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ORIGINAL RESEARCH

TRANSFUSION

How do transfusion services manage patients taking therapies such as anti-CD38 and anti-CD47 known to interfere with red blood cell compatibility testing?

Michael F. Murphy[1] | **Srijana Rajbhandary**[2] | **Sharon Carayiannis**[2] | **Claudia S. Cohn**[2,3]

[1]NHS Blood and Transplant, Oxford University Hospitals NHS Foundation Trust and the University of Oxford, Oxford, UK

[2]AABB, Bethesda, Maryland, USA

[3]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota, USA

Correspondence
Michael F. Murphy, NHS Blood and Transplant, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, and the University of Oxford, UK OX3 9BQ, Oxford, UK.
Email: mike.murphy@nhsbt.nhs.uk

Abstract

Background: Drugs such as daratumumab (Darzalex, anti-CD38) and Hu5F9-G4 (magrolimab, anti-CD47) may interfere with red blood cell compatibility testing as CD38 and CD47 are expressed on red blood cells.

Study Design and Methods: A survey of AABB member transfusion services was undertaken to understand their experiences of managing patients taking therapeutic monoclonal antibodies that are known to interfere with blood grouping and compatibility testing.

Results: The survey was distributed to the contact person at US-based AABB member transfusion services. The response rate was 27%. 172 of 240 (72%) indicated they had difficulties in performing compatibility testing in patients taking daratumumab and 66 of 91 (73%) reported difficulties in performing compatibility testing in patients taking magrolimab. Actions taken to provide compatible blood for these patients included referral of all samples to a reference center, blood group pheno/genotyping the patient in advance of starting the drug, treating reagent cells with 0.2 M dithiothreitol and using K-negative red cell units for patients taking daratumumab, and Gamma-clone (Immucor) anti-IgG for indirect antiglobulin testing for patients taking magrolimab. Lack of communication from clinical services about drug treatment was identified as a concern.

Conclusion: The results of the survey demonstrate that transfusion services are having challenges with the transfusion management of patients taking therapeutic monoclonal antibodies, and further education is needed.

KEYWORDS

ABO typing interference, anti-CD38, anti-CD47, daratumumab, Darzalex, Hu5F9-G4, magrolimab, pretransfusion testing interference, serological interference, transfusion interference

Abbreviations: AABB, Association for the Advancement of Blood and Biotherapies; AGT, Antiglobulin test; DTT, dithiothreitol; EMR, Electronic Medical Records; IRL, Immunohematology Reference Laboratory; RBC, Red blood cells.

1 | INTRODUCTION

Monoclonal antibodies are increasingly being used to treat patients with hematological malignancies and other disorders. Drugs such as daratumumab (Darzalex, anti-CD38) and Hu5F9-G4 (magrolimab, anti-CD47) may interfere with red blood cell compatibility testing as CD38 and CD47 are expressed on red blood cells.[1-4] Pan-reactive agglutination may occur in the standard indirect antihuman globulin (Antiglobulin test [AGT]) test used for antibody screening and crossmatching. Consequently, clinically relevant red blood cell alloantibodies may not be recognized in patients who need blood transfusion.

Various measures have been developed to overcome problems with compatibility testing. To safely test daratumumab samples, reagent red cells can be treated with 0.2 M dithiothreitol (DTT) to denature CD38 binding sites. A drawback of DTT treatment is the disruption of a limited number of blood group antigens such as Kell, and so it is usual practice to provide Kell negative units to patients treated with daratumumab.[1] For patient samples affected by magrolimab, an anti-CD47 IgG4 monoclonal antibody, Gamma-clone anti-IgG, can be used as it lacks IgG4 reactivity.[4] While these methods are regularly used by immunohematology reference laboratories (IRL), they may be beyond the scope of most transfusion services and blood banks.

We undertook a survey to understand the experiences of hospital transfusion services in managing patients taking these drugs, how they are dealing with any problems encountered with compatibility testing, and how they are managing the provision of blood for transfusion. The intention was that it will result in greater awareness of the problems that these drugs cause in compatibility testing and how they can be overcome.

2 | METHODS

The survey (see Table S1) was distributed to the contact person at US-based AABB member hospital transfusion services within the 50 states, the District of Columbia and Puerto Rico, and the Armed Services Blood Programs from August 28 to October 2, 2023. We asked the survey to be shared with appropriate contacts, but that only one survey should be completed for each institution. Duplicate responses for a facility were possible, but we think unlikely. It was not distributed to free-standing IRLs, as it was assumed that they have the capability of managing patients with complex transfusion problems such as interference with pretransfusion testing caused by therapeutic monoclonal antibodies. Display logics were applied to the online survey questionnaire (Table S1) to prompt respondents with relevant questions, and as a result, the denominators are not uniform throughout the survey. For multiple selection questions, frequencies are presented as percentage of the number of respondents for the question. The open-ended text responses for "Other/something else" options were reviewed and re-categorized where possible to appropriate options provided in the respective questions.

