Transplantation has become an accepted therapeutic modality for patients suffering from end organ failure since 1950s after the first milestones set independently by Peter Medawar’s group in the form of successful skin transplantation following splenic and bone marrow transplantation in neonatal mouse from adult, and Murray’s group in Boston and Hamburger's group in Paris simultaneously performing kidney transplantation (1-3). Much water has run under the bridge since then however there is no respite from chronic rejection of the graft in spite of life-long immunosuppressive medications. In addition to the cost, these medications have their own side effects and hazards in the form of acute/chronic life threatening fungal, bacterial and viral infections, immuno-compromised status with its own side effects and malignancy over long term.

The only answer to this problem is transplantation with minimum or no immunosuppression. This will give the gift of good quality of life to the patient by helping him/her return to mainstream of life and save the financial and health burden on the system.

Rejection of the grafted organ is believed to be

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T-cell and/or B-cell mediated, later being antibody mediated. There is one school of thought which believes in Burnet’s theory of clonal deletion, the other school following Medawar’s theory of chimeric tolerance believes in addressing T-cells (4-12).

“Transplantation Tolerance” may be defined as survival of the grafted organ in the recipient’s immune system without causing rejection, while maintaining host immune response intact and performing normal function without requiring immunosuppressive medications (13).

Few groups have shown promising results of long term transplant tolerance in a cohort of few patients. They achieved this feat using bone marrow transplantation for achieving mixed hematopoietic chimerism, or total lymphoid irradiation and central clonal thymic deletion (14-17).

As against these anecdotal reports, Ahmedabad team under the leadership of Prof. Trivedi has shown the definite path of transplant tolerance (18,19). When all the workers are failing in fulfilling their dreams of tolerance, our group under Prof. Trivedi has reached the promised land of tolerance (20,21). This has occurred because of combination of cell therapy and solid organ transplantation along with initial very important steps of clonal deletion of rejecting cells that has helped in winning this race with unequivocal results.

The steps followed by this group are clonal deletion using total lymphoid irradiation followed by unique therapy of combination of infusion of indigenously developed donor adipose tissue derived mesenchymal stem cells and bone marrow derived hematopoietic stem cells in thymus and portal circulation via superior mesenteric artery under C. arm guidance by femoral catheterization. Direct administration of cells in thymus has created central thymic tolerance in addition to solving problems of immune correction of lesions like focal segmental glomerulosclerosis.

Portal infusion helps in sustaining tolerance, since liver is the most tolerogenic organ of the body. After favorable immune response measured by CDCC, flow-cross-match for T/B cells and single antigen testing by luminex platform, kidney transplantation is performed under the cover of methylprednisone and rabbit-antithymocyte globulin. This additional immune induction is required since kidney acts as a major antigen load and rejecting cells are deleted immediately. Post-transplant immunosuppression consists of Prednisone, 20 mg/day tapered to 10 mg/day after one month and Tacrolimus, 0.05 mg/kgBW or Cyclosporin, 3 mg/kgBW/day. After 6 months CNI are replaced by mycophenolate. After 2-4 days of stability of the graft, Bortezomib, 1.3 mg/m² body surface area is given on days 1,4,7,11 of transplantation to abrogate antibody mediated responses initiated by plasma/B cells. Immune monitoring includes measurement of donor specific antibodies (DSA), regulatory T-cells in peripheral blood [pTregs] (127low/CD4+/25high) and graft biopsy. The routine monitoring of graft function like serum creatinine, blood counts and Doppler and ultrasound studies are followed as per standard guidelines. Biopsy proven rejections are treated as per standard guidelines.

Prof. Trivedi has more than 1000 patients with minimum rejections (<10%) doing well on 2 drug immunosuppression of Prednisone, 5-10 mg/day and Azathioprine, 50-100 mg/day or Mycophenolate sodium, 360 mg, once or twice a day (19,22). His group also has about 100 patients living a normal life for mean 2.5 years (ranging from 1 year to 15 years) with zero rejections, on 5-10 mg Prednisone/day or no immunosuppression at all. Now further addition to his armamentarium is regulatory T-cells generated in our lab infused posttransplant, which further protect the graft from any immune injury and help in earlier
withdrawal of immunosuppression (unpublished data). Thus he has reached the final destination of transplant tolerance. The acid test of tolerance is clinical tolerance which he has achieved. Laboratory signature is combination of peripheral T-regs of >2.5%, normal graft biopsy and serum creatinine. Chimerism and DSA do not form sustainable reliable signatures since we have several patients doing well with normal graft biopsy in absence of chimerism/presence of DSA for years. Perhaps the answer is presence of T-regs which act as strong bodyguards of the graft.

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