Original article

Multicenter evaluation of soluble CD38: neutralizing anti-CD38 pan-reactivity to enable alloantibody detection

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Background - Anti-CD38 is a monoclonal antibody treatment for multiple myeloma, B-cell malignancies, and autoimmune diseases that targets CD38 antigens on the cell surface. Red blood cells are CD38+, therefore anti-CD38 causes panagglutination, hindering immunohematology testing such as antibody screen, antibody identification, and crossmatch. This interference masks detection of clinically significant alloantibodies in pre-transfusion testing.

Materials and methods - To assess the effectiveness of soluble CD38 (sCD38) in neutralizing anti-CD38 in the clinical setting and user satisfaction, plasma samples from patients receiving anti-CD38 therapy were collected between 0 and 150 days after the last infusion and tested according to routine laboratory procedures with an established sCD38 neutralization method (15 minutes incubation at 37°C with up to 6 µL of sCD38 per 25 µL of plasma). Neutralization was evaluated using antibody screening or crossmatching, by tube or gel card. Some samples were spiked with irregular antibodies to evaluate the impact of sCD38 on antibody detection. A survey assessed user satisfaction.

Results - In total, 273 patient samples were evaluated (263 patients treated with daratumumab and 10 with isatuximab). sCD38 completely neutralized anti-CD38 present in 79.8% of samples tested using either 2 or 4 µL of sCD38. When either 2-4 or 6 µL of sCD38 was used, 98.5% of samples were neutralized. Except for anti-Fya and anti-Fyb, all spiked alloantibodies (anti-D, -c, -E, -K, -Jk^a, -Kp^a, -Lu^a, -S) were detected. The mean score for general satisfaction with sCD38 was 4.44 (with 5 [very satisfied] the highest score).

Discussion - sCD38 has demonstrated strong potential in neutralizing anti-CD38 drugs in the clinical setting. While tested against isatuximab and daratumumab, it could be a potentially universal solution. By mimicking CD38 antigen on red blood cells, sCD38 is likely to interact with a broad range of anti-CD38 antibodies, suggesting its possible applicability across various settings.

Keywords: *pre-transfusion testing, CD38, neutralization, antibody, multiple myeloma.*

Arrived: 19 June 2025
Revision accepted: 26 August 2025
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INTRODUCTION

CD38 antigen is an integral transmembrane glycoprotein that is ubiquitously expressed in the bone marrow environment and on the surface of red blood cells (RBC)[1]. In addition, CD38 has been found to be overexpressed on the surface of multiple myeloma (MM) cells. This overexpression makes CD38 one of the main targets of immunotherapies against MM and initially led to the development of anti-CD38 monoclonal antibodies (mAb)[2] as a therapeutic agent to treat this disorder. Anti-CD38 mAb daratumumab (Darzalex®, Janssen-Cilag Pty Ltd, Macquarie Park, Australia) has been shown to be an efficient treatment in relapsed and refractory MM, being the first anti-CD38 mAb (hIgG1 Kappa) approved for the treatment of relapsed and refractory MM[3]. Other anti-CD38 mAb were also clinically developed as isatuximab (IgG1, Sarclisa®, Sanofi, Paris, France), MOR202 (IgG1λ, MorphoSys AG, Planegg, Germany) and TAK-079 (IgG1λ, Takeda, Tokyo, Japan)[4]. Among these four agents, daratumumab is the most widely used in therapy and has also been approved for first line combination therapy in newly diagnosed MM patients[5]. Since then, anti-CD38 is gaining broader application in other diseases including more recently cold agglutinin disease and warm autoimmune hemolytic anemia[6,7], rheumatoid arthritis and systemic lupus erythematosus[8], for HLA antibody mediated rejection[9], and in the setting of refractory acute leukemia[10].

These patients often require blood transfusion as part of their supportive care[11,12]. As CD38 is weakly expressed on the surface of all RBCs[1], serum/plasma from patient treated with anti-CD38 interferes in indirect antiglobulin test (IAT) phase[13], causing panagglutination in the antibody screen, antibody identification, and crossmatch, potentially masking a clinically relevant alloantibody[14-16]. Notably the direct antiglobulin test (DAT) and the auto-control are often negative, suggesting a potential antigen downregulation or the clearance of patient's RBC with high levels of CD38[17]. Anti-CD38 does not interfere with ABO or RhD typing.

