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Prednisone-Free Maintenance Immunotherapy in Kidney Transplantation-Long Term Results

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Prednisone continues to be part of long-term maintenance immunotherapy in most renal transplant centers. Weaning recipients with stable renal function one-year or more after transplantation carries high risk of rejection episodes (20-30 percent). Consequently most centers are reluctant to discontinue maintenance prednisone.

Prednisone is the least specific among immunosuppressive agents in current use. It suppresses and destroys T-and B-lymphocytes, monocytes/macrophages and other cells in the lymphoid series. Although its use prevents rejection, an unwanted side effect of long-term prednisone may be to suppress early development of beneficial immunoregulatory mechanisms that are necessary for long-term graft survival. After weaning from prednisone, stunted regulatory protection may be insufficient to prevent a rejection episode.

By late 1998 the team at Northwestern believed that recipients might fare as well or better by avoiding maintenance prednisone altogether. A regimen of basiliximab, intra operative methylprednisolone, and maintenance tacrolimus, mycophenolate mofetil and prednisone had achieved more than 95% graft survival at one-year with rejection episodes less than 15% and median onset of 60 days. The decision was made to delete prednisone from the regimen. Only those recipients who were already taking prednisone for another medical condition continued maintenance doses after transplantation.

Outcomes of prednisone-free renal transplantation

Northwestern has treated more than 800 transplant recipients without maintenance prednisone since 1998. Eliminating maintenance prednisone from the basiliximab, methylprednisolone tacrolimus and MMF regimen had no adverse effect on first year survival of recipients, death censored grafts or incidence of rejection. The only adverse effect was to advance onset of first rejection episodes from a median of 60 days with prednisone to 10 days without maintenance prednisone. In September 2001 basiliximab was replaced by alemtuzumab which pushed onset of rejection back to a median of 153 days after transplantation. Patient survival, graft survival and incidence of rejection were not affected by choice of basiliximab vs. alemtuzumab. Outcomes were reported in July, 2005 (ref#1) and are available in the United States Scientific Registry of Transplant Recipients to which all 250 U.S. renal transplant centers must report long-term outcomes (ref#2). Northwestern operates the tenth largest renal transplant program in the United States; according to the national registry it is one of only eighteen centers whose three-year patient and graft survival are significantly higher than would be predicted from national experience for its patient population and mix of living and deceased donors.

Recipient Survival %			
	1 year	***3 years***	***5 years***
Northwestern	98.25	97.0	95.9
United States	95.9	90.23	------
Death Censored Graft Survival %			
	1 year	***3 years***	***5 years***
Northwestern	99.3	96.41	93.8
United States	95.4	90.1	------

Alemtuzumab (Campath-1H) is a lymphocyte depleting monoclonal antibody that is used primarily to treat lymphoma. Alemtuzumab reacts with the CD52 cell-surface antigen, which is densely expressed on T-and B-cells, eosinophils and some populations of monocytes, macrophages and dendritic cells. A single intraoperative intravenous injection of 30 mg at the time of transplantation induces profound lymphopenia within a few hours that recovers slowly over four to six months. Calne first reported use of alemtuzumab in a prednisone-free monotherapy regimen (cyclosporine) for kidney transplantation. He reported uncensored one and five year survival of 97% and 88% for recipients, and 94% and 79% for grafts with median onset of first rejection at 170 days (ref#3).

Patient and death censored graft survival have been very stable between the third and fifth post-transplant years. Moreover, renal function (serum creatinine) remains stable over 36 months.

Post transplant months	**Serum creatinine**
1	1.52+.6
6	1.38+ .55
12	1.39+.53
24	1.43+.60
36	1.47+.67

The beneficial effects of steroid-free immune suppression are well known. Many

Side effects associated with chronic steroid exposure were reduced in the prednisone-free recipients, including significant reduction of CMV disease, which occurred in only 4.5% of recipients. Alemtuzumab induction followed

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by prednisone-free maintenance therapy with tacrolimus and MMF provided a practical immunosuppression protocol after renal transplantation in an ethnically diverse group of recipients who received their grafts from deceased or living donors.

References

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