Open Journal of Nephrology, **2013, 3, 168-180**
http://dx.doi.org/10.4236/ojneph.2013.33030 Published Online September 2013 (http://www.scirp.org/journal/ojneph)

Cyclosporine-Associated Nephrotoxicity

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Received July 11, 2013; revised August 9, 2013; accepted August 24, 2013

ABSTRACT

Cyclosporine (CsA) has revolutionized transplant medicine and is currently one of the most important immunosuppressive agents for a wide range of organ transplantations and of autoimmune and inflammatory diseases, such as rheumatoid arthritis, uveitis, psoriasis, and atopic dermatitis. Renal impairment represents the main limitation to CsA long-term continuous therapy. However, it has been shown that nephrotoxicity is associated with longer treatment duration, larger cumulative doses and higher daily dose of CsA. With low dose regimens (<5 mg/kg/day), stable serum creatinine levels have been observed up to 15 - 20 years after kidney transplantation. Intermittent therapy may offer a good therapeutic strategy to limit long-term renal dysfunction, given the fact that renal structural changes are dose- and time-dependent. The best predictor of permanent renal damage is a persistent increase in serum creatinine level one month after treatment withdrawal. In patients with autoimmune diseases, the percentage increase in serum creatinine above baseline value during CsA therapy has been shown to predict CsA-induced nephropathy. Before CsA therapy initiation, patients should undergo a thorough baseline evaluation including laboratory assessments, in particular electrolytes, serum creatinine, and urea levels. Furthermore, patients should be evaluated for factors that might increase the risk of nephrotoxicity, such as obesity, older age, hypertension, concomitant use of nephrotoxic drugs, and pre-existing renal conditions. In the present paper, CsA-induced nephropathy will be reviewed in terms of pathophysiology, pathologic and clinical findings, and strategies for prevention and management.

Keywords: Cyclosporine; Nephrotoxicity; Immunosuppression; Transplant; Creatinine

1. Introduction

Since its discovery in Sandoz laboratories in 1972, cyclosporine (CsA) has revolutionized transplant medicine. CsA is currently one of the most important immunosuppressive agents for a wide range of organ transplantations, including kidney, liver, heart, lung, pancreas, and intestine [1]. CsA has been found to have many immunologic properties that make it an attractive agent for immunosuppression: it is found to inhibit both *in vitro* cell-mediated lysis as well as lymphocyte sensitization by allogeneic target cells [2]. Clinically, as summarized by Hariharan *et al.* in 2000, who reviewed 93,000 transplants from 1988 and 1996, CsA obtained one-year graft survival rates in 94% and 88% in living related and deceased donor allografts respectively [3]. More recent data from the United Network for Organ Sharing (UNOS) from 1998 to 2007 show one-year adjusted survival rates of 96.6% and 91.6% in living related and deceased donor allografts respectively. In its 40 years of life, CsA was shown to be also an effective treatment option in autoimmune and inflammatory diseases, such as rheumatoid arthritis, uveitis, psoriasis, and atopic dermatitis [4-8].

The fact CsA was nephrotoxic was discovered early after its initial use, when Calne *et al*. found a significant and unexpected nephrotoxicity that had not been observed in animal experiments in their first attempt to use CsA following transplantation using a dose of 25 mg/kg [9]. Currently, it is well known that renal damage may be an important side effect of CsA therapy, but it is also known that most persistent renal dysfunction is related to prolonged therapy, or doses of greater than 5 mg/kg/day, both of which can result in structural renal changes. Furthermore, it has been reported that nephrotoxicity is also related to individual susceptibility [10]. In the present paper, CsA-induced nephropathy will be reviewed in terms of pathophysiology, pathologic and clinical findings, and strategies for prevention and management.

