To the editor:

Leukocyte reduction and HTLV-I: is the glass half empty or half full?

We read with interest the recent article by Pennington et al.[1] Based on the ability to detect Tax DNA in the blood of asymptomatic carriers with proviral loads exceeding 10^8 DNA copies/L, the authors conclude that leukocyte depletion (LD) may not provide complete protection from human T-cell leukemia virus–I (HTLV-I) transmission by transfusion.

Lau et al[2] proved that cytomegalovirus (CMV)–infected blood, another example of a cell-borne viral infection, transfected with as many as 3×10^8 infected cells, contains a residual of 10^5 viral copies following LD, consistent with the present study's observations. These findings were confirmed in asymptomatic seropositive donors by Dumont et al.[3] However, in spite of the residual polymerase chain reaction (PCR) detectability of the CMV DNA in the postfiltration blood, little controversy exists concerning the ability of LD to greatly reduce the potential for transfusion-transmitted CMV infection.[4,5]

Okochi and Sato[6] conclude that approximately 10^8 infected lymphocytes are required to transmit HTLV-I infection by transfusion. This conclusion is further supported by the fact that plasma derived simultaneously from donations of whole blood whose red cells have transmitted HTLV-I infection have not transmitted the infection nor, as stated by the authors, has plasma ever been documented to transmit the infection. A unit of non-LD plasma delivers an average 3×10^6 leukocytes to a recipient.[7] Kobayashi et al[8] confirmed the infectivity of 7 units of native red cells from HTLV-I–positive donors using a syncytium induction assay in which cocultivation of HTLV-I–permissive (ME-80) cells and donor lymphocytes effect the development of multinucleated giant cells. Following LD, only 1 of the 7 filtered units showed infectivity using this assay.

Shinzato et al[9] quantified the HTLV-I viral genome load in the blood of 133 asymptomatic carriers and found that 95% of the individuals had 10 infected cells per 100 peripheral blood mononuclear cells (PBMCs), which approximates less than 10^8 cells per unit of blood. Levin et al found the number of infected cells to be as low as 1 per 10 000 PBMCs in patients with HTLV-I–associated disease.[10] Accepting the findings of the current study (ie, LD imposes a 3-4 $\log_{10}$ viral titer reduction), the residual number of proviral genomes in the blood of asymptomatic carriers is substantially less than that of plasma from infected donors and the infectious viral load requirement of Shinzato et al.[9]

As a final point, we believe use of MT2 cells as carriers of HTLV-I underestimates the benefit of LD because filtration of these cells results in a reduction of 1 $\log_{10}$ less than that of native leukocytes.

Only clinical experience can confirm the extent to which LD will be effective in minimizing the incidence of transfusion-transmitted HTLV-I infection. We agree with Pennington et al[1] that LD will not "provide complete protection" because no precautions, including nucleic acid testing, can. However, based on the information above, we believe LD will provide significant protection and, perhaps as for CMV, protection comparable to that afforded by serologic screening. Casting the conclusion this way appears more consistent with the authors' own data taken within the context of the available literature.

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Response:

Infectious dose of HTLV-I in transfusion recipients

We certainly agree with Wenz and Ortolano that leukocyte depletion (LD) reduces the risk of human T-cell leukemia virus–I (HTLV-I) transmission by transfusion just as they agree with us that this reduction does not equate zero risk. It is therefore important to be precise as to whether we consider LD to achieve risk reduction or risk removal.

In their rebuttal of our conclusions, Wenz and Ortolano quote studies regarding cytomegalovirus (CMV) and HTLV-I. We are not

convinced that CMV is a relevant model to compare with HTLV because the biology of herpesviridae is radically different from human retroviruses. Specifically, retroviruses are integrated into the host cell genome, whereas CMV is a cytoplasmic virus and thus could potentially be released during LD processes if cellular damage occurs. However, one aspect that posttransfusion HTLV-I and CMV transmission have in common is that clinical infectivity and pathogenicity of infection (or reactivation in the case of CMV) is more a function of the competence of the host immune system than of viral load. The rare development of clinical expression of HTLV-I infection after transfusion may well be more likely to occur in immunodeficient individuals.[1] Similarly, the disastrous consequences of CMV infection or reactivation have been observed essentially in premature neonates and bone marrow or organ transplant recipients. Although HTLV-I proviral load can be accurately measured, the threshold of susceptibility of patients with various levels of immunodeficiency cannot be predicted. It is therefore prudent to assume that, in these immunocompromised individuals who are the primary recipients of platelet concentrates, very low viral load can be not only infectious but could lead to clinical sequelae. Under such circumstances, it is likely that proviral loads considerably lower than the 10^8 infected cells calculated by Okochi and Sato in immunocompetent recipients of red cells can be infectious.[2]

We agree with Wenz and Ortolano that only clinical evidence could solve the problem. However, the low prevalence of HTLV-I infection and the extreme rarity of posttransfusion clinical consequences of HTLV-I infection make it doubtful that such evidence would ever be provided. Only a systematic follow-up of transfusion recipients in an area where anti–HTLV-I is not currently part of blood screening may provide an answer; but who would be willing to bear the massive cost involved?

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To the editor:

Factor XIII activation by thrombin depends on FXIIIVal34Leu genotype

Brummel et al[1] reported interesting results on different thrombin functions during tissue factor–induced whole blood coagulation. Thrombin generation, platelet activation, and activation of fibrinogen, factor V, and factor XIII (FXIII) were analyzed. FXIII activation was reported to occur slightly prior to fibrinopeptide A (FPA) release at a rate of 10.3 ± 0.9 nM/min and at a thrombin concentration of 0.84 ± 0.28 nM. However, these results by Brummel et al[1] must be interpreted with caution.

FXIII activation is known to be strongly influenced by a common polymorphism in the FXIII A-subunit gene (FXIIIVal34Leu),[2,3] which has been shown to be protective against myocardial infarction,[4] ischemic stroke,[5] and deep vein thrombosis.[6] This common G>T point mutation in codon 34, exon 2 of the A-subunit gene, which codes for the Val→Leu change, is only 3 amino acids from the thrombin activation site. The Leu allele is associated with increased cross-linking activity determined by an incorporation assay[3,7] and a reduced clot formation time measured by thrombelastography.[8] Kinetic studies on the activation reaction of FXIII by thrombin revealed increased catalytic efficiency (k_{cat}/K_m) for FXIII Leu34 compared with Val34.[9,10] Activation of FXIII Leu34 occurred at a similar rate as FPA release; FXIII Val34 was activated slower.[9] Based on these findings, altered fibrin structures[9] and wasteful, premature FXIII activation[10] have been proposed as mechanisms of the protective effect of FXIIIVal34Leu.

Knowledge of the FXIIIVal34Leu genotype in these 6 individuals taking part in the study by Brummel et al[1] is essential. Because of the high allele frequency of this polymorphism (approximately 0.25 for the Leu allele[4]) in the general population and the significant kinetic differences between genotypes, the Val34Leu polymorphism has to be taken into account when FXIII activation rates are studied.

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