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Immunosuppressive Drugs in Renal Transplantation
A Review of the Regimens

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Contents

Summary

Currently, expected 10-year first graft survival rates for kidneys from HLA-identical sibling, 1-haplotype-matched relative, and cadaver donors are 74, 51, and 40%, respectively. Histocompatibility, immunological conditioning with blood products, and immunosuppression with glucocorticoids, azathioprine, cyclosporin, and the antithymocyte (antilymphocyte) antibody preparations have been significant factors in the gradual improvement of kidney graft survival rates.

Nearly all immunosuppression regimens are cyclosporin-based. Antithymocyte antibody induction therapy with delayed administration of cyclosporin is widely practised to avoid cyclosporin nephrotoxicity while the kidney graft is recovering from preservation injury. Late cyclosporin withdrawal results in inferior cadaver kidney transplant survival rates. Rejection crises usually respond to high dose glucocorticoid therapy. Glucocorticoid-resistant rejection usually responds to treatment with antithymocyte antibody. FK-506 is a promising new immunosuppressant that has properties similar to cyclosporin. Prophylaxis against viral, bacterial and fungal infections is necessary to reduce the morbidity of immunosuppression. The incidence of malignant conditions associated with viral infections is significantly increased with immunosuppression.

New immunopharmacological agents and advances in genetic procedures may allow the induction of specific transplantation tolerance and successful xenotransplantation within the next decade.

The years 1959 to 1962 saw the development of mercaptopurine, azathioprine and glucocorticoids as immunosuppressants for organ transplants and the first successful human cadaveric kidney transplant (Calne 1991; Caralps 1988; Hamilton 1988; Murray 1991). Glucocorticoids and azathioprine remained the 2 most important maintenance drugs for nearly 20 years until cyclosporin was introduced for clinical use in 1978 (Calne et al. 1979). By the mid-1980s, most maintenance immunosuppression protocols were cyclosporin-based, and triple therapy with glucocorticoids, azathioprine and cyclosporin was introduced to reduce the dosage and toxicity of the 3 agents while maintaining immunosuppression (see section 3.2.2; Slapak et al. 1985). High doses of glucocorticoids have remained the most common treatment for rejection crises.

Antithymocyte (antilymphocyte) antibody therapy was introduced into renal transplant protocols in the mid-1960s, first with polyclonal antithymocyte globulin and, more recently, with monoclonal antithymocyte globulin (Cosimi et al. 1981). These preparations are used for induction immunotherapy and the treatment of rejection crises, especially when the latter are steroid-resistant. Preliminary clinical information is available on FK-506, a promising new drug with steroid-sparing properties (Shapiro et al. 1991). It is briefly reviewed here along with the currently used immunosuppression protocols in clinical renal transplantation.

1. Immunology of Rejection

Most kidney transplant losses are due to rejection, a phenomenon due to donor/recipient incompatibility of tissue antigens. The incidence and severity of rejection are modified by histocompatibility, immunological conditioning (usually with transfusion of blood products), and immunosuppression with drugs. The goal of immunosuppression is preservation of transplant function while preserving immune competence against infection and malignancy.

Although minor histocompatibility systems exist, the 2 systems of greatest importance in renal transplantation are ABO blood group and the HLA (human leucocyte antigen) systems (Dallman & Morris 1988). Usually the donor and recipient must be ABO compatible because A and B substances are present on endothelial cells and most individuals have antibodies to the red blood cell antigens they lack. However, successful renal transplantation has been performed with kidneys from blood group A2 donors into O recipients when the recipients' anti-A2 titres are low and immunological modification of the recipients with immunoadsorption, plasma exchange and splenectomy has been done (Alexandre et al. 1987).

