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Review

Interference of Monoclonal Antibody Therapy in Transfusion: An Update

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Abstract: Monoclonal antibody (MoAb) therapy has been increasingly used in recent years for hematologic malignancies. The MoAbs anti-CD38 and anti-CD47 are immunoglobulins directed against epitopes that are highly expressed not only on cancer cells, but also on red blood cells (RBCs), as well as platelets. Additionally, producing an off-target effect interferes in pre-transfusion testing, having the potential to unchain hemolytic anemia. Blood banks must assure the availability and safety of blood products for patients in need. Thus, MoAbs have become a challenge for blood banks, since methods to overcome interferences must be adopted. Several strategies have been proposed to mitigate pan-reactivity in pre-transfusion indirect antiglobulin tests, such as the treatment of reagent RBCs with enzymes or reducing agents, allogeneic RBC adsorptions, and drug-specific neutralization assays. All of these have some kind of limitation. This review summarizes the interferences of MoAbs in pre-transfusion testing, focusing on the available strategies to mitigate them in order to provide a safe transfusion.

Keywords: monoclonal antibody; Daratumumab; transfusion; anti-CD47

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1. Introduction

Monoclonal antibody (MoAb) therapy has been increasingly used in recent years for hematologic malignancies. Rituximab was the first MoAb approved by the FDA for treating an oncologic disease in 1997 [1]. Since then, more than 25 MoAbs have been introduced in clinical practices as a therapy for solid and hematological diseases [2]. Monoclonal antibodies are developed by hybridoma cultures and are directed against specific antigens. Interferences of MoAbs in different laboratory tests may occur depending of their specificity, although they have not been a problem until recently. The MoAbs anti-CD38 and anti-CD47 are immunoglobulins directed against epitopes that are highly expressed on red blood cells (RBCs) and platelets, and as an off-target effect, they interfere in pre-transfusion compatibility testing, in addition to having the potential to unchain hemolytic anemia [3].

Pre-transfusion testing consists of two main determinations—the ABO/Rh (D) typing and the screening for unexpected antibodies at 37 °C (antibody screen) using the indirect antiglobulin test (IAT). ABO typing consists of a forward type that identifies antigens present on the RBC surface and a reverse type to detect if anti-A and/or anti-B antibodies are present in the patient's plasma/serum. Screening for underlying alloantibodies or antibody screen tests, in general, involves the incubation of patient's plasma or serum with reagent RBCs at 37 °C, followed by an anti-human globulin phase for the detection of IgG alloantibodies. In addition, cross-matching in the antiglobulin phase between patient serum and RBCs being transfused is a mandatory test in patients who have been alloimmunized against RBC antigens [4]. Both antibody screening and cross-matching are IATs. Interferences with pre-transfusion tests were firstly detected in patients treated with the anti-CD38 Daratumumab [5]. Later, clinical trials using anti-CD47 agents were launched and stronger interferences were detected in pre-transfusion testing [6]. MoAbs

binding to reagent RBCs expressing CD38 and CD47 antigens lead to false-positive pan-agglutination during the anti-human globulin phase of pre-transfusion testing. If the blood bank has no previous knowledge on these treatments, finding pan-agglutination leads to an unnecessary laboratory workload in order to discard an autoantibody or alloantibody against high-incidence alloantibodies that could delay the provision of a blood transfusion. In addition, pan-agglutination masks underlying alloantibodies and puts the patient at risk for a post-transfusion hemolytic reaction [7]. Moreover, anti-CD38 and anti-CD47 MoAbs are used in patients who often have anemia and require periodic RBC transfusion support [8]. As such, the use of these MoAbs has raised relevant concerns about transfusion safety [9].

Blood banks must assure the availability and safety of blood products for patients who need them. Hence, the use of MoAbs has become a challenge for blood banks, since methods to overcome interferences must be adopted. Several strategies have been proposed, such as the treatment of reagent RBCs with enzymes or reducing agents, allogeneic RBC adsorptions, and drug-specific neutralization assays. All of them have limitations [2].

The objective of this review is to describe the interferences of MoAbs in pre-transfusion tests, and update the different approaches to overcome them.

