

# Implications of HLA in Transfusion Related Immune Complications Like TRALI and Platelet Refractoriness



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**Abbreviations :** TRALI: Transfusion-Related Acute Lung Injury; ALL: Acute Lung Injury; HLA: Human Leukocyte Antigens; HNA: Human Neutrophil Antigens; PRA: Panel Reactive Antibodies; MFI: Mean Fluorescence Intensity; CCI: Corrected Count Increment; DIC: Disseminated Intravascular Coagulation; eMMs: eplet Mismatches; HIMMs: Highly Immunogenic Mismatches; FNHTR: Febrile Non-Haemolytic Transfusion Reactions

## TRALI

Transfusion-related acute lung injury (TRALI) is defined as a new acute lung injury (ALI) that develops during or within 6 hours of transfusion and is a leading cause of transfusion-related morbidity and mortality [1]. The causative antibodies in TRALI may be directed against class I or II human leukocyte antigens (HLA) or human neutrophil antigens (HNA). It may also be caused by lipid products from the cellular breakdown, which accumulates in stored blood products and prime, activate neutrophils. TRALI can occur in patients undergoing repeated platelet transfusions and has mortality rates between 6-20%. Thus, it is important to identify these cases and address the issues related to the patients and implicated donors.

### Mechanism for the development of TRALI

There are two working hypotheses - the 'two hit' model and leukocyte antibodies (HLA antibodies). The 'two-hit' model mentions neutrophil priming as an initial requirement which can be a consequence of hematologic malignancy [2]. The introduction of neutrophil-binding antibodies, cytokines, and bioactive lipids from the transfused product, may lead to activation of the primed and sequestered neutrophils. Silliman et al. [3] mentioned that the patients with acute leukemia undergoing induction chemotherapy appeared to be at greater risk of developing TRALI. Another hypothesis suggests that transfused HLA antibodies may induce TRALI by direct contact with susceptible endothelial cells of the lung capillaries. It has been postulated that the transfused HLA Class I antibody binds to its cognate antigen present on the pulmonary endothelium. Passively transfused HLA Class II antibodies are also known to cause TRALI by activation of monocytes which lead to neutrophil activation [4]. A short duration of the clinical episode may

reflect the paucity of entrapped neutrophils. A recent study has demonstrated that donors serum positive for HLA class II antibodies, may induce monocytes and possibly platelets to secrete a variety of inflammatory mediators which subsequently activate neutrophils [5].

### TRALI after platelet transfusion

Previously, we have reported a 35 years old female with acute myeloid leukemia with prolonged neutropenia and thrombocytopenia secondary to chemotherapy-induced marrow suppression [6]. She was transfused with multiple platelets (single donor platelets) as she had prolonged thrombocytopenia and developed dyspnoea after one such transfusion. TRALI was diagnosed after excluding other causes of ALI. The Panel reactive antibodies (PRA) of the patient revealed HLA Class I and Class II antibodies. The implicated donor was a registered voluntary platelet donor with the hospital and his sample was sought immediately after this event for laboratory workup. The donor-specific antibody test between recipient and donor pair was positive with a high mean fluorescence intensity (MFI) value for Class I antibodies 10370 and class II antibodies 3454. The HLA typing of the implicated donor was A\*02,\*03; B\*51,\*58; DRB1\*03,\*04. Serum of implicated donor demonstrated HLA Class I antibodies and HLA class II antibodies. Therefore, the mechanism in the patient was a combination of the above factors. The patient had a haematological malignancy with superadded enterocolitis which made her susceptible to TRALI by the two-hit model. The donor-derived HLA-A\*02 antibodies by binding the pulmonary capillary endothelium may have facilitated the sequestration and activation of neutrophils despite a low ANC. A short duration of the clinical episode may reflect the paucity of

entrapped neutrophils. There was also an evidence of HLA Class II antibodies in the implicated donor.

Based on this observation it is suggested that the laboratory workup of all cases of TRALI should be performed to reduce the potential for further cases due to the implicated donor. Baseline PRA of repeat male donors should be studied to prevent TRALI due to passive transfer of antibodies. It is also important to perform PRA status of oncology patients at their 1st hospital visit to enable provision of epitope matched platelet transfusions to prevent the development of refractoriness.

### Platelet Refractoriness

Platelet refractoriness is the repeated failure to obtain acceptable responses to platelet transfusions [7]. Two consecutive platelet transfusions with corrected count increment (CCI) below 7,500 within 10-60 minutes after transfusion is an evidence of refractoriness [8].

Patients who are refractory as a result of HLA alloimmunization are given HLA-matched or crossmatched platelets. But these HLA matched donors can be potential candidates for stem cell harvest in future and patients can develop antibodies to minor antigens causing graft rejection. Another alternative is to provide platelets from donors matched at HLA-epitope level. This is based on the concept that HLA antibodies are produced for epitopes that can be structurally defined as eplets, which are present on different HLA alleles.

### Causes of platelet refractoriness

The causes of platelet refractoriness can be subdivided into immune and non-immune. Alloimmunization against HLA Class I antigens has remained the major immune cause of refractoriness of thrombocytopenic patients to random donor platelet (PLT) transfusions. Non-immune platelet consumption is associated with fever, sepsis, disseminated intravascular coagulation (DIC), splenomegaly and intravenous antibiotics (especially antifungal drugs such as amphotericin B) etc.