3 | RESULTS

3.1 | Respondents to the survey and their characteristics

A total of 272 institutions, 258 hospital transfusion services (221 without a reference laboratory and 37 with a reference laboratory) and 14 blood centers with an immunohematology reference laboratory, responded to the survey. The hospital transfusion services response rate was 258 of 944 (27%). There was much variation in the characteristics of the hospital transfusion services in relation to their location (urban, suburban, and rural), bed size, and the annual number of red cell units supplied (Table 1). The annual number of investigations referred to IRLs from hospital transfusion services varied from less than 25 to greater than 500, and shipping times (Table 1) varied from less than 30 min to several hours.

3.2 | Blood bank technology for compatibility testing

267 of 272 survey participants responded to the question about the technology used for routine antibody screening and crossmatching. 152 (57%) participants used column agglutination, 62 (23%) used solid phase, 29 (11%) used tube indirect antiglobulin test, and the remaining 24 (9%) used combinations of the three techniques.

3.3 | Capability to perform blood group genotyping

The capability for performing blood group genotyping was limited to 18 transfusion services. Of these sites, four were included because they belonged to a hospital system with this capability.

3.4 | Blood bank testing for patients taking daratumumab and magrolimab

The majority (88%) of transfusion services indicated they undertook pretransfusion testing for patients taking

TABLE 1 Characteristics of hospital transfusion service respondents.

	n
Hospital location (258 responses)	
Urban	157
Suburban	72
Rural	29
Hospital type (258)	
Academic	145
Non-academic	113
Bed size (256)	
0–100	30
101–200	43
201–300	46
301–400	43
401–500	23
500+	71
Annual RBC units supply (258)	
<500 units	20
501–1000 units	14
1001–5000 units	98
5001–10,000 units	59
10,001–20,000 units	37
>20,000 units	30
Hospital average shipping time (254)	
<30 min	14
<1 h	34
<3 h	111
>3 h	95
Number of investigations sent to IRL annually (251)	
<25	139
25–100	86
100–500	24
>500	2
Shipping time for urgent specimens (233)	
<30 min	20
31–60 min	79
61–150 min	82
151–240 min	40
241–480 min	6
481–600 min	1
601+ min	5

Abbreviations: IRL, immunohematology reference laboratories; RBC, red blood cells.

daratumumab, but less (33%) undertook this testing for magrolimab (Table 2). The most common method

TABLE 2 Responses regarding compatibility testing for daratumumab and magrolimab.

	Daratumumab, *n* (%)	Magrolimab, *n* (%)
Perform pretransfusion testing for patients taking these drugs		
Yes	240 (88)	91 (33)
No	28 (10)	124 (46)
Don't know	4 (1)	57 (21)
Clinical service Information Regarding Patients taking these drugs[a]		
On a written or electronic request	118 (52)	39 (48)
Phone call	71 (32)	18 (22)
Other	12 (5)	6 (7)
We are not notified	57 (25)	25 (31)
Pharmacy notification	17 (8)	5 (6)
Experienced difficulties with compatibility testing		
Yes	172 (72)	66 (73)
No	68 (28)	25 (27)
Have a formal policy for providing crossmatched RBC units for patients taking these drugs		
Yes	177 (78)	55 (68)
No	49 (22)	26 (32)

Abbreviation: RBC, red blood cells.

[a]Question limited to the transfusion services that performed pretransfusion testing for patients taking these drugs. Respondents could select more than one answer. It was not a mandatory question.

for informing the transfusion service regarding patients taking these drugs was by written or electronic request. No notification was received from the clinical service by 25% of transfusion services about the use of daratumumab and by 31% of transfusion services about the use of magrolimab. Of the services that do not get notification, 42% responded that the use of daratumumab was identified through the Electronic Medical Record (EMR) review and 24% responded identifying the use of magrolimab through the EMR review.

3.5 | Difficulties in compatibility testing experienced by transfusion services

172 of 240 (72%) respondents indicated they had difficulties in performing compatibility testing in patients taking daratumumab, and 66 of 91 (73%) reported difficulties in performing compatibility testing in patients taking magrolimab (Table 2).