2. Anti-CD38 Monoclonal Antibodies

Daratumumab was the first anti-CD38 MoAb to be approved by the FDA and EMA for relapsed or refractory multiple myeloma (MM). It is currently approved as the first-line treatment for transplant or non-transplant candidates [10]. The anti-CD38 MoAb Isatuximab was approved in 2021 by the FDA, in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received one to three prior lines of therapy [11]. Other anti-CD38 agents MOR202 and TAK079 are under investigation in ongoing clinical trials [5]. As such, there is an increasing number of patients who are receiving Daratumumab and Isatuximab. Fortunately, some studies have found that the risk of alloimmunization against RBC antigens in MM patients treated with the anti-CD38 Daratumumab is low and similar to the general patient population [8,12,13].

2.1. How Anti-CD38 Agents Work

Anti-CD38 Daratumumab is a humanized IgG1-k-type monoclonal antibody that binds to the CD38 molecule on the surface of human myeloma cells. CD38 is also expressed on the surface of some hematopoietic and non-hematopoietic stem cells, on plasma cells at a high level, and on RBCs in variable intensity [14]. Isatuximab is a chimeric humanized IgG1 kappa monoclonal anti-CD38 antibody that has been approved for a subset of patients with multiple myeloma as a second- and third-line treatment in combination with other anti-myeloma agents [15]. The main mechanisms by which anti-CD38 antibodies attack myeloma cells are antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity. Other mechanisms are the initiation of apoptosis due to crosslinks between CD38 on myeloma cells and effector cell Fcγ receptors, and immunomodulatory activity by depletion of myeloid-derived suppressor cells and regulatory T- and B-cells [16,17]. Daratumumab could also be effective in managing autoimmune disorders such as hemolytic anemia, pure red cell aplasia after ABO-incompatible hematopoietic stem cell transplantation, and antibody-mediated rejection in solid organ transplantation [18,19].

2.2. Interferences in Pre-Transfusion Tests

Anti-CD38 MoAbs (Daratumumab and Isatuximab) do not interfere with ABO or RhD typing, or immediate-spin crossmatching. However, CD38 expression on reagent RBCs used for IATs is the cause of the interference in pre-transfusion testing [20]. IATs use an IgG antibody directed against Fc of the immunoglobulin molecule. When reagent RBCs and the plasma/serum of a patient are incubated at 37 °C and Coombs antibody is added,

agglutination occurs if red blood cells have antibodies attached to the membrane. IATs are used not only for antibody screening, but also for full crossmatching, RBC alloantibody identification, and phenotyping. Anti-CD38 MoAbs bind to the CD38 antigen expressed on reagent RBCs and produce weak–moderate (+1–+2) pan-agglutination in all IAT tests, that may persist for up to 6 months after treatment ends [21]. Auto-control and direct antiglobulin tests (DATs) are often negative [5,17,22].

2.3. Strategies to Overcome Anti-CD38 Interferences in Pre-Transfusion Tests

Chapuy et al. [23] validated the dithiothreitol (DTT)-based method to overcome the interferences of anti-CD38 in pre-transfusion testing. These authors reported that 0.2 M DTT treatment of reagent RBCs could remove interference from Daratumumab by disrupting the structure of the CD38 antigen but maintaining the capacity for the identification of underlying clinically significant RBC alloantibodies. However, the DTT technique also denatures some clinically significant RBC antigens such as Kell, and other less immunogenic antigens such as Yt, Lutheran, JMH, Dombrock, and Cromer [17]. Thus, Kell-matched RBCs or Kell-negative RBCs, if K typing is unknown, must always be provided when using this method. Despite its efficacy, the DTT method is time-consuming and requires trained technologists; therefore, not all hospital blood banks have this test available. In order to simplify and to make the DTT technique available for 24 h, DTT-treated RBCs can be suspended in a RBC storage solution that extends the shelf life to 30 days [8,24]. Hosokawa et al. [25] proposed a simple method using 0.01 mol/L DTT for mitigating the Daratumumab interference and preserving K antigenicity. A method adapted for gel testing using DTT 0.04 M has also shown efficacy in alloantibody identification [26].