The major histocompatibility antigens are glycoproteins on the cell membrane (Hall 1991; Krensky et al. 1990; Strom 1990). They are encoded by major histocompatibility complex (MHC) autosomal genes on the short arm of chromosome 6. These antigens are subdivided into class I (HLA-A, -B, and -C) and class II (HLA-DP, -DQ, and -DR) antigens. Class I antigens are present on nearly all nucleated cells, while class II antigens are expressed on B lymphocytes, activated T lymphocytes, monocytes, macrophages, dendritic cells, and some endothelial cells, all of which can be antigen-presenting cells. Incompatibility of these MHC antigens on donor tissue stimulates the immune response (fig. 1). For example, a host macrophage processes class II antigens from the kidney graft, becomes activated by interleukin-1 (IL-1) and produces interleukin-6 (IL-6). The activated macrophage presents the incompatible class II antigens and IL-6 to T cell receptors on a resting CD4+ helper T lymphocyte. The helper T lymphocyte be-

comes activated and produces IL-2, which stimulates helper T lymphocytes to produce a series of lymphokines. B Lymphocytes, in the presence of incompatible tissue antigens and IL-4, IL-5, and IL-6 from the helper T cells, undergo proliferation and differentiation into plasma cells which make antibodies. These antibodies result in complement-mediated damage and antibody-dependent cell-mediated cytotoxicity to the kidney graft.

Antigen-presenting cells present class I antigens to the T cell receptors of CD8+ precursor cytotoxic T lymphocytes which, under the influence of IL-2 and IL-4 from the helper T cells, proliferate and differentiate into cytotoxic T lymphocytes which also attack the kidney graft. Helper T cells also produce IL-3 which stimulates proliferation of bone marrow stem cells, interferon-γ (IFNγ) and tumour necrosis factor (TNF). The latter 2 lymphokines upregulate class I and class II MHC antigen expression on kidney transplant cells and activate macrophages. These cellular and humoral events result in renal allograft rejection, a classification of which is presented in table I.

2. Drugs Used in Clinical Renal Transplantation

2.1 Azathioprine

Azathioprine is an imidazolyl derivative of mercaptopurine that acts as an antimetabolite and reduces lymphocyte proliferation by inhibiting DNA and RNA synthesis. It is very well absorbed from the gastrointestinal tract with a peak plasma concentration achieved within about 2 hours of oral administration (Walker & d'Apice 1988). Azathioprine is available as 25 and 50mg tablets and as 50

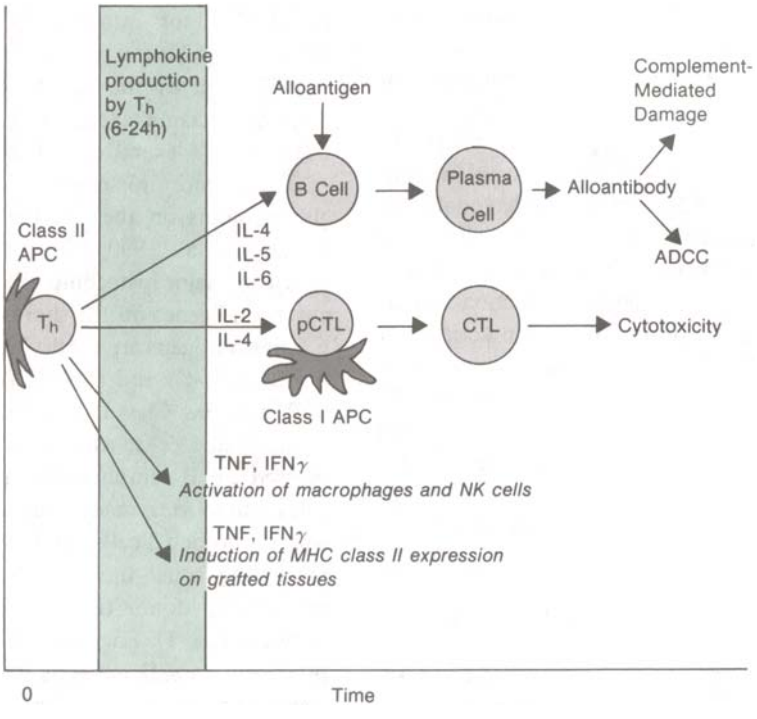

Fig. 1. Cellular interactions in renal transplant rejection. A CD4+ helper T lymphocyte (T_h) is activated by an antigen-presenting cell (APC) that expresses incompatible MHC class II antigens. The T_h cells produce lymphokines which promote proliferation of B lymphocytes, maturation of CD8+ cytotoxic T lymphocytes (CTL), activation of macrophages and natural killer cells (NK), and induction of MHC class I and class II antigens on kidney graft cells. ADCC denotes antibody-dependent cell-mediated cytotoxicity, and pCTL is precursor cytotoxic T lymphocyte (from Krensky et al. 1990).

