Delayed Immune Tolerance for Cardiac Allografts in Nonhuman Primates by Targeting CD154, CD2, and CD28 Costimulation Pathways

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Introduction

Long-term renal allograft acceptance has been achieved in macaques using a pioneering mixed-chimerism protocol, but similar regimens have proven unsuccessful in heart allograft recipients unless a renal graft was performed simultaneously. Here we test whether a modified protocol based on targeting CD28 and CD2 promotes expansion of peripheral regulatory T-cells and is sufficient to promote heart allograft acceptance.

Method

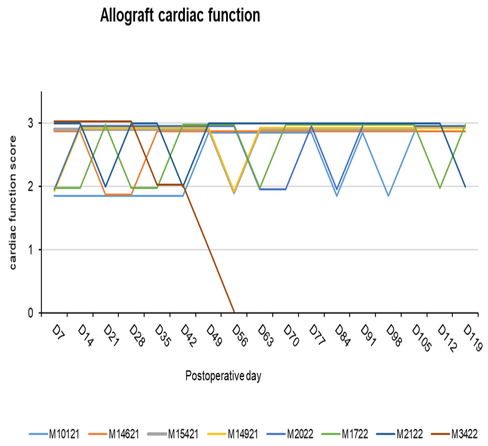
Donor bone marrow transplantation (BMT) was administered to recipients of MHC-mismatched heterotopic heart allografts after a 4-month delay period under TNX-1500 (anti-CD154). BMT induction was comprised of one (Group 1) or two (Group 2) doses of total body irradiation, thymic irradiation, and horse anti-thymocyte globulin (ATG) followed by two (Group 1) or five (Group 2) weekly doses of anti-CD2 and five weekly treatments with anti-CD28 and TNX-1500.

Results

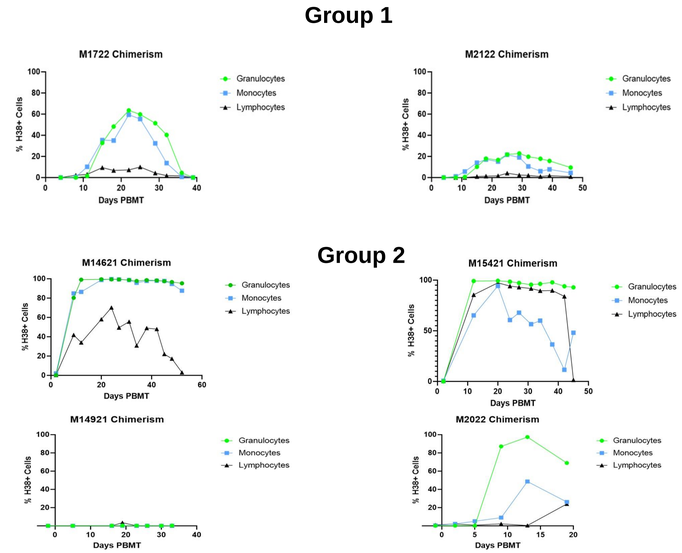
One Group 1 graft was rejected during the delay period; one in Group 1 and one in Group 2 with normal graft function exhibited moderate rejection on protocol biopsy prior to BMT, while five others exhibited normal histology. Lymphocyte chimerism >5% was observed in three of the five Group 2 animals but not in either Group 1 recipient. One Group 1 animal rejected 44 days after BMT while another succumbed to disseminated CMV infection. In Group 2, two monkeys succumbed to CMV disease or bacterial infection during the post-BMT treatment period. Two of three Group 2 animals developed >35% lymphocyte chimerism but succumbed to post-transplantation lymphoproliferative disease (PTLD) at 37, 41, and 51 days after BMT, with normal graft function and histology in all 3 at euthanasia.

Conclusion

The combination of anti-CD28 with multi-dose anti-CD2 often promotes lymphocyte chimerism in this delayed BMT model at levels that predict prolonged graft survival or long-term acceptance in kidney recipients. However, the high incidence of PTLD and opportunistic infection prevented assessment of the regimen's effectiveness in promoting alloimmune tolerance. Strategies to improve CMV control and PTLD prophylaxis merit investigation in this delayed heart allograft tolerance model



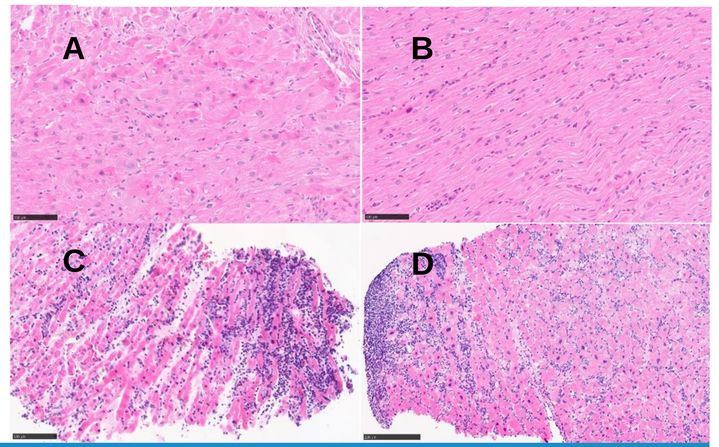
Graft survival was followed by ultrasound (USG) and palpation, and the contractility was subjectively classified as good [3], moderate [2], weak [1], or absent [0]



Heart biopsy histology:

A) In group 1 (M2122); there was no evidence of rejection. B) In group 2 (M10121, M14621, M14921, M2022); there was no evidence of rejection.

C) M1722 (group 1) had acute cellular rejection grade 1 along with antibody-mediated rejection. D) M15421 (group 2) exhibited acute cellular rejection grade 2.



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