Validation of HLAMatchmaker algorithm in identifying acceptable HLA mismatches for thrombocytopenic patients refractory to platelet transfusions

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BACKGROUND: HLAMatchmaker (HLAMM) is an algorithm that determines donor-recipient histocompatibility based on HLA type. This study determines the effectiveness of HLAMM in identifying suitable platelet (PLT) donors for refractory patients.

STUDY DESIGN AND METHODS: Data from a previous prospectively randomized multicenter study comparing cross-reactive group (CREG)-matched versus serologic crossmatch-selected PLT transfusions in refractory patients were analyzed. By use of HLAMM, the compatibility of donor-recipient pairings was determined as the number of donor triplet mismatches (TMMs) and eplet mismatches (EMMs) and compared against the posttransfusion PLT corrected count increment (CCI). The data included 73 patients who received up to two CREG-matched and crossmatch-selected PLT transfusions each (214 transfusions analyzed).

RESULTS: TMM and EMM values correlated well with CREG match grade. *A* and *BU* matches had TMM and EMM values of 0; *BX* matches had TMMs and EMMs of 4 and 6 respectively; and *C* and *D* matches had TMMs of 10 to 21 and EMMs of 13 to 24. Fewer mismatches (TMM or EMM) predicted better transfusion outcomes ($p < 0.05$). The median 1-hour CCI was 8000 with TMMs of not more than 9 versus 6000 with TMMs of more than 9. The median 1-hour CCI was 7954 with EMMs of not more than 11 versus 6356 with EMMs of more than 11. The positive predictive value of the different methods in producing a 1-hour CCI of more than 7500 were comparable: TMM, 56 percent; EMM, 54 percent; CREG, 50 percent; and crossmatching, 45 percent ($p > 0.05$).

CONCLUSIONS: HLAMM (both TMM and EMM) successfully identified donors associated with good transfusion outcomes in refractory recipients and represents an acceptable method of choosing donors for refractory patients.

Transfusion support of platelet (PLT)-refractory thrombocytopenic patients remains a complex issue.[1] Through sensitizing events such as pregnancies, blood transfusions, and organ/stem cell transplants, patients develop HLA antibodies and may become refractory to PLT transfusions. These antibodies, directed primarily against the HLA-A and HLA-B antigens present on PLTs, can result in the rapid immune-mediated clearance of transfused HLA-mismatched PLTs. Although HLA-identical PLTs would be the ideal choice for a PLT-refractory patient due to the presence of HLA antibodies, their availability is usually limited.[2,3] More frequently, HLA-compatible PLTs are selected by the use of cross-reactive group (CREG) matching or else by serologic crossmatching (XM).[3-6] For patients who have well-defined and limited HLA antibody specificities, donors can usually be readily identified by antibody specificity prediction methods that avoid these specificities.[7] For patients with broad and ill-defined HLA antibody specificities (i.e., reactivity against more than 80% of HLA types), the identification of HLA-compatible PLTs becomes more difficult.[7] CREG-matched PLT transfusions have been shown to

ABBREVIATIONS: CREG = cross-reactive group; EMM(s) = eplet mismatch(-es); HLAMM = HLAMatchmaker; TMM(s) = triplet mismatch(-es); XM = crossmatching.

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result in unsatisfactory PLT corrected count increments (CCIs) greater than 40 percent of the time.[8]