Some authors have shown that the manual polybrene method (MP) could overcome the interference caused by Daratumumab treatment. Comparing the MP method to DTT-IAT results in significant time and cost savings [27].

Although less effectively, proteolytic enzymes trypsin and papain have also been used in the immunohematologic studies of patients receiving anti-CD38 [5]. Data suggest that the use of papain panels for IATs avoids pan-reactivity and allows for the identification of the underlying alloantibodies [28]. As a disadvantage, proteolytic enzymes destroy some important blood group systems, such as Duffy and MNS, and therefore, phenotyped RBC units have to be transfused as a complement of this approach [29].

The most specific technique to eliminate pan-agglutination consists of neutralizing the anti-CD38 antibody in the patient serum before IATs. A recombinant monoclonal rabbit anti-DARA idiotype antibody has been used in 29 plasma samples from 29 patients receiving DARA. Pan-agglutination was eliminated and the detection of both alloanti-E and alloanti-K was allowed [30]. Selleng et al. [31] prepared $F(ab')_2$ fragments of Daratumumab by digestion with pepsin, and used them to block the binding to red blood cells by free Daratumumab in serum. This method has been successful for avoiding Daratumumab pan-agglutination in standard pre-transfusion testing. Other proposed methods are the supplementation of soluble CD38 to bind Daratumumab in patient serum [21]; the blockage of anti-CD38-adsorbed RBCs with antihuman globulin [32]; the use of cord red blood cells as reagent cells, since they express low levels of CD38 [33]; and the use of Darasorb for the pre-analytic depletion of anti-CD38 from patient plasma [34].

Allogeneic adsorptions using RBCs have not succeeded in eliminating pan-reactivity caused by anti-CD38 MoAbs; therefore, this method should not be used [21].

The DTT treatment of reagent RBCs is the most widely used method for avoiding pan-reactivity in pre-transfusion testing, and transfusion in patients receiving Daratumumab is considered to be safe [35].

3. CD47/SIRPα-Targeted Drugs

The CD47 transmembrane glycoprotein is highly expressed on a broad group of cell types including RBCs in the form of an Rh membrane protein complex, and CD47 expression is decreased in Rh-null RBCs. Platelets also have CD47 expression on the

membrane [3]. There are two classes of CD47/SIRPα-targeting agents currently under clinical investigation in phase I, II, and II clinical trials—IgG4 monoclonal antibodies (Hu5F9-G4, CC-90002, and Ti-061, SRF231) and SIRPα-Fc fusion proteins (TTI-621, TTI-622, and ALX148) [36]. Magrolimab (Hu5F9-G4) is a first-in-class humanized immunoglobulin G4 (IgG4) monoclonal antibody against CD47 that is under investigation in multiple clinical trials in combination therapies for solid tumor malignancies, MM, and relapsed/refractory acute myeloid leukemia [37,38]. ALX 148 is a fusion protein IgG1 containing a high-affinity engineered D1 domain of SIRPα. ALX148 binds CD47 with high affinity, inhibits wild-type SIRPα binding, and enhances the phagocytosis of tumor cells by macrophages. Moreover, ALX148 induces a broad antitumor immune response and enhances antitumor immunity, with a favorable safety profile [39,40]. Different new agents CD47/SIRPα are being tested in clinical trials [41].

3.1. How CD47/SIRPα-Targeted Drugs Work

The CD47/SIRPα pathway is an immune checkpoint in macrophages. Under physiological conditions, when CD47 binds to SIRPα on the surface of macrophages, it activates the "don't eat me" inhibitory signal. The overexpression of CD47 is a mechanism used by cancer cells to escape immune surveillance. On the contrary, CD47/SIRPα-targeted drugs make the tumor cells vulnerable to phagocytosis by macrophages [41]. CD47 seems to play a role in removing aged RBCs from circulation, since the amount of CD47 on the cell surface decreases when the RBC ages [2,42]. A transient hemolysis is observed after Magrolimab administration, probably due to the splenic clearance of aging RBCs [43].

3.2. Interferences in Pre-Transfusion Tests

MoAb Magrolimab strongly interferes in the reverse ABO group typing, producing ABO typing discrepancies in the non-O group patients, while forward typing is not affected.

