Role of post-marketing surveillance of blood products:

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Role of post-marketing surveillance in the safety of blood products:

- Plasma-derived medicinal products
- Blood components for transfusion

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Introduction -1-

✓ Blood and blood products are of biological origin
  • Complex molecules
  • Products of human origin: blood- or tissue-borne viruses or pathogens → no species barrier
  • Complex and fragile products
    → Difficult to handle, process, store, transport, deliver, and use
    → Batch-related or even single donor-related accident / incident

✓ Safety: in the meaning of
  • Microbiological safety: contaminants and transmissible agents
    → Risk of infectious diseases
  • Efficacy: denaturation/degradation
    → risk of loss of efficacy
  • tolerance profile: development of adverse drug reactions
    → mainly immunogenicity
Safety: a global approach and a built-up strategy:
- Several steps contribute to the overall safety of a product
- Each step has its role and importance

To explain the role of the vigilance systems for the safety of blood components and plasma derived medicinal products
Keys for safe products

✓ Quality management of the "production/supply chain"
  • For plasma-derived products: from the plasma pool to the finished product: production process, quality control tests, storage
  • For transfusion products: from the donor to the recipient – Collection chain, storage, distribution chain

✓ Viral safety management

✓ Post-marketing: vigilance system
Viral safety management: the three keys

3 COMPLEMENTARY APPROACHES

✓ Knowledge and adequate quality control of the starting material
  → to diminish the infectious load entering the process

✓ Production process, incorporating steps capable to remove or inactivate the contaminating agent(s) and validation of such steps
  → to diminish further the infectious load in the final product

✓ Control tests performed on intermediates and/or the final product
  → to monitor the quality all along the process
Knowledge and quality control of the starting material

✓ Plasma Master File:
  • Origin of plasma
    ▪ Blood/plasma collection establishments
    ▪ data on epidemiology of infection transmitted by blood:
      o absence of collection in high prevalence areas nor during epidemic
      o permanent reassessment of epidemiological data
  • selection/exclusion criteria according to the recommendations:
    ▪ Council of Europe R (95)15 on preparation, use and quality insurance for blood components,
    ▪ European Directives 98/463/; 2002/98; 2004/33
  • and specifying if donations are remunerated or not
Knowledge and quality control of the starting material

✓ Plasma Master File (contd):
  • screening tests for marker(s) of infection
  • Blood bags
  • Plasma quality criteria
  • storage and transport
  • Plasma pool preparation and specifications
  • Standard contracts

✓ Traceability system (in application to EU Directive)
  • system to trace the path of any donation → start of the traceability chain
Post-Marketing surveillance system

✓ Plasma-derived medicinal products (PDMP)
  • Pharmacovigilance
  • Traceability

✓ Blood components for transfusion
  • Haemovigilance
  • Traceability
Pharmacovigilance

✓ Plasma-derived products are considered as medicinal products (Directive 89/381) and as such are under the pharmacovigilance provisions

✓ French regulation: Decree (May 1995 Art R-5144-23/39) which describes and made mandatory
  • Notification
  • Traceability
Pharmacovigilance → Notification

✓ Obligation of notification

✓ Notification of Side effects to the pharmacovigilance system:
  • is mandatory for all side effects noticed
  • not restricted to severe and/or unexpected
  • is due immediately

✓ Centralisation of the information: any notification has to be copied to the central body (French Agency).
Traceability: European directives


• An adequate system to ensure traceability of whole blood and blood components should be established.

• Traceability should be enforced through:
  ▪ accurate donor, patient, and laboratory identification procedures,
  ▪ record maintenance,
  ▪ an appropriate identification and labelling system.

• Data needed for full traceability in accordance with this Article shall be kept for at least 30 years
Traceability is mandatory and is defined as follows:

• Set of actions taken to quickly retrieve history, use and localisation of a PDMD

• Traceability at each step of the supply chain:
  ▪ from the blood donation,
  ▪ through the production, the distribution, the dispensation
  ▪ Up to the administration

Traceability objectives:

• To allow the retrieval, from a PDMP batch number:
  ▪ of the blood donation numbers that were pooled for this batch preparation,
  ▪ and the recipients of this batch.
Traceability numbering system

Donors

Plasma pool

Product batches

Fractionation process

Patient

Medical records

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Traceability: ascending

✓ When a recipient develops a disease
  • Pharmacovigilance notification
  • Enquiry to investigate
    ▪ Implicated product(s) → need for batch number(s) recorded in the medical dossier
    ▪ Possible cause related to the product(s) « imputability »
    ▪ Check whether other patients experienced the same event
      o Need for traceability for each batch
      o Need for centralisation of the notifications
    ▪ If deemed necessary,
      o Batch quality testing
      o Quality of the plasma pool (retained samples)
      o Quarantine (during the investigations)
      o Withdrawal and appropriate action vis a vis the other recipient(s)
Traceability: descending

When a donor is found, post donation, as « at risk » (seroconversion, clinical stage of a disease..)

