BLOOD TRANSFUSION-RELATED IMMUNOMODULATION

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ABSTRACT

The phenomenon of transfusion-related immunomodulation (TRIM) has been studied since the observation of a higher kidney allograft survival in patients who had received a higher number of transfusions. Conversely, it has been suggested as one of the possible causes related to the development of infections in patients with multiple blood transfusions and/or after a major surgery, and has been also associated with a decreased function of natural killer cells (NK) and antigen-presenting cells (APCs), reduced cell-mediated immunity, and increased regulatory T cells (Tregs). This review aimed to conceptualize TRIM and discuss some aspects related to its mechanisms and the prevention of immunomodulatory events.

Keywords: *Immunomodulation; blood transfusion; immunosuppression; infection; leukocytes*

Blood component transfusion, as any other medical intervention, involves risks and benefits that should be individually assessed for each patient. Although blood transfusion guidelines usually do not follow a unique approach, there is growing amount of data in the medical literature to support individualized hemotherapy decisions¹. The immunosuppressive effects of red blood cell (RBC) transfusion were firstly reported in 1973, when a higher kidney allograft survival rate was observed in transplant patients who had received a greater number of packed red blood cells (PRBCs)². Subsequent clinical and laboratory investigations corroborated these data, which led to the deliberate use of allogeneic blood transfusions as a prophylaxis against graft rejection for a short period in the 1980s^{3,4}. Aggregate findings from previous studies seem to indicate that patients who need blood component transfusion have a higher risk of bacterial infection in the postoperative period compared to patients who did not receive transfusions⁵⁻⁷. Three possible mechanisms have been defined as the basis for the apparent association between transfusion-related immunomodulation (TRIM) and infection⁷⁻¹⁰: immunologically active allogeneic leukocytes, allogeneic leukocyte-derived soluble mediators, and human leukocyte antigen (HLA) peptides soluble in allogeneic plasma. These mechanisms are described below.

Immunologically Active Allogeneic Leukocytes

In blood transfusions, donor antigen presenting cells (APCs) may lose their ability to promote costimulation after being stored under refrigeration, either due to a reduction in the expression of B7-1 or B7-2 molecules or to the binding of these molecules to the recipient cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a T-cell receptor for B7 molecules. This interaction between donor APCs and recipient naive T cells may induce T cell anergy and promote immunosuppression (figure 1)⁷.

Donor dendritic cells, which express CD200 or OX-2 (an immunoglobulin transmembrane protein), bind to their receptors (CD200R or OX-2-R) in the recipient myeloid dendritic cells and T cells, which suppresses macrophage

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Figure 1: A) Normal immune response showing the binding of major histocompatibility complex class II molecules to the T-cell receptor (MHCII↔TCR) and between the costimulatory molecules B7-1/B7-2 and CD28 (B7-1/B7-2↔CD28), which activates the T cell and turn it into an effector cell. After refrigeration, T cells undergo anergy due to two mechanisms; B) donor antigen presenting cells (APCs) reduce the expression of B7-1/B7-2 molecules or C) the B7-1/B7-2 molecules of APCs bind to recipient cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) molecule⁷.

function, especially due to the release of transforming growth factor beta (TGF- β) from recipient T cells¹¹, with consequent host immunosuppression against infectious agents¹². This interaction between CD200 and CD200R has been suggested to be required for TRIM (figure 2)¹³.

Another mechanism related to immunomodulatory events is the phenomenon of microchimerism, which occurs when there is such a high HLA compatibility between donor and recipient that a small number of donor lymphocytes and APCs remain in recipient circulation or organs^{7,14}. Microchimerism may also induce the development of type 2 T-helper cell

(Th₂) response and the release of cytokines such as interleukin 4 (IL-4), interleukin 10 (IL-10), and TGF- β ^{15,16}. These biological products are able to inhibit type 1 T-helper cell (Th₁) response and macrophages activation¹⁵⁻¹⁷, a reaction mediated by host immune response and leads to reduced secretion of cytokines such as interleukin 2 (IL-2), interleukin 12 (IL-12), and interferon gamma (IFN- γ)¹⁸. Therefore, the presence of donor cells may cause a down-regulation of patient's immune response, resulting in donor tolerance to alloantigens and increased recipient predisposition to infections^{7,14,19}.

