Present and future of pathogen reduction for red cells

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Background: Pathogen reduction and leukocyte inactivation in red blood cells (RBC) are techniques implemented in order to improve transfusion safety by reducing the risk of transfusion transmitted infections (TTI) and transfusion-associated graft versus host disease (ta-GvHD), while RBC viability compared to gamma irradiated RBC seems to be improved. An alternative method to reduce the risk of TTI is pathogen testing. However, while pathogen reduction is a proactive way, testing requires the identification of a novel (re)emerging pathogen and the development of a new test, therefore testing is deemed reactive.

Aim: Clinical safety in adult cardiovascular surgery patients requiring transfusion support for acute anemia was assessed in a randomized, double-blind, controlled, multi-center clinical trial. Efficacy of the medical device using the S-303 pathogen reduction kit was also assessed in this trial.

Methods: Patients undergoing coronary artery bypass grafting, and/or valve replacement/repair were randomized to receive either S-303 treated or conventional RBC during a seven day treatment period. Clinical outcome regarding tissue oxygenation was assessed by diagnosis of renal insufficiency, hepatic insufficiency and cardiopulmonary function (six minute walking test; 6MWT). Adverse events (AE) were collected throughout the study. Immunogenicity was tested prior to transfusion, at the end of the study (day 28 to 40) and at day 90.

Results: 87 patients in two clinical centers were enrolled. 51 patients (25 pts. in the S-303 group; 26 in the control group) received study RBC and were evaluable. Overall, 73 S-303 treated RBC and 75 control RBC were transfused. Baseline characteristics and surgical variables were comparable between both groups. Overall incidence of renal insufficiency was 15.7% (5 in the S-303 group; 3 in the control group; p=0.41). Incidence of hepatic insufficiency was 2% (1 case in the S-303 group; 0 in the control group; p=0.37). 37 patients (17 in the S-303 group; 20 in the control group) were able to perform the 6MWT at the first evaluation. There were no differences in the mean [SD] distance in the 6MWT between days 0-6 (Test 44.8 m [48.6], Control 53.1 m [41.8]; 95%CI -37.0, 26.6) or at day 13 or discharge (Test 95.5 m [69.7], Control 97.7 m [51.1]; 95%CI -30.8, 50.3). Most patients (84.3%) experienced an AE. There were no statistical differences in the overall incidence of AE rates (22 in the S-303 group; 21 in the control group; p=0.412), or in possibly related AE (5 in the S-303 group; 3; in the control group; p=0.24). Overall, 22 (43.1%) patients experienced a serious adverse event (SAE), with similar distribution between groups (13 in the S-303 group; 9 in the control group; p=0.20). Three SAEs were considered possibly related to the transfusion of study RBC (1 in the S-303 group; 2 in the control group). Five patients died during this study (3 in the S-303 group; 2 in the control group; p=0.53). Deaths were not considered related to study drug. Observed AEs were within the expected range. No patients exhibited an immune response to S-303 treated RBC.

Summary: Clinical safety following the transfusion of S-303 treated RBC in this preliminary randomized controlled trial was comparable to conventional RBC. However, further clinical trial including greater numbers of patients are needed to further establish safety and efficacy of S-303 treated RBC.

Conclusions: Apart from RBC pathogen reduction, whole blood pathogen reduction offers a safety option in regions with high prevalence of different pathogens like malaria, viruses and bacteria, especially, if no sufficient testing (like nucleic acid testing; NAT) is in place yet. In addition, whole blood pathogen reduction does not require a full infrastructure like electricity “24/7”, cooling, delivery of products in different temperature zones, centrifuges, etc. Such technology could also be used in remote areas in order to improve safety of blood transfusion. Inline leukocyte depletion would probably add to the safety of pathogen reduced whole blood preparations, but the costs for leukodepletion filters are relatively high.

It has to be taken into account that whole blood pathogen reduction mainly conserves red cells, while platelets and coagulation factors are not very well preserved. Therefore, from the transfusion medicine point of view, it is mandatory to define very clearly, what indications are possible for this product. In addition, pathogen inactivation techniques do not inactivate all pathogens; e.g. hepatitis A and E with critical serotypes in some regions of the world or parvovirus B19 endangering immunocompromised haematological patients with the development of pure red cell aplasia (PRCA).

An additional benefit of whole blood pathogen reduction might be becoming accustomed to the pathogen reduction procedure. In financial contraints, whole blood pathogen reduction might be a “second best” solution to improve blood safety. If and when the infrastructure in such countries improves, component production and pathogen reduction of components (RBC, therapeutic plasma and platelet concentrates) is the next logical step. This might save money otherwise spent for a highly sophisticated testing procedure including e.g. NAT.