Locally administered immunomodulation for the maintenance of vascularized composite allotransplants

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INTRODUCTION: Advances in combat casualty care and body armor have resulted in improved soldier survival after sustaining catastrophic extremity and maxillofacial injuries. Reconstructive transplantation, or vascularized composite allotransplantation (VCA), offers a means for superior functional recovery following these devastating injuries compared to traditional reconstructive techniques. Using porcine models of VCA, we evaluated the efficacy of locally administered immunosupression to delay rejection in the absence of systemic immunosupression.

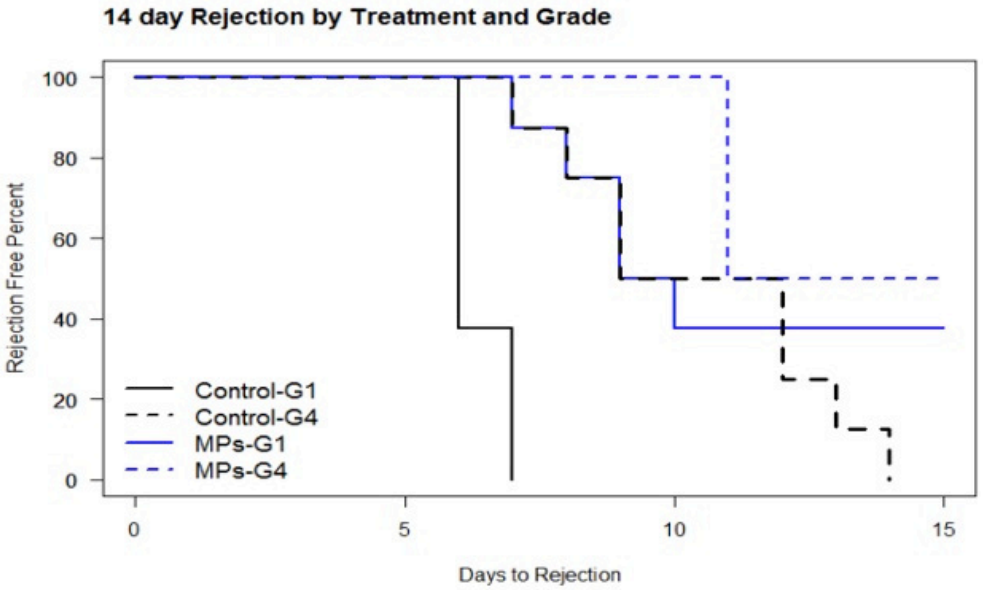
METHODS: Swine with a single swine leucocyte antigen (SLA) mismatch were used in two experiments. First, gracilis myocutaneous flaps were transplanted heterotopically into recipient necks. Group 1 (controls, n=8) received no additional intervention. In group 2 (experimental, n=8), 20μg of drug-eluting microparticles (loaded with IL-2, TGF-β, and rapamycin) were injected into subdermal donor tissues. Serum and tissue were collected until the end point at 14 days, then assessed for rejection based on the Banff scale. The second experiment employed a true orthotopic forelimb transplant. Group 3 (controls, n=4) received no additional intervention. Group 4 (experimental, n=4) received an enzyme responsive tacrolimus-eluting hydrogel injected into the subcutaneous space of the donor forelimb. Serum and tissue were collected with an endpoint of 90 days or limb rejection.

RESULTS: In Group 1, the mean time to grade 1 and grade 4 rejection was 6.4 days (SD=0.52) and 10.5 days (SD 2.6), respectively. In Group 2, on average, both grade 1 and 4 rejection was absent at the endpoint of 14 days. Group 3 animals rejected at 6-7 days. Two animals in Group 4 had no clinical signs of rejection in the absence of systemic immunosuppression for 32 and 63 days, respectively. These pigs were ultimately euthanized for weight loss. Of the remaining two animals, one expired from

CONCLUSION: Donor tissue-specific immunomodulation with drug-eluting compounds is evolving. Obviating the need for systemic immunosuppression through the use of locally applied agents will dramatically potentiate the field of reconstructive transplantation by increasing the reliability and safety of these transplant procedures. cardiopulmonary arrest on day 2 and one was euthanized for technical graft failure on day 9.

FIGURE LEGEND:

Table 1. Kaplan-Meyer curve of microparticle-treated gracilis allotransplants vs. controls


14 day Rejection by Treatment and Grade
Rejection Free Percent
100
80
60
40
20
0
0
5
10
15
Days to Rejection
Control-G1
Control-G4
MPs-G1
MPs-G4