### Eplet matched platelet transfusions

HLA epitope matching is expected to benefit platelet transfusion outcome and increase the number of compatible donors for refractory patients. It could lead to new strategies for HLA mismatch permissibility to reduce alloimmunization and thus increase platelet survival. Human leukocyte antigen (HLA) mismatches are important risk factors for HLA alloimmunization and cause an increase in the interval of platelet transfusions. It is known that HLA antibodies recognize epitopes instead of antigens, thus it has become evident that donor-recipient compatibility should be assessed at the epitope level [9]. A computer algorithm called HLA Matchmaker considers each HLA antigen as a series of small configurations of polymorphic residues, referred to as eplets, as essential components of HLA epitopes. By quantifying the total number of antibody-accessible eplet mismatches (EMMs) between donor and

patient, the probable success of the donor-recipient mismatch can be estimated [10]. The program evaluates the total number of triplet mismatches between the donor and recipient HLA collection. The triplet algorithm has helped to define the relative immunogenicity of mismatched triplets by analysis of serologic reactivity patterns of highly allosensitized patients. The program can identify the subset of highly immunogenic mismatches (HIMMs) [11]. Validation of this algorithm has been done previously for the prediction of kidney transplant survival [12]. It is hypothesized that platelet donors matched at the epitope level must be considered compatible, even if donor HLA antigens appear mismatched by conventional criteria. Hence, HLA Matchmaker should be applied at the time of HLA matching at epitope level rather than after failure of HLA-matched platelet transfusion. This hypothesis can be best tested by a prospective follow-up of platelet increments. The number of mismatched eplets (EMMs) has been shown to correlate with the CCIs of PLT-refractory patients with lesser; the mismatch more is the CCI [10].

HLA epitope matching approach in immune refractory patients can have very impressive 1 hour CCI results. It can be expected to benefit platelet transfusion outcome and increase the number of compatible donors for refractory patients. Because the HLAMM algorithm provides a quantitative method to measure donor-recipient mismatches, this method can be used for donor selection which will expand the available donor pool while improving PLT transfusion outcomes.

### Summary

HLA plays a crucial role in certain aspects of Transfusion Medicine. The main function of the HLA molecules is to present antigenic peptides to the immune system and thus regulate the induction of immune responses. HLA antigens and antibodies are responsible for some of the serious clinical complications of blood transfusion. HLA alloimmunisation, TRALI, platelet refractoriness, Febrile Non-Haemolytic Transfusion Reactions (FNHTR) etc are some of the complications of blood transfusion where HLA plays a crucial role [13]. This article highlights the HLA related immune mechanisms responsible for complications of transfusions and ways to detect and avoid the same.

### References

1. Toy P, Popovsky MA, Abraham E, Ambruso DR, Holness LG, et al. (2005) Transfusion-related acute lung injury: definition and review. *Crit Care Med* 33: 721-726.
2. Bux J, Sachs UJ (2007) The pathogenesis of transfusion-related acute lung injury (TRALI). *Br J Haematol* 136(6): 788-799.
3. Silliman CC, Boshkov LK, Mehdizadehkashi Z, Elzi DJ, Dickey WO, et al. (2003) Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. *Blood* 101(2): 454-462.
4. Looney MR, Su X, Van Ziffle JA, et al. (2006) Neutrophils and their Fc gamma receptors are essential in a mouse model of transfusion-related acute lung injury. *J Clin Invest* 116(6): 1615-1623.
5. Nishimura M, Hashimoto S, Takanashi M, Okazaki H, Satake M, et al. (2007) Role of anti-human leucocyte antigen class II alloantibody and

- monocytes in development of transfusion-related acute lung injury. *Transfus Med* 17: 129-134.
6. Jain P, Sharma N, Rajadhyaksha SB, et al. (2016) Transfusion Related Acute Lung Injury in a Platelet Refractory Neutropenic Patient. *Indian J Hematol Blood Transfus* 33(3): 436-437.
  7. Murphy MF (2014) Managing the platelet refractory patient. *VOXS* 9: 234-223.
  8. Fung MK, Grossman BJ (2014) *AABB Technical Manual* In: Hillyer C, Westhoff CM (Eds.), MT (ASCP) SBB, AABB (18<sup>th</sup> edn).
  9. Duquesnoy RJ (2013) HLA Matching at the Epitope Level: The Way to Go. *Clinical Transplants Terasaki Foundation Laboratory, Los Angeles, California*.
  10. Brooks EG, Bruce R (2008) Validation of HLA Matchmaker algorithm in identifying HLA mismatches for thrombocytopenic patients refractory to platelet transfusions. *Transfusion* (48): 2159-2166.
  11. Duquesnoy RJ, Marrari M (2002) HLA matchmaker: a molecularly based algorithm for bility determination, II: verification of the algorithm and determination of the relative immunogenicity of amino acid triplet-defined epitopes. *Hum Immunol* 63(5): 353-363.
  12. Duquesnoy RJ, Takemoto S, De Lange P, et al. (2003) HLA matchmaker: a molecularly based algorithm for histocompatibility determination, III: effect of matching at the HLA-A, B amino acid triplet level on kidney transplant survival. *Transplantation* 75: 884-889.
  13. Ogedegbe HO (2002) A Review of Immune Mediated Transfusion Reactions. *Laboratory Medicine* 33(4): 287-295.



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