HLAMatchmaker (HLAMM; R.J. Duquesnoy, University of Pittsburgh Medical Center, Pittsburgh, PA) is a computer algorithm that predicts donor-recipient compatibility by identifying the shared antigenic determinants in otherwise nonidentical HLA types and then quantifying the number of antigenic determinants that are unique to the donor and not present in the recipient (patient). This quantification is then referred to as the number of "mismatches." The algorithm assumes that patients do not form antibodies against antigenic determinants present in their own HLA types that are shared with the nonidentical HLA type, nor form antibodies against inaccessible portions of the HLA protein where additional differences between HLA types might be present. The original version of the HLAMM algorithm defined the antigenic determinants as linear sequences of three-amino-acid residues (i.e., triplets), one or more of which was polymorphic and quantitated differences between donor and recipient as triplet mismatches (TMMs).[9] The newer version expands the consideration of antigenic determinants to include both linear amino acid sequences and discontinuous polymorphic amino acid residues at the critical contact site for complementarity-determining regions of antibody-antigen interactions.[10,11] This new measurement of the degree of differences between donor and recipient HLA types is referred to as "eplet" mismatches (EMMs). By quantifying the total number of antibody-accessible triplet and/or eplet mismatches (EMMs) between patient and donor, the likely success of the donor-recipient mismatch can be estimated. The number of mismatched triplet amino acids (TMMs) and eplets (EMMs) has been theorized to correlate with the CCIs of PLT-refractory patients.[10-12]

Despite the potential benefits of these two proposed PLT selection algorithms, there are limited data evaluating its utility. One single-center retrospective study of 16 patients demonstrated the potential value of the triplet version of HLAMM in PLT-refractory patients.[12] No studies to date have tested the eplet version of the HLAMM algorithm. In this study, we evaluated the ability of the triplet and the eplet HLAMM algorithms to identify PLTs with successful transfusion responses using PLT transfusion outcomes data from a previous multicenter prospectively randomized study of CREG-matched versus serologic crossmatched PLTs in 73 patients.[6]

MATERIALS AND METHODS

Study design

This study is a post hoc analysis of data from a previously published multicenter prospective randomized trial of PLT-refractory patients treated with PLTs selected by CREG matching or serologic XM.[6] Patients were identified as PLT refractory when at least two random-donor PLT transfusions resulted in a 1-hour CCI of less than 10,000 per μL. Those patients with nonimmune factors that might shorten PLT survival (e.g., fever > 38.3°C, sepsis, disseminated intravascular coagulation) or those lacking a serologic crossmatch-compatible donor were excluded from the study. A total of 73 patients received at least one transfusion of PLTs selected by means of CREG matching and one by serologic XM in a crossover design, where patients were randomly assigned to receive a PLT transfusion via one method of selection and then by the other method. Patients could receive up to four transfusions in total in the study, with a total of 214 transfusions analyzed. Transfusion outcomes were reported as CCIs that were determined at 1 hour after transfusion and at 24 hours, if possible. Successful 1- and 24-hour CCI cutoffs were defined at 7500 or greater and 4500 or greater, respectively. We utilized the original raw data sheets from this study with the permission of the study's principal investigator. The original data sheets listed a total of 86 patients. Of these, 1 patient had received no transfusions, and 7 patients had received a single transfusion only. We excluded these patients from our analysis, on the grounds that they did not meet the original study criteria of receiving at least one CREG-matched and one crossmatched PLT transfusion. We excluded 5 patients whose pretransfusion PLT count exceeded 50,000 (i.e., did not meet standard indications for PLT transfusion in a nonbleeding, nonsurgical situation) for a total cohort of 73 patients.

HLAMM

The two HLAMM programs used in this study (triplet SER Version 1.3 and eplet ABC matching Version 1.3) are defined within a computer spreadsheet program (Excel, Microsoft Corp., Redmond, WA). Both donor and recipient HLA-A and HLA-B types were entered into the HLAMM spreadsheets, and the program then calculated the degree of mismatching based on the HLAMM algorithms. The degree of mismatching was expressed either as the sum of mismatched triplets (TMM) or as the sum of mismatched eplets (EMM) using the triplet and eplet versions of HLAMM, respectively. In cases in which the original recipient or donor HLA type needed to be further defined for the HLAMM algorithm, the predominant HLA type, most common HLA-A and -B haplotype, or predominant allele as identified through studies from the National Marrow Donor Program Registry was chosen.[13]

The HLAMM ABC eplet matching Version 1.3, as well as program instructions can be downloaded free of charge from the Web site http://www.hlamatchmaker.net. The HLAMM triplet version SER 1.3 is no longer posted on the Web site, but can be made available on request.

