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Immunosuppressant-Induced Nephropathy

Pathophysiology, Incidence and Management

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Abstract

Immunosuppressant-induced nephrotoxicity, in particular chronic progressive tubulointerstitial fibrosis/arteriopathy induced by the calcineurin inhibitors cyclosporin and tacrolimus, has become the 'Achilles heel' of immunosuppressive agents. The use of calcineurin inhibitors as primary immunosuppressants in hepatic and cardiac transplantation has led to end-stage renal disease and dialysis.

Calcineurin inhibitor–induced acute renal failure may occur as early as a few weeks or months after initiation of cyclosporin therapy. The clinical manifestations of acute renal dysfunction are caused by vasoconstriction of renal arterioles, and include reduction in glomerular filtration rate, hypertension, hyperkalaemia, tubular acidosis, increased reabsorption of sodium and oliguria. The acute adverse effects of calcineurin inhibitors on renal haemodynamics are thought to be directly related to the cyclosporin or tacrolimus dosage and blood concentration.

However, new clinical data indicate that calcineurin inhibitor–induced chronic nephropathy can occur independently of acute renal dysfunction, cyclosporin dosage or blood concentration. Several strategies have been evaluated to attenuate cyclosporin-induced nephropathy, but their efficacy remains unknown.

Cytokine release syndrome associated with the use of muronomab-CD3 (OKT-3) can also contribute to the pathogenesis of transient acute tubular necrosis and renal dysfunction following renal transplantation.

Continued research and clinical experience should provide information regarding the aetiology of cyclosporin-induced chronic progressive tubulointerstitial fibrosis/arteriopathy and its potential treatment.

The clinical use of selective and potent immunosuppressive drugs, improvements in surgical technique and refinement of preservation techniques have played pivotal roles in the remarkable success of solid organ transplantation. Immunosuppressive drugs are utilised not only in renal transplant recipients, but also in the treatment of refractory renal, haematological, dermatological, neurological and autoimmune disorders.[1-6]

The major adverse effect of immunosuppressive drugs that act as calcineurin inhibitors is nephrotoxicity.[7] Although calcineurin-induced nephrotoxicity was initially considered a dose-limiting adverse drug reaction, it is now recognised that calcineurin inhibitors can induce nephropathy even at low dosages.[8,9] Immunosuppressant-induced nephrotoxicity, in particular chronic progressive tubulointerstitial fibrosis/arteriopathy induced by calcineurin inhibitors, is considered the 'Achilles' heel' of immunosuppressive agents.[10-12] Although a number of clinical studies with short follow-up periods have documented impressive success rates in solid organ transplantation in the last decade, the average half-life of kidney allograft survival has improved only slightly.[13] The use of calcineurin inhibitors as primary immunosuppressants in hepatic and cardiac transplantation has led to end-stage renal disease and dialysis. In a study by Goldstein and co-workers[14] in cardiac transplant recipients, patients with cyclosporin-induced nephrotoxicity requiring dialysis were at a significantly greater risk of death compared with other patients without cyclosporin-induced end-stage nephropathy.

Therapeutic drug monitoring is used routinely to assess efficacy and avoid nephrotoxicity of immunosuppressive drugs.[15] It is important to note that a great amount of overlap exists between toxicity and efficacy with these agents. Clinically, it is almost impossible to separate or distinguish pharmacodynamic efficacy (immunosuppressive effect) from toxicity (nephrotoxicity, hypertension) of these agents with a single 12-hour drug concentration.[16,17]

This paper reviews the pharmacology and pharmacokinetics of nephrotoxic immunosuppressive drugs, the renal pharmacodynamics of calcineurin inhibitors, the incidence of nephrotoxicity in the context of renal, hepatic and cardiac transplantation and, finally, the prevention and treatment of immunosuppressant-induced nephropathy.

1. Pharmacology of Nephrotoxic Immunosuppressive Drugs

Cyclosporin, tacrolimus and muromonab-CD3 (OKT-3) have been associated with significant clinical nephropathy. The pharmacology, pharmacokinetics and clinical use of these agents have been reviewed and compared elsewhere.[17-25]

1.1 Cyclosporin

Cyclosporin is a highly insoluble cyclic polypeptide consisting of 11 amino acids. It was approved by the US Food and Drug Administration in the early 1980s for use as prophylactic therapy in solid organ kidney, liver and heart allogeneic transplants. Cyclosporin improved the 1-year graft

survival rate with conventional therapy (prednisone and azathioprine) in renal allografts from about 50% to 85%.[13] The advantages of cyclosporin over previous therapies include improved efficacy, shorter mean postoperative hospital stay, lack of myelosuppression, fewer postoperative infections, fewer rejection crises and reduced corticosteroid requirements.

