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Original article

Prevention of delayed hemolytic transfusion reaction

Prévention de la réaction post-transfusionnelle hémolytique

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ABSTRACT

Post-transfusion hemolysis is the most frequent immune reaction to transfusion in sickle cell disease. Its frequency is underestimated due to its biological and clinical characteristics. It results principally from the high incidence of alloimmunization in these patients, but no antibodies are detectable in 30% of cases. Prevention is based on the prevention of alloimmunization through the use of matched RBCs for highly immunogenic blood groups, taking into account the patient's transfusion history, particularly in patients undergoing occasional transfusion, which is associated with a higher risk of DHTR development than chronic transfusion. In addition to the use of matched RBCs, the prevention of alloimmunization through immunotherapy should be considered.

Mots clés :
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RÉSUMÉ

L'hémolyse post-transfusionnelle du patient drépanocytaire est une réaction fréquente chez les patients transfusés ponctuellement, mais sous-estimée du fait de ses caractéristiques immuno-hématologiques et cliniques. L'alloimmunisation anti-érythrocytaire reste la principale cause de cet accident, ceci étant, il existe un certain nombre de cas sans anticorps détectables. La prévention repose donc sur la prévention de l'alloimmunisation, mais tient aussi compte de l'historique transfusionnel des patients, et particulièrement chez les patients transfusés ponctuellement, présentant un risque plus élevé de DHTR. La prévention repose sur l'accès à des CGR phénotypés, mais aussi sur une prévention non spécifique par des traitements immuno-modulateurs, comme le rituximab.

DHTR is a very severe reaction to transfusion in patients with SCD. Its prevention is, thus, a key issue. This prevention must be based on risk factors. However, although some risk factors, such as alloimmunization, have been identified, much of the mechanism underlying DHTR remains a mystery, particularly in severe cases presenting hyperhemolysis. Alloimmunization is particularly frequent in SCD patients in Europe, largely due to the blood group polymorphism between the patients, who are of African ancestry, and the donors, who are mostly of European origin [1–3]. Different levels of RBC polymorphism can be detected in SCD patients. First, there is a difference in the distribution of common antigens, such as C, E, Fy^a, Jk^b and S, between the patients and donors (lower frequency in the patients). Antibodies against these antigens are the most frequently encountered in these patients. Despite the application of a care standard according to which all SCD patients should receive RH-matched RBCs, these patients frequently produce antibodies against the RH blood group antigens [4–6] The high frequency of these antibodies can be explained, in part, by the high frequency of partial RH variants in individuals of African origin. A patient carrying a partial D antigen may become immunized against the absent epitopes when receiving transfusion products carrying the common D antigen. The resulting anti-D antibody is, thus, an alloantibody of the same clinical significance as any other alloantibody displaying RH specificity. These variants can be identified by molecular analysis. An additional level of blood group complexity leading to alloimmunization results from the existence of specific rare blood groups in this population of patients. A rare blood group is defined as the absence of expression of an antigen that is generally universally expressed. In France, we consider an individual to have a rare blood group if the blood group concerned is found in less than 1/250 individuals. Individuals with such rare blood groups

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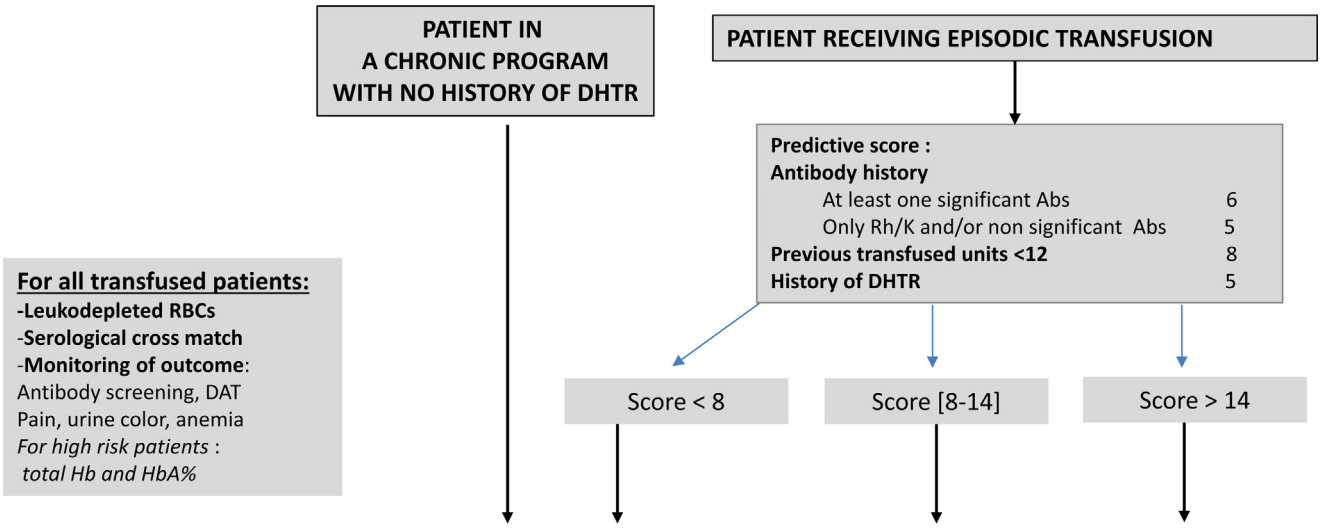

Immunization status of the patient before transfusion	Low risk of DHTR	Intermediate risk of DHTR	High Risk of DHTR
No previous immunization or only RH/K Abs and/or non major antibodies (auto, AUS*, low frequency)	Rh/K matched RBCs	**Case by case decision	Rh/K and extended matched (Fy, Jk, MNS)
At least one significant Abs FY,JK,MNS,DO, high frequency, other	Rh/K and matched to Ab specificity + if possible extended matched (Fy, Jk, MNS)	**Case by case decision	Rh/K and extended Matched (Fy, Jk, MNS) + Rituximab treatment (case by case decision)

Fig. 1. Strategy for preventing DHTR in SCD patients.

may develop antibodies against all common RBCs carrying the antigen concerned, and this may be associated with severe cases of DHTR in sickle cell disease.

