Managing a Side Effect: Cyclosporine-Induced Nephrotoxicity

Manasi Shirolikar, Sushil Pande, Milind Borkar, Sachin Soni
Department of Dermatology, NKP Salve Institute of Medical Sciences and Lata Mangeshkar Hospital, Nagpur; Consultant Nephrologist, United CIIGMA Hospital, Aurangabad, Maharashtra, India

INTRODUCTION
Cyclosporine (CsA), an immunosuppressant, is a calcineurin inhibitor (CNI) which is specific for T-cells. It was discovered in Sandoz Laboratories in Basel, Switzerland by isolating it from the soil fungus Tolypocladium inflatum gams.[1] Initially used for rheumatoid and psoriatic arthritis, it was later approved for prophylaxis of organ rejection. Dermatologists often prescribe CsA in the dose of 3–5 mg/kg/day for management of papulosquamous disorders, mainly psoriasis and autoimmune connective tissue disorders. It is also used off-label in atopic dermatitis. Nowadays, CsA is increasingly being used for the treatment of toxic epidermal necrolysis with good effects. Calne et al. used CsA following transplantation in a dose of 25 mg/kg and found unexpected nephrotoxicity that had previously not been seen in animal experiments.[2] Most of the persistent renal dysfunction is seen when the drug is used for a long duration of time and when dose of CsA is >5 mg/kg/day, especially in patients of psoriasis. This is an important side effect that needs to be recognized at early stages to avoid chronic kidney damage or irreversible nephrotoxicity.

PATHOPHYSIOLOGY OF NEPHROTOXICITY
Renal dysfunction can be functional or structural. Functional impairment is further split into vascular dysfunction and tubular dysfunction. Vascular dysfunction is caused by vasoconstriction of the afferent glomerular arterioles, resulting 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]

Acute nephrotoxicity
Activation of the renin–angiotensin system (RAS), afferent arteriolar vasoconstriction, increased vascular resistance of afferent and efferent arterioles, and decreased GFR are seen.[4,5] Activation of the RAS by CsA occurs by two mechanisms, a direct effect on juxtaglomerular cells[6] and indirectly through arterial vasoconstriction and reduced renal plasma flow. In addition to the RAS activation, it has been shown that CsA increases the vasoconstrictor factors – endothelin (ET) and thromboxane; and decreases the vasodilator factors – prostacyclin, prostaglandin E2, and nitric oxide (NO).[7,8] CsA may also increase superoxide,[9] upregulate angiotensin II receptors, and increase the concentration of calcium in smooth-muscle cells causing increased sensitivity to vasoconstrictive stimuli.[10,11]
Tubular changes also include isometric vacuolization of the proximal tubule.[12] Acute functional changes are typically reversible on withdrawal of CsA treatment.

Chronic nephrotoxicity
Chronic nephrotoxicity is due to structural changes in renal blood vessels and renal tubules. This includes an obliterator microvascular renal injury (vasculopathy) and a tubulopathy.[13]

Vasculopathy
Vasculopathy comprises glomerular or arteriolar thrombi (platelets or fibrin), arteriolopathy, and interstitial fibrosis with tubular atrophy.[14] Nodular protein deposits cause narrowing or occlusion of the vascular lumen.[15] Mucoid thickening of the intimal wall can also occur, leading to
arteriolar hyalinosis, interstitial fibrosis (striped form), tubular atrophy, and glomerular sclerosis.

**Tubulopathy**

Tubular structural changes include single-cell necrosis and microcalcification of Tamme–Horsfall protein in the distal tubule.[16] These changes are seen with higher doses of CsA and are, thus, uncommon these days.