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2. Risk Factors for CsA Nephrotoxicity

2.1. Systemic Levels of CsA

The main issue after renal transplantation is to maintain a reasonable balance between efficacy against rejection and toxicity, especially nephrotoxicity. Klintmalm *et al.* were the first to demonstrate a relationship between CsA doses, plasma levels, and renal allograft interstitial fibrosis [11,12]. This association between CsA nephrotoxicity and higher CsA doses (>5 mg/kg/day) was then confirmed by others [13]. After these findings, it became evident that CsA has a relatively narrow therapeutic window and great care has to be given to keep dosage within preset target ranges [14].

However, maintaining CsA concentrations within preset target ranges proved to be difficult due to its high inter-and intraindividual pharmacokinetic variability [15], which was especially observed with the first CsA formulation, Sandimmun. This variability appeared to be largely due to significant inter- and intraindividual variability in the expression and function of the metabolizing cytochrome P450 3A isoenzymes, mainly CYP3A4 and CYP3A5, and of the multidrug efflux transporter P- glycoprotein. This was partly attributed to interactions with other drugs, which cause either inhibition or stimulation of expression or activity of these enzymes and transporter. After development of a new CsA emulsion, Neoral, better absorption, less inter- and intraindividual variability, earlier stabilization of pharmacokinetics, and dose linearity in CsA exposure were observed compared with the old formulation [16-18]. However, it has been suggested that during chronic treatment of transplant recipeents, therapeutic drug monitoring of CsA may be useful and in fact, it is now adopted in clinical practice [19].

2.2. Local Renal Exposure to CsA

It has been demonstrated that levels of CsA in the renal tissue are much higher than in blood [20,21]. In addition to the degree of renal CsA exposure, there is also evidence that the susceptibility to CsA nephrotoxicity is determined by local renal factors, independent of local CsA levels. These factors include both the age of the recipient and of the transplanted kidney, the latter being independently associated with chronic histologic damage [22]. Second, local renal P-glycoprotein not only could play a role in renal accumulation of CsA, but could also be important for tubular epithelial cell detoxification and protection against apoptotic stress. Third, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to increase renal susceptibility to acute CsA nephrotoxicity, with decreases in renal plasma flow and GFR [23-26]. Finally, genetic polymorphisms in genes involved in the pathogenesis of CsA nephrotoxicity have been associated with the risk for chronic nephrotoxicity [27-37].

Given the above evidences, it could be anticipated that younger patients with native kidneys or recipients of transplanted kidneys from younger donors could be less susceptible to CsA nephrotoxicity. Moreover, great attention should be paid to drug interactions: **Table 1** lists the drugs that may increase the risk of CsA-associated nephrotoxicity. Finally, determination of a patient's or donor's genotype of drug-metabolizing genes or of molecules involved in CsA nephrotoxicity, like TGF-β, could provide a reasonable tool to determine which patients are most susceptible for CsA nephrotoxicity.

2.3. CsA-Independent Risk of Chronic Renal Failure Following Transplantation

Ojo *et al.* conducted a population-based cohort analysis to evaluate the incidence of chronic renal failure and the risk factors for it in 69,321 patients undergone non renal transplantation in the United States between 1990 and 2000 [38]. The 5-year risk varied depending on the type of organ transplanted, ranging from 7% among heart-lung recipients to 21% in recipients of intestine transplants. Other risk factors were increasing age, female sex, hypertension, diabetes mellitus, pre-transplantation heaptitis B infection, and postoperative acute renal failure. These data show that after transplantation of non-renal organs patients are at higher risk of chronic renal failure, independently from the post-transplantation immunosuppressive therapy.

3. Pathophysiology of CsA Nephrotoxicity

The etiology of chronic CsA nephrotoxicity has been studied extensively. A combination of CsA-induced hemodynamic changes and direct toxic effects of CsA on tubular epithelial cells is thought to play a role [19]. Renal dysfunction can be functional or structural. Functional impairment, which may begin soon after commencing

Table 1. Drugs that may increase the risk of CsA-associated nephrotoxicity [115].