Allogeneic Leukocyte-Derived Soluble Mediators

Proinflammatory soluble mediators accumulated in blood components during storage have also been implicated in TRIM pathogenesis²⁰⁻²². These mediators are usually located in the intracellular granules of donor leukocytes and are released over time during storage and granule deterioration²³. An observational study that investigated the possible mechanisms of TRIM found an association between the number of allogeneic blood transfusions and duration of mechanical ventilation, a finding that may be explained by the accumulation of leukocyte-derived soluble products in the supernatant of the stored PRBCs²⁴. Available evidence suggests that histamine may be a mediator of immune regulation²⁵ and that eosinophil cationic protein, eosinophil protein X²⁶, myeloperoxidase, and plasminogen activator inhibitor²⁷ may also contribute to the development of immunosuppression.

Two studies reported the presence of soluble Fas ligand (sFasL) molecules – coming from the membrane of the stored leukocytes – in the supernatant plasma of donor PRBCs^{28,29}. When sFasL is infused concurrently with blood components, these molecules may bind to Fas molecules of recipient natural killer (NK) and cytotoxic T (Tc) cells, which prevents the binding of Fas molecules of immune system cells to FasL molecules of infected cells^{30,31}. Thus, infusing sFasL together with blood components

may compromise the function of recipient NK and Tc cells, because it prevents the apoptosis of infected cells (figure 3)^{18,30,31}. Although there are no studies proving that blood cells undergo apoptotic changes during storage under refrigeration, the infusion of apoptotic cells has been recently found to have an immunosuppressive action in animal models³². Immunosuppression resulting from the infusion of these cells may be related to the release of TGF- β .

HLA Peptides Soluble in Allogeneic Plasma

It has been suggested that peptides derived from non-polymorphic HLA class I (HLA-I) molecules induce nonspecific antigen immunosuppression, whereas polymorphic HLA-I molecules have antigen-specific immunomodulatory effects³³⁻³⁶. Additionally, allogeneic plasma containing soluble HLA may possibly cause a clonal expansion of T cells directed against donor alloantigen and enter the circulation from the recipient thymus³⁷⁻³⁹. Soluble HLA may also be the responsible for the decrease in NK cell activity⁴⁰.

Other Possible Mechanisms

PRBC supernatant induces the activation of regulatory T cells (Tregs), which produce IL-10 and TGF- β and may suppress T cells and APCs^{41,42}. The mechanism that may lead to Treg activation in the recipient results from the presence of IL-2 in PRBCs and of thrombospondin-1, vitamin A metabolites,

Figure 2: The binding of the CD200 or OX-2 molecule of donor dendritic cells to CD200R or OX-2R molecules of recipient T cells leads to the release of transforming growth factor beta (TGF- β) and consequently to the suppression of macrophage function, thus reducing host immune defense¹¹⁻¹³.

Figure 3: Soluble Fas ligand (sFasL) molecules present in the blood component, when infused into the recipient, may bind to Fas molecules of recipient natural killer (NK) or cytotoxic T (Tc) cells, thus preventing the apoptosis of host infected cells.

heme oxygenase-1, and prostaglandin E₂ in the plasma fraction⁴¹. Other possible mechanism of immunosuppression is the production of anti-idiotypic antibodies. In this case, the transfusion stimulates a primary immune response against allogeneic antigens. The T-cell receptor (TCR) and the antibodies produced are considered “new antigens”; thus, the recipient produces an antibody matrix against these new antigens^{43,44}. After multiple transfusions, a network of anti-idiotypic antibodies may be present and react against multiple determinants of TCRs and antibodies^{43,44}. When a graft is performed, these anti-idiotypic antibodies reduce rejection by potentially interfering with TCRs and MHC molecules^{43,44}. Although there is no proof that these antibodies control immune response, renal transplant patients with detectable anti-idiotypic antibodies have been shown to have greater graft survival⁴⁵. Certainly none of these mechanisms occur in isolation but rather in synergy¹⁸.