While tubulopathic changes are reversible, vasculopathic changes are maintained in up to half of patients.[16,17]

CsA alters transcription of genes such as NO synthase, transforming growth factor beta (TGF-β), ET-1, Collagen I and IV, and Bel-2 which are proposed to be involved in the pathogenesis of chronic nephrotoxicity. Thus, both immunosuppression and nephrotoxicity are closely related to the suppression of calcineurin.[18,19]

**Risk Factors For Cyclosporine Nephrotoxicity**

Individual susceptibility also plays a role in susceptibility to renal toxicity.[20]

**Systemic levels of cyclosporine**

CsA has a relatively narrow therapeutic window. Thus, precautions must be taken to keep the dosage within a preset target range.[21] However, maintaining CsA concentrations within these ranges often proves to be difficult due to high inter- and intra-individual pharmacokinetic variability.[22] This is seen with Sandimmune® more often than with Neoral®.[23-25]

**Local renal exposure to cyclosporine**

Levels of CsA in the renal tissue are much higher than in blood.[26,27] This, in addition to local renal factors, contributes to nephrotoxicity. These factors include the age of the recipient and the kidney (if transplanted), local renal P-glycoprotein, and the use of nonsteroidal anti-inflammatory drugs.[28-31] Thus, it could be predicted that younger patients with native kidneys or those with kidneys transplanted from younger donors could be less susceptible to CsA nephrotoxicity.

There have been many studies of the safety of long-term CsA therapy in dermatology with regard to nephrotoxicity.

A study of renal biopsy specimens obtained from 30 psoriasis patients treated with CsA showed that all patients treated for 2 years or longer had an abnormal kidney biopsy specimen, with pronounced glomerular sclerosis after 4 years of continuous treatment.[32] A study of maintenance CsA for 3.5 years in psoriasis patients showed a moderate degree of interstitial fibrosis and glomerular scarring in two of 14 patients after 2.5 years, with minimal to mild change in all of the remaining 12 patients.[33] One year later, there was progression of fibrosis in nine of the 12 patients still enrolled in the study. Similarly, 1 month after drug withdrawal, tubulointerstitial scarring and arteriolopathy was seen in 27% of renal biopsy specimens taken from 15 psoriatic patients who had received CsA (<5 mg/kg/day) for 30 months.[34] These patients had marked increases in serum creatinine levels of >90% above baseline, and conversely, those showing no increase in serum creatinine levels did not have structural renal changes in 86% of cases. There was no correlation, however, with dose or treatment duration. In a study evaluating eight patients treated with a mean dose of 3.3 mg/kg/day for 5 years, renal biopsy specimens revealed tubular atrophy and arterial hyalinosis in six patients (75%), with interstitial fibrosis and obliteration of glomeruli.[35] Again, the best predictor of permanent renal damage was a persistent increase in serum creatinine level 1 month after treatment withdrawal.[36]

In psoriasis patients, nephrotoxicity is associated with longer use, higher cumulative and daily dosage, and 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 significance and the reversibility of the structural changes have not been fully characterized in the available studies.[37]

**Cyclosporine Nephrotoxicity and Hypertension**

Initiation and monitoring of antihypertensive therapy may be a reason why dermatologists have been apprehensive to include CsA in their clinical armamentarium. New-onset hypertension with CsA treatment has been reported in a wide range from 0% to 57% in different studies. A short-course of CsA therapy shows a decreased incidence of new-onset hypertension which is usually reversible on dose reduction or with antihypertensive medications.[38] There seems to be a lower incidence of new-onset hypertension as seen in studies of adults with atopic dermatitis compared with studies of psoriasis patients receiving short-term CsA treatment. This may be due to a younger mean age in the cohort of patients recruited to atopic dermatitis studies; however, psoriasis patients may have a higher inherent risk of developing hypertension because of an increased incidence of obesity and the metabolic syndrome and therefore hypertension.[39,40]

In patients receiving long-term treatment, hypertension is more frequent. Longer-term studies have shown the persistence of hypertension posttreatment in up to 35% of patients.[41]

The absence of an association between CsA dose and frequency of hypertension has been shown in other studies.[42] Thus, there may be subset of patients with increased sensitivity to CsA, who are predisposed to hypertension even at low doses. Consequently, it has been suggested that CsA-induced hypertension should be managed by antihypertensive therapy rather than dose reduction.[43]

**Prevention of Cyclosporine-Induced Nephrotoxicity**

CsA-induced nephropathy can be prevented by appropriate monitoring for the drug, avoidance of concomitant drugs, and giving proper drug interval.
Cyclosporine monitoring

Monitoring of serum creatinine, blood pressure, and various other parameters is to be done as shown in Figure 1 and 2.

