Alloimmunization against Fy3 is a serious threat in the era of cell therapy

In a recent article of *Haematologica*, Stone *et al.* described a case of a severe delayed hemolytic transfusion reaction due to an anti-Fy3 alloimmunization of a patient suffering from sickle cell disease and expecting gene therapy.[1]

This case report comes at the right time in the field of sickle cell disease management for two reasons: numerous protocols of cell therapy (i.e. gene therapy or allogeneic hematopoietic stem cell transplantation) are forthcoming and all advocate intensive transfusions before and during the procedure. It also reminds us of the real immunological transfusion issues related to the genetic distance between donors and recipients.

We currently treat about 100 sickle cell patients in our center, and we have been particularly concerned about this complication of alloimmunization. Three young women episodically transfused for sickle cell disease developed anti-Fy3 alloimmunization, between 2017 and 2021. All of them were homozygous for the allele *FY*02N.01* (*GATA-1* mutation). Their red cell concentrates were selected according to the international guidelines.[2,3] Consequently, before this alloimmunization, they received between four and 33 red cell concentrates, cross-matched and Rh (D, C/c, E/e), K and, if possible, S, s, Fy^a, Fy^b, Jk^a, Jk^b matched. In particular, special attention was paid to antigens of the FY protein and the majority of red cell concentrates were Fy^a negative. Interestingly, prior development of anti-Fy^a antibody was identified for only one of the three, as this antibody is considered a risk factor for developing anti-Fy3 by experts.[1] Two of these patients had prior alloimmunizations directed against other red cell antigens: one patient had anti-S, anti-D, anti-C, anti-E, anti-Jk^a; another one had anti-M, anti-S, anti-Le^a, anti-Fy^a, anti-Jk^b, and anti-Do^a. Due to the presence of the anti-Fy3 antibody, these two patients were in a transfusion deadlock in Switzerland.

The three cases suggest that immunogenicity of Fy3 antigen might be more important than previously thought. An alloimmunization directed against such a common antigen among Caucasian donors is a matter of great concern in small countries like ours, because of the limited availability of rare blood products.

Another interesting fact is that all of these antibodies directed against the Fy3 antigen were evanescent. This complicates the situation since this antibody is well-known for an acute or delayed hemolytic transfusion reaction and, in a less severe manner, hemolytic disease of the newborn.[4] In our center, two of the three patients developed a severe and delayed hemolytic transfusion reaction. It is worth adding that anti-Fy3 alloantibody was still undetectable at the moment of these two transfusion reactions. This clinical presentation, without detection of the causative antibody just after the triggering transfusion, can occur in more than one third of cases, as shown by the multi-center study of Habibi *et al.* in 2016.[5]

In conclusion, the well-known discrepancy in FY protein antigens between donors and recipients must be seriously taken into account because it can definitively harm a promising project of cell therapy for young patients. Moreover, as suggested by the authors, cell therapy providers must be aware of the risk of alloimmunizations. Indeed, it increases inevitably with the number of transfusions.

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BL and SWA conbributed equally.

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All data can be obtained by email request to the corresponding author.

References

1. Stone EF, Avecilla ST, Wuest DL, et al. Severe delayed hemolytic transfusion reaction due to anti-Fy3 in a patient with sickle cell disease undergoing red cell exchange prior to hematopoietic progenitor cell collection for gene therapy. Haematologica. 2021;106(1):310-312.
2. Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. Blood Adv. 2020;4(2):327-355.
3. Pirenne F, Yazdanbakhsh K. How I safely transfuse patients with sickle-cell disease and manage delayed hemolytic transfusion reactions. Blood. 2018;131(25):2773-2781.
4. Tormey CA, Hendrickson JE. Transfusion-related red blood cell alloantibodies: induction and consequences. Blood. 2019;133(17):1821-1830.
5. Habibi A, Mekontso-Dessap A, Guillaud C, et al. Delayed hemolytic transfusion reaction in adult sickle-cell disease: presentations, outcomes, and treatments of 99 referral center episodes. Am J Hematol. 2016;91(10):989-994.