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Transplantation tolerance; myth or reality?

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Implication for health policy/practice/research/medical education:
Transplantation is now a well-accepted therapy for end organ failure. However the recipients are required to take life–long immunosuppression to prevent rejection. This leads to immunosuppression associated morbidity in the form of viral/ fungal/ bacterial infections in addition to causing financial burden on the system. Over a long run these patients are at high risk to develop malignancies. In spite of all these efforts, the graft is lost over 7-10 years to chronic graft attrition/ rejection. The only answer to this problem is "Transplant tolerance" which means stable allograft function while maintaining third party immune response intact in absence of rejections on no immunosuppression. Since last 60 years transplanters across the globe are in search of this "Mackenna's gold". The following editorial discusses how far have we progressed in our search for the promised land of "Transplant Tolerance."

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Discussion

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 mycofenolate. After 2-4 days of stability of the graft, Bortezomib, 1.3 mg/m^2 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] ($127^{low/-}$/CD4+/25^{high}) 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 Mycofenolate 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.

Author's contribution

AV is the single author of the manuscript.

Conflict of interests

The author declared no competing interests.

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References

1. Billingham RE, Brent L, Medawar PB. Actively acquired tolerance to foreign cells. Nature 1953;172:603–606.
2. Guild WR, Harrison JH, Merrill JP, Murray J. Successful homotransplantation of the kidney in an identical twin. Trans Am Clin Climatol Assoc 1955; 67: 167–173.
3. Legendre Ch, Kreis H. A tribute to Jean Hamburger's contribution to organ transplantation. Am J Transplant 2010; 10 (11):2392-5.
4. Nishizuka Y. Studies and perspectives of protein kinase C. Science 1986;233: 305-12.
5. Berridge MJ, Irvine RF. Inositol triphosphate, a novel second messenger in cellular signal transduction. Nature 1984;312: 315-21.
6. Dinarello CA, Mier JW. Lymphokines. N Engl J Med 1987;317: 940-5.
7. Chalasani G, Lakkis FG. Immunologic ignorance of organ allografts. Curr Opin Organ Transplant 2001;6:83-8.
8. Nakajima H, Leonard WJ. Impaired peripheral deletion of activated T cells in mice lacking the common cytokine receptor gamma chain. J Immunol 1997;159: 4737-44.
9. Dorling A, Lechler RI. The passenger leucocyte, dendritic cell and antigen-presenting cell (APC). In: Tilney Nl, Strom TB, Paul LC, editors.Transplantation Biology: Cellular and Molecular Aspects. Philadelphia: Lippincott-Raven;1996. p. 355.
10. Terasaki PI, Cai J. Human leukocyte antigen antibodies and chronic rejection: from association to causation. Transplantation 2008; 86: 377.
11. Stegall MD, Park WD, Dean PG, Cosio FG. Improving long-term renal allograft survival via a road less traveled by. Am J Transplant 2011;11:1382.
12. Hachem RR, Yusen RD, Meyers BF, Aloush AA, Mohanakumar T, Patterson GA, et al. Anti-human leukocyte antigen antibodies and preemptive antibody-directed therapy after lung transplantation. J Heart Lung Transplant 2010; 29: 973.
13. Salama AD, Womer KL, Sayegh MH. Clinical transplantation tolerance. Many rivers to cross. J Immunol 2007; 178: 5419.
14. Strober S, Dhillon M, Schubert M, Holm B, Engleman E, Benike C, et al. Acquired immune tolerance to cadaveric renal allografts: a study of three patients treated with total lymphoid irradiation. N Engl J Med 1989; 321: 28-33.
15. Sayegh MH, Fine NA, Smith JL, Rennke HG, Milford EL, Tilney NL. Immunologic tolerance to renal allografts after bone marrow transplants from the same donors. Ann Intern Med 1991; 114: 954-955.
16. Spitzer TR, Delmonico F, Tolkoff-Rubin N, McAfee S, Sackstein R, Saidman S, et al. Combined histocompatibility leukocyte antigen-matched donor bone marrow and renal transplantation for multiple myeloma with end stage renal disease: the induction of allograft tolerance through mixed lymphohematopoietic chimerism. Transplantation 1999; 68: 480-484.
17. Burlingham WJ, Grailer AP, Fechner JH Jr, Kusaka S, Trucco M, Kocova M, et al. Microchimerism linked to cytotoxic T lymphocyte functional unresponsiveness (clonal anergy) in a tolerant renal transplant recipient. Transplantation 1995; 59: 1147-55.
18. Trivedi HL, Terasaki PI, Feroz A, Vanikar AV, Trivedi VB, Khemchandani SI, et al. Clonal deletion with bortezomib followed by low or no maintenance immunosuppression in renal allograft recipients. Transplantation 2010; 90: 221.

19. Vanikar AV, Trivedi HL. Stem Cell Transplantation in Living Donor Renal Transplantation for Minimization of Immunosuppression. Transplantation 2012; 94(8):845-50.
20. Kirk AD, Mannon RB, Kleiner DE, Swanson JS, Kampen RL, Cendales LK, et al. Results from a Human Renal Allograft Tolerance Trial Evaluating T-Cell Depletion with Alemtuzumab Combined with Deoxyspergualin. Transplantation 2005;80(8):1051-59.
21. Salama AD, Remuzzi G, Harmon WE, Sayegh MH. Challenges to achieving clinical transplantation tolerance. J Clin Invest 2001; 108: 943.
22. Vanikar AV, Goplani KR, Feroz A, Kanodia KV, Patel RD, Suthar KS, et al. Operational tolerance in living-related renal transplantation: a single-center experience. Transplant Proc 2011: 43(5): 1551-58.