Fasting (fasting 12 h, in the morning, no preceding strenuous exercise) serum creatinine should be measured in a standardized manner on at least two separate occasions and repeated again if there is a discrepancy of >10 μmol/L between these measurements. The average of these two values then serves as the baseline serum creatinine against which subsequent treatment values are compared.

Assessing CsA serum concentrations is a good tool to avoid CsA-induced side effects including nephrotoxicity. These are monitored mainly in transplant patients to avoid toxicity due to high concentrations of CsA and minimize possible organ rejection caused by low concentrations, because of the small therapeutic window. However, this has not been adopted or shown to be of benefit in monitoring efficacy or toxicity in dermatology patients. No correlation was established between immunosuppression and occurrence of adverse events. It can be used, however, if there is a query regarding patient adherence to treatment or to detect CsA levels above the recommended dosing range.

Avoidance of concomitant drugs increasing cyclosporine-associated nephropathy

CsA can delay the metabolism of multiple agents, including digoxin, simvastatin, prednisolone, diclofenac, and methotrexate, leading to increased concentration and toxicity of these drugs.

Drugs that may increase the risk of CsA-associated nephrotoxicity are shown in Table 1.

Drug-free interval

Since CsA nephropathy is strictly related to drug dose (>5 mg/kg/day) and treatment duration, it has been proposed 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 allow renal recovery and restoration of normal renal function.

Strategies to reduce local renal susceptibility to calcineurin inhibitor toxicity

As vasconstriction of the afferent arterioles appears to play a pivotal role in acute and chronic CNI nephrotoxicity, the potential role of vasodilatory agents for the avoidance of CNI nephrotoxicity cannot be underestimated. Various calcium channel antagonists such as nifedipine, verapamil, and diltiazem have shown their efficacy in reducing CNI nephrotoxicity in human studies.

Considering role of RAS activation in pathogenesis of CNI nephrotoxicity, therapeutic RAS inhibition appears an important approach. Beneficial effects have been observed in animal and human studies using losartan, lisinopril, and spironolactone.

In rats as well as human studies, vasodilatory prostanoids like misoprostol showed beneficial effect in reducing CNI nephrotoxicity. L-arginine or molsidomine by virtue of NO generation has also shown promise in animal studies.

Finally, other therapeutic approaches such as anti-TGF-β antibodies, statins, magnesium supplementation, and use of antioxidants have shown some beneficial effect in amelioration of CNI nephrotoxicity.

Treatment of nephrotoxicity-induced manifestations

Treatment of hypertension

- As there seems to be no relationship between the onset of hypertension and CsA dose, the introduction of

Figure 1: Management of renal toxicity during cyclosporine therapy proposed by Griffiths et al
Antihypertensives may be more appropriate than dose reduction

- Calcium channel blockers of the dihydropyridine class (amlodipine or isradipine) are the antihypertensives of choice in CsA-mediated hypertension because of their vasodilating effect on the afferent arteriole, which may confer protection against nephropathy. Nifedipine can potentiate the gingival hypertrophy caused by CsA. Verapamil and diltiazem should be avoided as they interfere with serum CsA levels

- Angiotensin-converting enzyme inhibitors reduce CsA nephrotoxicity and improve the cardiovasculone alterations observed in renal transplant recipients. However, some studies show a further decrease in GFR in CsA-treated hypertensive patients. Conversely, other studies have shown perindopril to be equally effective as amlodipine in lowering blood pressure without affecting GFR or effective renal plasma flow

- The use of thiazide diuretics may increase nephrotoxicity. Potassium-sparing diuretics should also be avoided, as CsA can increase serum potassium.