Table I. Classification of kidney transplant rejection

Type	Predominant mechanism		Prevention or treatment
	antibody-mediated	cell-mediated	
Hyperacute	+	–	Pretransplant crossmatch
Accelerated	+	+	↑ Immunosuppression
Acute	–	+	↑ Immunosuppression
Chronic	+	–	?

and 100mg powder for reconstitution for intravenous administration. The drug is administered as a single daily oral dose or as the same dose in an intravenous infusion, usually over 30 to 60 minutes. The usual initial dose is 3 to 5 mg/kg at the time of transplantation. This is rapidly tapered within the first week to a maintenance dose of 1 to 3 mg/kg depending on the peripheral white blood cell (WBC) count. Azathioprine is used for induction and maintenance immunosuppression, usually with glucocorticoids and often with cyclosporin.

The major toxic effects of the drug are leucopenia, thrombocytopenia and gastrointestinal problems including nausea, vomiting, pancreatitis, and hepatitis. Periodic measurements of WBC and platelet counts, pancreatic enzymes and liver function studies are necessary for the timely detection of azathioprine toxicity. Alopecia is a troublesome side effect that is often transient and may improve without reducing the dose (Walker & d'Apice 1988). Allopurinol, a xanthine oxidase inhibitor, significantly increases haematologic toxicity and immunosuppression and, when given concomitantly with azathioprine, the dose of azathioprine must be reduced by 66 to 75%.

2.2 Glucocorticoids

The primary mechanism of action of glucocorticoids, usually prednisone or prednisolone, is probably prevention of IL-1 and IL-6 production by macrophages (Strom 1990). Each drug is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations occurring within 1 to 3 hours (Walker & d'Apice 1988). Prednisone is metabolised in the liver to prednisolone. Much like cyclosporin, plasma concentrations can be influenced by drugs which induce or inhibit hepatic metabolism.

After induction immunosuppression with high intravenous doses, either prednisone or prednisolone is usually given as a single oral daily dose. Glucocorticoids may be given in relatively high doses as part of induction immunosuppressive therapy, or to ameliorate the cytokine release syndrome associated with muromonab CD3 (Chatenoud et al. 1991; Ortho Multicenter Transplant Study Group 1985), and to treat rejection crises. Lower doses are administered as part of maintenance immunosuppressive regimens with azathioprine and/or cyclosporin or FK-506. Some transplant units have in fact successfully withdrawn glucocorticoids from both induction and maintenance immunosuppression protocols (Bry et al. 1991; Griffin & Salaman 1991; Schleibner et al 1990).

High doses of glucocorticoids may result in Cushing's syndrome, metabolic bone disease, cataracts, peptic ulcer, hyperlipidaemia and poor wound healing. Prophylactic therapy against peptic ulcer disease is administered when patients receive high doses of glucocorticoids.

2.3 Cyclosporin

Cyclosporin is a cyclic polypeptide consisting of 11 amino acids, most of which are hydrophobic (Kahan 1989; Wenger 1983). The drug is mainly active against T helper cells, where it prevents the production of lymphokines, especially IL-2 (Kahan 1989; Strom 1990).

Cyclosporin is available in 25mg and 100mg capsules, as an oral solution containing cyclosporin

Table II. Drug interactions with cyclosporin (from Lemaire et al. 1990; Morris 1988; Physician's Desk Reference 1992)

Drugs which affect cyclosporin plasma concentrations		Drugs with nephrotoxic synergy
decrease	increase	
Rifampicin	Diltiazem	Gentamicin
Carbamazepine	Verapamil	Tobramycin
Phenobarbital	Danazol	Vancomycin
Phenytoin	Bromocriptine	Azapropazone
Isoniazid	Ketoconazole	Amphotericin B
	Fluconazole	Ketoconazole
	Itraconazole	Melphalan
	Erythromycin	Cotrimoxazole (trimethoprim/sulfamethoxazole)
	Methylprednisolone	Cimetidine
	Metoclopramide	Ranitidine
		Diclofenac