Statistical analysis

Owing to nonnormality of the distribution of the number of HLAMM TMMs and EMMs, and of the posttransfusion PLT CCI, nonparametric statistical methods were used when analyzing these continuous variables or outcomes, respectively. Continuous variables are described as the median and the first and third quartiles.

The relationship between the number of TMMs or EMMs, CREG match grade (*A*, *BU*, *BX*, *C*, and *D*), method of PLT selection, and posttransfusion PLT CCI at 1 and 24 hours was determined and analyzed by Wilcoxon rank sum or Fisher's exact tests where appropriate. Successful or satisfactory PLT transfusion responses were defined as a 1-hour CCI of 7500 or greater or 24-hour CCI of 4500 or greater. Comparison of the positive predictive values of using a particular TMM or EMM cutoff, CREG matching, or XM methods in choosing PLT donors was performed by Fisher's exact test.

All analyses were performed using a statistical package (STATA SE Version 8.2, StataCorp LP, College Station, TX). A p value of less than 0.05 was considered significant.

TABLE 1. Relationship between CREG match grade, TMMs, and EMMs*

	CREG match grade			
Variable	*A* and *BU*	*BX*	*C*	*D*
Number of transfusions	24	58	53	79
Median TMMs	0 (0-0)	4 (2-8)	10 (7-14)	21 (15-25)
Median EMMs	0 (0-0)	6 (4-9)	13 (10-17)	24 (18-29)

* The median numbers of TMMs and EMMs are presented with the first and third quartile values (in parentheses).

TABLE 2. Relationship between mismatches and method of PLT selection: CREG versus XM*

Mismatch	CREG-matched (n = 109)	Crossmatched (n = 105)	p Value
Median TMM	4 (1-10)	17 (12-23)	<0.0001
Median EMM	6 (2-11)	21 (15-26)	<0.0001

* Median numbers of TMMs and EMMs are presented with the first and third quartile values (in parentheses).

RESULTS

Patient characteristics

The patient characteristics of this study have been previously described in detail.[6] Briefly, 73 patients with previously demonstrated refractoriness to PLT transfusions from randomly selected donors were enrolled in the study. Of these, 37 were leukemic marrow transplant patients (mean age, 39.5 years); 23 were acute leukemic patients (mean age, 46.1 years); and 13 had myelodysplastic syndrome, aplastic anemia, or a solid tumor. The male-to-female ratio was 1.7:1. Each patient received at least two plateletpheresis components: one CREG-matched and the other serologically matched, with up to two PLT transfusions by each method of selection being allowed per patient. The total number of CREG-matched transfusions was 109, whereas the number of serologically matched transfusions was 105. One-hour CCIs were calculated for all 214 PLT transfusions, and 24-hour CCIs were obtained on 157 (73%) of the transfusions.

Relationship between CREG matching and HLAMM mismatches

All PLT transfusions (n = 214) were compared in terms of CREG match grade (*A*, *BU*, *BX*, *C*, and *D*) and median number of HLAMM mismatches (see Table 1). There was a close correlation between CREG match grade and number of HLAMM TMMs. Exact and nearly exact HLA matches such as *A* and *BU* (n = 24) had median TMMs of 0 (first and third quartiles, 0 and 0), whereas *BX* matches (n = 58) showed a median TMM of 4 (first and third quartiles, 2 and 8). Poorer matches such as *C* (n = 53) and *D* (n = 79) showed progressively greater median TMMs of 10 (first and third quartiles, 7 and 14) and 21 (first and third quartiles, 15 and 25), respectively. The number of HLAMM EMMs also showed a close correlation with *A* and *BU* matches with median EMMs of 0 (first and third quartiles, 0 and 0). With intermediate and poorer matches, however, the number of EMMs were higher than the TMMs. The median EMM for *BX* matches was 6 (first and third quartiles, 4 and 9), for *C* matches it was 13 (first and third quartiles, 10 and 17), and for *D* matches it was 24 (first and third quartiles, 18 and 29).