Although the precise mechanism of action of cyclosporin is incompletely understood, the major pathway involves the intracellular interaction of cyclosporin and calcineurin phosphatase, thus diminishing the production of interleukin-2 (IL-2).[26,27] Cyclosporin initially binds to a specific family of receptors called cyclophilins.[28] This drug-receptor complex inhibits the activation of calcineurin phosphatase, a secondary messenger in the dephosphorylation and activation of the nuclear factor of activation of T cells (NF-AT). NF-AT is a regulatory protein which increases transcription of IL-2. Inhibition of IL-2 transcription by cyclosporin, therefore, stops proliferation and activation of helper and cytotoxic T cells.[17,25]

The absorption of cyclosporin is slow, variable and incomplete (10 to 70%). Various factors may influence absorption, including bile production, food, duration of therapy (>50% increase in bioavailability during first 3 months) and gastrointestinal dysfunction (diarrhoea, changes in motility). The volume of distribution of cyclosporin ranges from 3.5 to 13 L/kg. Cyclosporin is highly tissue-bound and mostly accumulates in fat, liver, pancreas, kidney, spleen and blood fraction (50 to 60%). Cyclosporin distributes and binds extensively to red blood cells and the plasma fraction ranges from 30 to 40%. 90% of the plasma fraction is bound to plasma proteins, including lipoproteins.[16,17,29]

Cyclosporin is extensively metabolised in the liver by the cytochrome P450 (CYP) 3A4 enzyme system. More than 25 different metabolites have been identified. Some metabolites are immunosuppressive and nephrotoxic. The major route of excretion of cyclosporin is through the biliary system and renal excretion plays a minor role. Since many drugs are metabolised via the CYP3A4 enzyme system, they may directly or indirectly alter the rate of oral absorption or change the rate of metabolism of cyclosporin. These potential drug-drug interactions may increase the risk of under-immunosuppression (rejection), over-immunosuppression (infection) and toxicity (nephropathy, hypertension and tremor).[30]

1.2 Tacrolimus

Tacrolimus (FK-506) was originally discovered from *Streptomyces tsukubaensis* strains in soil samples from Japan.[31,32] Although cyclosporin and tacrolimus have different structures, both agents have similar mechanisms of action.[33,34] Cyclosporin is a cyclic polypeptide whereas tacrolimus is a macrolide antibiotic. Like cyclosporin, tacrolimus inhibits transcription of IL-2. Tacrolimus binds specifically to FK-506 binding protein (FKBP-12), an immunophilin receptor located in the cytoplasm. The complex of tacrolimus and FKBP-12 inhibits the calcineurin phosphatase enzyme which activates NF-AT.[35-37]

The absorption of tacrolimus is poor and incomplete, ranging from 4 to 93% with a mean of 21%.[38] Unlike cyclosporin, the oral administration of tacrolimus is not dependent upon the presence of bile, and hence biliary diversion in liver transplantation does not affect the absorption of tacrolimus.[39] Tacrolimus is highly protein bound, primarily to α_1-acid glycoprotein.[40]

Similar to cyclosporin, tacrolimus is an effective and well tolerated immunosuppressive agent for the prevention of acute rejection in kidney, liver and heart transplant recipients. Several clinical studies have demonstrated a lower incidence of acute rejection and use of antilymphocyte antibodies in tacrolimus-based immunosuppressive regimens compared with cyclosporin-based regimens.[32,41] In addition, accumulating evidence from several small clinical studies suggests that tacrolimus may be more effective than cyclosporin in the treatment of refractory rejection. Finally, tacrolimus has been used with some success for the treatment of chronic rejection and rescue therapy.[42-46]

1.3 Muromonab-CD3 (OKT-3)

Human T lymphocytes play a vital role in the induction of acute allograft rejection. Muromonab-CD3 is a murine monoclonal antibody that targets the ε subunit of the CD3 complex, a protein linked to the T cell receptor recognition site on the surface of mature T cells. Discovery of muromonab-CD3 in 1979 led to the availability of potent immunosuppressive agents to treat acute cellular rejection and delay episodes of rejection early after transplantation. Following intravenous infusion of muromonab-CD3, immature and mature T lymphocytes disappear from the circulation.[47-49] The mechanism of rapid disappearance of T cells from the circulation has yet to be defined. It has been postulated that muromonab-CD3 may coat the CD3 complex, which leads to depletion of circulating T cells by an opsonisation process.[50-53] In addition, muromonab-CD3 may induce modulation of CD3 receptors. Although the CD3 complex is undetectable during administration of muromonab-CD3, new types of T lymphocyte (CD2+ CD3– CD4+ and CD2+ CD3– CD8+) appear in the circulation.[54] These new T lymphocytes are not functional. The lack of surface membrane CD3 complex proteins or internalisation of this receptor during the modulation process leads to inability of the T cells to recognise antigens.

The major adverse drug reaction of muromonab-CD3 is cytokine release syndrome, particularly after the initial 3 doses.[55] It has been suggested that muromonab-CD3 may activate leucocytes by cross-linking the T cell CD3 complex with monocyte Fc receptors, resulting in activation of T cells and monocytes.[56] The activation of monocytes is associated with the release of tumour necrosis factor-α (TNFα), interferon-γ (IFNγ), IL-2 and IL-6 into the circulation within 2 hours of infusion of muromonab-CD3. Fever, chills, rash, nausea, vomiting, headache, myalgia and arthralgia have been attributed to the release of these inflammatory cytokines.[57]

Muromonab-CD3 may increase the incidence of acute tubular necrosis when used as an induction agent and worsen renal function initially when used for treatment of acute cellular rejection. Furthermore, allograft loss has been reported due to irreversible intragraft thrombosis.[58] Other rare but serious complications of muromonab-CD3 include aseptic meningitis, convulsions and potentially fatal pulmonary oedema.[59] Muromonab-CD3–induced nephropathy is a reversible disease entity without any long term adverse effects on the kidney.

2. Calcineurin Inhibitor–Induced Nephrotoxicity

2.1 Renal Pharmacodynamics of Calcineurin Inhibitors

Nephrotoxicity is the major adverse effect of cyclosporin and tacrolimus. Since the mechanism of nephrotoxicity is believed to be similar among both agents, we present the renal haemodynamics and pharmacodynamics of cyclosporin, which are analogous to those of tacrolimus.

