Cyclosporine began to be used as one of the immunosuppressive agents in transplantation in the beginning of the 1980s, and in the treatment of nephrotic syndrome in the pediatric nephrology. Therapeutic area of cyclosporine is narrow and its side effects limit its usage. Preference for cyclosporine and tacrolimus as a calcineurin inhibitor is left for the choice of the department. There are still countries with preferred-cyclosporine use because of economic reasons. Cyclosporine is currently being used in the treatment of nephrotic syndrome, but due to its high relapse rates in a short-term use, and nephrotoxicity in long-term use, search for new drugs with fewer side effects keeps continuing. As long as its use is indispensable, it will be necessary to keep track of kidney function and blood level of this medication closely to protect the patients from toxicity.

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INTRODUCTION

Cyclosporine, a molecule obtained from a fungus for the first time in 1969, began to be used as one of the rejection preventive agents in transplantation in the beginning of the 1980s, and began to be used in various fields such as in the treatment of nephrotic syndrome, in the autoimmune diseases, and in veterinary medicine in the later years. In its usage during childhood, it gave its place in transplantation to drugs which have the same effect potential and have fewer side effects. While it is still in use in nephrotic syndrome, it seems as it is going to give its place to other drugs herein as well. Nevertheless, understanding the pharmacodynamics of this drug, which is still in use, requires keeping its drug interactions in mind and being on the alert in terms of its side effects. The aim of this review is to compile nephrology usage area of cyclosporine, especially in childhood, its effects, and its long-term results.

MECHANISM OF ACTION

Overview

Cyclosporine is a cyclic protein with 11 amino acids, which is obtained from fungi called Tolypocladium inflatum. Because it is a lipophilic peptide, it can easily pass through the cell membrane. Cyclosporine is in an inactive form at first. It gets combined with cyclophilin, which is a cytosolic protein, and thus it represses the production of interleukin (IL)-2 by hindering the motion of complex transcription factors within the cell, thus it hinders the enzymatic activity of calcineurin (Figure 1). Calcineurin is accepted to be the target molecule that cyclosporine/cyclophilin complexes attach. What affects the signal production that calcineurin T cells trigger is an enzyme which is in bond with calmodulin and calcium and has serine/threonine phosphatase quality. Dephosphorylation, kinase activity, phosphatase activity, and protein expression can be included among the calcineurin activities. Dephosphorylation occurs in the target molecules within the cell as a result of cyclosporine/cyclophilin bonding with calcineurin, and as a result, inhibition of the IL-2 gene and other cytokine genes occur. Thus, IL-2 production is blocked, and proliferation signals of T cells disappear.1,2

Both in experimental and human studies, it was shown that cyclosporine was the two-edged
mechanism in the abolishment of proteinuria. While the first one is an immunosuppressive effect which it shows by directly affecting the release of glomerular permeability factor, the second one is the nonimmunologic effect on the glomerular permeability selectivity.3,4

Distribution

Although distribution volume is not different from that of adults, clearance is higher in little children compared to the body weight, the half-life of the cyclosporine is shorter. For this reason, some centers choose to divide the daily dose into 3 for the young patients. Necessary dose to create the target blood level is higher than adults.

Bioavailability

Bioavailability of oral formulas shows a great variation. It is affected by the factors like age of the patient, length of intestines, and presystemic metabolism in the intestinal wall.5 They showed that when cyclosporine is taken along with meals, it is absorbed better due to the increase in the secretion of bile, and there are fewer bioavailability variants.6 Some clinical studies were carried out related to metabolising the drug. It was observed that those who have ABCB1 and NR1I2 genes had higher bioavailability.7,8 Until the 1990s, the gel capsule form of the drug (Sandimum) was available. With the microemulsion form (Neoral), it has become easier to adjust the dose for children. It was also shown that the absorption of this form was better and had a higher time-drug-concentration curve and bioavailability as well.9

Drug Level

Due to its lipophilic quality, the highest concentration is found in the tissues with the highest fat proportion in the body.10 Higher concentrations are found in the liver, kidney, and pancreas and adrenal glands than plasma, and this is in proportion to the cyclophilin level, which is a cyclosporine binder protein.11,12 As cyclophilin cannot pass through the blood-brain barrier, its levels in cerebral tissue are lower. Seventy percent of it attaches to erythrocyte in the blood, 20% of it is in blood, and 5% to 20% of it is related to lymphocytes.13 As it attaches to the blood cells, their levels in the whole blood are 1.5 to 3 times less than that in plasma.14 In the cyclosporine level measurement, several methods can be used, and the most beneficial one is to measure with monoclonal radioimmunoassay. Using time-concentration curve to determine cyclosporine exposure reflects more accurate results instead of measuring plasma level at specific times.15 However, using this method is
both expensive and time-consuming and also it is very hard to implement in routine patient practice. Cyclosporine levels can be measured from plasma or from whole blood to be able to follow toxic complications. At first, C0 (the time right before taking the drug) levels were used. However, time length to reach the high concentrations after the cyclosporine application ranges between zero and 4 hours. It reaches to its highest level in the 2nd hour. For this reason, it was attempted to foresee the drug exposure and clinic outcome by following the plasma levels in the C2 after having taken the drug.16,17

