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Tolerance-inducing Strategies and Immunosuppression Minimization

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Kidney transplant outcomes have improved and become the best treatment option for end stage kidney disease. However, current immunosuppression has limitations in both efficacy and safety. Insufficient efficacy leads to chronic rejection and persistent, nonspecific immunosuppression results in safety concerns, such as infection, malignancy, cardiometabolic syndrome, and renal dysfunction. Therefore, induction of donor-specific tolerance or at least minimization of conventional immunosuppressants are main goal of kidney transplantation. Induction of chimerism is the main direction of tolerance induction in kidney transplantation. Durable full chimerism-based regimens using central deletion have a risk of graft-versus-host disease. Persistent mixed chimerism-based regimens using HLA full-matched donors showed successful outcomes in the recent phase III trial but need to expand to HLA-mismatched donors. Transient mixed chimerism-based regimens using central deletion and peripheral regulation has overcome chimerism transition syndrome and BKV infection but showed insufficient outcomes in highly HLA-mismatched donors. Costimulatory blockade can play an adjunctive role for immunosuppression minimization rather than tolerance induction. Or costimulatory blockade can participate in chimerism-based tolerance regimens to decrease current potential toxicity. Especially, the 3rd generation anti-CD154 monoclonal antibodies are promising to be applied to clinical trials. Immunosuppressive cell therapy includes regulatory T cells, tolerogenic dendritic cells, mesenchymal stem cells etc.; however the current position of cell therapy is immunosuppression minimization rather than tolerance induction and cell therapy is promising as an adjunctive therapy for mixed chimerism-based regimen with reduced toxicity. Furthermore, cell therapy has been evolving to engineered cell therapy, such as chimeric antigen receptor (CAR) regulatory T cell, T cell receptor (TCR) regulatory T cells, and B cell antibody receptor (BAR) regulatory T cells. Strategies of human tolerance induction or

immunosuppression minimization has been developed over the last thirty years and recent successes in a few clinical trials support their potential role in future clinical kidney transplantation.

Keywords: tolerance, chimerism, costimulatory blockade, cell therapy, minimization