In both experimental models and human clinical studies, it has been well established that calcineurin inhibitors produce dose-dependent, acute and reversible vasoconstriction of renal arterioles. Calcineurin inhibitor–induced acute renal failure may occur as early as a few weeks or months following the initiation of therapy.[60] Prolonged cold ischaemic time, advanced donor age, donor history of acute renal failure, hypotension and perioperative surgical complications may increase the incidence and manifestation of acute renal impairment caused by calcineurin inhibitors.[61] The clinical manifestations of renal arteriolar vasoconstriction or acute renal dysfunction include reduction in glomerular filtration rate, hypertension, hyperkalaemia, tubular acidosis, increased reabsorption of sodium and oliguria.[62] The adverse effects on renal haemodynamics caused by calcineurin inhibitors are thought to be directly related to blood concentrations. Interestingly, profound renal impairment after a single large infusion of cyclosporin has been described previously.[63,64] Afferent arteriolar vasoconstriction results in a decrease in effective renal blood flow, a rise in total intrarenal vascular

resistance and ultimately a decrease in glomerular filtration rate.[62]

The precise mechanism and the mediators implicated in the alteration of renal haemodynamics induced by calcineurin inhibitors have yet to be described. Increased production of endothelin and thromboxane A_2, decreased production of renal vasodilatory prostaglandins, inhibition of nitric oxide as well as activation of the sympathetic nervous system have all been suggested as causes of renal arteriolar vasoconstriction.[65-70] Experimental data and clinical studies have shown that some of these effects are reversible with dosage reduction or withdrawal of calcineurin inhibition.[71,72] In an important clinical study by Curtis and coworkers, an improvement in renal function was noted after cyclosporin withdrawal.[64] This effect was also observed in perceived stable renal transplant recipients who were doing well under cyclosporin immunosuppression. An overall 30% improvement in renal allograft haemodynamics and function was reported. The mean arterial pressure was also reduced in all participants.

Therapeutic drug monitoring is routinely used for reducing the risk of potential toxicity of these agents. However, it is not clear whether precise therapeutic drug monitoring can improve dosage selection and avoid chronic cyclosporin toxicity. Perico et al.[73] studied cyclosporin-induced renal hypoperfusion in patients with a recent renal transplant. A direct, proportional, dose-dependent decline in glomerular filtration rate was observed. As the mean trough blood concentration, area under the curve and maximum cyclosporin blood concentration declined, glomerular filtration rate and renal blood flow slowly and continuously returned to the baseline in a single dosing administration interval. These results have been supported by other investigators.[74]

Although several reports have correlated early acute reversible episodes of renal impairment with chronic interstitial fibrosis, the transition from acute haemodynamic changes to chronic injury has not been clearly established.[74-76]

Although rare and mostly observed in bone marrow transplant recipients, acute cyclosporin/tacrolimus nephrotoxicity can be manifested as *de novo* or recurrent haemolytic uraemia syndrome.[77,78] On the basis of functional and morphological findings, diffuse capillary thrombi with glomerular fibrin deposits have been associated with haemolytic uraemic syndrome. The exact mechanism(s) by which cyclosporin mediates haemolytic uraemic syndrome is still not clearly understood. Experimental studies indicate vascular endothelial injury from cyclosporin.[79]

2.2 Chronic Cyclosporin Nephropathy

In solid organ transplant recipients treated with calcineurin inhibitors, chronic progressive nephrotoxicity is the major long term toxic effect. Although the acute effects of cyclosporin on the kidney have been well documented, the effect of the haemodynamic changes discussed in section 2.1 may not be the only cause of progressive cyclosporin nephrotoxicity. Studies of biopsies from experimental models, patients with autoimmune diseases and extrarenal solid organ transplants have demonstrated strikingly distinct and specific pathological and morphological changes suggestive of cyclosporin chronic progressive nephropathy.[80-83] Histologically, progressive chronic nephropathy induced by cyclosporin and tacrolimus is characterised by destruction of arterial wall, myointimal necrosis and progressive narrowing of the arterial lumen. It is also associated with tubulointerstitial fibrosis in a striped pattern, beginning in the medulla and extending to the medullary rays of the cortex. This histological pattern has been documented in other general vasoconstriction processes. This specific disease entity has been documented in kidney, liver, heart and bone marrow transplant recipients and in patients with autoimmune diseases who have been exposed to long term cyclosporin therapy.[83-85] Unlike cyclosporin-induced acute renal impairment, chronic progressive nephropathy is not dose-dependent and has been observed in patients receiving oral cyclosporin in dosages as low as 2 mg/kg/day.[86]

Most commonly, chronic progressive nephropathy is associated with mild to moderate renal dysfunction. Retrospective clinical studies of chronic progressive nephropathy in renal transplant recipients have been based on serum creatinine and renal function without any histological or pathological data. Clearly, renal function (estimated by serum creatinine or even by more precise measurements of glomerular filtration rate) can stay relatively stable for long periods of time as the result of adaptive mechanisms within the kidney. Such mechanisms are seen in progressive tubulointerstitial diseases as exemplified by diabetic nephropathy and autosomal dominant polycystic kidney disease, and in renal transplant recipients not treated with cyclosporin. However, some concern has been expressed regarding the validity of these data. Although it is difficult to distinguish and separate chronic rejection and chronic progressive nephropathy induced by calcineurin inhibitors, the morphological changes associated with rejection involve mostly large blood vessels as opposed to cyclosporin-induced chronic progressive nephropathy which effect mainly arterioles.[87] It is also possible that the processes of chronic rejection and cyclosporin-induced chronic progressive nephropathy could coexist. For the most part, renal function as estimated by serum creatinine has been used as a surrogate marker for the presence or absence of chronic cyclosporin nephropathy.