Thus, CsA-induced nephrotoxicity can be prevented or treated effectively. This should allow dermatologist to use CsA in optimal and effective manner for various dermatology indications. Dermatologist should be vigilant to detect nephrotoxicity and should promptly seek nephrologist’s opinion for further management of CsA-associated nephropathy.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Borel JF, Feurer C, Gubler HU, Stähelin H. Biological effects of cyclosporin A: A new antilymphocytic agent. Agents Actions 1976;6:468-75.
2. Calne RY, White DJ, Thiru S, Evans DB, McMaster P, Dunn DC, et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet 1978;2:1323-7.
3. Colombo MD, Perego R, Bellia G. Cyclosporine-associated nephrotoxicity. Open J Nephrol 2013;3:168-80.
4. Barros EJ, Boim MA, Ajzen H, Ramos OL, Schor N. Glomerular hemodynamics and hormonal participation on cyclosporine nephrotoxicity. Kidney Int 1987;32:19-25.
5. Murray BM, Paller MS, Ferris TF. Effect of cyclosporine administration on renal hemodynamics in conscious rats. Kidney Int 1985;28:767-74.
6. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: Part II. J Am Acad Dermatol 2010;63:949-72.
7. Hortelano S, Castilla M, Torres AM, Tejedor A, Boscá L. Potentiation of nitric oxide of cyclosporin A and FK506-induced apoptosis in renal proximal tubule cells. J Am Soc Nephrol 2000;11:2315-23.
8. Textor SC, Burnett JC Jr., Romero JC, Canzanello VJ, Taler SJ, Wisner R, et al. Urinary endothelin and renal vasoconstriction with cyclosporine or FK506 after liver transplantation. Kidney Int 1995;47:1426-33.
9. Diederich D, Skopec J, Diederich A, Dai FX. Cyclosporine produces endothelial dysfunction by increased production of superoxide. Hypertension 1994;23:957-61.
10. Sekerova N, Christians U. Transplantation: Toxicokinetics and mechanisms of toxicity of cyclosporine and macrolides. Curr Opin Investig Drugs 2003;4:1287-96.
11. Avdonin PV, Cottet-Maire F, Afanasjeva GV, Loktionova SA, Lhote P, Ruegg UT, et al. Cyclosporine A up-regulates angiotensin II receptors and calcium responses in human vascular smooth muscle cells. Kidney Int 1999;55:2407-14.
12. Naesens M, Kuypers DR, Sarwal M. Calcineurin inhibitor nephrotoxicity. Clin J Am Soc Nephrol 2009;4:481-508.
13. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: Part II. J Am Acad Dermatol 2010;63:949-72.
14. Mihtsch MJ, Thié G, Ryffel B. Histopathology of cyclosporine nephrotoxicity. Transplant Proc 1988;20:759-71.
15. Mihtsch MJ, Thié G, Ryffel B. Renal side-effects of cyclosporin A with special reference to autoimmune diseases. Br J Dermatol 1990;122 Suppl 36:101-15.
16. Mason J. Renal side-effects of cyclosporin A. Br J Dermatol 1990;122 Suppl 36:71-7.
17. Morozumi K, Thiel G, Albert FW, Banfi G, Gudat F, Mihtsch MJ, et al. Studies on morphological outcome of cyclosporine-associated arteriolopathy after discontinuation of cyclosporine in renal allografts. Clin Nephrol 1992;38:1-8.
18. Campistol JM, Sacks SH. Mechanisms of nephrotoxicity. Transplantation 2000;69:SS5-10.
19. Busauschina A, Schnuelle P, van der Woude FJ. Cyclosporine nephrotoxicity. Transplant Proc 2004;36:2295-33S.
20. Kandaswamy R, Humar A, Casingal V, Gillingham KJ, Ibrahim H, Matas AJ, et al. Stable kidney function in the second decade after kidney