The panagglutination caused by anti-CD38 does not only increase the likelihood of missing a significant alloantibody that may cause hemolytic transfusion reactions, but also, it delays issuing of blood products[13,17-20]. In addition, the standard practice to use DTT-treated reagent screening cells is associated with a laborious in-house validation, with reagent RBCs having a significant short shelf life (1-4weeks) that require daily quality control.

Several strategies have been developed to overcome the interference caused by anti-CD38, either by inhibition of anti-CD38 in patient's plasma (such as blockage monoclonal antibody protocol[21], Daudi B-cell line[22]) or by blocking/destroying the CD38 antigen expressed on RBC (including dithiothreitol[23-25], 2-mercaptoethanol[26], or fab fragments[27-29]). Although these methods have been well established internationally and provided specific evidence that they are reliable and safe for routine test performed in the immunohematology laboratory, their use as routine procedure has limitations such as time-consuming testing methods or K antigen destruction, and consequent loss of antibody detection[23,30-34]. For the above reasons, there is a need for improved techniques and ready-to-use reagents.

Soluble CD38 (sCD38; Medion Grifols Diagnostics, Düdingen, Switzerland; CE-marked product) is a recombinant protein reagent for the pre-treatment of plasma of patients receiving anti-CD38 therapy, to counteract anti-CD38-mediated pan-reactivity without diluting the patient plasma significantly. Selective binding to anti-CD38 enables for its inactivation and subsequent screening and identification of irregular antibodies, previously masked by the presence of the anti-CD38, in DG Gel (Diagnostic Grifols SA, Parets del Vallès, Spain) and tube techniques, and crossmatch in DG Gel technique in plasma from patients undergoing anti-CD38 treatment. sCD38 reliably neutralizes anti-CD38 in clinical samples and when serum/plasma samples are spiked with the oncological drug daratumumab[35-37].

This study aimed to summarize the effectiveness of sCD38 in neutralizing anti-CD38 drugs in the clinical setting, i.e., using samples from patients treated with anti-CD38, and the user satisfaction level with the sCD38 testing method.

MATERIALS AND METHODS

Study design

This was a multicenter study in samples from patients treated with anti-CD38 in real-world clinical practice conducted at eight sites in the UK, Italy, Spain, France, and Switzerland to assess the effectiveness of sCD38 in neutralizing daratumumab or isatuximab anti-CD38 therapies.

Samples

In this study, a total of 273 samples were tested, including 182 plasma samples (70 fresh and 112 frozen), 71 serum samples (all frozen samples) and 20 frozen samples without information regarding whether the sample was plasma or serum. For 183 samples, pretreatment of plasma with sCD38 was performed internally (in the upper chamber of a DG Gel card), for 49 samples it was performed externally (in a glass tube), and for 41 samples with both methods in parallel. The volume of sCD38 used per 25 µL of plasma or serum was 2, 4, or 6 µL depending on the anti-CD38 neutralization achieved.

Main inclusion criterion was patients with anti-CD38 treatment ongoing or last dose within the last 150 days. Exclusion criteria included collected sample volume lower than 1 mL, and blood specimens exhibiting gross hemolysis or contamination. All patients signed the informed consent form (when applicable); in case of leftover samples, informed consent was not required. According to local regulations, ethics committee approval was not required for studies involving anonymized residual samples.

Data collection

For each sample, the following data were recorded in the results data sheet: the date of blood drawing, aliquot number, kind of material, volume of the aliquot, kind of treatment (daratumumab or others), the antibody screening results, and whenever available, the date of the last treatment infusion and the infusion program received by the patient.

Procedures

The samples were tested according to the work habits of the laboratory. The existing method (called comparative method) was carried out (when possible) according to each site protocol and the sCD38 method was added to the routine. For the sCD38 method, plasma samples from patients receiving anti-CD38 therapy were pretreated with sCD38 (incubation at 37°C for 15 minutes). For each testing, 25 µL of plasma containing anti-CD38 drug were treated first with 2 µL of sCD38; in case the 2 µL of sCD38 did not inhibit sufficiently the amount of anti-CD38 present in the plasma (residual positive reaction not due to any irregular antibodies), a new aliquot of 25 µL of plasma was treated with 4 µL of sCD38 according to Grifols sCD38 instructions for use (IFU). In addition, a research use only method was evaluated: if 4 µL of sCD38 did not neutralize the sample, the procedure (with the whole test cell panel) should be repeated with 6 µL of sCD38.