2.3 Pathophysiology of Cyclosporin Nephropathy

The chronic progressive nephropathy observed in recipients of long term therapy with calcineurin inhibitors has an unclear pathogenesis. It is widely accepted, but not conclusively proven, that low grade chronic ischaemia caused by continuing renal vasoconstriction may be an important factor in this lesion. This thesis is somewhat tenuous, since chronic arteriolar and tubulointerstitial changes with cyclosporin can be observed in patients given low doses of these drugs without any episodes of overt renal dysfunction and with normal blood pressures.

Research into the pathogenesis of this condition had been hampered until recent years because of the lack of an experimental model that would reproduce the clinical features of chronic cyclosporin nephropathy in animals. Elzinga and colleagues[72] have developed an experimental model of this clinical and pathological entity by exposing rats to extreme sodium depletion prior to administering cyclosporin. These animals developed striped tubulointerstitial fibrosis and a hyaline arteriolopathy similar to that observed in patients. The glomerular filtration rate declined, but the decline was reversible when the drug was stopped. However, the tubulointerstitial changes were relatively permanent, while the vascular lesions slowly resolved with the remodelling events that took place in the afferent arteriole.

Sodium depletion was the critical factor in producing this pathological lesion; prior attempts to increase dosage or other manipulations had failed to reproduce the histopathology observed in patients. Further studies examined the renin angiotensin system as an important mediator of cyclosporin-induced nephropathy.[88] These studies showed that the angiotensin II receptor antagonist losartan potassium, as well as the ACE inhibitor enalapril, prevented tubulointerstitial fibrosis in this animal model. This occurred without improvement in glomerular haemodynamics, dissociating the processes leading to tubulointerstitial fibrosis from any effects on renal haemodynamics. Further studies have shown the importance of nitric oxide inhibition by cyclosporin in this model.[11,89,90]

In a rat model of cyclosporin-induced nephropathy, sodium depletion enhanced fibrosis and the expression of matrix proteins.[91] Shihab et al.[91] proceeded to demonstrate that transforming growth factor β-1 (TGFβ-1) and the formation of renal lesions were reduced by blockade with losartan potassium. This experiment has led to the conclusion that the renin angiotensin system is activated intrarenally by cyclosporin and leads to the deposition of excess matrix proteins by stimulating production and/or diminishing their breakdown. Although this does not preclude other mechanisms,

including ischaemia, it should be noted that blockade of endothelin receptors does not affect tubulointerstitial fibrosis whereas treating animals with enalapril provides a protective effect.[92] A similar animal model can be produced with tacrolimus, using the manipulation of sodium depletion.[93,94]

The hypertension so frequently seen in patients can be reproduced in animal models with cyclosporin and tacrolimus. The former produces elevation in blood pressure much more regularly, which seemingly is also the case in humans. Roullet et al.[95] have shown that cyclosporin-induced hypertension *in vivo* and in resistance vessels *in vitro* is due to the inhibition of acetylcholine-mediated vasodilation. This, again, points to a major role that inhibition of nitric oxide synthase plays in the pathogenesis of hypertension with these drugs. Increased activity of the sympathetic nervous system has also been demonstrated with cyclosporin therapy in humans and animals. Drug-induced wasting of divalent cations such as calcium and magnesium associated with immunosuppressive therapy may also play an important role in blood pressure elevation. Experimental denervation of the kidneys, however, does not protect against drug-induced tubulointerstitial fibrosis by cyclosporin or tacrolimus.

Early in the time course of experimental nephrotoxicity, there is a macrophage infiltrate into the renal parenchyma. Later in the course, however, the cellular elements disappear and the kidney is involved in increased scarring. There is now evidence that cyclosporin induces programmed cell death, shown morphologically.[96] Furthermore, blockade of the renin angiotensin system seems to lessen the evidence of activation of these pathways. Further studies into the precise pathways and mechanism of programmed cell death mediated through stimulation of the renin angiotensin system are now being facilitated by the development of a mouse model of chronic cyclosporin nephrotoxicity.[97] By understanding the pathogenesis of this lesion, it may be possible to interrupt the pathway of progressive renal scarring and damage. Since others have shown that at least part of the immunosuppressive effect of calcineurin inhibitors is dependent on the activation of TGFβ-1,[71,72] the profibrotic cytokine involved in the renal effects, it is imperative to unravel mechanisms that can dissociate efficacy from toxicity if these drugs are to be used for other than lifesaving organ transplants.

3. Muromonab-CD3–Induced Nephropathy

Muromonab-CD3 is the most effective agent for the treatment of acute cellular rejection following solid organ transplantation. Several clinical studies have demonstrated the superiority of muromonab-CD3 over corticosteroids in reversing allograft rejection. Use of muromonab-CD3 in sequential immunotherapy with delayed cyclosporin administration has also been advocated to reduce the incidence of acute tubular necrosis early after transplantation.[98,99] The clinical use of muromonab-CD3 is limited because of cytokine release.[57]

3.1 Pathophysiology

Muromonab-CD3–induced nephropathy frequently occurs in patients who receive muromonab-CD3 during the induction period or in the first 3 days of treatment of acute rejection. Toussaint and co-workers[100] reported an increased incidence of acute tubular necrosis and postoperative dialysis after the prophylactic use of muromonab-CD3 in cadaveric renal allograft transplantation: 14 of 21 (66%) muromonab-CD3–treated patients and 6 of 21 (28%) cyclosporin-treated patients ($p = 0.03$) required dialysis after transplantation. Goldman et al.[101] and Batiuk et al.[102] have documented an increase in serum creatinine and decrease in renal function during the treatment of acute rejection in renal and heart transplant recipients.