When comparing the number of TMMs or EMMs of donor PLTs chosen by the CREG matching method versus serologic XM, CREG matching (n = 109) resulted in significantly lower TMMs (or EMMs) than did serologic XM (n = 105, $p < 0.0001$; see Table 2). The CREG-matched PLTs had a median TMM of 4 (first and third quartiles, 1 and 10) versus serologic crossmatched PLTs, which had a median TMM of 17 (first and third quartiles, 12 and 23). A similar trend was observed with EMMs where CREG-matched transfusions had a median EMM of 6 (first and third quartiles, 2 and 11) versus serologic crossmatch where the median EMM was 21 (first and third quartiles, 15 and 26).

Relationship between CREG matching versus XM and transfusion response

The PLT transfusion response as measured by the median 1- and 24-hour CCI was calculated for CREG-matched

versus crossmatched transfusions. These two traditional methods of PLT selection showed comparable posttransfusion increments ($p > 0.05$ for both 1- and 24-hr CCI). CREG matching resulted in a median 1-hour CCI of 7500 (first and third quartiles, 2678 and 12,706) versus 6778 for serologic XM (first and third quartiles, 3048 and 10,723). When the 24-hour CCI was considered, the median CCI was 2093 for CREG matching (first and third quartiles, 0 and 5856) versus 2250 for serologic XM (first and third quartiles, 0 and 4304).

Current literature suggests that PLT transfusions resulting in a 1-hour CCI of 7500 or greater are considered satisfactory in refractory patients.[14] When CREG-matched transfusions (n = 109) were evaluated, 50 percent were found to result in a satisfactory 1-hour CCI, whereas for serologically crossmatched transfusions (n = 105), 45 percent resulted in a satisfactory 1-hour CCI. However, both methods generated a comparable percentage of successful transfusions at 1 hour ($p > 0.05$). At 24 hours after transfusion, a CCI of 4500 or greater is generally deemed satisfactory in refractory patients. When all transfusions in which we had 24-hour posttransfusion data were examined, 36 percent of 80 CREG-matched transfusions resulted in a satisfactory response, while serologic XM resulted in a satisfactory response in only 21 percent of 77 cases. In contrast to the findings at 1 hour after transfusion, the percentage of successful transfusions after 24 hours by CREG matching was significantly superior ($p = 0.036$).

Relationship between HLAMM matching and transfusion response

When all transfusions with a satisfactory 1-hour CCI (7500 or greater) were examined (n = 101; see Table 3), the number of TMMs was found to be lower than the number of TMMs associated with unsatisfactory transfusions (n = 113, $p = 0.0481$), with a median TMM of 9 (first and third quartiles, 2 and 17) versus 13 (first and third quartiles, 4 and 18; see Table 3). The number of EMMs was also lower in transfusions with a satisfactory 1-hour CCI, but this difference was not significant ($p > 0.05$), with a median EMM of 11 (first and third quartiles, 4 and 22) versus 14 (first and third quartiles, 7 and 22). When all transfusions with a 24-hour CCI of 4500 or greater were examined (n = 45), the median TMMs and EMMs were similarly found to be lower than with transfusions where the CCI was less than 4500, with a median TMM of 9 (2-14) versus 10 (4-18) and a median EMM of 11 (3-17) versus 13.5 (6.5-22). These differences, however, were not significant. A regression analysis was also performed to determine if ABO incompatibility (i.e., group A PLTs transfused to group O recipient) played a significant role in the outcome of PLT transfusions, but none was found in this study (data not shown).