100 mg/ml, and as a concentrate for injection containing 50 mg/ml. It is usually administered orally as a single daily dose of 5 to 15 mg/kg and then tapered to a maintenance dose of about 5 mg/kg, depending somewhat on suspected nephrotoxicity and plasma concentrations. Some transplant units prefer twice-daily oral dosing. When oral administration is not possible, one-third the calculated oral dose is given as an intravenous infusion over 2 to 24 hours. Children may require higher or more frequent doses than adults to maintain therapeutic concentrations. Absorption of cyclosporin from the gastrointestinal tract is incomplete and variable. A peak plasma concentration is usually reached 2 to 6 hours after a single oral dose, and the half-life is 10 to 27 hours (Lemaire et al 1990; Physicians Desk Reference 1992). It is primarily metabolised in the liver through the cytochrome P450-III system. Thus, drugs that induce this system will increase the metabolism of cyclosporin, lower its plasma concentration, and result in under-immunosuppression. Conversely, drugs that inhibit these hepatic enzymes can result in high cyclosporin concentrations and toxicity. Nephrotoxic synergy has been reported with a variety of drugs. Table II lists generally accepted drug interactions (Castelao et al 1988; Morris 1988; Lemaire et al 1990; Physicians Desk Reference 1992).

Cyclosporin adverse effects have involved renal, hepatic, dermatological, gastrointestinal, metabolic, neurological, dental and hematological systems. Nephrotoxicity is the most common effect, and occurs in 3 clinical settings: immediately after transplantation as an additive effect on renal ischemia; 2 or 3 weeks after transplantation; and long term with a slow decline of renal function and interstitial fibrosis (Morris 1988). Although high plasma trough concentrations are often associated with nephrotoxicity and low values with rejection, biopsy may be necessary to exclude the latter.

Cyclosporin therapy is usually monitored with whole blood or plasma trough concentrations. Because of cyclosporin binding to red blood cells and the time it takes to perform high performance liquid chromatography when compared with radioimmunoassay, most transplantation units use the latter with whole blood for this determination (Consensus Document 1990). Plasma concentrations range from 20 to 50% of whole blood values, and they vary with the temperature and time of separation from red blood cells.

Because of nephrotoxicity, cyclosporin administration is often delayed (Sommer & Fergusson 1985) or initiated in a low dose (Leichtman & Strom 1988) until satisfactory renal function has occurred. Cyclosporin is used for induction and maintenance immunosuppression, usually in combination with glucocorticoids, with or without azathioprine.

2.4 Antithymocyte (Antilymphocyte) Globulins

2.4.1 Polyclonal Antithymocyte Globulins

Polyclonal antithymocyte antibodies are obtained by injecting animals, usually horses, with human lymphoid cells such as B cell lymphoblasts, peripheral T cell lymphocytes or thymus lymphocytes, and then harvesting and processing the immune sera to obtain purified globulin (Strom 1990). Examples of polyclonal antilymphocyte globulins are 'Atgam', 'Minnesota antilymphocyte globulin', 'ATG Fresenius' and 'ALG Institut Merieux' (table III).

The polyclonal antithymocyte globulins are useful as prophylactic or induction immunosuppressants to prevent or delay first rejection, or to protect a newly transplanted kidney from the combined nephrotoxic effects of preservation injury and cyclosporin (Grino et al. 1990; Najarian & Matas 1991; Sommer & Fergusson 1985). They are also used to treat rejection crises, especially those resistant to high dose glucocorticoid therapy (Widmer et al 1988).

The major mechanisms of action are complement-mediated lysis of lymphocytes, uptake of lymphocytes by the reticuloendothelial system, or masking of lymphocyte cell surface receptors. These preparations are usually infused for over 4 hours through an inline filter into a central venous catheter or arteriovenous fistula to minimise systemic reactions and the occurrence of phlebitis and local thrombosis. Potential adverse effects include fever, chills, thrombocytopenia, leucopenia, haemolysis, respiratory distress, rash, serum sickness, and rarely anaphylaxis. Many of these reactions can be prevented or relieved by increased doses of glucocorticoids and the administration of paracetamol (acetaminophen) and diphenhydramine.

2.4.2 Monoclonal Antithymocyte Globulin

Muromonab CD3 (OKT 3) is a murine monoclonal antibody of the Ig2a class to the CD3 portion of the T cell receptor (Cosimi et al. 1981; Todd & Brogden 1989). This immunoglobulin blocks T cell function and does not react with other haematopoietic cells or tissues. It is administered as an intravenous bolus, usually in a dose of 5 mg/day for 10 to 14 days. The effect can be monitored by an assay of CD3 antigen on circulating T cells. Within minutes of administration, circulating CD3-expressing cells are decreased. They usually become undetectable and remain so until termination of treatment with muromonab CD3, unless the patient develops neutralising antibodies. These neutralising antibodies develop in up to 50% of treated patients (Kreis et al. 1991) and can render retreatment with muromonab CD3 unsuccessful.