The mechanism by which muromonab-CD3 induces acute tubular necrosis or renal dysfunction is still unclear. The cytokine release syndrome associated with the use of muromonab-CD3 may contribute to the pathogenesis of transient acute tubular necrosis and renal dysfunction. In experimental models, injection of TNFα and IL-2 in-

duces renal dysfunction and acute tubular necrosis. It has been suggested that TNFα and IL-2 decrease cardiac contractility, induce capillary leak syndrome and promote the release of endothelin, a potent renal vasoconstrictor. These haemodynamic alterations ultimately lead to renal ischaemic insult and account for transient allograft acute tubular necrosis. Besides the release of TNFα and IL-2, the release of IL-1 and IFNγ have also been reported to induce renal tubular cell death. In addition to the activation of these cytokines, neutrophil activation may increase the release of oxygen free radicals and protease enzymes which cause renal impairment.[103]

Patients with the primary diseases of systemic lupus erythematosus, haemolytic-uraemic syndrome, protein C and/or S deficiency and patients with a history of a hypercoagulable state with multiple episodes of thrombosis are at a greater risk of intra-allograft thrombosis and potential allograft loss after treatment with muromonab-CD3.[58,104,105] In a study by Abramowicz et al.,[58] a total of 13 intra-graft thromboses were reported in 12 out of 211 patients (6.2%): 6 in glomerular capillaries, 5 in allograft veins and 2 in allograft arteries. An increase in thrombin-antithrombin III complex and tissue-type plasminogen activator suggests activation of the coagulation and fibrinolysis cascades. Muromonab-CD3 may induce intra-allograft thrombosis by activation of monocytes which release procoagulants. In addition, the release of TNFα, IL-1 and IFNγ is associated with inhibition of the effects of the naturally occurring anticoagulants proteins S and C.

3.2 Management

In the clinical setting, several strategies have been utilised to reduce the toxicity of cytokine release syndrome.[106-108] Use of corticosteroids within 4 hours before muromonab-CD3 administration resulted in suppression of cytokine production.[109] Premedication with methylprednisolone 4 to 8 mg/kg, paracetamol (acetaminophen) 650mg and diphenhydramine 25 to 50mg 1 to 2 hours before muromonab-CD3 administration attenuate muromonab-CD3–induced cytokine release syndrome and induced nephropathy.[55,56] Use of mini-dose heparin (3500 units every 8 hours) or low-molecular-weight heparins (dalteparin 2500 units subcutaneously daily) have reduced the incidence of intra-graft thrombosis.[110] The use of anti-TNFα antibody, IL-10 and pentoxifylline remain subjects of debate without clear evidence of efficacy in reducing the incidence or severity of muromonab-CD3–induced cytokine release syndrome.

3.3 Alternatives to Muromonab-CD3

Introduction of humanised/chimaeric monoclonal antibody technology has offered the possibility of the development of newer agents that could improve allograft survival without the adverse sequels associated with muromonab-CD3 and its associated cytokine release syndrome. Daclizumab and basiliximab are new monoclonal antibodies approved for the prophylaxis of acute organ rejection in renal allograft recipients.[111-115]

The efficacy of these agents has been established in a number of well-controlled clinical trials. These multicentre studies assessed the efficacy of daclizumab and basiliximab versus placebo when used as part of a regimen of double therapy (cyclosporin and corticosteroids) or triple therapy (cyclosporin, corticosteroids and azathioprine) to prevent acute renal allograft rejection. The primary endpoint for both studies was the incidence of acute rejection within the first 6 months after renal allograft transplantation. The incidence of acute rejection was 28% in double therapy and 22% in triple therapy regimens with daclizumab, versus 47 and 35% in the placebo group. These studies demonstrated that daclizumab significantly decreases the incidence of acute rejection at 6 months. Daclizumab when given in combination with other immunosuppressants did not show an increase in the number of serious adverse events compared with placebo.[114]

With basiliximab, the incidence of acute rejection was 34% with double therapy in the basiliximab group and 52% in the placebo group. The

incidence and types of adverse events were similar to those in placebo-treated patients. No drug interactions have been observed when daclizumab and basiliximab are administered with other immunosuppressive agents.[111]

4. Incidence of Chronic Nephropathy in Clinical Transplantation

4.1 Renal Transplantation

A number of systemic disease processes can lead to tubulointerstitial fibrosis and renal structural and functional deterioration. These include chronic rejection, hypertension, hyperglycaemia, hyperlipidaemia, recurrence of the underlying disease and aging. The renal haemodynamic effects of cyclosporin on renal structure/function in renal allografts is often difficult to distinguish from other processes. These confounding factors may complicate the differential diagnosis of renal dysfunction in renal transplant recipients. Some of the early clinical studies have demonstrated a stable serum creatinine over time and have suggested that the renal allograft is spared from cyclosporin-induced chronic progressive nephropathy. As mentioned in section 2.2, the main drawback of these retrospective studies are the absence of renal histology. Renal allograft structure and function were not measured concurrently. Some studies only evaluated structural changes while other studies used functional parameters alone.[7,12,116,117]

Klintmalm and co-workers[118] studied the effect of cyclosporin on renal allografts in the early 1980s. In this study, the renal allograft biopsies of 24 renal allograft recipients treated with cyclosporin were compared with those from 43 patients treated with azathioprine and corticosteroids over a 1- to 4-year period. The dosage of cyclosporin was higher initially, but was reduced to 10 mg/kg/day after 4 months. The average serum creatinine was 2.1 mg/dl in the cyclosporin-treated group and 1.5 mg/dl in the azathioprine-treated group. There was no difference between the 2 groups in the number of rejection episodes. In addition, blinded renal allograft biopsies revealed severe interstitial fibrosis and tubular atrophy in the cyclosporin group compared with the azathioprine group. This interstitial fibrosis correlated with a high cyclosporin trough blood concentration and the cumulative dose of cyclosporin in the first 6 months following transplantation.