Aminoglycosides
Melfalan
Diclofenac
Amphotericin B
Ketoconazole
Trimetoprim (with or without sulphametoxazole)
Fluoroquinilones
Acyclovir
Cidofovir
Foscarnet
Cimetidine, ranitidine
Tacrolimus
Colquicine
NSAIDs
Analgesics
Contrast media
Fibrates

treatment, can be subdivided into vascular dysfunction and tubular dysfunction. Vascular dysfunction is caused by vasoconstriction of the afferent glomerular arterioles, leading to increased vascular resistance. This results in decreased renal glomerular filtration rate (GFR) and renal blood flow with decreased clearance of creatinine. Tubular dysfunction is characterized by decreased magnesium reabsorption, decreased uric acid excretion, decreased potassium and hydrogen ion secretion, and distal tubular acidosis. Hypomagnesemia, decreased bicarbonate concentration, hyperuricemia, and hyperkalemia may also result. There is no loss of urinary concentrating power, as is the case with other nephrotoxins.

3.1. Acute Nephrotoxicity

Vasoconstriction of the afferent arterioles was first suggested by Murray *et al.* in 1985, which was proposed to be due to activation of the renal sympathetic nervous system, since a concomitant stimulation of plasma renin activity was demonstrated [39]. These authors also noted a reduction in the rate of decline of renal blood flow in denervated rats. Barros *et al.* also demonstrated an increase in vascular resistance in both afferent and efferent arterioles with a reduction in renal plasma flow and glomerular filtration rate (GFR), an effect that was attenuated by the administration of the angiotensin-converting enzyme (ACE) inhibitor captopril and the calcium channel blocker verapamil [40]. In addition to its activation of the renin-angiotensin system (RAS), CsA has been shown to increase the vasoconstrictor factors endothelin and tromboxane. It also demonstrated to reduce vasodilator factors, prostacyclin, prostaglandin E2 and nitric oxide (NO) [41,42]. Activation of the RAS by CsA occurs by two mechanisms, a direct effect on juxtaglomerular cells [43] and indirectly through arterial vasoconstriction and reduced renal plasma flow. Another pathogenic mechanism was that observed by Hoecherl *et al*. who demonstrated a marked reduction of COX-2 expression and of the down- stream production of arachidonic acid metabolites, and a consequent vasoconstriction [44].

The role of the innate immune system has also been implicated in the nephrotoxicity of CsA. Injured tubular epithelial cells may activate toll-like receptors (TLR) and TNF-alfa which, in turn, stimulate secretion of chemokines that initiate phagocytic activity and immune activation [45]. This mechanism may provide a link between innate immunity and the direct effects of CsA on renal tubular cells.

3.2. Chronic Nephrotoxicity

Chronic nephrotoxicity is the main drawback of current CsA immunosuppressive regimens [46]. Myers *et al.* in 1984 were the first demonstrating that high doses of CsA not only induce reversible alterations in renal vascular resistance, but may also be associated with irreversible damage of the renal architecture [46]. In cardiac transplant recipients surviving more than 12 months and treated with CsA at very high doses (up to 17 mg/kg/day), which are no longer used even in transplant recipients, they observed significant reduction in GFR, renal plasma flow, and renal blood flow. Biopsies of five CsA-treated patients showed tubulointerstitial injury and focal glomerular sclerosis, which seemed to correlate in intensity with the degree of renal impairment47. Further evidence of chronic nephrotoxicity related to high dose (>5 mg/kg/die), long-term CsA use (>2 years) was the finding of impaired renal function in heart, liver, and lung transplant recipients as well as in patients with autoimmune diseases [47-49].

More recently, other authors reported much more encouraging results following long-term use of CsA in kidney transplant recipients. Sandrini *et al.* reported on renal function in 638 cadaveric kidney transplant patients treated with CsA for up to 15 years. At 15 years, patient and graft survival rates were 82.7% and 56.1% respecttively, renal function remained stable in 266 patients (46.6%) with preserved serum creatinine values observed even after a 15-year treatment period [50]. Kandaswamy *et al* studied the impact of continuing CsA-based immunosuppression in the second decade after kidney transplantation in a total of 1263 patients [10]. They observed that not all transplanted patients on CsA developed progressive renal changes, but conversely in a subset or patients on long term CsA, serum creatinine levels were stable up to 20 years post-transplantation. The authors' conclusions were that identifying recipients' predisposetion to CsA toxicity and individualizing immunosuppressive therapy might be important in order to improve long-term kidney function. They also noted that reducetion in CsA exposure over time might preserve renal function.