- Blood collection establishment is notified
- Enquiry to investigate
  - Fate of the donation(s) → need for a numbering system for any donation
  - Identification of the concerned plasma pool(s)
  - Identification of the concerned plasma-derived product batch(es)
- Quantitative risk analysis (depends on the original risk identified, the process(es) and the resulting products)
- Action taken depending on the results of the risk analysis
- Action could envisage recall of batches and information of the recipients …
Traceability examples -1-

☑️ HIV seroconversion post donation
  • Identification, by chance, few months post donation (donation tested by serology)
  • Plasma pool retested by PCR → negative
  • Quantitative risk analysis: risk is deemed minimal
  • No further action

☑️ HCV seroconversion in an Ig-IV treated patient
  • Patient found HCV-antibody positive
  • Other risk factors (blood transfusion)
  • No other reports with the concerned batch
  • No further action deemed necessary
Traceability examples -2-

✓ vCJD clinical symptoms in a donor, four years post donation
  • Risk is theoretical but
  • Identification of all past donation (10 years)
  • Identification of all plasma pools concerned and resulting batches of medicinal products
  • For in-date products still on the market, withdrawal and information of the patients who had stocks at home
Application to blood components: haemovigilance

- More simple chain as compared to plasma products, but more « weak » points
  - Direct from the donor to the patient
  - No « process »
    - to standardised the product (no pool effect)
    - To remove, inactivate pathogens
  - No holding time (to be use in less than 5 days)

- Essentially rely on
  - The donor selection
  - The follow-up and monitoring of the donor and of the recipients → need for an haemovigilance system and traceability
Traceability/Notification in transfusion

✓ Directive 2002/98: setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending:
  • Traceability
  • Notification system


✓ Directive 2005/61: specifies the traceability and notification system to be put in place in blood collection establishment
Haemovigilance

✓ Directive 2002/98:
✓ ‘haemovigilance’ shall mean a set of organised surveillance procedures relating to
  - serious adverse or unexpected events or reactions
  - in donors or recipients,
  - and the epidemiological follow-up of donors

✓ Haemovigilance is not only for recipients
Traceability numbering system

✓ Donor identification – donation number
✓ Identification (coding system, numbering) of the obtained blood components:
  • Red blood cells
  • Platelets
  • Plasma (fresh frozen, for fractionation)
✓ Distribution chain → to trace any blood component distributed in an health care establishment
✓ Patient:
  • Blood component received are recorded in the medical dossier
  • Information on the recipient is sent back to the blood Collection establishment
✓ Traceability is mandatory but should not be a breach in confidentiality of the data
Usefulness of traceability
Recent examples

✓ vCJD and blood donation
  • In France, 17 suspected or confirmed vCJD cases, 3 were blood donors
  • Traceability allowed to trace back all their donations (30 within 15 years) and corresponding transfused patients
  • Information and counselling of the alive recipients

✓ Chikungunia epidemic in La Reunion
  • No screening test available at the start of epidemic
  • Asymptomatic donors may have donated while viremic
  • Suspected cases of chikungunya symptoms in platelet-transfused patients
  • Retained samples tested using PCR and found negative
  • Further evaluation undertaken and decision was made to stop blood collection at La Reunion, during the epidemic, except for platelet concentrates (supply problems) which should however be
    ▪ PCR tested
    ▪ Put through an inactivation treatment
Key role of the various actors in the Vigilance system

✔ **Donor**: to refer back to the collection center in case anything wrong after donation

✔ **Recipient (patient)**: if he(she) detects something wrong with the medication

✔ **Physician or health care professionals**: to notify the relevant hemo- or pharmaco-vigilance system so as to trigger any further action

✔ **Need for well structured and reactive system**,
  - To identify, as early as possible a signal
  - To treat it accordingly: → evaluation and decision-making process

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Safety of blood / blood products

✔ To be built-up

✔ To be evaluated

✔ To be monitored

✔ To be built-up considering
  • The product of origin
  • The possible method(s) of obtention
  • The intended use

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Safety of blood / blood products

- To be built-up
- To be evaluated
- To be monitored

- To be evaluated
  - Process description and validation data (consistency)
  - Collection description
  - Viral inactivation steps
  - Viral safety level (should be assessed before going to human clinical trials)
Safety of blood / blood products

- To be built-up
- To be evaluated
- To be monitored

- Safety profile monitoring
  - Ponctual accident may occur, due to individual factors
    - Donor
    - Process
    - Supply and storage chain
  - New emerging risks (particularly infectious agents)
  - New technology are developed
    - Inactivation techniques
    - Screening tests
The safety loop

Product

Development

Characteristics specification

Evaluation

Authorisation

Use

PATIENT

Surveillance

Re-assessment Corrective action

Importance of Traceability Notification

Additional information
New findings
Conclusion

✓ Safety is achieved as the result of a multi-approach system
✓ Safety should be monitored permanently
✓ Pharmacovigilance and haemovigilance are part of the tools to ensuring safety, but
• Need for a well structured notification system
• need for a well standardised and operating traceability (up-and backward) system