A pan-agglutination (3+ or greater reactivity) is observed in the plasma samples of patients under Magrolimab treatment in all phases of antibody screening (saline, room temperature, 37 °C, and IAT). The titration of pan-reactivity is, in some cases, very high [44]. A variable positivity was found for DAT, and the eluate showed pan-reactivity [6,45]. The pattern of interference is highly variable among anti-CD47 agents, and depends on plasma drug concentrations, the IgG subclass, the characteristics of the drug molecule, the strength of the monoclonal affinity/avidity, and the methods used for blood typing [46]. Magrolimab also interferes in platelet testing [6].

ALX148 produces weak pan-reactivity (+2) in IATs and two-stage papain testing. However, there were no interferences at the immediate spin, room temperature, and 37 °C phases of antibody screening. DAT and auto-control were positives, and the eluate showed pan-agglutination [47]. The duration of the interference remains unknown. Pan-reactivity was found to disappear to a mean of 127 days after the last anti-CD47 treatment, based on data from a few patients [48].

Table 1 summarizes the interferences in the pre-transfusion testing of MoAbs.

Table 1. Characteristics of interferences in pre-transfusion testing caused by MoAbs.

	Anti-CD38	**CD47/SIRPα-Targeted Drugs**
ABO typing	No	Interference in reverse ABO typing
Rh/extended antigen typing	No	Possible
Antibody screening and cross-matching (IATs)	Pan-agglutinin (+1–+2)	Pan-agglutinin (+3–+4)
Direct antiglobulin test	Negative/Weak Positive	Positive
Eluate	Negative	Pan-agglutinin
Auto-control	Negative	Pan-agglutinin

3.3. Strategies to Overcome CD47/SIRPα-Targeted Drug Interferences in Transfusion Tests

The treatment of reagent RBCs with ficin, papain, trypsin, 0.2 M DTT, or W.A.R.M. reagent failed to mitigate the interferences. Multiple adsorptions [4] carried out with papain-treated allogeneic RBCs or pooled single-donor platelets succeeded in eliminating the interference [6]. Plasma is adsorbed three or four times at 37 °C with an equal volume or allogeneic RBCs or pooled platelets. This method is laborious, requires trained technicians, and carries the risks of diluting plasma and adsorbing alloantibodies against high-incidence antigens. Moreover, in some cases, a weak pan-reactivity may persist, depending on the plasma drug titration. Since Magrolimab is an IgG4, antibody screening in anti-human globulin phase using the Capture method with Gamma-Clone anti-IgG reagent (Immucor) eliminated the interferences. Capture is a solid-phase automated method that uses an anti-human immunoglobulin IgG reagent that does not recognize IgG4 for antibody screening, antibody identification, or serologic crossmatching. This method allows for the performance of IATs in an automated and easy way. As a disadvantage, it is useful only for IgG4 monoclonal antibodies, such as Magrolimab.

Recently, a new method using Daudi cells to eliminate anti-CD47 MoAb interferences in immunohematology testing has been published [49]. Again, it is a lengthy method that requires cell culture and cell preservation, and is, therefore, not available for most blood banks.

Fortunately, the preliminary data show, similar to anti-CD38, that the rate of alloimmunization in patients receiving anti-CD47 therapy is especially low [48]. Table 2 summarizes the usefulness of different strategies to avoid interferences of MoAbs in pre-transfusion testing.

Table 2. Strategies to mitigate interferences in pre-transfusion tests caused by MoAbs.

		CD47/SIRPα-Targeted Drugs	
Methods	**Anti-CD38**	**Anti-CD47 IgG4**	**ALX148**
IATs using DTT-treated RBCs	Yes	No	No
IATs using RBCs treated with papain or trypsin	Yes	No	No
IATs with anti-human globulin that does not detect IgG4	No	Yes	No
Multiple adsorptions 4–6 using allogeneic RBCs or pooled platelets	No	Yes	Yes
Soluble antigens	Yes	Yes	Unknown
Antibody fragments	Yes	Unknown	Unknown

4. How to Manage Transfusion in Patients Receiving Anti-CD38 and CD47/Sirpα-Targeted Drugs

Patients who are treated with anti-CD38 and CD47/SIRPα-targeted drugs often have anemia and will likely receive blood at some point during their illness. Moreover, interferences in pre-transfusion tests persist long after the treatment ends. Establishing a good communication between the clinical teams and hospital blood bank is critical to optimize transfusion support in patients receiving MoAbs. First of all, clinicians must inform blood banks about patients who receive any treatment that produce interferences in pre-transfusion testing. A lack of knowledge of these treatments leads to unnecessary imnunohematologic studies and delays in transfusion, thus compromising patient care and safety [7].