4. Pathologic Findings

The hallmark finding in CsA nephrotoxicity is arteriolar hyalinosis, characterized by nodular hyaline deposits in the tunica media of afferent arterioles. Another common finding is interstitial or so-called striped fibrosis. This is hypothesized to be secondary to the above mentioned vasoconstriction effects of CsA with subsequent arterial narrowing. The subsequent tissue ischemia/hypoxia leads to a reperfusion type injury, with the formation of reactive oxygen species and free radicals, leading to cellular injury and apoptosis [19,51].

Activation of the RAS is also implied in the pathogenesis of CsA nephrotoxicity, not only for its vasoconstrictive effects but also due to the action of angiotensin

II, which has been shown to possibly induce fibrosis [19, 52,53].

Nankivell *et al* in 2004 gave one of the most important contributions to the documentation of the long-term nephrotoxic effects of CsA and the associated pathologic findings [54]. These authors examined serial kidney biopsies, performed at the time of organ implantation, at weeks 1, 2 and 4, at months 3, 6 and 12, and then yearly for 10 years. In total 888 biopsies were obtained in 99 patients. At 10 years these authors observed lesions consistent with chronic CsA toxicity in 100% of patients, but it has to be taken into account that immunosuppression protocols in those years were complex, with transplanted patients usually receiving triple therapy, including CsA, prednisone and azathioprine, so that renal damage cannot be attributed to CsA alone [55].

Table 2 summarizes the histological lesions associated with CsA acute and chronic use. However, the differential diagnosis between CsA-related nephrotoxicity and other injury phenomena is very difficult, especially in kidney transplantation. The calcineurin inhibitors nephrotoxicity score proposed by Kambham *et al.* in 2007 [56] represents a first step in the standardization of the composite histological changes induced by CsA, but further validation studies are necessary. In non-renal organ transplantation the picture may be clearer and the study of CsA nephrotoxicity in native kidneys seems to be less troublesome [38,57].

5. CsA-Induced Nephropathy in Patients with Autoimmune Diseases

Feutren *et al.* in 1992 [4] studied the incidence of and the risk factors for CsA-induced nephropathy in patients with various autoimmune diseases. They retrospectively analyzed clinical and renal biopsy data from 192 patients (152 with insulin-dependent diabetes mellitus, 23 with posterior uveitis, 11 with psoriasis, 5 with Sjoegren, 1 with polychondritis), including 63 children of ≤15 years of age. The duration of CsA therapy ranged from 4 to 39 months and in most patients CsA doses were higher than currently recommended (8.2 ± 2.8 mg/kg/day) and were increased during the first months of therapy. Renal biopsies were performed in all patients and CsA-induced nephropathy was defined as the presence of moderate or more severe alterations of the tubulointerstitial space, the glomerular arterioles or both. Forty-one of the 192 patients had evidence of CsA-induced nephropathy: 25 had diabetes, 14 had uveitis, and 1 each had polychondritis and Sjoegren's syndrome. Interstitial fibrosis with tubular atrophy were the predominant morphologic lesions in CsA-induced nephropathy. The percent increase in serum creatinine above baseline values was the best predictor of nephropathy. The impairment of renal function did not seem to be a direct consequence of the morphologic alterations, since it was reversible in most patients after a reduction in the dose or discontinuation of CsA therapy, even when morphologic lesions were present. The dose of CsA, the type of underlying disease, and the patient's age were additional risk factors for nephropathy. The incidence of nephropathy was lower in children than in adults, probably because the clearance of CsA is greater in children [58]. In the authors' opinion, the results of this study suggest that CsA-induced nephropathy may not be the result of long-term and cumulative toxic effects on arterioles and tubules, but rather a consequence of a brief insult brought about by the administration of excessive doses of CsA (≥ 10 mg/kg/day), which were rather frequent in early nineties. This analysis suggests that in patients with autoimmune and inflammatory disease and normal renal function, the likelihood of the development of CsA-induced nephropathy can be minimized by using doses ≤ 5 mg/kg/day and avoiding increases in serum creatinine concentrations greater than 30% above the patient's baseline value by appropriate dose.