The long term effect of cyclosporin on allograft function has been a subject of controversy. The long term efficacy and safety of cyclosporin in 1663 renal transplant recipients was studied by Burke and colleagues.[119] In this retrospective multicentre analysis the majority of patients tolerated long term cyclosporin therapy (median 36 months) without major evidence of chronic progressive cyclosporin nephropathy. The major methodological flaws in this study include the short duration of follow-up (only 25% were followed up for 4 years), unclear definition of chronic rejection and lack of histological data to support the long term safety of cyclosporin in renal transplant recipients. In addition, only 2 centres utilised antilymphocyte induction therapy and all 4 centres had different immunosuppressive regimens.

The long term efficacy and safety of cyclosporin in living-donor renal transplantation has been studied in several clinical trials.[120-125] In a report by Sanfilippo et al.[120] for the South-Eastern Organ Procurement Foundation (SEOPF), the impact of cyclosporin use and blood transfusion on the outcome of renal transplantation was studied. Interestingly, no blood transfusions with the use of cyclosporin was associated with the lowest 6-month and 3-year allograft survival in recipients of living related renal transplantation. In a similar study, Gill et al.[125] compared the long term efficacy and safety of cyclosporin and azathioprine in recipients of renal transplantation from HLA-identical siblings. Although both treatment groups had equally excellent outcomes, cyclosporin-treated patients had significantly higher serum creatinine levels compared with azathioprine-treated patients (1.7 *vs* 1.3 mg/dl, $p = 0.018$). However, some studies have documented lower incidence of acute cellular rejection with equivalent patients and allograft survival. MacPhee et al.[126] reported improved

renal function after conversion from cyclosporin to azathioprine at 1 year following renal transplantation in adult patients with stable renal function and without history of rejection within the last 6 months. However, some studies have found a better serum creatinine level in cyclosporin-treated patients. For example, Flechner et al.,[127] in a small study of 48 patients (20 azathioprine-treated *vs* 28 cyclosporin-treated), documented a significantly better 5-year allograft survival in cyclosporin-treated patients compared with azathioprine and prednisone immunoprophylactic therapy (96 *vs* 76%, $p < 0.02$). Similar results have been reported by Chan et al.[128] and Monaco et al.[129] Unfortunately, none of these studies reported the results of renal allograft histology.

The role of chronic progressive cyclosporin-induced nephropathy in the course of chronic renal allograft failure leading to allograft loss is still unknown. Mihatsch et al.[87] studied 90 renal transplant recipients and compared the renal allograft histology of 3 groups of patients: those with serum creatinine levels less than 2 mg/dl, those with biopsy-proven rejection with serum creatinine levels greater than 2 mg/dl, and those with pathologically defined evidence of cyclosporin-nephrotoxicity with serum creatinine levels greater than 2 mg/dl. Regardless of history of acute rejection episodes, only high cyclosporin trough blood concentrations were correlated with cyclosporin nephrotoxicity.

Although it has been suggested that arteriolopathy and tubulointerstitial fibrosis are irreversible processes, recent studies have questioned these assumptions. Morozumi et al.[123] studied the morphological outcome of cyclosporin-associated arteriolopathy after discontinuation of cyclosporin in 20 renal allografts. Nine patients continued to demonstrate arteriolopathy, while in 11 patients complete regression and remodelling of arterioles as reported. Vascular rejection was responsible for allograft loss after discontinuation of cyclosporin therapy. Mourad and co-workers[130] studied the effect of dosage reduction or cyclosporin withdrawal in 23 transplant and nontransplant patients with biopsy-proven cyclosporin-induced nephropathy. Of the 23 patients, 12 had interstitial fibrosis and the other 14 showed some evidence of arteriolar insudative lesions and/or arterial wall medial necrosis. Some histological improvement was noted after cyclosporin withdrawal in small number of patients. This finding was consistent with previous findings from our group in an experimental model of cyclosporin-induced nephropathy.[71]

In conclusion, after 2 decades of cyclosporin-based immunosuppressive therapy, there are still no prospective studies available that document the long term renal safety of cyclosporin or the role of cyclosporin-induced renal structural and functional changes on the longevity of renal transplants.

4.2 Heart Transplantation

Cyclosporin-associated chronic nephropathy in the cardiac transplantation setting was first described by Myers et al.[131] The renal haemodynamics of 17 heart transplant recipients who were treated with cyclosporin for at least 12 months were compared with those of 15 patients who received azathioprine and prednisone. Chronic cyclosporin nephrotoxicity and end-stage renal disease were documented in 7 and 2 patients, respectively. In addition, cyclosporin treatment was associated with reduced renal blood flow, increased renal vascular resistance and a decreased glomerular filtration rate despite an equivalent cardiac output. Furthermore, these structural and functional changes were associated with hypertension. Histology of the native kidney in 5 cardiac transplant recipients revealed glomerulosclerosis, striped interstitial fibrosis and afferent arteriolopathy. This study was criticised because of the high dosage of cyclosporin (17 mg/kg/day) utilised as induction therapy.