Table III. Polyclonal antithymocyte antibody preparations

Product	Frequency	Dose (mg/kg)	Duration (days)	Indication	Reference
Minnesota antilymphocyte globulin	Daily	20	7 14 7-10	Adult induction Paediatric induction Rejection	Najarian & Matas (1991)
'Atgam' (Upjohn)	Daily	15	14	Induction	Physicians Desk Reference (1992)
	Daily	10-15	14	Rejection	
'ATG' (Fresenius R)	Daily	3	10-14	Rejection	Greger et al. (1988)
'ATG' (Fresenius R)	Daily	3	8-10	Induction	Widmer et al. (1988)
'ALG' (Institut Merieux)	Alternate days	10	Up to 12	Induction	Grino et al. (1990)

Muromonab-CD 3 has been effectively used as part of induction immunosuppressive therapy (Monaco 1989; Norman et al. 1991), as first treatment for rejection crisis (Ortho Multicenter Transplant Study Group 1985), and as 'rescue' treatment for acute rejection unresponsive to high dose glucocorticoids and/or polyclonal antithymocyte globulin (Norman et al 1985; Widmer et al 1988).

The administration of muromonab CD3 is nearly always accompanied by a cytokine release syndrome characterised by (with decreasing frequency) fever, dyspnoea, nausea, vomiting, chest pain, diarrhoea, tremor, wheezing, headache, tachycardia, chills and hypertension. This usually occurs within 2 days of the first dose. The severity of the cytokine release syndrome can be reduced by the administration of intravenous methylprednisolone (Chatenoud et al. 1991; Ortho Multicenter Transplant Study Group 1985), diphenhydramine, and paracetamol prior to the first dose of muromonab CD3, and by a cooling blanket and intravenous hydrocortisone 30 minutes post-injection. One of the most serious side effects, pulmonary oedema, can be prevented by weight reduction to $\leq$ 3% above the minimum weight reported in the week prior to muromonab CD3 administration and the demonstration of no pre-existing pulmonary oedema or pleural effusion on chest radiograph taken within 24 hours preinjection.

2.5 FK-506

FK-506 is a macrolide antibiotic that shares many characteristics with cyclosporin (Goto et al 1991). It is mainly active against T helper cells, where it prevents the production of lymphokines, especially IL-2, by inhibiting lymphokine gene expression. It is available as an intravenous preparation and as an oral capsule formulation.

The oral bioavailability of FK-506 ranges from 5 to 67%, with a mean value of 27% (Venkataramanan et al. 1991). In 14 patients peak plasma concentrations occurred 0.5 to 4 hours after a single oral dose, and the half-life was 3.5 to 40.5 hours. Like cyclosporin, FK-506 is primarily metabolised in the liver through the cytochrome P450 system.

FK-506 is used for induction and maintenance immunosuppression, usually in combination with glucocorticoids which are often successfully withdrawn (Shapiro et al. 1991). Protocols with FK-506 are still evolving. One example is a continuous infusion of 0.1 mg/kg/day until patients can tolerate a solid diet, then an oral dose of 0.15 mg/kg twice daily (Shapiro et al. 1991).

The adverse effects are similar to those associated with cyclosporin, and include nephrotoxicity and neurotoxicity. Therapy is usually monitored with whole blood or plasma trough concentrations. Whole blood may be preferable to plasma because, like cyclosporin, plasma FK-506 concentrations are modified by temperature and haematocrit on separating plasma from whole blood (Beysens et al. 1991; Kobayashi et al. 1991).

3. Immunosuppression Protocols

A glossary of terms describing immunosuppressive therapy is presented in table IV. Table V provides an example of a typical immunosuppression protocol in renal transplant recipients.

3.1 Azathioprine and Glucocorticoids

Although cyclosporin is currently the preferred immunosuppressive agent for induction and maintenance immunosuppression in renal transplantation, azathioprine and glucocorticoid immunosuppression is appropriate in some circumstances: (a) HLA-identical sibling renal transplantation; (b) financial inability to afford cyclosporin; and (c) significant early cyclosporin nephrotoxicity unresponsive to dose reduction.