Evaluation of neutralization was carried out with different immunohematological methods, i.e., antibody screening or crossmatching, and using tube method or DG Gel technique. Pretreatment of plasma with sCD38 could be internal (in the upper chamber of a DG Gel card) or external. The method used for neutralization assessment and pretreatment with sCD38 was chosen by each site. The sCD38 testing method is primarily manual when used with tube and gel techniques. However, when plasma is pretreated externally with sCD38, automated systems may be used for subsequent testing, depending on the laboratory setup. The method is compatible with both plasma and serum samples.

Additionally, because none of the samples contained natural alloantibodies, some samples were spiked with irregular antibodies to evaluate the impact of sCD38 pretreatment on antibody detection.

Study outcomes

The main outcome was the evaluation of the effectiveness of the methods on anti-CD38 neutralization (complete or incomplete neutralization) and their impact on antibody detection (whether antibodies spiked to the samples can be detected after anti-CD38 neutralization pretreatment). Additional outcomes included the level of user satisfaction with the sCD38 test method. A satisfaction survey was filled in by the eight sites at the end of the study. Each survey item rated from 1 to 5, where 1 was very dissatisfied and 5 was very satisfied. The likelihood of recommending the sCD38 method to a colleague was rated from 1 (not likely at all) to 10 (extremely likely).

Statistical analysis

All variables were categorical and described by counts and percentages per category. Microsoft Excel was used to analyze the data sets (Microsoft, Redmond, WA, USA).

RESULTS

Samples

A total of 273 samples from real patients were evaluated in eight sites. Of them, 263 patients were receiving or received treatment with daratumumab and 10 patients with isatuximab. **Figure 1** shows the testing methods used. A comparative method with DTT (gel or tube) was used for a total of 157 samples in four sites. According to study

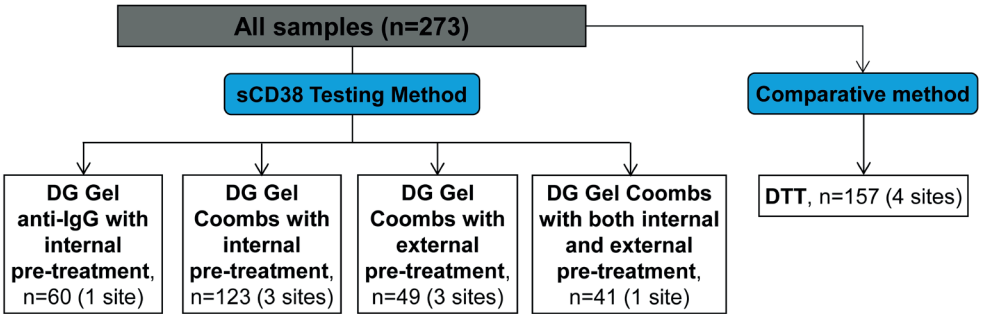

Figure 1 - Testing methods used for sCD38 and for the comparative reagent

protocols, DTT concentrations and method used: Udine and Vitoria-Gasteiz: gel technique - DTT concentration 0.2 mol/L; Zurich: tube - DTT concentration 0.01 mol/L; Napoli: gel technique - DTT concentration 0./04 mol/L.

Neutralization assessment

In 79.8% (218 out of 273) of the samples tested in this study, the anti-CD38 was completely neutralized by either using 2 or 4 µL of sCD38 to treat 25 µL of plasma. It was possible to reach 98.5% (269 out of 273) complete inhibition by using 6 µL of sCD38. Only 4 out of 273 (1.5%) samples, all containing daratumumab, showed very weak panagglutination after treatment with sCD38. However, even in these cases, a decrease in the initial interference intensity (untreated plasma) was observed (**Table I**).

The comparison DTT method could completely neutralize the interference caused by anti-CD38 in 78.3% (123 out of 157) of the samples. Of these, 46 samples were tested using the gel card technique and 77 using the tube test. In some of the 80 samples tested with DTT in gel card, a small ring of RBC was retained at the top of the column, making the result less neat. The 34 samples partially neutralized by DTT (all tested using the gel card technique) were completely neutralized by 2 or 4 µL of sCD38.

Antibody detection

A total of 25 patient samples containing 10 different alloantibody specificities were tested with sCD38 (gel technique) in 3 sites: anti-D (5 samples), anti-c (3 samples), anti-E (3 samples), anti-K (3 samples), anti-Jk^a (1 sample), anti-Fy^a (6 samples), anti-Fy^b (1 sample), anti-Kp^a (1 sample), anti-Lu^a (1 sample), anti-S (1 sample). All alloantibodies were detected after using sCD38 except for the 6 anti-Fy^a and 1 Fy^b samples.

