Abstract Type : Oral Presentation
Abstract Submission No. : F-009047

Factors Affecting the Long-Term Graft Survival after pig to NHP renal Xenotransplantation

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Introduction: The xenotransplantation research team at Konkuk University performed 30 pig-to-NHP (Non-Human Primate) renal xenotransplantation since 2011. Among them, 12 NHPs showed survival from 30 to 80 days and 5 showed survival of more than 80 days. We regarded survival for less than 30 days as a technical failure. As such, in this study, to find out what factors made the difference in survival, we analyzed different types of medi pig and immunosuppressants, the weight of NHPs, and date of surgery.

Methods: Average age of donor medi pigs was about 1~2 months old (body weigh: 1.7 to 11.5 kg). All transgenics were Gal-knockout (GTKO) based, and the knock-in genes were thrombomodulin (TBM), ectonu-cleoside triphosphate diphosphohydrolase-1 (CD39), membrane cofactor protein (CD46), and complement decay-accelerating factor (CD55), as well as multiple-edited genes, similar to GGTA1/CMAH/ B4galNT2 (Triple-knockout; TKO) transgenic pigs. Cynomolgus monkeys weighing 2.6 to 6.13 kg were used. The transplantation technique was similar to allotransplantation. We extracted the right kidney of the host monkey before intraabdominal anastomosis of the pig kidney. Anti-CD154 antibody, rituximab, anti-thymocyte globulin, tacrolimus, mycophenolate mofetil, and steroids were used as immunosuppressants. Remained host kidney was extracted after the 2 weeks as the second-look operation. All data are expressed as mean±SEM. The statistical differences in mean values between various groups and GTKO groups were analyzed by one-way analysis of variance followed by Tukeys multiple comparison tests as a post hoc test using statistical software (Prism, version 5.01; GraphPad Software Inc., San Diego, CA). A value of $p < 0.05$ was considered statistically significant.

Results: The average life expectancy of these two groups was 48 days and 117.2 days, respectively. CVF + ATG + Rituximab + aCD154 as immunosuppressants were used equally in all experimental groups. Other factors included the use of calcineurin inhibitor (CNI) in the immunosuppressive agents used, the different types of medi pig, the weight of the NHPs used in the experiment, and the timing of surgery. Compared to the GTKO group, the graft survival rate increased significantly at 80 days after transplantation compared to 30 to 80 days after transplantation (***$p<0.001$ vs. GTKO

group; Fig. 1A). Graft survival rate when rapamycin and tacrolimus were administered was significantly increased when tacrolimus was administered compared to the GTKO group (**$p<0.01$ at rapamycin and ***$p<0.001$ at tacrolimus, vs. GTKO group, respectively). When comparing survival rates in several medi pigs knocked-in, there were no significant results, and although the n number of experimental groups was small, CD39 and CD55 were knocked in based on TKO. and the 2nd-look period, the graft long-term survival rate showed a tendency to increase. Although no significant results were found between NHPs body weight and graft long-term survival rate, in terms of transplant technique and primate management proficiency, technical failure of less than 30 days was higher than the suspected survival rate in previous studies. As a result, the long-term survival rate tended to increase compared to previous studies.

Conclusion: In this study, factors such as the development of various knock-in (e.g., CD39 and CD55) transgenic technologies based on TKO, appropriate immunosuppressive control, improvement of techniques, and increased proficiency in primate management may affect long-term survival.