An example of an azathioprine and glucocorticoid protocol is presented in the second and third columns of table V. Withdrawal of cyclosporin from maintenance cadaver kidney transplant immunosuppression protocols and conversion to dual protocols of azathioprine plus glucocorticoids has resulted in acute rejection rates of 30 to 38% (Freedman et al. 1991; Hiesse et al. 1991) and significantly poorer graft survival rates (Stiller & Opelz 1991). The lack of a significant benefit of cyclo-

Table IV. Classification of immunosuppression therapeutic regimens

Regimen	Definition
Induction	Immunosuppression given around the time of transplantation
Maintenance	Immunosuppression given after induction therapy
Rejection crisis	Immunosuppression change or increase given to treat an acute rejection, usually addition of an antithymocyte antibody preparation or increased glucocorticoids
Conventional	Standard local immunosuppression therapy, formerly azathioprine and a glucocorticoid
Monotherapy	Induction and/or maintenance immunosuppression with one drug, usually cyclosporin
Dual therapy	Induction and/or maintenance immunosuppression with 2 drugs
Triple therapy	Induction and/or maintenance immunosuppression with 3 drugs, usually a glucocorticoid plus cyclosporin plus azathioprine
Quadruple (or sequential, or overlap) therapy	Antithymocyte antibody induction, usually with a glucocorticoid plus azathioprine followed by delayed administration of cyclosporin

sporin in a series of 2413 HLA-identical sibling renal transplants was also reported by Stiller and Opelz (1991).

3.2 Cyclosporin Protocols

3.2.1 Cyclosporin Monotherapy

Cyclosporin monotherapy has two definitions. The first refers to when cyclosporin is the only immunosuppressant administered from the time of engraftment, and the second to when it is the only remaining immunosuppressant after others have been withdrawn. An example of the first type of cyclosporin monotherapy protocol is presented in the fourth column of table V.

Data from the Canadian and European multicentre, randomised prospective studies indicated that 33 to 53% of recipients assigned to cyclosporin monotherapy did not require maintenance glucocorticoid therapy, and that kidney graft survival was significantly better in patients who received cyclosporin monotherapy than in those assigned to azathioprine and maintenance glucocorticoid immunosuppression (Land 1988; MacDonald et al. 1987). The single centre, randomised prospective study of Tarantino and associates (1991) compared cyclosporin monotherapy in 74 renal transplant recipients (61 cadaveric and 13 living donor transplants) with cyclosporin plus glucocorticoid plus azathioprine therapy in 77 other recipients (64 cadaveric and 13 living donor transplants). During a 2-year follow-up, 40% of the cyclosporin monotherapy patients did not require another drug for maintenance immunosuppression, although there were significantly more rejection crises and nephrotoxic episodes. Two-year kidney graft survivals were not significantly different (84 *vs* 90%).

Cyclosporin monotherapy from the time of transplantation can therefore give good results, although maintenance glucocorticoids will probably be necessary in more than half of the cases because of recurrent rejection episodes or difficulty differentiating nephrotoxicity from rejection. Successful cyclosporin monotherapy after withdrawal of glucocorticoids from maintenance dual immunosuppression protocols, and withdrawal of glucocorticoids and azathioprine from triple drug protocols 3 or more months after transplantation has been reported by several groups (Gulanikar et al. 1991; Jain et al. 1988; Maiorca et al. 1988).

3.2.2 Cyclosporin Dual and Triple Therapy

Cyclosporin dual therapy consists of cyclosporin and glucocorticoids or cyclosporin and azathioprine, while triple therapy consists of all 3 drugs (table V). A Collaborative Transplant Study report of 19 514 first cadaver kidney transplants reported no significant differences in 3-year graft survivals when cyclosporin plus glucocorticoid, cyclosporin plus azathioprine, cyclosporin plus azathioprine plus glucocorticoid, and cyclosporin monotherapy were compared (Opelz 1988). At 1 year, mean daily

Table V. Example of maintenance immunosuppresssion protocol in renal transplant recipients

