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Original article

## Delayed hemolytic transfusion reaction in the French hemovigilance system

### Réaction transfusionnelle hémolytique retardée dans le système d'hémovigilance français

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French hemovigilance network

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#### ABSTRACT

In France, reporting of adverse events related, or likely to be related, to transfusion is mandatory. Since its creation in 1993, the French hemovigilance system has contributed to a better recognition of unappreciated risks like delayed hemolytic transfusion reactions (DHTR) in sickle-cell disease (SCD) patients. Long under-reported or misclassified, reports of this serious complication of transfusion have improved, particularly through the dissemination of information within the hemovigilance network. To our knowledge, the French hemovigilance system has one of the largest series of DHTR in SCD patients. Guidelines for diagnosis and reporting to hemovigilance system as well as a specific reporting form are being developed, which should contribute to the quality of data essential for epidemiological studies.

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#### RÉSUMÉ

En France, la déclaration de tout effet indésirable, dû ou susceptible d'être dû à la transfusion, est obligatoire. Depuis sa création en 1993, le système d'hémovigilance a contribué à une meilleure reconnaissance de certains risques comme les hémolyses post-transfusionnelles chez les patients drépanocytaires. Longtemps sous-déclarée ou classée sous un autre diagnostic, les déclarations de cette complication grave de la transfusion se sont améliorées, en particulier grâce à la diffusion d'informations au sein du réseau d'hémovigilance. Actuellement, le système d'hémovigilance français possède une des plus grandes séries d'hémolyses post-transfusionnelles chez les patients drépanocytaires. Un guide de déclaration et un recueil de données spécifiques sont en cours et devraient permettre d'améliorer la qualité des données et de réaliser des études épidémiologiques.

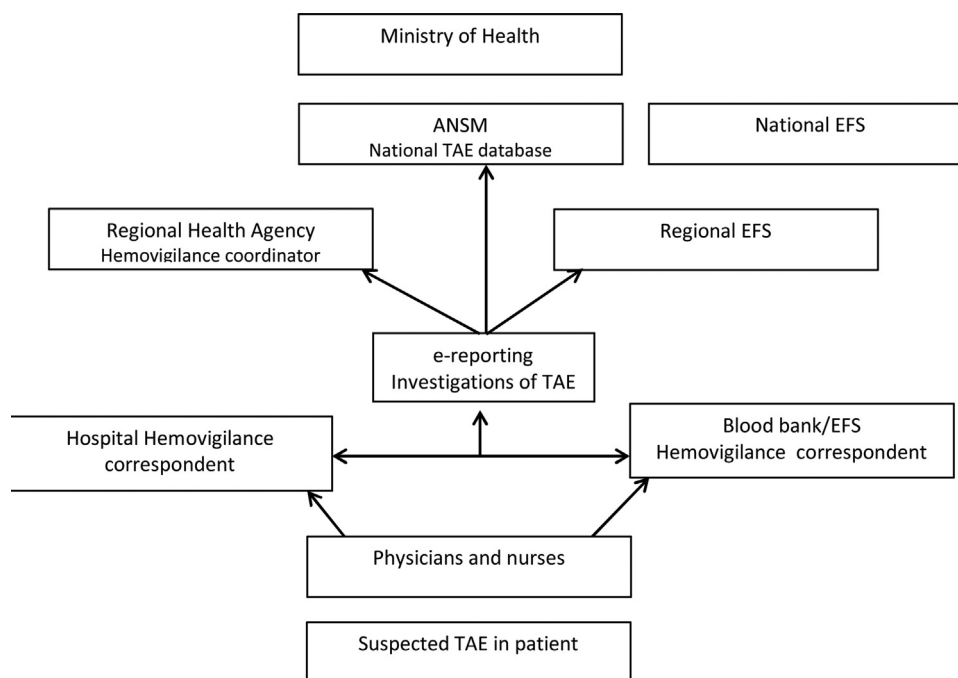
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### 1. French hemovigilance system

