A randomized, placebo-controlled trial of complement inhibition in ischemia-reperfusion injury after lung transplantation in human beings

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Objective: Complement activation has been shown to play a significant role in ischemia-reperfusion injury after lung transplantation. TP-10 (soluble complement receptor 1 inhibitor) inhibits the activation of complement by inactivating C3a and C5a convertases. This was a clinical trial of TP-10 to reduce ischemia-reperfusion injury in lung transplantation.

Methods: In a randomized, double-blinded, multicenter, placebo-controlled trial, 59 patients from four lung transplant programs received TP-10 (10 mg/kg, n = 28) or placebo (n = 31) before reperfusion. This dose achieved 90% complement inhibition for 24 hours, and activity had returned toward normal by 72 hours.

Results: At 24 hours, 14 of 28 patients in the TP-10 group (50%) were extubated, whereas only 6 of 31 patients in the placebo group (19%) were ($P = .01$). The total times on the ventilator and in the intensive care unit both tended to be shorter in the TP-10 group, but these differences did not achieve statistical significance. Among patients requiring cardiopulmonary bypass (n = 5 in placebo group and n = 7 in TP-10 group), the mean duration of mechanical ventilation was reduced by 11 days in the TP-10 group (10.6 ± 5.0 days vs 21.5 ± 5.9 days in placebo group, $P = .2$). Operative deaths, incidences of infection and rejection, and length of hospital stay were not significantly different between the two groups.

Conclusions: Short-term complement inhibition with TP-10 led to early extubation in a significantly higher proportion of lung transplant recipients. The effect of TP-10 was greater among patients undergoing cardiopulmonary bypass, with a large reduction in ventilator days. Complement inhibition thus significantly decreases the duration of mechanical ventilation and could be useful in improving the outcome of lung transplant recipients.

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Lung transplantation has become a standard therapy for patients with end-stage lung disease. More than 15,000 lung transplantations have been performed worldwide, and approximately 1500 are performed every year.[1] Despite the recent expansion both in the number of centers performing lung transplantation and in the number of patients undergoing transplantation, ischemia-reperfusion (IR) injury remains an important problem after lung transplantation.[2,3] It occurs in as many as 10% to 20% of patients, despite the recent introduction of low-potassium dextran solution (Perfadex; Vitrolife, Goteborg, Sweden) to preserve the lungs, and still represents the prime cause of early morbidity and mortality.[4] In addition, there is

TABLE 1. Patient characteristics

	TP-10 (n = 28)	Placebo (n = 31)	*P* value
Age (y)			
Mean ± SEM	53.4 ± 10.5	51.8 ± 7.8	.5
18-60 (No.)	24	28	.6
>60 (No.)	4	3	
Sex (No.)			.6
Male	19	19	
Female	9	12	
Lung transplantation (No.)			.7
Single	16	16	
Bilateral	12	15	
Pathology (No.)			.8
Emphysema	19	20	
Pulmonary fibrosis	3	6	
Pulmonary hypertension	4	4	
Other	2	1	

some evidence to suggest a relationship between IR injury and both acute rejection and chronic graft dysfunction.[5,6]

Prediction of early lung dysfunction has been difficult because of the complexity of the interactions between the donor lung and the recipient.[7] A large number of interventions have been performed experimentally to limit the release of inflammatory mediators and to improve the quality of the lung.[8] However, relatively few treatment options have been translated into clinical practice.[9]

Complement is a collective term used to describe a group of plasma and cell membrane proteins that play a key role in the cell defense process.[10] Animal experiments have shown that activation of the complement system may lead to cellular injury through direct and indirect mechanisms during lung ischemia and reperfusion.[11,12] Complement receptor 1 is a natural complement antagonist that has been cloned and the transmembrane portion removed to obtain a soluble form (sCR1). sCR1 can suppress both the classic and the alternative pathways of complement activation by inhibiting C3 and C5 convertases. We and others have shown in a swine single-lung transplantation model that the administration of sCR1 to the recipient before reperfusion significantly reduces lung edema and improves lung function.[13,14] In response to these results, we undertook a multicenter trial to evaluate whether complement inhibition with sCR1 (TP-10) would lead to reduced IR injury and improved outcomes in human lung transplantation.

Materials and Methods

We performed a randomized, double blind, placebo-controlled trial at four North American lung transplant centers. These centers were the University of Toronto, Duke University, the University of Colorado, and Washington University. The study drug and placebo were provided by T Cell Sciences Inc. Patients with end-stage pulmonary disease undergoing lung transplantation surgery were enrolled in the trial. Patients with cystic fibrosis or with infectious conditions such as bronchiectasis were excluded from the study because of the theoretic possibility that complement inhibition might impair the ability to fight infection. All patients received standard care, including immunosuppressive therapies, antirejection therapies, and anti-infection therapies, as determined by the principal investigator at each institution. Pharmacists in each center randomly assigned patients at the time of transplantation and provided drug or placebo in a blinded fashion. Lung preservation methods were similar between the centers, with a bolus of 500 μg prostaglandin E_1 followed by an anterograde flush of Euro-Collins solution injected through the pulmonary artery and hypothermic preservation during transport.

A total of 59 patients enrolled in the study were randomly assigned to either the TP-10 group (n = 28) or the placebo group (n = 31). One patient was excluded because of incomplete dose administration. One patient received placebo instead of the drug and was perforce transferred to the placebo group. There was no significant difference between groups in age, sex, type of transplantation, and underlying lung disease (Table 1). The drug was administered at a dose of 10 mg/kg through a period of 30 minutes before reperfusion of the first allograft. This dose has been shown to achieve >90% complement inhibition for 24 to 48 hours, with a return to normal activity by 72 hours.[15]

The primary end point was the time to extubation. We considered the duration of mechanical ventilation to be a clinically important end point for a phase III study, because it reflects the severity of IR injury, intensive care unit (ICU) morbidity, and resource use. Secondary end points were as follows: Pao_2/inspired oxygen fraction ratio, ICU and hospital stays, and survival. Chest radiographs performed on postoperative day (POD) 1, POD 2, and POD 3 were blindly reviewed by a radiologist, and scores of 0 to 5 were attributed to the upper, middle, and lower zones of each transplanted lung. A score of 0 defined a clear chest radiograph, and a score of 5 was given when the entire zone was consolidated. The total score (0-15 for each lung) was multiplied by 2 for patients with single-lung transplants. The incidences of acute rejection and infection were also recorded. Safety parameters and pharmacokinetics of the drug were also analyzed. All surviving patients were prospectively followed up for 6 months after the transplantation.

Assessment of Complement Activity

The inhibitory effect of TP-10 on the complement system was determined by the Mayer hemolysis method to measure complement activity (CH_{50}) and by the level of C3a in the blood, as described previously elsewhere.[13] To carry out these assays, blood was collected before administration of the drug and at 12, 24, 48, and 72 hours after reperfusion, as well as on the POD 5.

Statistical Analysis

Data collection and management was carried out by T Cell Sciences. All data analysis was supervised by the principal investigators (S.K., R.D.D., M.R.Z., G.A.P.). Results are expressed as mean ± SEM. Categoric variables were analyzed by Fisher exact test or χ^2 test, and continuous variables were analyzed by Student *t* test. Repeated-measures analysis of variance and planned com-