Adverse Effects Related to Immunomodulation

TRIM has been associated with a decreased function of NK cells and APCs, reduced cell-mediated immunity, and increased Tregs^{17,46}. However, the effects that

these changes may cause on the organism are still under investigation. Table 1 shows studies evaluating the effects attributable to immunomodulation⁴⁶⁻⁵⁴. In an article published by Rogers et al.⁴⁷, a dose-dependent relationship was observed between the number of PRBC units (U) received during hospital stay and the prevalence of infection: 13.6% for 1-4 U, 25.3% for 5-49 U, 30.8% for 50-99 U, and 33.3% for 100 U or more. In a retrospective analysis of trauma patients to assess the relationship of immunomodulation with acute respiratory distress syndrome (ARDS), Chaiwat et al.⁴⁹ observed that, regardless the type or severity of injury or pneumonia, transfusion of more than 5 U of PRBCs during the first 24 hours after admission increased the risk of ARDS in 6% and hospital mortality in 5%. Conversely, Shorr et al.⁵¹ focused their research on the development of ventilator-associated pneumonia (VAP). Based on an analysis of 1,518 patients on mechanical ventilation for at least 48 hours after adjustment for confounding factors, the authors concluded that RBC transfusion was independently associated with VAP ($p<0.05$) and that patients who received more than 2 U of PRBCs had a more than twofold increased risk of developing VAP.

Table 1: Studies on the main effects of transfusion-related immunomodulation.

Authors	Year of publication	Type of Study	Transfusion-related infection	Increase in transfusion-related mortality	Blood component
Rogers et al. ⁴⁷	2006	Cohort	Infection of respiratory, digestive and urinary tracts, cardiac infection, and sepsis	Yes	PRBC
Banbury et al. ⁴⁶	2006	Retrospective	Bacteremia, sepsis, sternal infection, and deep infection in surgical site	Not available	PRBC, FFP, PC and CR
Walz et al. ⁴⁸	2006	Retrospective Multicenter	Deep infection in surgical site	Not available	PRBC
Chaiwat et al. ⁴⁹	2009	Retrospective Multicenter	ARDS	Yes	PRBC
Bernard et al. ⁵⁰	2009	Prospective Multicenter	Pneumonia, sepsis, and deep infection in surgical site	Yes	PRBC
Shorr et al. ⁵¹	2005	Prospective Multicenter	Increased probability of infection	Not available	PRBC
Zilberberg et al. ⁵²	2007	Cohort Multicenter	ARDS	Not available	PRBC
Shorr et al. ⁵³	2004	Retrospective Multicenter	Ventilator-associated pneumonia	Not available	PRBC
Sarani et al. ⁵⁴	2008	Retrospective	Ventilator-associated pneumonia, bloodstream infection, and sepsis	Not available	FFP

PRBC=packed red blood cells; PC=platelet concentrate; FFP=frozen fresh plasma; CR=cryoprecipitate; ARDS=acute respiratory distress syndrome.

Most studies aimed to investigate the relationship between PRBC transfusion and immunomodulation, but Banbury et al.⁴⁶ analyzed the association of transfusion with PRBCs, platelet concentrates, Fresh Frozen Plasma (FFP), and cryoprecipitate with postoperative infection. Results showed that, in general, a greater use of PRBCs was associated with a higher probability of infection. However, patients who received an average of six or more RBC units together with FFP or platelet concentrates had a lower probability of developing deep sternal wound infection compared to those who received only PRBCs. This finding was attributed to the fact that the patient receives a greater amount of IgG and IgM antibodies from the donor dissolved in FFP and platelet concentrates than in PRBCs, which would help in fighting against recipient infections⁴⁶. Moreover, Sarani et al.⁵⁴ found that FFP transfusion was associated with increased risk of several types of infection in critical patients, except for catheter-related sepsis. However, the fact that their study was retrospective makes it difficult to establish a causal relationship between FFP transfusion and infectious complications. Previous investigations

suggest that transfusion of soluble proteins in FFP may cause immunosuppression similar to that possibly observed in PRBC transfusion. These proteins may include HLA molecules or fibrinogen/fibrin, which show immunosuppressive properties and are found in FFP⁵⁵⁻⁵⁷.

Prevention of TRIM

The use of leukocyte reduction filters to prevent TRIM has been widely studied in the literature⁵⁸⁻⁶². More than 99.9% of leukocytes are removed when RBC units pass through these filters before or after storage⁸. Another technique commonly used in many European countries is the transfusion of buffy-coat depleted RBCs^{63,64}, which are obtained through a process that removes nearly two thirds of white cells without using filters as the result of the separation of whole blood into blood components⁸.

There are also other methods to reduce immunomodulation, such as autologous blood donation⁶⁵ or the transfusion of blood components with shorter storage time⁶⁴, but both have been little studied in recent years. Table 2 presents a description of studies

Table 2: Studies assessing TRIM prophylaxis.