Reporting of delayed hemolytic transfusion reactions (DHTR) to the French hemovigilance system is mandatory, in the same

manner as all transfusion-related adverse events (TAE). Created in 1993 by law, the French hemovigilance covers all procedures for monitoring, evaluating and preventing adverse reactions occurring in donors or recipients of labile blood products (red cells, platelets, plasma and granulocytes) and serious incidents of the transfusion process from the collection of blood components to the follow-up of recipients [1]. The French National Agency for Medicines and Health Products Safety (ANSM) is responsible for implementation of hemovigilance organized in a dedicated net-

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**Fig. 1.** French Hemovigilance system and reporting. ANSM: *Agence nationale de sécurité du médicament et des produits de santé* (French National Agency for Medicines and Health Products Safety); EFS: *Établissement français du Sang* (French blood service); TAE: transfusion adverse events.

work working at national, regional and local levels (Fig. 1). At the local level, hemovigilance correspondents, usually physicians, are responsible for reporting transfusion events, ensuring traceability of blood transfusions, complying with best practices, and training health professionals. Regional coordination is made by the Regional Agency of Health. ANSM centralizes all the hemovigilance data and has a role in the supervision and control of blood activities.

Reporting of adverse events related, or likely to be related, to transfusion, post-donation events, and errors in the transfusion chain is mandatory. Reporting is made via an Information Technology (IT) system, e-FIT, allowing real-time sharing of information between authorized members. This tool allows for rapid analysis, alert and immediate action but also provides a national database. The report form is the same for all adverse events but additional data can be added (hospitalization report, results of biological investigations). Incidence and analysis of transfusion and blood collection related events are published in the ANSM annual hemovigilance reports [2]. Every year, about 3 million labile blood products (LBP) are transfused to 500,000 patients. Between 14,000 and 15,000 adverse events are reported equally distributed in patients and in donors.

Hemovigilance has identified previously unrecognized or unappreciated transfusion risks, led to prevention measures, and then contributed to their reduction. As an example, between 2000 and 2015, ABO incompatible red cells transfusion has been reduced by 6-fold and bacterial transfusion-transmitted infection by 5-fold [2]. Hemovigilance has also contributed to a better recognition of unappreciated risks like TRALI and, more recently, DHTR in sickle-cell disease (SCD) patients.

## 2. DHTR in the French hemovigilance system

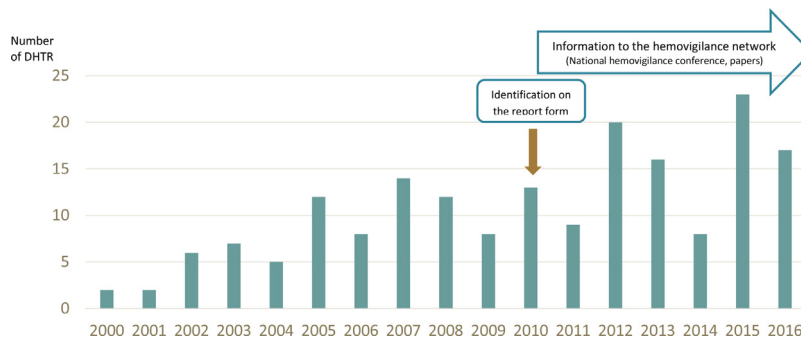
DHTR in SCD patients are a severe complication occurring usually between 5 and 15 days after transfusion. Fever, pain and hemoglobinuria with a decrease in hemoglobin level and a significant increase in lactate dehydrogenase (LDH) are the main clinical

and biological features. New allo-immunization is found in 60 to 70% of cases [3–5]. DHTR can be complicated by the hyperhemolysis syndrome with destruction of both autologous and transfused red blood cells resulting in a fall in the hemoglobin concentration to below the pre-transfusion level. Hyperhemolysis can induce multiorgan failure and death. Overall, the death rate of DHTR ranges from 5% to 10% [4–6]. Early recognition is essential as additional transfusions may exacerbate the process and new strategies for management are being developed [7,8].

