Published in final edited form as:

Transplant Proc. 2009 ; 41(1): 429–430. doi:10.1016/j.transproceed.2008.08.147.

COMPARISON OF LUNG AND KIDNEY ALLOGRAFTS IN INDUCTION OF TOLERANCE BY A MIXED-CHIMERISM APPROACH IN CYNOMOLGUS MONKEYS

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Abstract

We have previously reported the successful induction of renal allograft tolerance in non-human primates using a non-myeloablative conditioning regimen to produce a mixed-chimeric state in the recipient. In the present study, we applied this same technique to lung allotransplantation in cynomolgus monkeys.

METHODS—Nine pairs of fully MHC-mismatched cynomolgus monkeys were used. The conditioning regimen consisted of total body irradiation, thymic irradiation, and anti-thymocyte globulin. The recipients underwent lung and bone marrow transplantation, followed by anti-CD154 mAb, and a one-month course of cyclosporine. The regimen included anti-CD8 mAb in the last five recipients and alpha 1-antitrypsin in the last three recipients. The results were compared with eight recipients that received kidney allografts using the same regimen.

RESULTS—Transient chimerism developed in all lung recipients, as was previously seen in the kidney recipients. Nonetheless, the lung recipients rejected their allografts significant earlier than the kidney recipients ($p < 0.01$).

CONCLUSIONS—Despite the successful induction of mixed chimerism in recipients of fully MHC-mismatched lung allografts, we have not observed long-term graft survival, as has been seen in an analogous kidney model. Strategies to overcome this problem include organ-specific modifications of the transplant regimen.

Lung transplantation is an established therapeutic option for a variety of end-stage lung diseases. However, despite improvements in immunosuppression, five-year survival is only approximately 50% (1). One of the most robust means of inducing transplantation tolerance is through the creation of a mixed-chimeric recipient. (2–6). Based on studies in mice, we have developed a non-myeloablative regimen that can induce mixed chimerism and renal allograft tolerance in MHC-mismatched cynomolgus monkey kidney recipients (4,5). Here we applied the analogous approach to MHC-mismatched lung allografts in cynomolgus monkeys and compared the results with those previously reported in kidney recipients (5).

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MATERIALS AND METHODS

Eighteen male cynomolgus monkeys weighing 2–5 kg were used. Recipient and donor pairs were selected for compatible ABO blood types and mismatched MHC antigens. The transplant regimen was previously reported in detail (5). In brief, the regimen consisted of total body irradiation (1.5 Gy $\times$ 2), thymic irradiation (7 Gy), anti-thymocyte globulin (50 mg/kg/day $\times$ 3), and orthotopic left lung and bone marrow cell transplantation, followed by anti-CD154 mAb (20 mg/kg $\times$ 2 and 10 mg/kg $\times$ 4). In the last five transplantations, the regimen was modified by adding two doses of anti-CD8 mAb. Post-transplant administration of alpha 1-antitrypsin was also added in the last three transplantations. Animals received a one-month course of cyclosporine to maintain therapeutic serum levels.

RESULTS

Transient chimerism was detected postoperatively in 8 out of 9 animals (chimerism in one lung recipient was not assessed). The levels of myeloid chimerism reached $88.1 \pm 7.6\%$ in the lung recipients versus $72.8 \pm 23.8\%$ in the kidney recipients ($p=0.104$). Slightly higher maximum levels of lymphocyte chimerism were also found in lung recipients than in kidney recipients ($7.6 \pm 4.4\%$ vs. $4.0 \pm 2.1\%$, $p=0.048$). Nonetheless, six of nine lung recipients rejected their allografts revealing acute cellular rejection (ISHLT grade 3 to 4) by day 85, 68, 55, 35, 26, and 22 days, while the same regimen induced long-term allograft survival in the kidney recipients (>2500 , >2000 , 837, 755, 401, 373, 206, and 58 days) ($p<0.01$). The other three lung recipients died or were sacrificed due to non-immunological causes.

DISCUSSION

We previously reported that transient chimerism can induce allograft tolerance in MHC-mismatched cynomolgus monkey kidney transplantation (4,5). In the current study, we attempted to induce lung allograft tolerance using an analogous regimen. However, none of lung recipients acquired allograft tolerance despite levels of mixed chimerism comparable to those seen in renal allograft recipients. We suspect that the lung allografts exist in a higher state of innate immune activation and that further modification of the regimen is necessary to achieve durable tolerance in lung allografts.

Acknowledgements

This work was supported by NIH U19 AI066705, the American Society of Transplant Surgeons-Wyeth Collaboration Scientist Award (J.S.A.), and a Scholarship to Study Abroad from the Yoshida Scholarship Foundation (A.A.)

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