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Immunological and non-immunological factors implicated in TRALI — Polish experience

Immunologiczne i nieimmunologiczne czynniki powodujące TRALI — doświadczenie polskie

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Abstract

This article is a summary of a 10-year experience (2001–2011) in TRALI diagnostics in Poland including clinical observation of TRALI and results of leukocyte antibody detection in both recipients and donors of blood components. We also present our recent investigations on concentrations of lysophosphatidylcholine, cytokines, and microparticles released from erythrocytes, platelets, and leukocytes during storage of blood components.

Key words: TRALI, anti-leukocyte antibodies, lysophosphatidylcholine, cytokines, membrane microparticles

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Streszczenie

Artykuł podsumowuje 10 lat doświadczeń (2001–2011) dotyczących diagnostyki TRALI w Polsce, wraz z obserwacjami klinicznymi TRALI i wynikami wykrywania przeciwciał leukocytarnych zarówno u biorców, jak i dawców składników krwi. Przedstawia także nasze ostatnie badania odnośnie do stężenia lizofosfatydylocholiny, cytokin i mikrocząstek uwalnianych z erytrocytów, płytek i leukocytów w czasie przechowywania składników krwi.

Słowa kluczowe: TRALI, przeciwciała przeciwleukocytarne, lizofosfatydylocholina, cytokiny, mikrocząstki błonowe

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Transfusion-related acute lung injury (TRALI) is recognized as a severe transfusion-related adverse reaction. This paper is a summary of Polish experience in TRALI diagnostics routinely performed since the mid 1990s in the reference laboratory of our Institute. TRALI diagnostics was performed according to the recommendations of ISBT Working Party on Granulocyte Immunobiology [1].

The immunological pathomechanism of TRALI is well documented with both clinical and serological evidence as well as studies on animal models [2–7]. In Poland the first case of TRALI due to anti-HNA-3a was described by Żupańska et al. [8] in a patient with paroxysmal nocturnal haemoglobinuria. The next TRALI observations were published in several other papers [9–12]. A data sum-

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mary for the 2001-2005 period by Żupańska et al. [11] reported 44 TRALI cases; in 68.2% anti-HLA/ /anti-granulocyte antibodies were detected. In the period 2006–2011, Maślanka et al. [13] reported 28 TRALI cases; anti-HLA/anti-granulocyte antibodies were found in 64.3%. For these reported 'immune' TRALI cases, anti-leukocyte antibodies were found more often in patients than in donors of blood components.

In Poland we do not perform routine donor screening for HLA class I & II and HNA antibodies, but all donors of blood components transfused to patients who have been observed to develop adverse reactions (sudden onset of respiratory distress, dyspnoea included, tachypnoea and typically acute hypoxemia) are tested for anti-leukocyte antibodies. Donors with anti-leukocyte antibodies are deferred from donating blood for clinical use.

In a prospective study (2004–2006) antibodies were examined in 1043 donors, and anti-HLA class I or II were found in 9.8% of women; none in men. In the same study the look-back procedure was performed for one recipient with TRALI developed as result of red blood cell concentrate (RBCs) transfusion from a donor with anti-HLA antibodies. Cognate HLA antigens were found in TRALI patients as well as in 11/26 recipients who were transfused with blood components from the same donor with anti-HLA but developed no TRALI [14].

The pathomechanism of 'non-immune' TRALI is not equally well documented. Experimental evidence shows that TRALI can be induced by substances other than antibodies. Also, the age of blood components has been found to be significant for TRALI pathogenesis [15–17]. Blood components are human biological material, which, during storage, accumulate metabolic products such as bioactive lipids, cytokines, and microparticles. For the last few years we have investigated the levels of such products released during blood component storage.

The hypothesis of biologically active lysophosphatidylcholine (LysoPCs) accumulated during storage of blood components being involved in the pathomechanism of TRALI was mainly supported by Silliman et al. [18, 19]. According to our observations the concentrations of LysoPCs during storage underwent the following changes: in platelet concentrates (PCs) — it increased almost two fold; in RBCs — it remained within limits or dropped below the level of control plasma; and in FFP — it was comparable to control samples [20, 21]. Furthermore, no LysoPCs were found in RBCs transfused to TRALI patients (data not published). Our investigations confirmed the results of Sachs et al. [22] and Vlaar et al. [23].

Cytokines are released from leukocytes following their activation or destruction that occurs during storage of blood components. Our study demonstrated that during storage a 5-10 fold higher concentration of IL-8, sCD40L, and IL-1 beta cytokines occurs but only in non-leukoreduced RBCs. TNF-alfa and IL-6 were not detected in any other blood components [24]. We also found that IL-1beta, IL-8, and sCD40 cytokine concentration in RBCs, PCs, and FFP transfused to TRALI patients were within the same range as those found in blood components transfused to the recipients who presented no adverse reactions (data not published).

Microparticles (MPs) are small phospholipid vesicles ($< 2\ \mu$m), released from erythrocytes, leukocytes, and platelets during routine blood component storage. Compared to plasma of healthy donors, we found significantly elevated counts of platelet and erythrocyte MPs released during storage of RBCs and PCs but not of leukoreduced RBCs [25]. We also found that in RBCs transfused to patients who developed TRALI the levels of platelet and leukocyte MPs were within the range for control groups while the percentage of erythrocyte MPs was significantly higher than in RBCs transfused to the patients of the control groups (data not published).

Neutrophils are postulated as the effector cells in both 'immune' and 'non-immune' TRALI [4, 6]. In 2007, a threshold model of TRALI was presented by Bux & Sachs [26], which may explain the pathomechanism of TRALI. The authors suggest that neutrophils in critically ill patients are preactivated, and once their priming overcomes a certain threshold value the interactions with anti-leukocyte antibodies or other biological substances may be sufficient to trigger TRALI.

Finally, attention should be drawn to the decrease in the annual TRALI incidence rate observed in Poland: from 8.8 cases annually in 2001–2005 [11] to 4.7 in the 2006–2011 period [13]. A declining tendency was observed although a TRALI-oriented educational program was introduced and more advanced tools for effective anti-leukocyte antibodies recognition were implemented (additional methods of anti-HLA detection: ELISA in 2005, FlowPRA in 2007). On the other hand, the declining tendency may be attributed to wider implementation of leukoreduction in blood components [27], reduction of plasma volume in PCs by partial replacement with new generation additive solution (PAS III M) [28], and pathogen inactivation methods [29].

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