
- **Patients** for granting access to their medical records, with permission
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**THANK YOU FOR YOUR KIND ATTENTION!**