Several studies have been conducted specifically in psoriasis patients treated with CsA. Nine studies evaluated changes in renal structure, assessed in kidney biopsy specimens, together with the variation in GFR, in patients with psoriasis treated with CsA [59,67]. Different grading and scoring systems were used to evaluate CsA nephrotoxicity, making it difficult to combine the results. Biopsy studies included a total of 104 patients receiving CsA for a period ranging from 1 to 10 years at doses commonly ranging between 1.9 and 5 mg/kg/day, with some patients receiving up to 7.5 mg/kg/day. These studies showed slight to moderate interstitial fibrosis after 1 year of CsA in some subjects, and after 3 to 4 years, interstitial fibrosis was moderate to severe [59,61-64]. The frequency of glomerular sclerosis in biopsies increased from 12.5% at 3 years to 26% at 10 years [60,66]. Tubular atrophy has also been described. Renal arteriolar abnormalities, consisting of either necrosis of smooth-

Table 2. Histological lesions associated with cyclosporine use (modified from Naesens *et al.* [19]).

Acute CsA nephrotoxicity	• Acute arteriolopathy = renal dysfunction without histological alterations • Tubular vacuolization • Thrombotic microangiopathy
Chronic CsA nephrotoxicity	• Interstitial fibrosis and tubular atrophy • Medial arteriolar hyalinosis • Glomerular capsular fibrosis • Global glomerulosclerosis • Focal segmental glomerulosclerosis • Juxtaglomerular apparatus hyperplasia • Tubular microcalcification

muscle cells and nodular protein deposits in the wall of afferent glomerular arterioles or arteriolar intima hyalinosis may also be seen [68]. The percentage of increase in serum creatinine above 30% of baseline was found to be a predictor of structural kidney changes. Moreover, the severity of recurrent acute nephrotoxicity was shown to correlate with chronic histological changes ($r = 0.8$, $p = 0.0003$) [64]. Increases in serum creatinine were reversible 1 month to 10 years [65,66,69] after stopping CsA therapy. It seems that structural kidney damage can be expected in patients in whom serum creatinine does not decrease after cessation of CsA therapy. Young *et al.* [62] showed that older patients may be more vulnerable to CsA-induced renal injury and that CsA-associated hypertension was associated with a greater degree of progressive renal interstitial fibrosis on serial biopsies. Other six studies described the incidence of increases in serum creatinine by more than 30% above the baseline value in psoriasis patients [4,70-74]. Overall, more than 50% of the patients had a significant increase in serum creatinine (>30% of baseline) if treatment was prolonged for ≥2 years. Comparing the incidence of in- creases in serum creatinine >30% in patients receiving continuous or intermittent CsA treatment no significant difference was found (OR 1.35, $p = 0.66$). In conclusion, in psoriasis patients nephrotoxicity was associated with longer use, larger cumulative dose, higher daily dose and the occurrence of acute increases in serum creatinine. Slight to moderate interstitial fibrosis was observed in patients treated for at least 1 - 2 years, while glomerular sclerosis or severe interstitial fibrosis were seen in some cases after 3 years or more. The functional signification and the reversibility of the structural changes have not been fully characterized in the available studies.