87 out of 127 (69%) academic hospitals reported difficulties in performing compatibility testing in patients taking daratumumab compared with 77 of 99 (78%)

nonacademic hospitals. 33 of 49 (67%) academic hospitals reported they had difficulties in performing compatibility testing in patients taking magrolimab compared with 25 of 32 (78%) nonacademic hospitals. There was little difference in the responses about difficulties in compatibility testing when analyzed by the bed size of the hospital.

3.6 | Policies for providing compatible blood

177 of 226 (78%) respondents indicated they had policies for providing compatible blood in patients taking daratumumab and 55 of 81 (68%) reported they had policies for providing compatible blood in patients taking magrolimab. 103 of 127 (81%) academic hospitals reported they had policies for the management of patients taking daratumumab compared with 74 of 99 (75%) nonacademic hospitals. 33 of 49 (67%) academic hospitals reported they had policies for the management or patients taking magrolimab compared with 22 of 30 (73%) nonacademic hospitals.

3.7 | Actions taken to overcome the difficulties with compatibility testing

The most common answers to questions about actions taken to provide compatible blood for patients taking daratumumab were to refer all samples to a reference center, blood group pheno/genotype the patient in advance of starting the drug and provide antigen-matched red blood cell units for transfusions, and treat reagent cells with 0.2 M dithiothreitol (DTT) and use K-negative red cell units (Table 3). Of the "Other" responses for the question related to actions taken to provide compatible blood for patients taking daratumumab, 68% of responses stated the use of ABO/Rh-compatible K-negative units.

46 of 103 (45%) academic hospitals reported they referred all samples to a reference center for patients taking daratumumab compared with 42 of 74 (57%) nonacademic hospitals. 9 of 33 (27%) academic hospitals reported they referred all samples to a reference center for patients taking magrolimab compared with 15 of 22 (68%) nonacademic hospitals. The bed size of hospitals also influenced the referral to a reference center for both daratumumab and magrolimab, for example, only 25% of hospitals with a bed size of over 500 referred samples from daratumumab patients and only 22% of hospitals with a bed size of over 500 referred samples from magrolimab patients.

The most common answers to questions about actions taken to provide compatible blood for patients taking magrolimab were to refer all samples to a reference center, blood group pheno/genotype the patient in advance of starting the drug and provide antigen-matched red blood cell units for transfusions only if other compatibility tests do not work or are temporarily unavailable, blood group pheno/genotype the patient in advance of starting the drug and provide antigen-matched red blood cell units for transfusions, and use Gamma-clone (Immucor) anti-IgG for indirect antiglobulin testing. Most

TABLE 3 Actions taken to overcome difficulties in compatibility testing (respondents could select more than one answer).

Daratumumab	***n* = 177**
a. Refer all samples for testing at a reference center	88
b. Provide ABO/Rh-compatible RBCs and advise the clinicians to monitor the patient for evidence of hemolysis	29
c. Treat reagent cells with 0.2 M DTT and use K-negative red cell units	63
d. Use lower concentrations of DTT (e.g., 0.01 M) to preserve the K antigen	0
e. Neutralize daratumumab in plasma with soluble CD38 or anti-daratumumab idiotype antibodies	0
f. Blood group pheno/genotype the patient in advance of starting the drug and provide antigen-matched red blood cell units for transfusions	73
g. Blood group pheno/genotype the patient in advance of starting the drug and provide antigen-matched red blood cell units for transfusions only if other compatibility tests do not work or are temporarily unavailable	46
h. Other	31
Magrolimab	***n* = 55**
a. Refer all samples for testing at a reference center	24
b. Provide ABO/Rh-compatible RBCs and advise the clinicians to monitor the patient for evidence of hemolysis	8
c. Conduct multiple RBC alloadsorptions to minimize interference	1
d. Use Gamma-clone (Immucor) anti-IgG for indirect antiglobulin testing	21
e. Blood group pheno/genotype the patient in advance of starting the drug and provide matched red blood cell units for transfusions	24
f. Blood group pheno/genotype the patient in advance of starting the drug and provide antigen-matched red blood cell units for transfusions only if other compatibility tests do not work or are temporarily unavailable	24
g. Other	8

Abbreviations: DTT, dithiothreitol; *n*, number of respondents; RBC, red blood cells.