Finally, all 214 PLT transfusions were separated according to the number of mismatches (Fig. 1), using a TMM of 9 or less and an EMM of 11 or less as a criterion for identifying PLTs that would be found acceptable for transfusion using the HLAMM algorithm. Transfusions with a TMM of 9 or less (n = 97) resulted in significantly greater 1-hour CCIs than did transfusions with TMMs greater than 9 (n = 117; $p = 0.005$), with a median 1-hour CCI of 8000 (first and third quartiles, 4411 and 12,977) versus 6000 (first and third quartiles, 1595 and 10,102). Transfusions with EMMs of 11 or less (n = 101) compared to those with EMMs of greater than 11 (n = 113) showed a similar, though less pronounced, difference in 1-hour CCIs ($p = 0.020$), with a median 1-hour CCI of 7954 (first and third quartiles, 4002 and 12,739) versus 6356 (first and third quartiles, 1600 and 10,102). There was no significant difference in the 24-hour CCI when analyzed in terms of acceptable TMMs or EMMs (i.e., ≤ 9 or ≤ 11, respectively) versus unacceptable TMMs or EMMs (i.e., >9 or >11, respectively), a finding that can likely be attributed to the smaller number of transfusions analyzed where 24-hour CCI values were available (number range, 72-85). The positive predictive value of TMM versus EMM (percentage of transfusions with an acceptable number of TMMs or EMMs that resulted in satisfactory CCIs) was roughly equivalent. TMM was slightly better than EMM at 1 hour (56% vs. 54%) and slightly worse at 24 hours (32% vs. 34%), but these differences were not significant ($p > 0.05$ for both comparisons).

Previous studies have demonstrated the superiority of *A* and *BU* CREG-matched PLTs over *BX*, *C*, and *D* matches.[6] Because HLAMM algorithms are not needed to choose *A* or *BU* CREG-matched PLTs, these groups were excluded from the analysis to determine whether HLAMM would still be effective. After exclusion of *A* and *BU* CREG-matched transfusions, we found that transfusions with a

TABLE 3. Relationship of mismatches to CCIs*

	No. of transfusions		Median number of TMMs			Median number of EMMs		
1 hr CCI	≥7500	<7500	≥7500	<7500	p Value	≥7500	<7500	p Value
	101	113	9 (2-17)	13 (4-18)	0.0481	11 (4-22)	14 (7-22)	0.109
	No. of transfusions		Median number of TMMs			Median number of EMMs		
24 hr CCI	≥4500	<4500	≥4500	<4500	p Value	≥4500	<4500	p Value
	45	112	9 (2-14)	10 (4-18)	0.164	11 (3-17)	13.5 (6.5-22)	0.143

* Median numbers of TMMs and EMMs are presented with the first and third quartile values (in parentheses).