transplantation while on cyclosporine-based immunosuppression. Transplantation 2007;83:722-6.
21. Ptachinski RJ, Burekatt GJ, Venkataramanan R. Cyclosporine concentration determinations for monitoring and pharmacokinetic studies. J Clin Pharmacol 1986;26:358-66.
22. Fehr A. Cyclosporin clinical pharmacokinetics. Clin Pharmacokinet 1993;24:472-95.
23. Holt DW, Mueller EA, Kovarik JM, van Bree JB, Richard F, Kutz K, et al. Sandimmun neoral pharmacokinetics: Impact of the new oral formulation. Transplant Proc 1995;27:1434-7.
24. Masri MA, Barbari A, Stephan A, Kamel G, Fream G, Younan F, et al. Cyclosporine pharmacokinetics in stable renal transplant patients: Effect of formulation sandimmun versus consupren versus neoral. Transplant Proc 1996;28:1318-20.
25. Humbert H. Variability of the bioavailability of cyclosporine: Benefit of the new oral formulation. Therapie 1997;52:337-3.
26. Halloran PF, Helms LM, Kung L, Noujaim J. The temporal profile of calcineurin inhibition by cyclosporine in vivo. Transplantation 1999;68:1356-61.
27. Iwasaki K, Shiraga T, Matsuda H, Teramura Y, Kawamura A, Hata T, et al. Absorption, distribution, metabolism and excretion of tacrolimus (FK506) in the rat. Drug Metab Pharmacokinet 1998;13:259-65.
28. Altman RD, Perez GO, Sfakianakis GN. Interaction of cyclosporine A and nonsteroidal anti-inflammatory drugs on renal function in patients with rheumatoid arthritis. Am J Med 1992;93:396-402.
29. Sturrock ND, Lang CC, Struthers AD. Indomethacin and cyclosporin together produce marked renal vasoconstriction in humans. J Hypertens 1994;12:919-24.
30. Kovarik JM, Kurki P, Mueller E, Guerret M, Markert E, Alten R, et al. Diclofenac combined with cyclosporine in treatment refractory rheumatoid arthritis: Longitudinal safety assessment and evidence of a pharmacokinetic/dynamic interaction. J Rheumatol 1996;23:1073-8.
31. Soubbia RM, Mendes GE, Mendonça FZ, Baptista MA, Cipullo JP, Burdmann EA, et al. Tacrolimus and nonsteroidal anti-inflammatory drugs: An association to be avoided. Am J Nephrol 2005;25:327-34.
32. Zachariae H, Kragballe K, Hansen HE, Marcussen N, Olsen S. Renal biopsy findings in long-term cyclosporin treatment of psoriasis. Br J Dermatol 1997;136:531-5.
33. Lowe NJ, Wieder JM, Rosenbach A, Johnson K, Kuncl R, Bainbridge C, et al. Long-term low-dose cyclosporine therapy for severe psoriasis: Effects on renal function and structure. J Am Acad Dermatol 1999;41:294-306.
34. Pei Y, Scholey JW, Katz A, Schachtler R, Murphy GF, Catran D, et al. Chronic nephrotoxicity in psoriatic patients treated with low-dose cyclosporine. Am J Kidney Dis 1994;23:528-36.
35. Powles AV, Cook T, Hulme B, Baker BS, Lewis HM, Thomas E, et al. Renal function and biopsy findings after 5 years’ treatment with low-dose cyclosporine for psoriasis. Br J Dermatol 1993;128:159-65.
36. Ho VC, Griffiths CE, Albrecht G, Vanaclocha F, Leon-Dorantes G, Atakan N, et al. Intermittent short courses of cyclosporin (Neoral(R)) for psoriasis unresponsive to topical therapy: A 1-year multicentre, randomized study. The PISCES study group. Br J Dermatol 1999;141:283-91.
37. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, et al. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296:1735-41.
38. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM, et al. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55:829-35.