Regarding rheumatoid arthritis (RA), following the estimation of potential risk factors for the development of CsA-induced nephropathy in autoimmune diseases4, dosing recommendations for the use of CsA in RA were established, stating that the starting dose should be 2.5 - 3.5 mg/kg/day, the maximum daily dose should not exceed 5 mg/kg/day and that the dose should be reduced whenever serum creatinine increases by ≥ 30% [75,76]. The 1994 International Consensus Report on the treatment of RA by CsA concluded that CsA-induced nephropathy can be avoided when these rules are observed. Subsequently, data from the Kidney Biopsy Registry on 60 first and 14 second renal biopsies performed in RA patients treated with CsA for up to 87 months were reviewed by Rodriguez *et al*. in order to describe the biopsy findings in all evaluable RA patients, collect information about the long-term follow-up of renal function and discuss the risk factors for the development of nephrotoxicity [5]. Of the 22 patients who started CsA at dosages <4 mg/kg/day and did not exceed 5 mg/kg/day, none developed CsA-associated nephropathy. Continuous assessment of renal function did not show any evidence of deterioration over time in patients maintained on long-term, low-dose CsA.

A single-center prospective cohort study was conducted to assess the long-term renal tolerance of a low-dose CsA treatment in patients affected by sight-threatening posterior idiopathic uveitis, having healthy kidneys before CsA therapy [6]. Forty-one patients were included in the study undergoing a mean CsA treatment duration of 44.9 ± 3.6 months and receiving no other nephrotoxic drugs. Mean CsA daily dosage was gradually tapered from 4.3 ± 1.6 mg/kg/day to 1.8 ± 0.9 mg/kg/day over 5 years. Renal effects were evaluated by creatinine clearance, GFR and effective renal plasma flow; additionally 11 patients underwent kidney biopsies before and after 2 years of CsA treatment. The authors suggest that in order to obtain the expected benefits to patients with uveitis, CsA should be used at the lowest effective dose, possibly ≤ 3 mg/kg/day, so that CsA-associated nephrotoxicity might be prevented.

A large cohort of 285 recently diagnosed type 1 diabetic patients having received CsA for a mean of 20 months was monitored for 13 years and compared with a parallel group of 100 similar patients treated with insulin alone. The CsA-treated patients showed a transient increase in creatininemia during the first 18 months of treatment, associated with a transient increase in renal vascular resistance, both of which disappeared later, with values remaining then normal [77]. The authors conclude that low-dose CsA combined with tight and careful monitoring should not result in long-term renal dysfunction.

6. Prevention of CsA Nephrotoxicity

Despite the above mentioned evidences of CsA-associated renal toxicity, the exclusion of CsA from the immunosuppressive regimens following organ transplantation does not allow to preserve the allograft function, due to the inadequate rejection prophylaxis obtained with other immunosuppressive regimens [78-81]. Therefore, different strategies aimed at prevent- ing renal damage during long-term CsA treatment have been developed. For example, the week-end therapy was evaluated in the PREWENT study, which assessed the impact on efficacy and safety of a two consecutive days a week regimen in psoriasis patients, no difference in the incidence of adverse effects was observed between placebo and CsA [82].

6.1. CsA Minimization

There is increasing interest in CsA minimization protocols, in which the doses of CsA are adjusted to lower target levels, both in de novo immunosuppressive proto-

cols both from time of transplantation and for rescue therapy after detection of renal histologic damage or dysfunction [80]. These CsA-sparing regimens appear to be relatively safe [79-81]. By minimizing CsA levels, nephrotoxicity might be partially avoided, but it has become clear that the increased risk of allograft rejection could annihilate these positive effects. It will be important to develop and apply new tools for clinical immunologic monitoring in order to avoid that minimization strategies will result in under-immunosuppression with the risk of chronic rejection.

6.2. Calcium Antagonists

Because vasoconstriction of the afferent arterioles appears to play a pivotal role in acute and chronic CsA nephrotoxicity, many authors have studied the preventive effects of vasodilatory agents. The calcium antagonist nitrendipine and later lacidipine were shown to prevent the fall in renal plasma flow and GFR associated with CsA administration [83-85]. In a randomized trial in renal transplant recipients, patients treated with the combination of CsA and nifedipine had better renal function with the same degree of blood pressure control [86]. A similar effect was shown by lacidipine in another randomized trial [87].

