Asian Transplantation Week 2023

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Session Title : Mechanisms and biomarkers of immune tolerance

T cell responses in transplantation

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Transplantation induces a potent and complex immune response, which ultimately leads to tissue destruction. Although the use of immunosuppressive drugs allows the immune response, directed towards the allograft, to be inhibited to a greater or lesser extent, delayed graft loss and management of the side effects of lifelong immunosuppression, including cancer, remain major problems.

Regulatory T cells (Treg) are a subset of T cells that act physiologically to prevent autoimmune disease and provide immune homeostasis. In animal models, tolerance can be adoptively transferred to naïve transplant recipients by administering purified preparations of regulatory immune cells. Adoptively transferred Tregs can mediate an 'infectious tolerance' in the recipient, whereby they promote a self-perpetuating regulatory response through the recipient's own native T cells, which persists even after the disappearance of the original tolerising cells. Our group having been the first to demonstrate human Treg ability to prevent rejection of human vessel allografts, went on to prove that Tregs home to the allograft and that allograft tolerance can be sustained by Tregs residing within the allograft. Having demonstrated the efficacy of Treg therapy in humanised mouse models, we then went on to design a Phase I clinical trial to test safety and feasibility of Treg-based therapy in renal transplantation. In this study, termed the ONE Study, 12 living donor kidney transplant recipients were infused with autologous polyclonally-expanded Tregs in a dose escalation safety trial administering at doses of $1x10^6$; $3x10^6$; $6x10^6$ and $10x10^6$ cells/kg at day five post-transplant. No infusion reactions were noted, and no biopsy-proven rejection episodes were observed. Importantly, all patients demonstrated stable allograft function. The clinical results of the ONE Study demonstrated the clinical safety and feasibility of GMP-quality autologous polyclonally-expanded Tregs. We are currently running a large Phase II trial, which we hope will provide further evidence for Treg efficacy and provide the impetus to further develop cellular therapies for transplantation.