A complete pre-transfusion testing should be performed before starting treatment, including [50]:

- ABO/Rh (D) group typing
- Antibody screening (IATs) and identification, if positive
- DAT
- Phenotyping (if no transfusion/pregnancy/transplantation three months before) or genotyping (if recent transfusions or DAT positive) for Rh (CcDEe), K, JKa, JKb, Fya, Fyb, S, and s

Taking into account the high transfusion requirements of patients with acute leukemia, this information is critical for providing antigen-matched (at least Rh and K) blood in a timely manner, when needed, that can be as early as after the first Magrolimab dose.

Some centers recommend providing patients with an Alert Card that includes the baseline testing and information about treatment [50].

Once patients start treatment and pre-transfusion tests became pan-reactive, the studies to be performed to mitigate interferences will be different according to the drug involved. All the methods have limitations and there is no universal solution for the immunohematologic problems raised from MoAb therapy. Each transfusion service must establish specific protocols based on the available techniques, workflow, and expertise. In hospitals with few resources, samples should be sent to referral centers.

In the case of patients receiving anti-CD38 MoAbs, the most accurate and widely used approach is to perform IATs with DTT-treated RBCs [21]. This technique is implemented in many transfusion laboratories and Immunohematology Reference units. If the DTT method is not available, patients could be transfused with RBCs that are phenotype-matched for Rh (CcDEe), K, JKa, JKb, Fya, Fyb, M, N, S, and s, if possible [29]. In the case of complete phenotype-matched RBCs not being available, partially phenotype-matched RBC units can be issued (ABO > Rh (DCcEe) > K > JK > Fy > Ss > MN). RBC units should be negative for any antigen for which there were known alloantibodies.

The development or RBC alloantibodies is a major concern in transfusion medicine. In patients treated with Daratumumab, a low rate of alloimmunization has been found [51,52]. Consequently, some authors have questioned the need of patients receiving Daratumumab to be provided with phenotypically matched RBC units to prevent the development of clinically significant alloantibodies. Moreover, they suggest that universal pre-transfusion genotyping or extended phenotyping may be unnecessary [51,53].

Interferences produced by anti-CD47 agents are stronger and more challenging to mitigate. The available methods are time consuming and not always effective. In the case of Magrolimab, the use of the Capture technique is the best approach and interferences are successfully avoided. In ALX148, successive adsorptions should be performed, and expanded phenotype-matched RBC units should be provided to avoid alloimmunization [50]. The concern about transfusing phenotype-matched RBCs is the development of alloantibodies against minor antigens or non-matched antigens that may complicate future transfusions.

Many transfusion services also provide extended antigen-matched RBC units to individuals on cross-reactive therapies to mitigate novel alloantibody formation and to avoid compatibility complexities in future care.

In emergency situations, un-crossmatched group O RBCs should be issued. Expanded antigen phenotype-matched (as compatible as possible) RBC units should be transfused if available on site. Figure 1 summarizes the workflow to mitigate interferences caused by MoAbs.