Likewise, in heart transplantation, treatment with nifedipine normalized BP and improved renal function [88]. More recently, another randomized trial with amlodipine confirmed these positive effects of calcium antagonists on CsA nephrotoxicity again in heart transplant recipients [89]. In contrast, a long-term follow-up study did not find a protective effect of calcium channel blockers in preventing CsA nephrotoxicity [90], but it has to be pointed out that the type of calcium antagonist is not specified in this study.

6.3. RAS Inhibition

Given the pivotal role of RAS activation in the pathogenesis of CsA nephrotoxicity, it can be expected that RAS inhibition will be useful in preventing its development. In human studies, ACE inhibitors showed to reduce CsA nephrotoxicity [91] and to improve the cardiovascular alterations observed in renal transplant recipients [92]. On the other hand, results with the angiotensin-receptor blocker (ARB) losartan are currently contradictory [93,94] and it is therefore not clear whether combination with ARB could effectively slow the progression of CsA-associated renal toxicity. Similarly inconsistent are the results of the comparison between nifedipine and lisinopril [95,96].

6.4. Other Pharmacological Approaches

Vasodilatory prostanoids, like misoprostol, did not prevent CsA nephrotoxicity both in transplant recipients and in rheumatoid arthritis patients [97,98]. Despite promising results in rats, the nitric oxide donor L-arginine showed no effect on CsA nephrotoxicity prevention in humans [99].

Other therapeutic approaches are promising, such as anti-TGF-β antibodies [100,101], antioxidants [102-105], statins [106] and magnesium supplementation [107,108], but no human studies are yet available with these agents.

7. Management of CsA Nephrotoxicity

A protocol for the management of nephrotoxicity associated with long term CsA administration has been proposed by Griffith *et al.* in their international consensus statement on CsA in psoriasis clinical practice [7]. Based on the observation that CsA nephropathy is strictly related to drug dose (>5 mg/kg/day) and treatment duration [60,70,109], these authors propose that the risk of renal toxicity during CsA treatment is reduced by the use of intermittent, short courses of the drug. The drug-free days should allow renal recovery and restoration of normal renal function [109]. Renal safety during short course CsA therapy has been shown in studies where only a minority of patients (4%, 17% and 10% - 27%) [72,110-112] experienced an elevation in serum creatinine, which was typically transient and commonly returned to baseline within 4 weeks following dose reduction or treatment cessation [72].

According to Griffiths *et al.* [7], the chance of developing renal impairment during CsA therapy should be minimized by screening patients at baseline for any risk factors of renal toxicity: hypertension, advanced age, pre-existing renal conditions, and abnormalities in absorption of CsA. Concomitant medications and weight may represent additional risk factors [4]. Most importantly, the dose of CsA should only exceptionally exceed 5 mg/kg/day and the duration should be only as long as is necessary to achieve clearance or near-clearance of the disease. Further management guidelines for monitoring renal safety during CsA therapy proposed by Griffiths *et al* are summarized in **Figure 1**.

8. Conclusions

Renal impairment represents the main limitation to CsA long-term continuous therapy. However, it has been shown that nephrotoxicity is associated with longer treatment duration, larger cumulative doses and higher daily dose of CsA. Its prevalence with doses ≤5 mg/kg/day is low. Renal structural changes including slight to moderate interstitial fibrosis were mainly observed in patients treated for ≥2 years consecutively with high dosages, significant lesions such as glomerular sclerosis or severe interstitial fibrosis seen after 3 years or more.