39. Markham T, Watson A, Rogers S. Adverse effects with long-term cyclosporine therapy for severe psoriasis. Clin Exp Dermatol 2002;27:111-4.
40. Christophers E, Mrowietz U, Henneicke-von Zepelin HH, Bachmann H, Welzel D, Christophers E, et al. Long-term maintenance therapy with cyclosporine and posttreatment survey in severe psoriasis: Results of a multicenter study. German multicenter study. J Am Acad Dermatol 1995;33:470-5.
41. Feutren G, Friend D, Timonen P, Laburte C. Cyclosporin monitoring in psoriasis. Lancet 1990;335:866-7.
42. Feutren G, Friend D, Timonen P, Barnes A, Laburte C. Predictive value of cyclosporin A level for efficacy or renal dysfunction in psoriasis. Br J Dermatol 1990;122 Suppl 36:85-93.
43. Mahalati K, Belitsky P, Setriks I, West K, Panek R. Neoral monitoring with simplified sparse sampling area under the concentration-time curve: Its relationship to acute rejection and cyclosporine nephrotoxicity early after kidney transplantation. Transplantation 1999;68:55-62.
44. Heyndendael VM, Spuls PI, Ten Berge JJ, Opmeer BC, Bos JD, de Rie MA, et al. Cyclosporin trough levels: Is monitoring necessary during short-term treatment in psoriasis? A systematic review and clinical data on trough levels. Br J Dermatol 2002;147:122-9.
45. Katz HI. Potential drug interactions with cyclosporin. Int J Dermatol 2008;36 Suppl 1:18-24.
46. Mihatsch MJ, Belghiti D, Bohman SO. Kidney biopsies in control or cyclosporin A treated psoriatic patients. Br J Dermatol 1990;122 Suppl 36:95-100.
47. Ruggenenti P, Perico N, Mosconi L, Gaspari F, Benigni A, Amuchastegui CS, et al. Calcium channel blockers protect transplant patients from cyclosporine-induced daily renal hyperperfusion. Kidney Int 1993;43:706-11.
48. Morales JM, Rodriguez-Paternina E, Araque A, Andres A, Hernandez E, Ruijlope LM, et al. Long-term protective effect of a calcium antagonist on renal function in hypertensive renal transplant patients on cyclosporine therapy. A 5-year prospective randomized study. Transplant Proc 1994;26:2598-9.
49. Kuypers DR, Neumayer HH, Fritschle L, Budde K, Rodicio JL, Vanrenterghem Y, et al. Calcium channel blockade and preservation of renal graft function in cyclosporine-treated recipients: A prospective randomized placebo-controlled 2-year study. Transplantation 2004;78:1204-11.
50. Mervaala E, Lassila M, Vaskonen T, Krugerus L, Lähteenmäki T, Vapaatalo H, et al. Effects of ACE inhibition on cyclosporine A-induced hypertension and nephrotoxicity in spontaneously hypertensive rats on a high-sodium diet. Blood Press 1999;8:49-56.
51. Li C, Sun BK, Lim SW, Song JC, Kang SW, Kim YS, et al. Combined effects of losartan and pravastatin on interstitial inflammation and fibrosis in chronic cyclosporine-induced nephropathy. Transplantation 2005;79:1522-9.
52. Sun BK, Li C, Lim SW, Choi BS, Lee SH, Kim IS, et al. Blockade of angiotensin II with losartan attenuates transforming growth factor-beta1 inducible gene-h3 (beta-g3) expression in a model of chronic cyclosporine nephrotoxicity. Nephron Exp Nephrol 2005;99:e9-16.
53. Hann vedouche TP, Natov S, Boitard C, Lacour B, Grünfeld JP. Angiotensin converting enzyme inhibition and chronic cyclosporine-induced renal dysfunction in type 1 diabetes. Nephrol Dial Transplant 1996;11:673-8.
Shirolikar, et al.: Cyclosporine induced nephrotoxicity