Elimination

Cyclosporine is metabolized with the cytochrome P450 3A (CYP3A) enzyme within the liver and gastrointestinal system microsomal enzyme. A minor part of it, to be disposed of by kidneys, is disposed of through biliary tract. Clearance of cyclosporine and distribution volume decreases with the increase in plasma cholesterol and haematocrit, and on the other hand, decreases with the decrease in serum creatinine.18

Drug and Food Interactions

It has many drug interactions. As it is metabolised with cytochrome P450, giving drug components that stimulate this system may lead to decrease in plasma cyclosporine levels, in contrast with this drugs which inhibit this may lead the plasma levels of cyclosporine to increase. They are rifampicin, nafcillin, phenobarbital, and carbamazepine CYP3A4 inducers, and they lead to a decrease in cyclosporine levels.19

In contrast, as some calcium channel blockers such as macrolides, azole antifungals, diltiazem, and verapamil inhibit CYP3A4, it leads to an increase in cyclosporine levels.20 Glucocorticoids affects glomerular filtration rate estimation by increasing the cyclosporine level and decreasing cysteine C levels after the transplantation, and this emerges as the early nephrotoxic effect of cyclosporine. Cyclosporine usage increases the toxicity effect of amphotericin in the simultaneous diuretic application.21,22 On the other hand, drugs such as metoclopramide which affect gastrointestinal motility cause cyclosporine levels to increase by affecting cyclosporine levels. In its use of hyperlipidemic drugs such as lovastatin, serious myolysis, myopathy was reported.23 In its use with FK 506, as cyclosporine increases its nephrotoxicity, using both of these agents together must be avoided.24 Not to give grapefruit or grapefruit juice to the patients who take cyclosporine is the most important thing in drug interactions. Grapefruit, along with the decrease in CYP3A4, by inducing the membrane transporter P-glycoprotein, affects the intestinal absorbment and tissue distribution.25 During the consumption of other drugs, cyclosporine serum levels help in the follow-up as well. Effect of the body weight on cyclosporine blood levels is also stated in some studies. Less cyclosporine dose is required for the patients with a higher body mass index.26

CLINICAL USAGE

Overview

Therapeutic area of cyclosporine is narrow. It is used both in adults and children. It first began to be used to prevent acute rejection.27 In some later years, it began to be used in the treatment of nephrotic syndrome.28 Apart from that, it is also used in autoimmune diseases such as inflammatory bowel diseases and psoriasis which do not respond to some other treatments.29

Transplantation

In 1978, cyclosporine began to be used as an alternative to azathioprine and steroid.27 Cyclosporine is used in the transplantation of solid organs such as the heart, liver, and bone marrow as well. In the induction treatment, the dose of cyclosporine was 8 mg/kg/d (165 mg/m²) for those aged under 6 years old and 4.5 mg/kg/d for those older than 6 years, during the 24 hours of infusion. Within 48 hours oral dose started as 500 mg/m²/d for an age less than 6 years and 12 mg/kg/d to 15 mg/kg/d for an age greater than 6 years, once in 12 hours. Target blood levels for the first 6 months is 100 ng/mL to 125 ng/mL, and 50 ng/mL to 100 ng/mL after 6 months. For the levels above 250 ng/mL, nephrotoxicity risk is higher. However, it was observed that some patients developed toxicity at levels as low as 100 ng/mL and some developed rejection at levels as low as 250 ng/mL.30

In the comparisons made with muromonab-CD3 in the induction regimens, no difference was found in the antibody formation.31 There is no evidence
regarding preventative effect of cyclosporine against the relapse of nephrotic syndrome after the transplantation. However, a high dose of cyclosporine (15 mg/kg/d to 35 mg/kg/d) may be effective in the repetition of the disease after the transplantation. It is used as combined with other immunosuppressives, yet it is not advised to use it together with tacrolimus, which is another calcineurin inhibitor as it increases posttransplant lymphoproliferative disease risk.