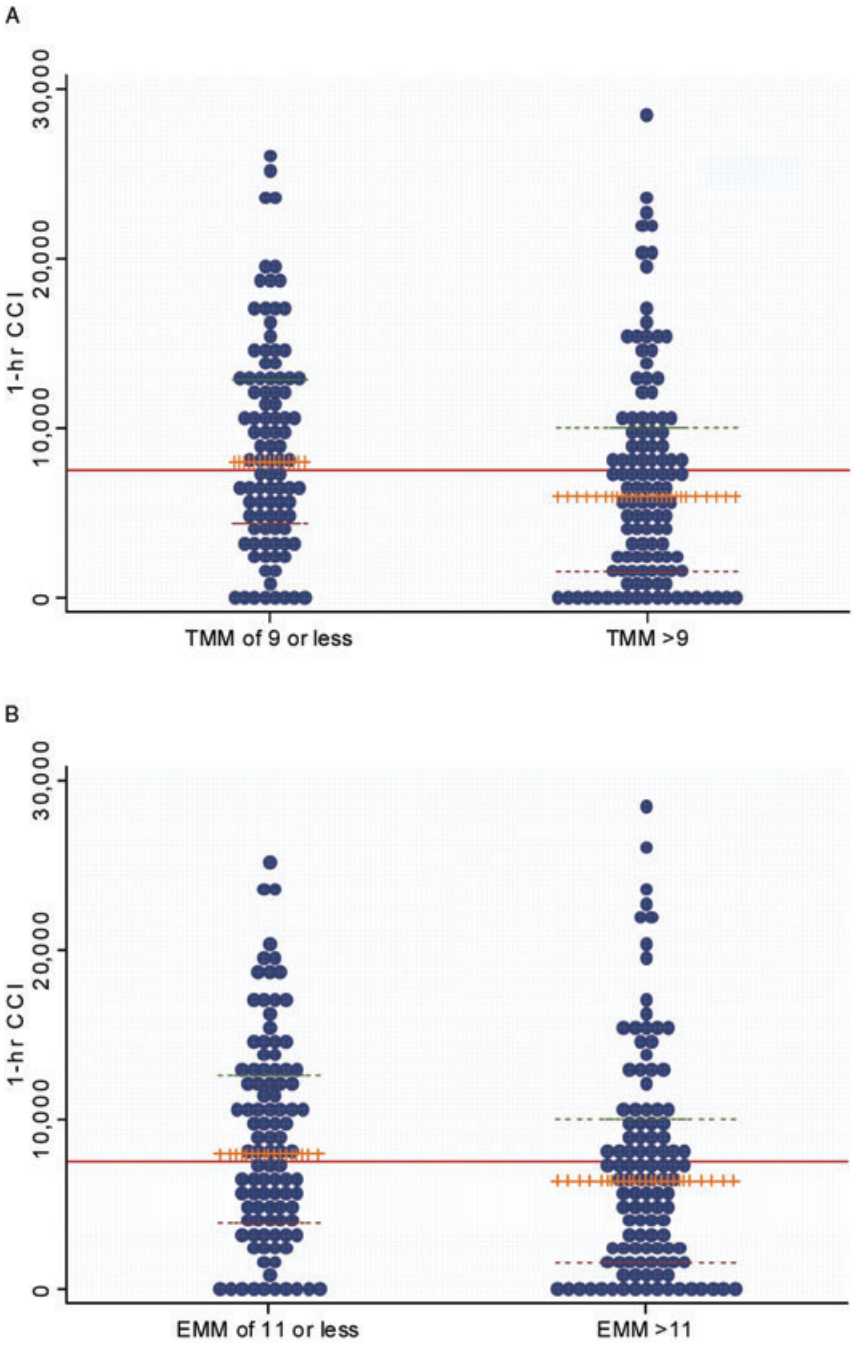

Fig. 1. A dot plot of 1-hour CCI when divided by TMM of 9 or less (n = 97) versus a TMM of more than 9 (n = 117). +++ = median (50th percentile); --- = quartile boundaries; solid line = 1-hour CCI of 7500. p = 0.005. (B) Dot plot of 1-hour CCI when divided by an EMM of 11 or less (n = 101) versus an EMM of more than 11 (n = 113). +++ = median (50th percentile); --- = quartile boundaries; solid line = 1-hour CCI of 7500. p = 0.020.

TMM of 9 or less (n = 73) continued to result in significantly greater 1-hour CCIs than did transfusions with TMMs greater than 9 (n = 117, p = 0.024), with a median 1-hour CCI of 7754 (first and third quartiles, 4324 and 12,739) versus 6000 (first and third quartiles, 1595 and 10,102). Transfusions with EMMs of 11 or less (n = 77) compared to those with EMMs of greater than 11 (n = 113) showed a similar trend that was not significant (p = 0.08), with a median 1-hour CCI of 7740 (first and third quartiles, 3629 and 12,444) versus 6356 (first and third quartiles, 1600 and 10,102). In comparison, *BX* CREG-matched transfusions (n = 58) had a median 1-hour CCI of 7475 (first and third quartiles, 2462 and 12,444), and *C* CREG-matched transfusions (n = 53) had a median 1-hour CCI of 6720 (first and third quartiles, 3580 and 10,800).