In addition, one site tested 11 samples spiked with nine different alloantibody specificities with sCD38 (gel technique) and DTT (tube technique): anti-D (1 sample), anti-E (2 samples), anti-K (1 sample), anti-Jk^a (1 sample), anti-Fy^a (2 samples), anti-Fy^b (1 sample), anti-Kp^a (1 sample), anti-Lu^a (1 sample), anti-S (1 sample). Overall, five alloantibodies were missed after using DTT method (anti-E, anti-Fy^a, anti-K, anti-D, anti-Kp^a), whereas 3 anti-Fy (anti-Fy^a/Fy^b) were not detected after sCD38 neutralization.

Satisfaction level

The survey items with highest mean satisfaction score when using sCD38 were those related to reagents management (5 out of 5 points), ability to provide matched blood units in a timely manner (4.78 out of 5 points), and ability to solve the current challenges related to treating daratumumab patients (4.67 out of 5 points). The mean score for the general satisfaction level with sCD38 was 4.44. When comparing the mean scores between sCD38 and the comparative method (current method used whenever the client has a method implemented or a current workflow whenever the client does not have a method on site but has to send the

Table I - *Samples neutralization by volume of sCD38*

Treatment	Completely neutralized with 2 µL	Completely neutralized with 4 µL	Completely neutralized with 6 µL	Partially neutralized	Total
Isatuximab	9 (90%)	1 (10%)	0 (0%)	0 (0%)	10 (100%)
Daratumumab	138 (52.5%)	70 (26.6%)	51 (19.4%)	4 (1.5%)	263 (100%)
Total	147 (53.8%)	71 (26.0%)	51 (18.7%)	4 (1.5%)	273 (100%)

Table II - *Mean score of the main points of the satisfaction survey*

Evaluated topic	Current method	sCD38
Hands on time	3.00	4.22
Reagents management (i.e., shelf-life, preparation, number of sub-reagents, consumption)	3.33	5
Ability to provide matched blood units in a timely manner	3.29	4.78
Ability to solve the current challenges related to treating daratumumab patients	3.67	4.67
Ability to provide matched units due to the method limitation (i.e., Kell neg for DTT, Fy neg for sCD38)	4.67	3.50
General satisfaction level concerning the product	3.29	4.44

Each item rated from 1 (very dissatisfied) to 5 (very satisfied).

sample to a reference center, for example), all items were scored higher for sCD38 except for the ability to provide matched units due to the method limitation (3.50 vs 4.67, respectively). Users stated that this issue can be overcome by providing Fy^a/Fy^b matched units (**Table II**). The mean likelihood that one of the testing sites would recommend the sCD38 testing method to a colleague was 8.4 (being 10 [extremely likely] the maximum possible score).

DISCUSSION

In this multicenter study carried out in plasma samples from patients treated with anti-CD38 drugs under routine clinical practice, sCD38 completely neutralized anti-CD38 in 79.8% of the patient samples using the testing method according to Grifols sCD38 IFU (2 and 4 µL sCD38). Adding the research use method (6 µL sCD38), this effectiveness increased up to 98.5%. In both cases, the effectiveness was higher than neutralizing samples with DTT (78.3%). Furthermore, the samples partially neutralized by DTT were completely neutralized by 2 or 4 µL of sCD38, showing that sCD38 was more effective than DTT in neutralizing anti-CD38. These sCD38 findings in real-world samples are in line with previously reported data in samples spiked with anti-CD38[35-37].

Given that the use of 6 µL sCD38 increased the effectiveness of neutralization, it could be hypothesized that higher volumes, such as 8 µL, might further enhance this effectiveness. However, this was not evaluated in the present study, as during the design of this study we decided not to exceed 6 µL to avoid the potential dilution of low-titer antibodies in the plasma. Therefore, further research would be needed to assess the impact of higher sCD38 volumes on both neutralization efficiency and antibody detection.

Considering that sCD38 was designed as high affinity epitope and that all samples containing isatuximab were completely neutralized by either 2 or 4 µL of sCD38, this seems to confirm that sCD38 could potentially be a universal and broad solution for neutralization of any anti-CD38 drugs. Even so, more studies are needed to fully validate this finding and the use of sCD38 with other therapies than daratumumab.