Measurement of the drug level is important to be protected from immunosuppression and probable side effects. The most suitable method found as the concentration time curve. Twelve hours of time-drug-concentration curve profile is the determiner which shows the drug absorbment and cleaning best. As using it in the practice is hard, target C2 level is found to be appropriate to be 1500 μg/L in the early period after the transplantation. Low serum levels were found to be related to rejection and high serum levels were found to be related to toxicity. 32

Due to side effects of cyclosporine, another calcineurin inhibitor, tacrolimus, began to be used and found as effective as cyclosporine in preventing acute rejection and long-term survival. 33 We have been using tacrolimus instead of cyclosporine in the transplantation induction protocol in our clinic since 2004.

Glomerulonephritis

Cyclosporine is effective in various immune-mediated glomerular diseases as well. It is used both in the steroid-responsive and steroid-resistant nephrotic syndromes. 28,34-47 It is used in minimal lesion disease, focal segmental glomerulosclerosis (FSGS), immunoglobulin A nephropathy, lupus nephritis, and membranous nephropathy. 48

Steroid-sensitive Nephrotic Syndrome

The first-line treatment of steroid-sensitive nephrotic syndrome is steroids. Cyclosporine is one of the agents used as a rescue agent of steroids like levamisole, cyclophosphamide, and mycophenolate mofetil in the steroid-responsive cases. In steroid-dependent nephrotic syndrome, cyclosporine decreased the relapse rates by 75% to 90%. This helps protect patients from long-term side effects of the steroid. Its effect was shown in many studies, and in the 2013 the Kidney Disease: Improving Global Outcomes guideline, cyclosporine use was advised for steroid-sensitive nephrotic syndrome children to be at the dose of 3 mg/kg/d to 5 mg/kg/d. 50 Cyclosporine has an antidiuretic effect, as it will increase water retention during the nephrotic syndrome attack, and it is advised to start it after nephrotic syndrome entires the remission phase. In steroid-dependent nephrotic syndrome, cyclophosphamide is used as an alternative to steroid, and long-term remission is observed. However, as this drug can cause azoospermia especially in male children and its long-term results are not clearly known, cyclosporine seems to be in the direction of becoming the first choice after steroid instead of cyclophosphamide. 34,35,50

In most studies, relapses due to short-term consumption of cyclosporine were observed after having stopped using the drug. 34,37 Hulton and coworkers 34 found that restarting the drug after having stopped the cyclosporine resulted in more relapses and steroid was also needed for remission. For this reason, it is advised to continue to use cyclosporine for at least 1 or 2 years after having started to use it. 35,47 Tejani and coworkers 28 compared patients using low-dose steroid and cyclosporine with those using high-dose steroid; the remission rate was found to be lower in the group using only steroid.

Steroid-resistance Nephrotic Syndrome

Remission rates with cyclosporine was found to be zero to 71%. While Meyrier and colleagues 43 determined the remission rate to be 23%, Ingulli and associates 42 obtained a remission above 80% by using a high dose (7 mg/kg/d). Cattran and colleagues 51 administered prednisolone and prednisolone plus cyclosporine in 49 steroid-resistant FSGS patients for 26 weeks, and the remission rate was found to be 4% and 70%, respectively. The reason for this discrepancy might be related to concurrently using steroid treatment regimen or histological differences. 38-40,42,43,47,51,52 Cyclosporine is suggested among the treatment options for the children with steroid-resistance nephrotic syndrome in the Kidney Disease: Improving Global Outcomes. 53 Also, long-term use of cyclosporine decreased the progression to end-stage renal disease. By pointing that a renal damage which was triggered before in the patients with FSGS may become worse with cyclosporine, it was highlighted that it should
not be used with the patients below glomerular filtration rate 40 mL/min/1.73 m².45

SENSITIVITY, DEPENDENCY, AND RESISTANCE

Most of the children with nephrotic syndrome are sensitive means response to cyclosporine. Unfortunately relapse rate is higher after cessation of cyclosporine; in other words, it shows dependency to the drug.54 This situation was attempted to be resolved by prolonging the treatment process by at least 12 months.40,55-57

Cyclosporine resistance is defined as stopping the treatment after receiving a response to cyclosporine or not receiving a response after restarting the drug after having cut it down.58 In the biopsies carried out at the beginning or at the later periods of the treatment, they determined that detecting FSGS or C4 or C1q is an increased risk for cyclosporine resistance as well. Shaat and colleagues41 found while all of the patients with steroid-dependent nephrotic syndrome respond to cyclosporine, the response to cyclosporine was 22% in steroid-resistant nephrotic syndrome patients and concluded that cyclosporine resistance is higher in case of steroid resistance. Mahmoud and colleagues44 determined that hypertension and kidney dysfunction side effects were higher in the group with cyclosporine resistance as well.