To address potential violations of data independence due to repeated transfusions in the same patient (between two and four transfusions per patient), we also repeated our analyses in data subsets wherein each patient was represented only once with their first CREG match and first XM PLT transfusion. A trend similar to the original aggregate analysis showing transfusions from donors with acceptable TMM with satisfactory 1-hour CCI was seen, but was no longer significant due to small patient numbers in each subset (data not shown).

DISCUSSION

The utilization of the HLAMM algorithm offers a standardized, quantitative method for the selection of donors for PLT-refractory patients. In contrast, there is possible institutional variation in how CREG matching is applied. This is in part due to different definitions of public epitopes, particularly the HLA types that would be included in the A1, B5, and B8 CREGs.[15] In addition, the CREG-matching method is limited to five broad grades of matching of donor to recipient (*A*, *BU*, *BX*, *C*, *D*). In particular, no distinction is made within the *BX* or *C* grade of CREG matches. Our review of the distribution of TMM values compared to CREG match grade demonstrated that a number of poor "*C*" matches by CREG matching would have been found acceptable by the HLAMM triplet algorithm, and thus avoid being erroneously excluded, whereas simultaneously some of the better "*B*" matches by CREG matching would have been

appropriately excluded by the HLAMM algorithm. Because the HLAMM algorithm provides a quantitative method to measure donor-recipient mismatches, using this method for donor selection could expand the available donor pool while improving PLT transfusion outcomes.

Although a number of studies have examined the effectiveness of the HLAMM algorithm in renal transplantation,[16-20] studies of its effectiveness in guiding PLT selection are limited. Nambiar and colleagues[12] retrospectively examined the CCIs of 16 PLT-refractory patients with aplastic anemia. Their data showed the triplet version of HLAMM to be a valid means of predicting the overall success (i.e., CCI $\geq$ 8000) of PLT transfusions in their patients at a single institution. However, the number of transfusions per patient in their study was unequally distributed with the transfusion outcomes of a single patient representing approximately 30 percent of transfusions analyzed. In contrast, our data set was derived from a multicenter prospectively randomized study with a greater number of patients transfused and a more uniform number of transfusions per patient analyzed (two to four transfusions total). To date, there are no published data validating the eplet version of HLAMM for either renal transplants or PLT transfusions. This study represents the largest cohort of PLT-refractory patients assessed in terms of triplet HLAMM compatibility (n = 73) and the first report of PLT transfusion outcomes assessed via the eplet version of HLAMM.

Our analysis of 214 PLT transfusions revealed that the HLAMM triplet and eplet algorithms successfully identified PLTs associated with good transfusion outcomes in refractory recipients. The median number of TMMs was found to be significantly lower in satisfactory (CCIs $\geq$ 7500) versus unsatisfactory (CCIs < 7500) transfusions, that is, TMM of 9 versus 13. Furthermore, transfusions where the number of TMMs were 9 or less resulted in significantly greater 1-hour CCIs (median, 8000) than did transfusions where the number of TMMs were greater than 9 (median, 6000). These findings are similar to those of Nambiar and coworkers[12] who reported median TMMs of 11 versus 13 as correlating with satisfactory (CCIs $\geq$ 8000) and unsatisfactory outcomes (CCIs < 8000), respectively. They also found 9 or less TMMs to be the cutoff point for successful transfusions. Our study showed that the median number of EMMs was also lower with satisfactory than with unsatisfactory 1-hour CCIs, but this difference was not significant: an EMM of 11 versus 14. Transfusions from donors with EMMs of 11 or less resulted in significantly higher 1-hour CCIs (median, 7954) than did transfusions with EMMs of greater than 11 (median, 6356). The higher median EMM values, compared to TMM values, are likely attributable to the differences between the two HLAMM algorithms. The triplet version considers a smaller number of loci of polymorphic sequences compared to the eplet version. The end result is that the eplet version of HLAMM may have a larger range within which to identify potential mismatches than does the triplet version.