In a subsequent study by the same group of investigators, the physiological and morphological effects of chronic injury with low dosage cyclosporin (4.6 ± 0.4 mg/kg/day) were compared with those of high dosage cyclosporin (6.3 ± 0.3 mg/kg/day).[132] A marked increase in renal vascu-

lar resistance and a 45% decrease in the glomerular filtration rate from baseline was noted even in patients treated with a low dosage of cyclosporin. The morphological changes associated with the use of a lower dosage of cyclosporin were similar to those seen with the higher dosage, with only marginally less obliterative arteriolopathy and/or glomerulosclerosis and striped interstitial fibrosis. Although serum creatinine was within the normal range in the control (azathioprine and prednisone) group, the mean serum creatinine was significantly higher for the high dosage cyclosporin-treated patients compared with the low dosage group (1.7 ± 0.1 *vs* 2.1 ± 0.1 mg/dl, $p < 0.01$). Further, renal biopsies revealed progressive, irreversible histopathological changes in both cyclosporin groups despite drug withdrawal.

Greenberg et al.[133] studied early and late presentations of cyclosporin-induced nephrotoxicity in heart transplant recipients. In this study, the renal function of azathioprine-treated patients, cyclosporin-treated patients and patients who had undergone cardiopulmonary bypass surgery were compared. Mild to moderate azotaemia and hypertension was documented in the early phase post transplantation in 58% of cyclosporin-treated patients *vs* 34% of azathioprine-treated patients and 4% in the cardiopulmonary bypass group. Interestingly, at 36 months after transplantation none of the cyclosporin-treated patients retained normal renal function. Renal function was improved in 5 patients in whom dosage reduction was attempted, although pathological documentation of histological improvement was not available. In a 7-year follow-up study of 228 cardiac transplant recipients who survived at least 1 year and had normal renal function, the average serum creatinine was increased from 1.2 mg/dl at the time of initial hospital discharge to 3.3 mg/dl at 7 years after transplantation.[134]

Similar results have been reported by Lloveras et al.[135] and Zietse et al.[136] Lloveras et al.[135] studied the glomerular filtration rate and renal plasma flow of 39 cyclosporin-treated cardiac transplant recipients. A biphasic reduction in glomerular filtration rate was noted; a rapid decline in the first 3 months, followed by a stabilisation without further decline in renal function. Zietse et al.[136] also documented that more than 50% of cardiac transplant recipients treated with cyclosporin had a serum creatinine greater than 2 mg/dl at 2 years and 13% had a serum creatinine greater than 3.5 mg/dl at 4 years following transplantation. No pathological material was available, but the dosages of cyclosporin used in the study were similar to currently used clinical dosages of 10 mg/kg/day for induction and then 5 to 10 mg/kg/day as maintenance therapy, according to cyclosporin blood concentration.

Therefore, in cardiac transplant recipients treated with cyclosporin, progressive nephropathy and moderate renal failure associated with obliterative arteriolopathy and glomerular ischaemia may occur after 2 years of cyclosporin therapy, and there is no correlation between renal structural damage and renal function as measured by serum creatinine.[137]

4.3 Liver Transplantation

A number of factors and pathological insults may affect renal function in liver transplant recipients.[138,139] Renal impairment in the liver transplant setting may result from pre-existing renal disease, hepatorenal syndrome, acute tubular necrosis from postoperative sepsis and calcineurin inhibitors.

Rimola et al.[140] reported renal impairment in 67% of patients in a study of 102 liver transplant recipients. There was no relationship between renal impairment and the daily dosage of cyclosporin or the measured whole blood trough concentrations. The glomerular filtration rate decreases soon after liver transplantation, with a 40% reduction in the first 6 months post transplantation.[139] Although it is unusual, there have been reports of renal function progressing to end-stage renal failure and/or dialysis requirement.[141,142] In 1 small study, investigators were able to demonstrate that renal fibrosis and arteriolopathy are independent of serum creatinine, cyclosporin concentration and

blood pressure in liver transplant recipients receiving cyclosporin.[141]

Recently, Fisher et al.[142] retrospectively studied the incidence of chronic renal failure in 883 consecutive adult liver transplant recipients. The mortality rate was 44% for patients who experienced end-stage renal disease within the first year after transplantation. Early rise in serum creatinine in the first 3 months was correlated with chronic renal failure. Mild to moderate renal impairment was documented in 78% of all patients. These investigators concluded that the cyclosporin trough concentrations should be kept below 250 μg/L, cyclosporin dosage should not exceed 5 mg/kg/day and patients at the risk of renal failure should be considered for immunosuppressive maintenance therapy with corticosteroids and mycophenolate together with complete withdrawal of cyclosporin.