62. Nast CC, Hirschberg R, Artishevsky A, Adler SG. Misoprostol partially inhibits the renal scarring of chronic cyclosporine nephrotoxicity. Am J Ther 1995;2:882-5.

63. Moran M, Mozes MF, Maddux MS, Veremis S, Bartkus C, Ketel B, et al. Prevention of acute graft rejection by the prostaglandin E1 analogue misoprostol in renal-transplant recipients treated with cyclosporine and prednisone. N Engl J Med 1990;322:1183-8.

64. Chander V, Chopra K. Effect of molsidomine and L-arginine in cyclosporine nephrotoxicity: Role of nitric oxide. Toxicology 2005;207:463-74.

65. Ling H, Li X, Jha S, Wang W, Karetukaya L, Pratt B, et al. Therapeutic role of TGF-beta-neutralizing antibody in mouse cyclosporin A nephropathy: Morphologic improvement associated with functional preservation. J Am Soc Nephrol 2003;14:377-88.

66. Pere AK, Lindgren L, Tuomainen P, Krogerus L, Rauhala P, Laakso J, et al. Dietary potassium and magnesium supplementation in cyclosporine-induced hypertension and nephrotoxicity. Kidney Int 2000;58:2462-72.

67. Tariq M, Morais C, Sobki S, Al Sulaiman M, Al Khader A. N-acetylcysteine attenuates cyclosporin-induced nephrotoxicity in rats. Nephrol Dial Transplant 1999;14:923-9.

68. Bárány P, Stenvinkel P, Ottonson-Seeberger A, Alvestrand A, Morrow J, Roberts J 2nd, et al. Effect of 6 weeks of Vitamin E administration on renal haemodynamic alterations following a single dose of neoral in healthy volunteers. Nephrol Dial Transplant 2001;16:580-4.

69. Luke RG. Mechanism of cyclosporine-induced hypertension. Am J Hypertens 1991;4:468-71.

70. van der Schaaf MR, Hené RJ, Floor M, Blankestijn PJ, Koomans HA. Hypertension after renal transplantation. Calcium channel or converting enzyme blockade? Hypertension 1995;25:77-81.

71. van den Dorpel MA, Zietse R, Ijzermans JN, Schalekamp MA, Weimar W. Effect of isradipine on cyclosporin A-related hypertension. Blood Press Suppl 1994;1:50-3.

72. Hausberg M, Kosch M, Hohage H, Suwelack B, Barenbrock M, Kisters K, et al. Antihypertensive treatment in renal transplant patients – is there a role for ACE inhibitors? Ann Transplant 2001;6:31-7.

73. Curtis JJ, Laskow DA, Jones PA, Julian BA, Gaston RS, Luke RG, et al. Captopril-induced fall in glomerular filtration rate in cyclosporine-treated hypertensive patients. J Am Soc Nephrol 1993;3:1570-4.

74. Abu-Romeh SH, el-Khatib D, Rashid A, Patel M, Osman N, Fayyad M, et al. Comparative effects of enalapril and nifedipine on renal hemodynamics in hypertensive renal allograft recipients. Clin Nephrol 1992;37:183-8.

75. Sennesael J, Lamote J, Violet I, Tasse S, Verbeeelen D. Comparison of perindopril and amlodipine in cyclosporine-treated renal allograft recipients. Hypertension 1995;26:436-44.

76. Deray G, Le Hoang P, Aupetit B, Achour A, Rottembourg J, BAumelou A. Enhancement of cyclosporine A nephrotoxicity by diclofenac. Clinical Nephrology. 1987;27:213-4.