Fortunately, not all patients develop antibodies in these various mismatch situations. High and low responders can be identified. Some patients receive hundreds of RBC units without ever developing a single antibody. Studies are underway to differentiate between these two groups of patients, with a view to developing specific prevention measures for those identified as. Inflammation, and several immunogenetic markers have been identified as possibly important factors in this context, but it is not yet possible to define precise cutoffs between potential high and low responders [7–9]. The only factor known with any certainty to be predictive is the prior immune-hematological status of the patient. A patient who has already developed one or more antibodies following transfusion can certainly be considered a high responder.

In 70% of cases, antibodies are identified in the patient's blood after transfusion. However, only about half these antibodies are precisely identified and linked to known blood group polymorphism [10] The other half are autoantibodies, antibodies of unknown specificity, or antibodies against low-frequency antigens of unknown clinical significance. Two levels of prevention of alloimmunization must therefore be considered. The first consists of avoiding exposure to highly immunogenic antigens (RH/KEL) in all patients, and avoiding exposure to other significant but less immunogenic blood groups (FY, JK, MNS) in patients who are already immunized and considered at a higher risk of developing new antibodies. However, such prevention measures are not always possible due to the lack of matched units, which are generally obtained from donors of the same ethnic background as the patients. Additional prevention against alloimmunization would be useful for high responders and patients with history of severe DHTR. Ideally, for these patients, matching should be performed for a much larger range of blood group antigens, given that many other antibodies can be involved. However, matching for all 36 blood groups, with almost 350 different antigens, is not realistic, and other types of antibodies, including autoantibodies have also been implicated in DHTR. Nonspecific measures for preventing RBC immunization have been implemented in highly immunized patients who have already experienced DHTR. These measures were found to decrease antibody production, but were not entirely effective for DHTR prevention. However, DHTR, when it occurred, was milder than the previous severe episodes in the patients treated.

The results of rituximab-based prevention in some cases highlight the complex mechanism of DHTR, a condition for which no antibodies are detectable in 30% of cases [11].

There was, therefore, an urgent need to identify the biological and clinical risk factors associated with DHTR development in patients undergoing transfusion. A prospective single-center observational study was conducted over 30 months in adult patients with SCD [3]. In total, 694 transfusion episodes (TEs) in 311 patients were included, classified as occasional TEs (OTEs: 360) and chronic transfusion program transfusion episodes (CTEs: 334). During follow-up, 15 cases of DHTR were recorded, exclusively after OTEs. The incidence of DHTR was 4.2% per OTE (95% CI [2.6; 6.9]) and 6.8% per patient over the 30 months of the study (95% CI [4.2; 11.3]). Data were collected for a large number of parameters: age, sex, transfusion history, age of the units transfused, simple versus exchange transfusion, volume, indication for transfusion,

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treatment of the patient. A predictive score was constructed for DHTR. The variables retained in the multivariate model were history of DHTR, number of units previously transfused and immunization status before transfusion. The resulting predictive score for DHTR was of high negative predictive value. Based on these results and a knowledge of the clinical significance of antibodies, the risk of alloimmunization and efficiency of rituximab, a strategy for preventing DHTR in SCD patients was then proposed (Fig. 1). Patients with no history of DHTR on chronic transfusion have a lower risk of developing DHTR. Within this group of patients, a history of RBC immunization and previous DHTR greatly increase in the risk of DHTR. These three risk factors (number of previous transfusions, history of immunization and previous DHTRs) should thus be carefully considered when evaluating a patient for transfusion. If transfusion is necessary in high-risk patients, the prevention of alloimmunization should be a matter of priority, because alloimmunization can trigger DHTR. For patients with anti-Fy, -Jk or -Ss antibodies, we recommend extended matching (Fy, Jk, Ss), because the risk of producing additional antibodies increases with each new transfusion[19,38]. Given the high likelihood of alloimmunization against any blood group antigen in these patients, we also recommend prophylaxis with rituximab before transfusion.

This represents a first attempt to stratify DHTR risk. It is certainly not perfect, because the history of the patient is not always known and because decisions must be taken on a case-by-case basis for patients with intermediate scores. For example, should patients with a history of DHTR followed by subsequent uneventful transfusion episodes be considered at risk? What about highly immunized patients with no history of DHTR. Another key group is the patients who develop DHTR without detectable antibodies. The first occurrence of DHTR in these patients is entirely unpredictable, as is recurrence. Is DHTR dependent on a particular state of the patient at the time of transfusion, such as an increase in complement activation, an increase in free heme levels? Is it linked to characteristics of the blood units transfused (what about G6PD deficiency in the donor, for example)? For the moment, we have no definitive answers to these questions. Further research on this aspect is urgently required and would be facilitated by the creation of a register for this syndrome, collating epidemiological and pathophysiological data, with a collection of samples from these patients.

Thus, DHTR prevention is currently based on the prevention of alloimmunization, and a knowledge of the transfusion history of the patients. There is a need to increase the number of matched RBC units, provided by donors from the same ethnic background as the patients.

Disclosure of interest

The author declares that he has no competing interest.

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