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EFFICACY OF RECOMBINANT HUMAN AND RHESUS THROMBOPOIETIN STIMULATED BLOOD TRANSFUSIONS IN COMPARISON TO UNSTIMULATED WHOLE BLOOD OR THROMBOCYTE TRANSFUSIONS IN A NON-HUMAN PRIMATE MODEL

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Background: Pre-treatment of allogeneic blood donors with thrombopoietin or other c-mpl ligands to increase thrombocyte counts would reduce apheresis volume, increase transfusion efficacy, decrease volume donated per recipient and the number of donors needed, and reduce the number of thrombocyte transfusions required and thus the cumulative risk of immune responses.

Aims: We tested the efficacy of recombinant rhesus TPO (rrTPO) and human TPO (rhTPO) treatment of non-human primate blood donors on the total number of thrombocytes per transfusion and its effect on platelet and hematocrit increments in irradiated recipient monkeys. In addition, we used a pre-treatment regimen predicted by biomathematical modeling[1] for optimal efficacy and reduced immunogenicity, and measured the humoral immune response to TPO after up to 4 times challenging of donors.

Methods: Healthy male rhesus monkeys (n=11) were treated with 5 μg/kg/d rrTPO or rhTPO (Genentech Inc.), administered subcutaneously for 4 consecutive days and served as donors up to 4 times for lethally or sublethally irradiated pancytopenic monkeys (n=21). Data were compared to regular thrombocyte transfusions or whole blood transfusions obtained from untreated animals and infused into irradiated control monkeys (n=23). Transfusions were collected in citrate and exposed to 20 Gy γ-rays delivered by a ^{137}Cs source. Antibodies to TPO were demonstrated using a sensitive ELISA with a detection limit of 10 pg/mL.

Results: Each transfusion was standardized to contain on average 10^{10} thrombocytes, independent of the source or stimulation status of the platelets. The average transfused volume was 10.3±4.2 mL for rrTPO stimulated transfusions, 14.6±3.4 mL for rhTPO, 32.1±6.4 mL (from 100 mL of blood) for regular platelet transfusions and 38.1±10.8 mL for whole blood transfusions. Transfusion with rrTPO or rhTPO stimulated blood products resulted in platelet increments of 33.4±26.0 and 28.0±19.7x10^9/L, respectively, the former significantly different from 25.4±19.2x10^9/L observed for regular platelet transfusions ($P<0.05$). Hematocrits were not affected by infusions of TPO stimulated platelet transfusions, contrasting an average 6.1% unstimulated whole blood transfusion. The average increment of thrombocytes per mL infused volume was 0.8±0.6x10^9/L for

both whole blood and thrombocyte transfusions and was significantly higher for both rrTPO with an increase of $3.4\pm2.4x10^9$/L ($P<0.01$) and rhTPO with an increase of $2.0\pm1.6x10^9$/L ($P<0.01$). Even after 4 cycles of rr or rhTPO pretreatment, antibodies to TPO were not detected using the regimen predicted by the biomathematical model.

Conclusions: A mathematically predicted non-immunogenic TPO administration regimen adapted for multiple pre-treatment of blood donors resulted in a significant increase of blood platelets and in well-tolerated collection of the required 10^{10} thrombocytes per transfusion unit. Despite the significantly lower total volume obtained from the donor monkeys after TPO stimulation, platelet increments in recipients were significantly higher for both the rrTPO and rhTPO pretreated transfusions. These data demonstrate that use of TPO or a TPO-mimetic can considerably reduce blood volume required per recipient (in our study 5- to 10-fold) while significantly promoting transfusion efficacy.

[1]Skomorovski K, et al. Br J Haematol. 2003 Nov;123(4):683-91