After anti-CD38 neutralization with the existing method (DTT) in the participating sites, five alloantibodies (anti-E, anti-Fy^a, anti-K, anti-D, and anti-Kp^a) were not detected. This denaturation of DTT-sensitive antigens, such as those of the KEL blood group system, is well known and recognized as a significant limitation of the DTT method[23,38]. The reported missed detection of antibodies from the RH and FY systems must be attributed to other intra-laboratory factors. In contrast, following the neutralization of anti-CD38 with sCD38, all assessed antibodies specific to blood group antigens were successfully identified via the IAT, except for those specific to the Fy antigen. This interference of sCD38 with anti-Fy detection was previously discovered during clinical performance activities and was added in the IFU[39]. In that sense, we must consider that some studies mention an extremely low rate (up to 0.4% and 0.6%) of alloimmunization of MM patients undergoing anti-CD38 therapy[40,41]. This rate of alloimmunization means that the likelihood of detecting any irregular antibody in a sample from a patient receiving anti-CD38 drug is extremely low. Nevertheless, an investigation to clarify the reason for the sCD38 interference with Fy antibodies is ongoing.

Overall, the satisfaction level with the product and the likelihood of recommending it was high, and higher than the satisfaction level with the current method used

in the sites (DTT). Due to the detected sCD38: anti-Fy interference, users pointed out a likely need for Fy^a/Fy^b matched units. To mitigate future alloimmunization from multiple or chronic transfusions, patient phenotyping on presentation and before transfusion using IgM-based antisera or broad-based genotyping with its accompanying efficiencies is a longstanding recommendation[13-15].

This study has several limitations that should be acknowledged. First, the samples were collected from a limited number of sites, which may restrict the generalizability of the findings. Second, the study mainly evaluated the effect of sCD38 on daratumumab, with only a small number of patients treated with other anti-CD38 drugs such as isatuximab. Although daratumumab is the most widely used in MM therapy, the effect of sCD38 on other anti-CD38 drugs needs to be evaluated. Third, the number of samples spiked with known irregular antibodies was relatively small, particularly those involving antibodies against the FY system. Further research is needed to confirm the findings in larger and more diverse patient cohorts and to better understand the interference observed with Fy antibodies. Despite these limitations, the main strength of this study is that it shows the results of real-world clinical use of sCD38, by real, unbiased end-users, and with real samples from patients treated with anti-CD38.

CONCLUSIONS

sCD38 has exhibited significant potential in neutralizing anti-CD38 drugs, a common treatment for MM, in a real-world setting. The sCD38 product successfully neutralized anti-CD38 mAb in 98.5% of the patient samples, demonstrating its high effectiveness and suggesting its potential as a universal solution for any anti-CD38 drugs. However, further studies are required to validate the use of sCD38 with therapies other than daratumumab and to understand the observed interference in the detection of Fy antibodies. The design of sCD38 as a high-affinity epitope and its demonstrated ability to successfully inhibit both isatuximab and daratumumab mAb in patient samples further supports its potential as a broad solution for neutralizing any anti-CD38. The results of this study in real-world conditions are consistent with and support the findings reported in previous studies conducted in controlled or laboratory conditions.

Data availability

The data that support the findings of this study are available from the corresponding Author upon reasonable request.

ACKNOWLEDGEMENTS

Irene Mansilla, MSc and Eugenio Rosado, PhD (Grifols) are acknowledged for medical writing and editorial support in the preparation of this manuscript.

SOURCES OF SUPPORT / FUNDING

This study was funded by Grifols, manufacturer of sCD38. Grifols provided the reagent sCD38, as it was not commercially available at the time of the study.

AUTHOR CONTRIBUTION

CE, ES, JF, DL, CP, IL, NDM, MLB, CN, LP, SDM, and MEP: acquisition of data. AC, and LA: protocols preparation, data collector, meetings to explain the use of the product, reagent provision, compiling the data, analyzing the data. TB: review, presentation, and approval of study design; management of the shipments to provide testing material at the different sites. All Authors have critically reviewed the draft manuscript for important intellectual content and have approved the final manuscript.

CONFLICT OF INTEREST

AC, TB, and LA are full-time employees of Grifols and have no other conflicts of interests to declare. CE, ES, JF, DL, CP, IL, NDM, MLB CN, LP, SDM, and MEP declare they have no conflicts of interest.

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