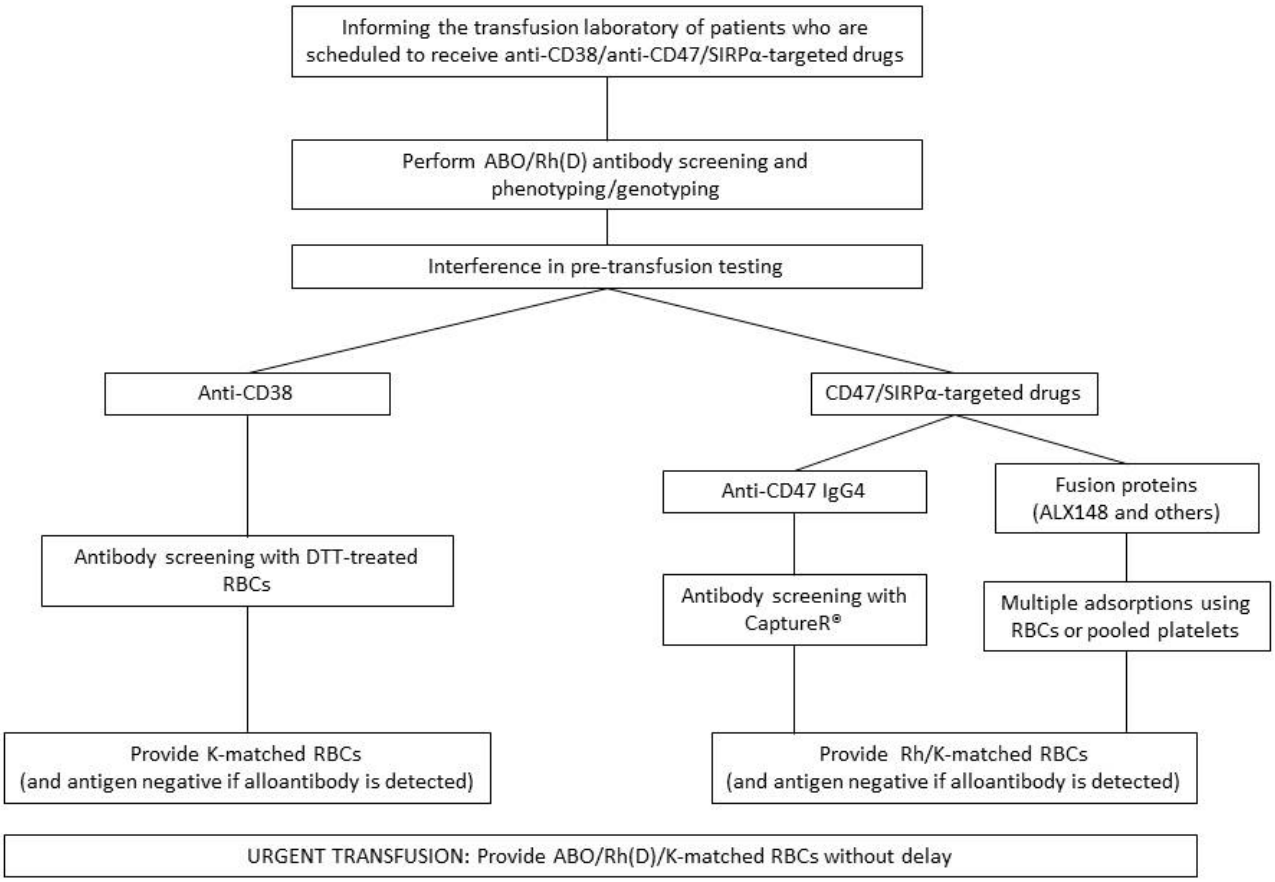

Figure 1. Workflow to address the interferences of MoAbs in pre-transfusion testing.

5. Conclusions and Future Directions

We live in the era of new drugs, in which monoclonal antibodies are emerging. Interferences in pre-transfusion testing have risen as an off-target effect of some MoAbs. Anti-CD38 and anti-CD47 may be the tip of the iceberg. As an aggravating circumstance, these treatments are used for patients with hematologic malignancies, such as acute leukemia, who are among the greatest proportion of blood product consumers.

Blood banks must be prepared to recognize drug immunohematologic effects, to innovate and rapidly implement new methods and protocols to overcome interferences in pre-transfusion testing, and to provide a safe transfusion. There is no universal and simple solution for all cases; on the contrary, there are a variety of methods that can be applied in different scenarios. The goal is to provide a safe transfusion and minimize the risk to patients as much as possible. In addition, new affordable methods and strategies to overcome strong interferences produced by CD47/SIRPα-targeted drugs are needed.

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