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Review

Relevance of RH variants in transfusion of sickle cell patients

Intérêt clinique des variants du système RH au cours de la drépanocytose

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Abstract

Transfusion remains the main treatment of sickle cell disease patients. Red cell alloimmunization is frequent because of the antigen disparities between patients of African descent and donors of European ancestry. Alloimmunization is associated with severe hemolytic transfusion reaction, autoantibody formation, and difficulties in the management of transfusion compatibility. Beside common antigens, a number of different RH variant antigens found in individuals of African descent can be involved in alloimmunization. If some variants, such as Hr^S negative antigens, are known to prone significant alloantibodies and delayed hemolytic transfusion reactions, it is not clear whether all the described variants represent a clinical risk for sickle cell disease patients. The knowledge of the clinical relevance of RH variants is a real issue. An abundance of molecular tools are developed to detect variants, but they do not distinguish those likely to prone immunization from those that are unlikely to prone immunization and delayed hemolytic transfusion reactions. A strategy of prevention, which generally requires rare red blood cells, cannot be implemented without this fundamental information. In this review, we discuss the relevance of RH variants in sickle cell disease, based on the published data and on our experience in transfusion of these patients.

Keywords: RH; Sickle cell disease; Blood groups; Variants; Immunisation; Hemolysis

Résumé

La transfusion reste un des traitements majeurs de la drépanocytose. L'allo-immunisation antiérythrocytaire est fréquente du fait du polymorphisme des antigènes de groupes sanguins entre les patients d'origine Africaine et Antillaise et les donneurs essentiellement d'origine Européenne en France métropolitaine. L'allo-immunisation est associée au risque d'hémolyse post-transfusionnelle avec mise en jeu du pronostic vital. Au-delà des antigènes communs, un certain nombre de variants du système RH peuvent être impliqués dans ces accidents, d'autant que ces variants sont fréquents dans la population afro-antillaise. Si certain variants sont clairement associés à un risque d'allo-immunisation et d'hémolyse chez les patients, tel le phénotype RH : −18, pour la grande majorité, les données sont peu claires. La connaissance de l'impact clinique des variants RH chez les drépanocytaires est d'un intérêt majeur. De nombreux outils moléculaires sont développés pour caractériser ces variants, mais ils ne permettent pas de distinguer ceux réellement d'intérêt pour les patients, et qui donc nécessitent une prévention de l'allo-immunisation. Dans cette revue, nous faisons état de l'ensemble des données de la littérature sur ce sujet, ainsi que de notre expérience au cours de la transfusion des patients drépanocytaires.

Mots clés : RH ; Drépanocytose ; Groupes sanguins ; Transfusion ; Variants ; Immunisation ; Hémolyse

1. Introduction

Blood transfusion is a cornerstone of the management of sickle cell disease [1]. The goals of blood transfusion are to increase oxygen distribution to tissues, and/or to replace rigid sickle-shaped red blood cells by deformable red blood cells. However, blood transfusion in patients affected with sickle cell disease is associated with a high rate of delayed hemolytic transfusion reactions. One major cause of these reactions is the development of alloantibodies to red blood cells promoted by the high polymorphism of blood group antigens between the patients of African ancestry and the donors primarily of

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European descent [2]. In these situations, the rate of allo-immunization is about 10 to 45% [3–5]. It is likely that in Africa, where there is homogeneity between donors and patients, the rate of allo-immunization is lower [6]. The common antigens expressed in donors and causing allo-immunization in patients are well known. They are C and E in the RH blood group. Few individuals of African descent express C and E when they are D positive. In Caucasians, the presence of D antigen is always accompanied by the presence of either C or E antigen. In the other blood groups, the disparities are mainly for Fy^a, Jk^b, and S antigens. In every country with a European background, there is a shortage of matching units. Limited antigen matching for E, C, and Kell has become the standard of care [7]. Matching for the other antigens is generally extended when alloantibodies are developed. This approach reduces the rate of allo-immunization considering that patients who form antibodies show an increased risk for additional alloantibodies upon further transfusion exposure [8]. It remains that this approach does not take into account the numerous RH variants that are encountered in these patients of African ancestry, representing potentially an additional risk for allo-immunization and delayed hemolytic transfusion reactions. They are encoded by altered alleles at the RH locus. The RH variants may prone allo-immunization when the antigen is incomplete (or partial) and when the carrier is exposed to the complete antigen through transfusion or pregnancy.