Some races show different responses in terms of response and resistance.59 It was shown that especially those who have a mutation in NPHS2 gene show a resistance against cyclosporine like in the steroid as well.41 Nonetheless, Caridi and colleagues60 showed that partial remission could be available for the patients who had podocin mutation.

SIDE EFFECTS

Nephrologic Side Effects

Nephrotoxicity is the most important side effect (Figure 2). The first effect of cyclosporine is vasoconstriction in the glomerular afferent arteriole. In the experimental studies, thromboxane B2, a strong vasoconstrictor was found in urine and the production of vasoconstrictor prostaglandin E2 decreased. With calcineurin inhibition, along with IL-2, another IL, transforming growth factor-β, endothelin (ET1), nitric oxide synthase, and other proteins protecting the cell from apoptosis are blocked as well.61 While this effect provides immunosuppression, mechanisms which cause renal toxicity are triggered as well. Another mechanism which is thought to be responsible for nephrotoxicity is oxidative damage that it makes by increasing the free oxygen radicals which are the result of lipid peroxidation that it creates in the cell membrane.62

The last part of the proximal tubules, which especially is concentrated in the medulla cortex, is richer than peroxisomes which include P450 oxidases that are in charge in the cyclosporine metabolism, and material accumulation within the cell occurs because of the oxidase inhibition when cyclosporine broke down into its metabolites.63 Also, direct toxic effect of cyclosporine on the renal tubules is seen especially on proximal tubules. Renal cell apoptosis and free oxygen radicals and lipid peroxidation are well-known nephrotoxicity mechanisms. The most often observed electrolyte abnormalities are hyperkalemia, hyperuricemia, and hypomagnesemia. Urinary magnesium loss is observed due to the downregulation of cyclosporine and paracellin.64 Calcium binding-D28k causes downregulation hypercalciuria and hyperkalaemia.
Cyclosporine may cause stone formation by causing calciuria.\(^{65}\)

While acute nephrotoxicity can be asymptomatic clinically, it manifests as an increase in serum creatinine and blood pressure. It emerges after a short while after the drug consumption and is reversible in a short time after the consumption of the drug is stopped.\(^{66}\)

The effect of cyclosporine on the kidneys is vasoconstriction and hyperfiltration. Due to its direct toxic effect on the renal veins, it causes a decrease in the plasma flow and glomerular filtration rate. Various observations were obtained regarding the hemodynamic changes of cyclosporine; activation of renin-angiotensin system, sympathetic nervous system, an increase in the release of potent vasoconstrictor ET1, and degenerated production of nitric oxide. As a result of vasoconstrictor and vasodilator, unbalance plays a supporting role in the nephrotoxicity, as well.\(^{67}\) Inhibition of the renin-angiotensin system with angiotensin-converting enzyme inhibitors and angiotensin-1 receptor antagonists correct these functional and structural changes and are an indicator of this situation. In the studies done on the rats, due to the increase in the renin in cyclosporine treatment, juxtaglomerular hypertrophy and hyperplasia were detected. Again in the rats, after the ET1 release that cyclosporine stimulates, an increase in the mesentery in the aorta and in the number of the ET receptors in the renal cortex was determined.\(^{68}\) Von Willebrand factor, which is an indicator of endothelial damage related to the endothelium injury that cyclosporine causes, showed that selectin and thrombin complexes increased.\(^{69}\)

Clinically, distinguishing these findings from the acute rejection is difficult. Even though toxicity does not have specific diagnostic findings, histopathology requires for distinguish this situation. Histopathological findings are occlusive vasculopathy in the afferent arterioles, nodular IgM positivity in the apical side of the arteriole in the immunofloresan staining, and necrose and smooth muscle cell damage in the electron microscopy. It is seen as hyalinosis in the optical microscope. Although patch-like isometric tubular vacuolisation is not specific, it is a predictor. Some cases may be related to serious vascular injury and glomerulosclerosis collapsed due to ischemia, or cyclosporine toxicity.\(^{70}\)

Chronic nephrotoxicity means the irreversible deformation of kidney function and it is not dose dependent. Here again, it is thought that arteriolar damage is developed because of the accumulation of the extracellular matrix molecules due to that nitric oxide synthetase, transforming growth factor-β, endothelin-1, collagen I and IV, and bcl-2 affect its mechanisms.\(^{71,72}\) The reversible histologic findings of the chronic nephrotoxicity is vacuolisation in the smooth muscle cells of the afferent arterioles. After a while, these cells with vacuole progress into necrose and leave their place to proteinosis material. Interstitial fibrosis is related to osteopontin in the tubulointerstitial area, and transforming growth factor-β expression and macrophage infiltration.\(^{73}\)