Postop day	Prednisone (mg/kg/day)[a]	Azathioprine (mg/kg/day)[a,b]	Cyclosporine (mg/kg/day)[c]
0	2.0-7.0	3-5	5-15, usually
1	2.0	2	5-10, usually
2	1.0	2	5-10
3	0.9	2	5-10
4	0.8	2	5-10
5	0.7	2	5-10
6	0.6	2	5-10
7	0.5	2	5-10
30	0.5	2	5-7, usually
60	0.4	2	5-7
90	0.3	2	5, usually
120	0.2	2	5
150	0.15	2	5
180	0.10	2	5

a Intravenous dose is same as oral dose.
b Reduce for leucopenia.
c Oral dose; intravenous dose is one-third oral dose. Monitor blood concentrations periodically, and reduce for nephrotoxicity or high concentrations. Administration often delayed by poor renal function or sequential therapy with antithymocyte globulin.

cyclosporin doses were highest for patients receiving cyclosporin monotherapy and lowest for those receiving triple therapy. Triple therapy is popular because it allows adequate immunosuppression with lower doses of nephrotoxic cyclosporin and the eventual tapering and/or elimination of glucocorticoids as maintenance drugs in many patients (Slapak et al. 1991).

3.3 Sequential Therapy

Sequential (overlap or quadruple) therapy refers to induction immunosuppression with an antithymocyte antibody preparation, a glucocorticoid and azathioprine followed by delayed administration of cyclosporin. The goal is potent immunosuppression while allowing renal recovery from preservation injury before initiating cyclosporin with its high potential for nephrotoxicity (Sommer & Fergusson 1985). Duration of antibody induction therapy varies from 5 to 14 days (Monaco 1989; Najarian & Matas 1991; Norman et al. 1991; Sommer & Fergusson 1985). The doses and frequency of administration depend on the potency and toxicity of the drug and, in some programs, peripheral blood CD3 lymphocyte levels (Grino et al. 1990) or rate of recovery of renal function (Belitsky et al. 1991; Brinker et al. 1990).

First cadaver kidney graft survival rate was pooled and reported in 3505 recipients treated by sequential immunosuppression (Opelz 1990a). There was no significant difference in graft survival rates up to 3 years after transplantation when compared with 18 593 first cadaver kidney transplants treated with cyclosporin from day 1. Belitsky et al. (1991) compared sequential therapy with continuous intravenous cyclosporin as induction immunosuppression in a prospective randomised study of 110 cadaver kidney transplants. Cyclosporin was given to the antithymocyte globulin-treated recipients after demonstration of good renal function. All patients received azathioprine and glucocorticoids; the latter were discontinued 105 days after transplantation. Although graft and patient survival rates were nearly identical, the patients who received sequential therapy had a more rapid recovery of renal function, a longer interval

to first rejection and lower serum creatinine level at 3 months.

A comparison between sequential therapy with ATG (n = 3817) or muromonab CD3 (n = 414) revealed no significant differences in 1- and 2-year first cadaver kidney transplant survival rates (Opelz 1990b). Two recently reported randomised prospective studies comparing sequential muromonab CD3 with polyclonal antithymocyte globulin have confirmed this observation (Frey et al. 1991; Hanto et al. 1991).

3.4 Rejection Crisis Treatment

In this setting, increased dosages of corticosteroids (table VI) may be used or, in steroid-resistant rejection, muromonab CD3 5 mg/day intravenously for 10 to 14 days or a polyclonal antithymocyte globulin.

3.4.1 Increased Glucocorticoids

The most frequent treatment for acute cellular rejection is a brief course of increased glucocorticoids, often called 'pulse therapy'. Some units prefer intravenous administration of methylprednisolone, while others prefer oral administration of prednisone or prednisolone (table VI). All, however, involve the equivalent of 3 to 15 mg/kg/day of oral or intravenous prednisolone for 1 to 5 days with a taper to maintenance glucocorticoid doses within a few weeks. Most transplant groups favour oral prednisone or prednisolone in a dose of 3 to 5 mg/kg/day for 3 to 5 days. Two-thirds to three-quarters of acute cellular rejection episodes are reversed by this 'pulse therapy' (Leichtman & Strom 1988; Ortho Multicenter Transplant Study Group 1985). Favourable response to treatment is characterised by loss of fever, diuresis and decreased serum creatinine level, usually in that order.