4.4 Bone Marrow Transplantation

Acute and chronic graft-versus-host disease (GVHD) are the major complications in bone marrow transplantation. Cyclosporin and tacrolimus are routinely used prophylactically against GVHD disease (heterologous transplantation) or conversely to induce GVHD (autologous transplantation).[143] In a study by Dieterle et al.,[144] 48% of renal autopsies or biopsies from bone marrow transplant recipients showed striped interstitial fibrosis and 18% showed arteriolopathy. Serum creatinine levels increased 40 to 80% by 3 months after transplant and then stabilised. In general, bone marrow transplant recipients are younger and without any major pre-existing atherosclerotic diseases compared with recipients of solid organ transplants. The presence of striped interstitial fibrosis and arteriolopathy in patients without a history of vascular diseases demonstrates that chronic cyclosporin nephropathy may occur in patients without pre-existing renal disease. Similar findings have been reported in patients with autoimmune diseases.[145]

5. Management of Immunosuppressant-Induced Nephropathy

Apart from using reduced dosages of calcineurin inhibitors, several approaches have been evaluated to attenuate the nephropathy associated with their use in both experimental models and clinical studies; none has proven to be effective.[146-153]

Calcineurin inhibitor–induced nephropathy has been demonstrated to be partially reversible. Discontinuation of cyclosporin has been advocated for the treatment of nephrotoxicity. However, clinical studies evaluating cyclosporin withdrawal have been inconclusive and conflicting.[154,155] In a rapid cyclosporin elective withdrawal schedule tapered over a 6-week period, a 20 to 50% occurrence of acute rejection has been reported.[154] With the use of a slow taper schedule over a 6-month period with an increase in azathioprine (2.5 mg/kg/day) and prednisone dosages, only 9.1% of 165 patients experienced rejection.[156] Pedersen et al.[154] compared the outcome of allograft survival in patients who discontinued cyclosporin with patients in whom cyclosporin was continued. At the end of the 1-year follow up, although a reduction in blood pressure and vasculopathy was noted in the patients who were withdrawn from cyclosporin, no differences in tubulointerstitial fibrosis were observed. Conversely, improvement in renal function at 3 months after cyclosporin discontinuation was shown by Hollander et al.[157] in a randomised clinical study.

Since the introduction of mycophenolate mofetil, a potent and effective purine antagonist, several small clinical studies have advocated discontinuation of cyclosporin in patients who are intolerant to cyclosporin therapy. Zanker et al.[158] converted 13 patients with a history of cyclosporin toxicity to mycophenolate mofetil monotherapy. After 118 days of follow-up, renal function was improved with serum creatinine decreasing from 1.9 ± 1.2 to 1.5 ± 0.7 mg/dl ($p = 0.001$). In the second part of the study, 12 renal transplant recipients >50 years of age or with donor age >50 years were enrolled in a cyclosporin-free induction im-

munosuppression regimen. The median serum creatinine was 1.3 ± 0.21 mg/dl at 6 months and only 1 patient experienced reversible allograft rejection. In a similar study with a longer follow-up, Duloux et al.[159] reported that, in selected renal transplant patients with biopsy-proven cyclosporin nephrotoxicity, a significant improvement in renal function can be obtained following cyclosporin withdrawal with concomitant switch to mycophenolate mofetil.

TGFβ-1 has been recognised as an important fibrogenic growth factor in the development of chronic calcineurin inhibitor–induced nephropathy.[160-162] In an experimental study by Shahib and co-workers, salt-depleted animals were given placebo, nilvadipine, hydralazine/hydrochlorothiazide, enalapril and losartan potassium. Some antihypertensive effect and reduction in glomerular filtration rate was achieved in all groups. However, only losartan potassium and enalapril decreased the expression of TGFβ-1.[91] There is some evidence to suggest that the plasma renin level is low following renal transplantation; however, cyclosporin activates synthesis and accumulation of intrarenal renin and the angiotensin system. As in diabetes mellitus, increase in the intra-renal renin content may play an important role in fibrosis and chronic calcineurin inhibitor–induced nephropathy. The effect of cyclosporin on the renin angiotensin system includes low plasma renin activity, high plasma pro-renin, a high incidence of hypertension and nephrotoxicity with evidence of afferent arteriopathy.[91]

Calcium antagonists are routinely used for treatment of post-transplant hypertension. The major renal pharmacodynamic effects of calcium antagonists are decreased mean arterial pressure and total renal vascular resistance, increased renal blood flow and increased glomerular filtration rate. The use of calcium antagonists immediately after renal allograft transplantation has been associated with lower serum creatinine and greater urine output.[163,164] Calcium influx into the smooth muscle may lead to the generation of free radicals, mitochondrial dysfunction and calcium accumulation. It has been postulated that calcium antagonists may modulate the influx of calcium into the vascular cell and prevent acute tubular necrosis during an ischaemic insult. In addition, calcium antagonists may protect renal system via vasodilation. However, the long term effects of calcium antagonists on allograft survival remain to be determined.

6. Conclusion

It is not clear why some patients develop cyclosporin-induced nephropathy and others do not. Clinical and experimental models of chronic nephropathy induced by cyclosporin or tacrolimus suggest that several factors play a role in the pathogenesis and outcome of the impaired renal function of transplant recipients. Pharmacodynamic or pharmacokinetic drug-drug interactions, cyclosporin/tacrolimus blood concentrations and prolonged exposure to cyclosporin/tacrolimus even at low dosages have been implicated in immunosuppressant-induced nephropathy. Cytokine release syndrome associated with the use of muromonab-CD3 can also contribute to the pathogenesis of transient acute tubular necrosis and renal dysfunction following renal transplantation. Several strategies have been evaluated to attenuate immunosuppressant-induced nephropathy, but their efficacy remains unknown. Understanding the interactions of immunosuppressive agents, renal physiology and the basic science of immunobiology may lead clinicians to an increased understanding of acute rejection, treatment of allograft rejection and chronic cyclosporin nephrotoxicity. In addition, alternative forms of immunosuppressive therapy that do not have long term renal adverse effects can be developed to minimise post-transplant nephropathy.

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