Current and Evolving Immunosuppressive Regimens in Kidney Transplantation

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• **The advent of novel immunosuppressive agents with increased potency now offers multiple treatment options for transplant physicians. However, variable efficacy, drug-drug interactions, and adverse effects associated with long-term immunosuppression continue to complicate the clinical management of kidney transplant recipients. Currently, investigators are challenged to develop regimens that take into account not only efficacy, but also dosing, monitoring, safety, and patient quality of life. Recent research has focused on evaluating new combinations of approved agents that seek to improve outcomes by improving control of immunologic events with fewer complications. This article reviews current practice and recent studies to give all health care providers who manage kidney transplant recipients a better understanding of current regimens and general trends in immunosuppressive therapy.** ***Am J Kidney Dis*** **47(S2):S3-S21.**
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INDEX WORDS: Tacrolimus (TAC); cyclosporine (CsA); antibody induction; mycophenolate mofetil (MMF); sirolimus (SRL); corticosteroids; kidney transplant.

DURING THE PAST DECADE, the availability of newer immunosuppressive agents has been associated with improved outcomes in kidney transplantation. These newer agents have distinct mechanisms of action, allowing investigators to formulate alternative combinations and therapeutic strategies. Traditionally, these approaches focused on decreasing the risk for acute rejection to achieve prolonged graft and patient survival. More recently, increasing attention has been devoted to developing regimens that preserve immunologic benefits while reducing complications (nephrotoxicity, cardiovascular risk, infections, glucose intolerance), addressing financial issues, and improving quality of life.

Currently, the calcineurin inhibitors (CNIs) tacrolimus (TAC; Prograf; Astellas Pharma US Inc, Deerfield, IL) and cyclosporine (CsA; Neoral; Sandimmune; Novartis Pharmaceuticals Corp, East Hanover, NJ) remain the cornerstones of standard immunosuppression therapy. These agents commonly are coadministered with an antiproliferative agent, such as mycophenolate mofetil (MMF; CellCept; Roche Pharmaceuticals, Nutley, NJ), sirolimus (SRL; Rapamune; Wyeth Pharmaceuticals Inc, Philadelphia, PA), or azathioprine (AZA; Imuran; Prometheus Laboratories Inc, San Diego, CA), with or without corticosteroids. Inclusion of therapeutic antibody administration at the time of transplantation to initiate immunosuppression (eg, basiliximab [BAS; Simulect; Novartis Pharmaceuticals Corp, East Hanover, NJ], daclizumab [DAC; Zenapax; Roche Pharmaceuticals, Nutley, NJ], antithymocyte globulin [ATG], and alemtuzumab [Campath-1H; Campath; Genzyme Corp, Cambridge, MA]) is increasingly common. Currently used transplant immunosuppressive agents are listed in Table 1.

CALCINEURIN INHIBITORS

Immunosuppressive protocols built around CNIs remain the standard for kidney transplant recipients. Although the mechanisms by which they induce immunosuppression are similar, CsA and TAC can be distinguished by structure and receptor interactions, attributes that translate into differences in clinical efficacy.[1,2] The introduction of CsA in 1983 resulted in less acute rejection and improved graft survival compared with previous immunosuppressive regimens.[3] Although clinical studies indicated similar efficacy

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Table 1. Immunosuppressive Agents Currently Used in Kidney Transplantation

CNIs	Antiproliferative Agents	Corticosteroids	Therapeutic Antibodies
TAC (Prograf)	MMF (CellCept)	Prednisone	Alemtuzumab (Campath-1H, Campath)
CsA (Sandimmune)	MPS (Myfortic)	Methylprednisolone	Equine ATG (Atgam)
CsA-ME (Neoral and generics)	SRL (Rapamune)		Rabbit ATG (Thymoglobulin)
	AZA (Imuran)		Muromonab-CD3 (OKT3; Orthoclone OKT3)
			DAC (Zenapax)
			BAS (Simulect)

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for TAC and CsA in terms of patient and graft survival,[4-7] further reduction in risk for acute rejection and a favorable profile in terms of adverse events have made TAC the CNI of choice in the United States.[8,9] To date, discontinuation of CNI therapy, although successful in some studies,[10] has not gained widespread acceptance because of ongoing concerns about acute and chronic rejection.[3]

Dosing and Administration

The recommended starting oral dosage of TAC for adult kidney transplant recipients is 0.2 mg/kg/d administered every 12 hours in 2 divided doses.[1] However, recent studies, more reflective of current practice, have initiated (0.15 mg/kg/d) and maintained (0.07 to 0.1 mg/kg/d, 6 to 36 months posttransplantation) therapy with TAC, in conjunction with MMF or SRL, at lower doses (Table 2).[11-15] For treatment with TAC/AZA, TAC was maintained at a median dose of 0.08 to 0.11 mg/kg/d at 12 to 36 months posttransplantation.[12,14,15]

For new kidney transplant recipients, the recommended initial oral dose of CsA is 9 ± 3 mg/kg/d administered in 2 divided doses, although this can vary based on the immunosuppressive protocol.[2] In several studies in which

Table 2. Maintenance Dosing Levels for TAC/MMF, TAC/AZA, and TAC/SRL

	Gonwa et al,[11] 2003	Johnson et al,[12] 2000	Mendez et al,[13] 2005	Ahsan et al,[14] 2001	Gonwa et al,[15] 2003
Follow-up (mo)	6	12	12	24	36
Treatment group					
TAC/MMF					
Median TAC dose (mg/kg/d)	0.08	0.10	0.08	0.09	0.07
Median MMF dose (mg/d)	1,500	1,500	1,500	1,500	1,000
CsA/MMF					
Median CsA dose (mg/kg/d)	NA	4.0	NA	3.77	3.54
Median MMF dose (mg/d)	NA	2,000	NA	2,000	1,500
TAC/AZA					
Median TAC dose (mg/kg/d)	NA	0.11	NA	0.08	0.08
Median AZA dose (mg/kg/d)	NA	1.44	NA	NR	NR
TAC/SRL					
Median TAC dose (mg/kg/d)	0.07	NA	0.07	NA	NA
Median SRL dose (mg/d)	3.0	NA	3.0	NA	NA

NOTE. All patients were treated with corticosteroids; only patients who developed delayed graft function were eligible for antilymphocyte antibody induction therapy.

Abbreviations: NA, not applicable; NR, not reported.

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