Low levels of interleukin-10 in patients with transfusion-related acute lung injury

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Transfusion related acute lung injury (TRALI) is the leading cause of transfusion-related fatalities (FDA Report 2016) (1) and is characterized by the acute onset of respiratory distress within 6 hours following blood transfusion (2,3). The clinical diagnosis is confirmed in case of newly developing acute respiratory distress: PaO_2/FiO_2 ratio (ratio of arterial oxygen partial pressure to fractional inspired oxygen) <300 mmHg or arterial oxygen saturation <90% at room air; newly developed or worsened bilateral pulmonary infiltrates indicative of pulmonary edema on chest X-ray; emergence of all symptoms within 6 hours upon blood transfusion and exclusion of cardiac ischemia and transfusion associated circulatory overload (TACO). Apart from supportive measures, such as oxygen or ventilation, no specific therapies are available. The pathogenesis is incompletely understood, however, a two-hit model is usually assumed to underlie the disease pathology. The first hit consists of a pre-disposing factor present in the recipient such as inflammation while the second hit is conveyed by factors present in the transfused blood product such as anti-leukocyte antibodies (3). For example, the acute phase protein C-reactive protein (CRP) which rapidly increases during infection and inflammation was shown to enhance antibody-mediated TRALI in mice (4) and in line with that data, CRP was found to be elevated in human TRALI patients (5) confirming its role as a first hit risk factor in human TRALI.

Little is known about the protective mechanisms against TRALI, however, recently it was demonstrated that T regulatory cells and dendritic cells convey protection against murine TRALI via interleukin (IL)-10 (6). This study found low levels of plasma IL-10 in mice which suffered from antibody-mediated TRALI and IL-10 knock out mice were also susceptible to TRALI induction. Interestingly, administration of IL-10 was able to protect and rescue the mice from TRALI development (6). Low IL-10 levels may therefore perhaps be a risk factor in human TRALI as well. A previous study indeed found IL-10 levels to be low in human TRALI patients (n=70) while IL-10 levels were increased in patients with TACO (n=29) (7). The same group, however, found IL-10 levels to be increased in TRALI (n=38) in an earlier study (8). This discrepancy might be explained by the fact that in the first study, they investigated fold-changes of paired samples prior to and following transfusion (8) whereas in the later study, they compared post-transfusion TRALI samples versus controls undergoing blood transfusion without developing TRALI (7). To shed more light on IL-10 levels in human TRALI patients, we also measured plasma IL-10 levels in our previously described cohort of transfused patients that developed TRALI reactions (n=12) and transfused control individuals that did not develop TRALI or any other pulmonary reactions upon transfusion (n=12) (5). Both groups had comparably low levels of IL-10 and this was in contrast to non-transfused septic patients with acute lung injury (septic ALI patients; n=21) who had increased IL-10 levels versus healthy non-transfused

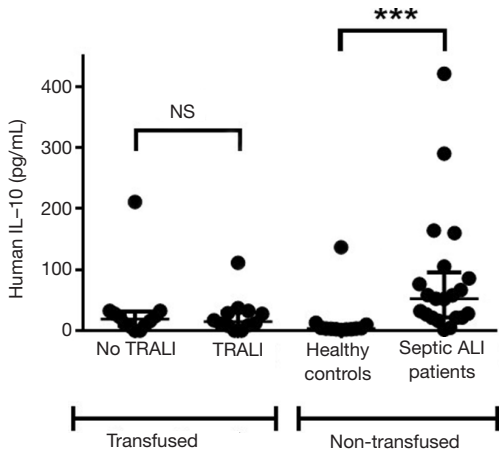

Figure 1 Plasma IL-10 measurements in TRALI patients (n=12) *vs.* transfused control patients who did not develop TRALI (n=12) and non-transfused septic ALI patients (n=21) *vs.* healthy control patients (n=12). Only statistical comparisons of interest are shown, statistical analyses were
made with a two-tailed Mann-Whitney test. ***, P<0.001. IL, interleukin; TRALI, transfusion-related acute lung injury; NS, non-significant.

controls (n=12) (*Figure 1*). These data should be interpreted with caution, however, in order to induce IL-10 secretion, particular induction signals are required such as triggering by specific molecular events or pathogen-derived products (9) or by antibodies as was demonstrated in TRALI-resistant mice (6). In TRALI, it seems likely that such triggering has taken place through antibodies (or perhaps via biological response modifiers) present in the transfused blood product and our data indicates that there is a lack of IL-10 secretion in human TRALI patients. These data at least, support low IL-10 levels as a predisposing risk factor in human TRALI. The recently described beneficial therapeutic effect of IL-10 infusion in TRALI-mice (6) may therefore also have potential to be effective in human TRALI. However, this approach may not be successful in other inflammatory pulmonary disorders such as septic ALI or other transfusion-related disorders such as TACO, in which IL-10 levels appear to be elevated.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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