However, both triplet and eplet HLAMM versions successfully predicted satisfactory PLT transfusion outcomes, and both appeared to perform as well as CREG matching and serologic XM in this respect. The positive predictive value of the different selection methods (defined as the percentage of transfusions expected to be successful which actually resulted in a satisfactory CCI) showed a trend toward better improvement with TMM (56%) > EMM (54%) > CREG matching (50%) > XM (45%) at 1 hour. At 24 hours, the positive predictive value of CREG matching was slightly higher than either version of HLAMM, but the differences were comparable, and not significant. It is interesting to note that both in terms of 1- and 24-hour positive predictive value, XM lagged behind both CREG matching and using the HLAMM algorithms. Transfusions where the TMM and EMM was below our designated cutoff (TMM $\leq$ 9 or EMM $\leq$ 11) resulted in higher median 1- and 24-hour CCIs than did CREG or serologic XM, although the difference was not significant ($p > 0.05$). Although the positive predictive value of any of the PLT selection methods evaluated in this study may seem low, this is still superior to the lack of response to unselected (random) PLT transfusions that these patients had as entry criteria into the original study. Furthermore, nonalloimmune factors may also adversely influence PLT outcomes even in patients receiving HLA-compatible or HLA-identical PLTs.

Limitations of this study include the post hoc design of analysis of existing prospective data. Further validation of the HLAMM algorithms with superior study designs would be of value. However, the ability to perform a multicenter prospectively randomized study of the efficacy of the HLAMM algorithms will be difficult with the greater use of leukoreduced blood in the United States and universal leukoreduction in Canada and many of the European countries. Overall, there are likely fewer numbers of HLA-alloimmunized and PLT-refractory patients available for future study. Therefore, our approach of a post hoc analysis of data from a well-designed multicenter prospectively randomized trial of PLT-refractory patients may represent the only practical means of validating the two HLAMM algorithms.

The lack of antibody specificity is another major limitation of this study. Owing to the number of years that have passed since the original data were gathered, this information is no longer readily available. Personal as well as anecdotal evidence, however, indicates that HLAMM is of greatest utility in situations where the percentage of reactive antibody is greater than 80 percent and where not all specificities can be readily defined. Analysis of the correlation between patient serologic antibody specificities

and HLAMM predictive properties is beyond the scope of the current work but would make for interesting future research.

Another limitation is that the HLAMM algorithm gives equal weight to all possible antibody specificities as defined as mismatched triplets or eplets. Therefore, it does not account for the relative frequencies of certain antibodies/epitopes in the population or the relative immunogenicity of different epitopes. For instance, anti-Bw4 is a potential alloepitope found in a majority of PLT donors. Even with a TMM or EMM score of 1, a patient with this broad antibody specificity might not respond to the PLTs selected by HLAMM unless Bw4 is avoided. Therefore, some knowledge of a patient's HLA antibody specificities remains of value in choosing appropriate PLT products for a refractory patient. The strength of HLAMM over CREG or XM, however, lies in its ability to find otherwise perfectly acceptable mismatches (i.e., TMM or EMM score of 0) when an *A* or *BU* CREG match is not available. This is often the case when HLA-matched or -compatible PLTs are needed immediately.

In conclusion, our data validate the use of both triplet and eplet versions of HLAMM for identifying acceptable HLA mismatches in thrombocytopenic patients refractory to PLT transfusions. We found that the predictive value of HLAMM (triplet or eplet version) was comparable to that of CREG matching. The low relative positive predictive value of XM as well as low 1-hour median CCIs suggest the HLAMM algorithm may be superior to XM, although further studies are needed to corroborate this. At minimum, both the triplet and the eplet versions of HLAMM represent reasonable additional tools for assisting in the selection of PLTs for refractory patients.

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