Immunomodulation in Vascularized Composite Allotransplantation – Preliminary Results in a Non-human Primate Model with Tocilizumab

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INTRODUCTION: Tolerance in vascularized composite allotransplantation (VCA) remains elusive and patients are faced with a lifetime of immunosuppression and associated risks. Tocilizumab (anti-IL-6 receptor monoclonal antibody) is currently FDA approved for use in rheumatoid and idiopathic arthritis. It mitigates inflammation, reduces the incidence of GvHD, and is potentially pro-tolerogenic. We investigated the utility of a short course of tocilizumab in a non-human primate model (NHP) of facial VCA to achieve prolonged survival and/or tolerance.

MATERIALS AND METHODS: VCAs were transplanted into MHC-mismatched NHPs (n=4) after induction with anti-thymocyte globulin. Post-operative maintenance consisted of triple immunosuppression (FK506, methylprednisolone, MMF) before further conditioning (irradiation, lymphocyte depletion) in preparation for co-stimulatory blockade-based donor bone marrow transplantation (DBMT) on POD 60. Tocilizumab was administered on the day of DBMT, and at weekly intervals thereafter for a total of 5 doses. Post-DBMT, the recipient was maintained on a tapering course of cyclosporine before complete withdrawal 28 days later. VCAs were assessed by serial clinical assessment and histopathology. Mixed chimerism in peripheral blood was monitored by flow cytometry and *in vitro* immunologic responses were assessed through mixed lymphocyte reaction (MLR) assays.

RESULTS: Two recipients were euthanized within 2 weeks of DBMT due to neutropenic sepsis and post-transplant lymphoproliferative disorder but both VCAs remained viable up to experimental endpoint. M4515 (full MHC-mismatched recipient) has been off of all immunosuppression for 3 weeks without any evidence of rejection. M3815 (haplomatched) developed mixed chimerism transiently at 6 weeks after DBMT and corresponding MLR assays demonstrated decreased anti-donor responses; immunosuppression was then successfully withdrawn for a total of 5 weeks before rejection developed. Although the rejection episode could be reversed with steroid bolus and a tapering course of FK506, recurrence occurred after another 2 weeks off immunosuppression.

CONCLUSION: As with the clinical experience with tocilizumab, vigilant monitoring is required following drug administration due to increased susceptibility to neutropenia and infections[1]. Tocilizumab appears to promote engraftment after DBMT to allow short-medium term immunosuppression-free VCA survival across haplomatched barriers in this NHP model. Continued follow-up is required to determine if similar results can be achieved across a full MHC mismatch. Further studies in our laboratory are focused on optimizing the current protocol to achieve stable engraftment and durable mixed chimerism for tolerance of VCA.

REFERENCES:

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