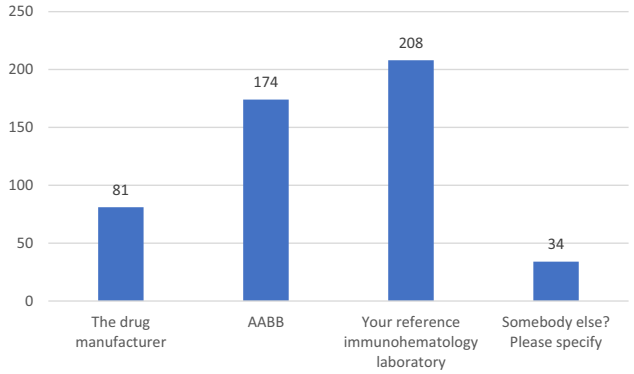

FIGURE 1 Provision of advice for management of patients taking drugs known to interfere with compatibility testing (respondents could select more than one answer). [Color figure can be viewed at wileyonlinelibrary.com]

transfusion services applied more than one action. Of the "Other" responses, for question related to actions taken to provide compatible blood for patients taking magrolimab, 38% of responses stated the use of ABO/Rh-compatible K-negative units.

3.8 | Advice on compatibility testing

Transfusion services were asked from whom they would expect advice for patients taking drugs known to interfere with compatibility testing (Figure 1). The most common answer was their IRL, followed by AABB and the drug manufacturer. A minority of respondents would seek expert advice from other sources. In relation to other sources of advice, 35% responded seeking advice from their medical directors.

4 | DISCUSSION

The therapeutic use of monoclonal antibodies that target antigens expressed by cancer cells that are also present on red blood cells produces challenges for pretransfusion testing. If not managed appropriately, test turnaround times may be prolonged, and the provision of blood products delayed thus compromising patient care and safety.[4] It is uncertain how transfusion services are dealing with any problems encountered with compatibility testing and how they are managing the provision of blood for patients taking these drugs.

This survey was conducted by contacting AABB member hospital transfusion services contacts. The participation rate was 27% of transfusion services. The variation in the characteristics of the transfusion services that responded in terms of location (urban, suburban, and rural), bed size, and the annual number of red cell units supplied were in line with expectations. There was also the expected variation in the technology used for routine antibody screening and crossmatching, with the most common being column agglutination and solid phase. The capability for performing blood group genotyping was limited to around 8% of the total respondents. The shipping times of samples to reference centers were variable and sometimes it took several hours, even for urgent samples.

The majority of transfusion services indicated they undertook pretransfusion testing for patients taking daratumumab, but this was much less for magrolimab, possibly reflecting the more recent and less widespread use of this drug. It is concerning that 12% of transfusion services reported that they were not notified that patients were taking daratumumab when compatibility testing requests were made, and this was even higher at 25% for magrolimab.

Over 70% of transfusion services indicated they had problems with compatibility testing for both daratumumab and magrolimab. The general actions taken to provide compatible blood for these patients were appropriate, including referral of all samples to a reference center and to blood group pheno/genotype the patient in advance of starting the drug and provide antigen-matched red blood cell units. Specific actions were to treat reagent cells with 0.2 M dithiothreitol (DTT) and use K-negative red cell units for patients taking daratumumab and to use Gamma-clone (Immucor) anti-IgG for indirect antiglobulin testing for patients taking magrolimab. Transfusion services indicated they would seek advice about difficulties with compatibility testing for patients taking drugs known to interfere with compatibility testing from their IRL, AABB, or the drug manufacturer. Perhaps not surprisingly, nonacademic hospitals reported slightly higher rates of difficulties in compatibility testing than academic centers and higher rates of referral of samples to a reference center for patients taking daratumumab and magrolimab. The bed size of the hospital had a similar effect with a lower referral rate in hospitals with a large bed size.

This study has the obvious limitations of a snapshot survey, but it clearly demonstrates that transfusion services are having challenges with the transfusion management of patients taking therapeutic monoclonal antibodies. A recent review article summarized mitigation strategies such as blood group pheno/genotyping the patient in advance of starting the drug and emphasized the importance of timely communication between clinicians and transfusion services.[4] The lack of such communication was one of the most important findings of this survey. Another important finding was the recognition that advice about the transfusion management of these

patients can be obtained from several sources. The survey collected information on the difficulties that transfusion services are having, suggesting that further efforts are needed to provide information and education on this issue. Although magrolimab use in acute myeloid leukemia and myelodysplastic syndrome was halted by the FDA in February 2024 due to significant clinical risks found in clinical trials and there has been a pause in enrollment in solid tumor studies, the findings of this survey are relevant for current and future use of monoclonal antibody therapies that affect transfusion testing.

CONFLICT OF INTEREST STATEMENT

The authors have disclosed no conflicts of interest.

ORCID

Michael F. Murphy https://orcid.org/0000-0002-2375-7503
Srijana Rajbhandary https://orcid.org/0000-0001-8283-1921
Claudia S. Cohn https://orcid.org/0000-0001-9847-0470

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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