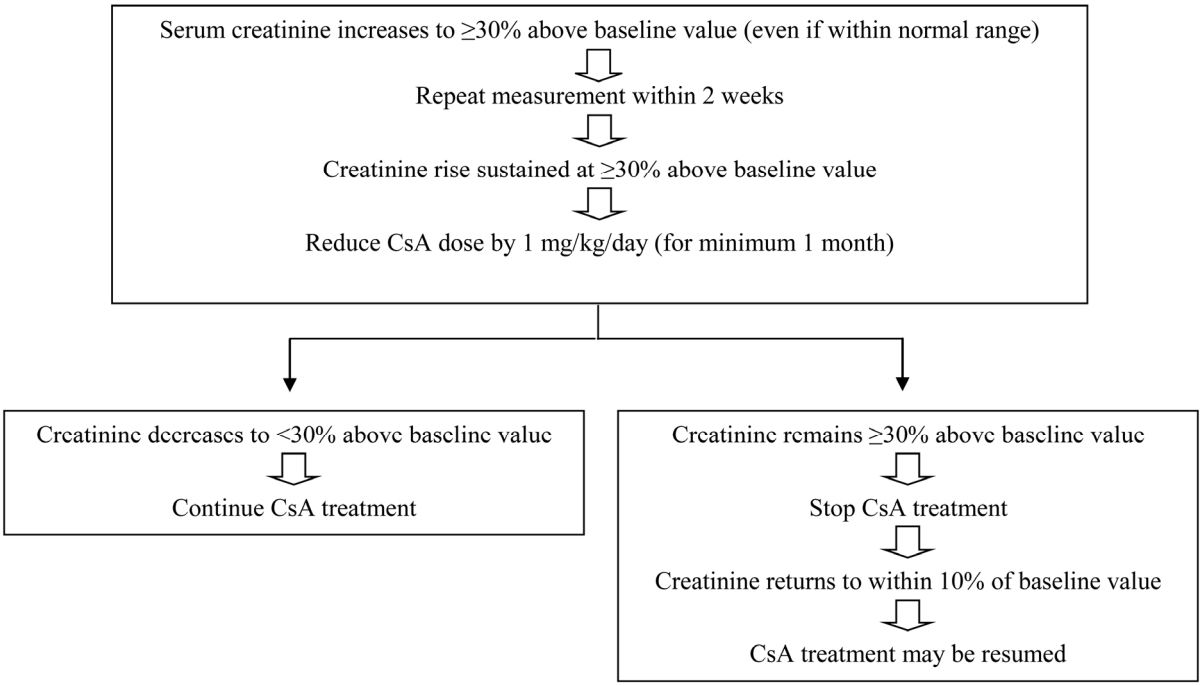

Figure 1. Management of renal toxicity during CsA therapy proposed by Griffiths *et al.* [7].

With low dose regimens, stable serum creatinine levels have been observed up to 15 - 20 years after kidney transplantation [10,50]. Intermittent therapy may offer a good therapeutic strategy to limit long-term renal dysfunction, given the fact that renal structural changes are dose- and time-dependent. Besides, the conventional CsA dose must be adapted to the ideal and not the real weight in obese patients to limit the risk of nephrotoxicity.

The best predictor of permanent renal damage is a persistent increase in serum creatinine level one month after treatment withdrawal. The percentage increase in serum creatinine above baseline value during CsA therapy has been shown to predict CsA-induced nephropathy in patients with autoimmune diseases [4]. Thus, patients must be examined and have serum creatinine levels measured monthly, in order to monitor increases >30% of baseline value, which may precede histological lesions and should prompt dose reduction.

Initiation of CsA therapy requires a thorough baseline evaluation including laboratory assessments with full blood counts, electrolytes, serum creatinine, urea, liver enzymes, cholesterol and triglycerides [113]. Furthermore, patients should be evaluated for factors that might increase the risk of nephrotoxicity. These risk factors include obesity [66], older age [60], hypertension, concomitant use of nephrotoxic drugs [114], and pre-existing renal conditions.

In general, if CsA is administered at a dose of 5 mg/kg/day or less and patients' serum creatinine levels are carefully monitored to ensure that they do not increase to more than 30% above baseline, renal side effects will be fully reversible after discontinuation of the drug.

In summary, CsA has with no doubt revolutionized transplant medication and has proven to be effective in autoimmune and inflammatory diseases. Despite the discovery of acute and chronic nephrotoxicity, its use continues to be a mainstay in immunosuppression, and CsA remains irreplaceable despite the enormous efforts otherwise. Available data indicate that low-dose CsA regimens (2.5 - 5 mg/kg/die) would provide an interesting balance between efficacy and toxicity.

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