It is important to mention that it is not clear which RH variants induce allo-immunization when the carrier of the variant is exposed to the normal antigens. It also remains unclear which alloantibodies to RH variants are clinically significant. This knowledge is a major issue to determine which variants have to be considered in the prevention of allo-immunization and delayed hemolytic transfusion reactions. The RH variants have been widely described. There is a consensus to recognize DNA analysis as the best tool to detect and characterize RH variants [9–11]. In the last years, industrials have developed many tools to detect variants. They are qualified as “high throughput genotyping” because of the numerous detected alleles in one assay [12,13]. With those commercial tools, all biologists can type variants for sickle cell disease patients. Therefore, they are supposed to assist the clinician to make an informed decision regarding selection of units. However, they remain frequently puzzled because they do not really know the clinical significance of the variant they have found. After a long period of describing new variant alleles, the next goal is to determine which variants represent a risk for the sickle cell disease patients frequently exposed to foreign antigens, to adapt DNA-based typing to the clinical situation [14], and to implement prevention only when necessary.

2. RH blood group and variants

The RH blood group is composed of two highly homozygous genes, the *RHD* and the *RHCE* genes.

The *RHD* gene produces the D antigen, and the *RHCE* gene produces a polypeptide carrying two antigens: C or c and E or e [15]. In Caucasians, the main haplotype is *DCe*, in Afro-Americans and Afro-Caribbeans, the main haplotype is *Dce* [16]. The result of this distribution is a high frequency of sickle cell disease patients with the D+C–E–c+e+ phenotype. Only 20% of patients express the C antigen [5]. Within the five main antigens (D, C, E, c, e), schematically, two types of variants are described, and they are encoded by point mutations, multiple missense mutations or hybrid alleles [17]. First, those named partial, because they lack some immunogenic epitopes, as shown by alloimmunization of the carriers against missing epitopes when exposed to the complete antigen through transfusion or pregnancy. Second, are the weak antigens. Individuals carrying weak antigens do not get immunized when exposed to the normal antigen. Therefore, a carrier of a partial antigen should receive red blood cells, which do not express the antigen to prevent alloimmunization. When a new variant is discovered because the carrier has developed an antibody, the variant is classified as partial on an immunological point of view. When a new variant is described, because of a weak reactivity, it is much more difficult to decide the category [18]. There is a consensus to classify the variant based on the predicted localization of the substitution. The Rhesus index determining the antigen density can help also to decide [19]. Schematically, when localized at the outer surface of the membrane, the variant is considered partial, when localized in the intramembrane or in the intracellular domain, the variant is considered only weak. But it has been shown that carriers of some variant categorized as weak did get immunized. It is the case for the weak D type 11, type 15, and also for the weak D type 4.2, which is found in sickle cell disease patients [20,21]. Then, as stated by the Bristol team, the weak D/partial D dichotomy is artificial [18]. Therefore, the risk of alloimmunization in a “variant” situation is fundamental to know to manage safely and efficiently the transfusion of the carrier. There is already a register for anti-D immunization [49], but there are no data regarding the clinical significance of the antibodies. There is no register for RHCE variants prone to immunization.

3. RH variants in sickle cell disease patients and the associated risk of alloimmunization

Sickle cell disease patients are highly polymorphic at the RH locus compared with individuals of European ancestry. In the *RHD* gene, the first difference is the molecular basis of D-negative individuals. As compared with D-negative European individuals who display mainly a deletion of the *RHD* gene [22], D-negative individuals of African ancestry exhibit a silent gene produced either by a 37 base pair insertion that lead to a premature stop codon or a hybrid *RHD-CE-D* gene characterized by the production of a partial C antigen but no D [23,24]. These differences do not bring any specific risk for sickle cell disease patients, as serologically there is no difference between D negative individuals from European or African ancestry. This background has to be considered only when determination of D is based on DNA-based typing methods. The variants that have to be taken into account are those prone to allo-immunization. They are the partial variants of the five main antigens (D, C, E, c, e), the variants characterized by absence of expression a high frequency antigen, mainly produced by abnormalities within the