Authors	Year of publication	Type of study	Techniques used	Results/Conclusion
Fergusson et al. ⁵⁸	2004	Randomized	NLR vs LRPR	Infection and mortality < LPRBC*
Phelan et al. ⁵⁹	2007	Retrospective	LR vs NLR	No difference was observed between the two techniques in terms of mortality, length of hospital stay, and interventions
Fung et al. ⁶⁰	2004	Double blind Randomized	CHL vs LRPR	No difference was observed between the two techniques in terms of acute lung injury and ARDS.
Bilgin et al. ⁶³	2004	Double blind Randomized	PS-LR vs BCD	Mortality twice as high with BCD*. Lower infection rates with PS-LR*
van de Watering et al. ⁶⁴	2006	Retrospective	ST in BCD	The higher storage time, the lower mortality*
Innerhofer et al. ⁶⁵	2005	Prospective Observational	ABD vs LR	Infection: LR>ABD*
Llewellyn et al. ⁶⁶	2004	Retrospective	NLR vs PS-LR	No difference was observed between the two techniques in terms of length of hospital stay and infection
Fung et al. ⁶⁷	2004	Cohort	NLR vs PS-LR	Length of hospital stay: < PS-LR*; Mortality: no difference was observed between the two techniques
Phelan et al. ⁶⁸	2007	Cohort	NLR vs PS-LR	No difference was observed between the two techniques in terms of length of hospital stay and mortality
Nathens et al. ⁶⁹	2006	Double blind Randomized	NLR vs PS-LR	No difference was observed between the two techniques in terms of length of hospital stay, mortality, and infection
Watkins et al. ⁷⁰	2008	Double blind Randomized	NLR vs PS-LR	No difference was observed between the two techniques in terms of acute lung injury and ARDS

LR=poststorage leukoreduction; NLR=non-leukoreduced packed red blood cells; PS-RL=prestorage leukoreduction; ARDS=acute respiratory distress syndrome; BCD=buffy coat depleted red blood cells; ABD=autologous blood donation; ST=storage time; *=Statistically significant difference.

on TRIM prophylaxis⁵⁸⁻⁶⁸. One of the procedures mentioned in literature is intraoperative autologous blood transfusion, a method in which blood collected during the surgical procedure by suction from the surgical site or from the extracorporeal circulation circuit is centrifuged, washed and filtered, and then reinfused into the patient during or immediately after surgery^{71,72}. According to previous research, in addition to possibly preventing TRIM, intraoperative autologous blood transfusion has advantages such as:

- Removal of leukocytes activated by extracorporeal circulation in cardiac surgery⁷³;
- Lower RBC transfusion in cardiac surgeries⁷⁴⁻⁷⁶, orthopedic surgeries⁷⁷⁻⁷⁹, and in liver transplantation⁸⁰;
- Improvement in hemoglobin concentration after surgery⁷³.
- Strategy for blood management safer for the patient⁸¹.

Final Considerations

It can be observed that no consensus has been achieved regarding immunomodulatory mechanisms related to the use of blood components or regarding which is the best way to prevent TRIM. This lack of consensus is believed to result from the fact that the immune system is extremely complex and its functioning has not been completely understood yet. Some studies have demonstrated that immunosuppression increases

proportionally with the number of transfusions⁵⁻⁷, which shows the importance of well established protocols and an active transfusion committee. Based on previous research showing that intraoperative cell saving procedures may reduce the number of transfusions, a literature review aimed to search for studies on the association between this technique and decreased immunomodulation was performed using the following keywords: cell saver, immunosuppression, and immunomodulation. Although not finding any study related to this topic, this review allowed us to investigate the differences in the evolution of patients who received leukocyte-filtered blood, buffy-coat depleted RBCs, or blood components with shorter storage time⁵⁸⁻⁶². According to the researchers, these data should be discussed so as to establish the cost-benefit relationship of observing the storage time of the blood component and expanding the use of filtered blood components or buffy-coat depleted RBCs in patients who will knowingly receive regular or multiple transfusions after surgery. Because of their debilitated status, patients who need transfusion are usually immunosuppressed and thus more predisposed to infection, a fact that creates a major bias and raises difficulties for randomized studies. Therefore, further studies are needed to elucidate the mechanisms involved in immunomodulation and the implication of this phenomenon for patients, which would help to determine the best strategy to prevent immunomodulatory events.

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