3.4.2 Antithymocyte Globulins

The monoclonal preparation muromonab CD3 and a variety of polyclonal antithymocyte antibody preparations (table III) are very effective for treatment of first rejection episodes. A multicentre, randomised, prospective trial of 123 cadaver kidney transplant recipients demonstrated a significantly higher percentage (94%) of reversal of first rejection episodes when a 14-day course of muromonab CD3 was administered, compared with a 75% reversal with high dose glucocorticoids (Ortho Multicenter Transplant Study Group 1985).

Because of toxicity, expense, development of antibodies to the preparations, duration of therapy, and risk of activation of viral infection, many units prefer to reserve these drugs for the treatment of biopsy-proven, glucocorticoid-resistant rejection. In nonrandomised, uncontrolled studies, antibody preparations reversed > 60% of steroid-resistant rejection crises (Kreis et al. 1991; Norman et al. 1985; Tellis et al. 1987; Widmer et al. 1988).

Table VI. Glucocorticoid protocols for the treatment of acute, cellular renal allograft rejection

Reference	Drug	Route of administration	Adult daily dosage	No. of doses
Barry et al. (1988)	Prednisone	PO	5 mg/kg	5
Brinker et al. (1990)	Methylprednisolone	IV	3 mg/kg	5
Jain et al. (1988)	Prednisolone	PO	200mg	3
Salaman et al. (1987)	Methylprednisolone	IV	0.5-1.0g	1-3
Slapak et al. (1991)	Methylprednisolone	IV	500mg	3
Walker & d'Apice (1988)	Prednisolone	PO	200mg	3

Abbreviations: PO = oral; IV = intravenous.

4. Results of Immunosuppression in Renal Transplantation

4.1 Graft Survival

The routine use of cyclosporin-based immunosuppression has resulted in significant improvement in patient and graft survival for all types of human kidney transplants, with the possible exception of grafts from HLA-identical siblings (Stiller & Opelz 1991). Based on 45 020 cases, projected 10-year survival estimates for first kidney grafts from HLA-identical siblings, HLA 1-haplotype-matched related donors, and cadaveric donors are now 74, 51 and 40%, respectively (Opelz et al. 1991). Although graft survival for subsequent cadaver kidney transplants has also significantly improved in the cyclosporin era, it is still considerably worse than graft survival for first grafts (Stiller & Opelz 1991).

4.2 Infection Associated with Immunosuppression

Bacterial, viral and fungal infections are increased in recipients of kidney transplants, especially when the total doses and number of drugs are increased because of repeated rejection crises (Simmons & Migliori 1988). Prophylaxis against bacterial infections includes pneumococcal vaccination, perioperative antibacterial agents (usually a second-generation cephalosporin), antibacterial wound and bladder irrigations, and 3 to 4 months of oral cotrimoxazole (trimethoprim/sulfamethoxazole). Cotrimoxazole also prevents *Pneumocystis* infection. Prophylactic measures against viral infections include vaccination against hepatitis B, donor and blood product selection, aciclovir administration, and hyperimmune globulin administration. Prophylaxis against oral and upper gastrointestinal tract *Candida* infection is with oral nystatin. Amphotericin B should be avoided because of nephrotoxicity.

4.3 Cancer Associated with Immunosuppression

An increased incidence of cancer is a well recognised complication of organ transplantation (Penn 1991; Sheil et al. 1991). The greatest increase is for malignant conditions possibly associated with viral infections, such as lymphoma (especially of the central nervous system), Kaposi's sarcoma, cancers of the vulva and vagina, invasive squamous cancer of the cervix, liver cancer, cancer of the oropharynx and oesophagus, and cancers of the genitourinary system, except prostate (Sheil et al. 1991). The probability of developing non-skin malignancy is about 4% after 4 years, irrespective of cyclosporin treatment. Complete regression of cyclosporin-related non-Hodgkin's lymphoma has been associated with reduction or cessation of cyclosporin therapy (Penn 1991).

5. The Future

While we await advances in immunobiology that will allow the induction of specific transplantation tolerance, perhaps even to xenografts, immunopharmacology continues to provide exciting new developments (First 1992). Examples of new immunosuppressive agents include the antibiotics mizoribine, RS-61443, rapamycin, NKT-01 (deoxyspergualin), and SKF-105685; the monoclonal antibodies BMA 031, OKT-4A, anti-CD54, anti-Tac, and 33B3.1; and drugs that affect the prostaglandin-thromboxane system, such as misoprostol.

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