The first report of DHTR in SCD to ANSM was made by our hemovigilance unit in the University Hospital Henri-Mondor in 2000, thanks to an early recognition of this complication by the physicians of the SCD referral centre located in our hospital. At this time, the case of DHTR was considered an “unknown diagnosis” because the serology was antibody-negative and this situation had not been foreseen in the national hemovigilance report form.

DHTR is still an under-reported event. Both missed diagnosis and misdiagnosis of DHTR in SCD are common. Clinical and biological features mimic those of vaso-occlusive crisis, no detectable red blood cell antibodies are identified in a substantial fraction of patients and a link to previous transfusion is often overlooked. DHTR were often misclassified as “unknown diagnosis”, “other diagnosis” or “hemolysis from other causes than transfusion” [6]. At present, reporting is improving since DHTR in SCD was identified as a formal diagnosis in the hemovigilance report form and members of the hemovigilance network have been better informed about the diagnosis of DHTR (Fig. 2).

To assess DHTR in the hemovigilance national database, we reviewed all reports of hemolytic transfusion reactions (HTR) in SCD patients from 2000 to 2016. HTR was defined by at least one clinical symptom among fever, pain, dark urine and one biological feature among a decrease in hemoglobin concentration, an increase in LDH and a reduction in hemoglobin A percentage occurring between 2 to 28 days after transfusion. Cases were reviewed by a hemovigilance expert and a SCD specialist. We found 205 cases and excluded 23 for insufficient information. Selected characteristics of



**Fig. 2.** Annual reports of DHTR in the French hemovigilance system 2000-2016.

**Table 1**  
 Characteristics of DHTR reported in the French hemovigilance system (2000–2016, n = 182).

|  |               |
|--|---------------|
| Sex ratio, F/M                           | 2.1           |
| Median age in years                      | 26            |
| Previous allo-immunization               | 89 (48.9%)    |
| Previous DHTR                            | 37 (20.3%)    |
| Transfusion indication, (n = 167)        |               |
| Acute setting                            | 129 (77.3%)   |
| Pregnancy setting                        | 35 (19.2%)    |
| Median time between transfusion and DHTR | 8 days (2–29) |
| Deaths                                   | 10            |

the 182 remaining cases are presented in Table 1. Women were twice as frequent as men partly due to transfusion in the setting of pregnancy. Previous allo-immunization was documented in half of the cases and 20.3% of the DHTR episodes had a history of previous DHTR. The majority of cases were transfused for acute complications. More than 80% of the DHTR occurred between 4 and 15 days. Ten patients died, yielding an overall mortality rate of 5.5%. Additional analyses are in progress in particular immuno-hematological features.

These preliminary results illustrate the value of the centralized French hemovigilance database. To our knowledge, the French hemovigilance system has one of the largest series of DHTR in SCD patients. This work has also emphasized the need of exhaustiveness, completeness of reports and reporting of additional data that do not appear on the hemovigilance form. Guidelines for diagnosis and reporting to hemovigilance system as well as a specific complementary form are being developed by ANSM and national experts. A national expert group including SCD physicians, transfusion specialists and hemovigilance experts could be created with the aim to review all cases and give advice on management. These actions will contribute to further improvement in the quality and standardization of data that is essential for

epidemiological studies. A common approach of reporting DHTR could be considered in Europe as some countries are facing this “emerging” complication in national hemovigilance systems.

In conclusion, the French hemovigilance network has a key role to play in the recognition and the description of DHTR in SCD and to contribute to raising the awareness of authorities of this transfusion risk. Coordination between physicians, transfusion specialists and hemovigilance experts is crucial to improve management of patient and implement prevention measures.

#### Disclosure of interest

The authors declare that they have no competing interest.

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