The frequency of nephrotoxicity in the 10-year follow-up protocol biopsies in transplantation is 96%.\(^{74}\) Studies were carried out to determine the toxic effects after the cyclosporine use in the children with the nephrotic syndrome and found 23% to 63% proven histologically.\(^{75-78}\) Chronic nephrotoxicity in cyclosporine use emerges within 2 years in the extrarenal transplantations and in other autoimmune treatments.\(^{79}\) Although chronic structural cyclosporine toxicity findings were observed in the protocol biopsies after the transplantation, this situation was found to be rare or cause loss of graft in the transplant nephrectomies. The decrease in cyclosporine nephropathies was detected with a decrease in the dose in the immunosuppression protocols to prevent nephrotoxicity.\(^{80,81}\) Secondly, it was attempted to switch cyclosporine with sirolimus from the protocols in the early period. By this, it was observed that controlling the blood pressure became easier without a rejection.\(^{82}\) It was determined that kidney function did not recover and patients with low glomerular filtration rate or those who had proteinuria became worse in the transitions in the late period. Flechner and colleagues\(^{83}\) regarded the switch to using less nephrotoxic agents before a serious renal damage was observed after having used cyclosporine for a short time in the protocols to be the best choice. As cyclosporine represses cytokine production, it results in serious glomerular damage with the rebound increase in the cytokine levels after having stopped the treatment.\(^{84}\)

Several studies are carried out for prevention cyclosporine-induced renal toxicity. Some of
them were with many antioxidants, vitamin E, curcumin, propionyl carnitine, N-acetylcysteine, alpha tocopherol, superoxide dismutase/catalase, L-arginine, and erythropoietin. Some publications showed that cyclosporine caused microsomal lipid peroxydation in the kidneys, lipid peroxydation-repressive effect of vitamin E decreases cyclosporine nephrotoxicity. It was shown that malondialdehyde which is a lipid peroxydation product following the cyclosporine application increased in the kidney cortex. Mansour and coworkers showed in their study that L-arginine which is an agent that does vasodilatation from nitric oxide in rat kidney, decreased the degeneration in the kidney function and histologic structure that cyclosporine caused. In our study, we showed the tubular arteriolar changes with the application of low- and high-dose erythropoietin, that it decreased apoptosis and oxidative stress yet had no effect on kidney function and chronic fibrotic changes. McCulloch and colleagues found effects of nifedipine on fibrosis in the transplantation patients, as a result of treatment for a year, they showed that interstitial volume decreased in the patients who did not use nifedipine and their glomerular filtration rate was protected better. However, none of the studies achieved enough success to find their place in daily practice.

**Hypertension**

Hypertension is reported as the most frequent side effect of cyclosporine in transplantation. Systemic renal hemodynamic changes by activation of sympathetic system and renin-angiotensin system demonstrated in many animal and human studies. Blocking the neural calcineurin epinephrine increases the catecholamine levels. Also, increasing in nitric oxide and endotheline-1 production causes vascular resistance as a result of endothelial dysfunction. Endothelin-1 receptor antagonists like bosentan and avosentan contribute to the decrease in the blood pressure by decreasing the endothelin releasement. angiotensin-converting enzyme inhibitors and angiotensin receptor blockers combinations have an important place in the reduction of both hypertension and proteinuria. Also, calcium channel blockers are useful to prevent hypertension and chronic allograft damage. This side effect is much less with another calcineurin inhibitor, tacrolimus. The frequency of hypertension in the children using cyclosporine in the nephrotic syndrome treatment is less than that observed in the transplantation (14% to 36%).

**Hemolytic Uremic Syndrome**

Hemolytic uremic syndrome can be triggered by cyclosporine after transplantation. Cyclosporine causes endothelial cell injury, but its mechanism is still not fully explained.

**Dyslipidemia and Diabetes Mellitus**

Dyslipidemia induced by cyclosporine after the transplantation is shown in some studies. In our study, we found that C0 levels with cyclosporine were more meaningful to predict dyslipidemia. Steroids have additive effects of the cyclosporine. In the regimens using cyclosporine without steroids, dyslipidemia rate was found to be much lower. Hyperlipidemia and diabetes mellitus should be avoided by a good metabolic control after transplantation. Although the effect of diabetes mellitus is not as much with tacrolimus, it should not be disregarded.

**Bone Metabolism**

Although after renal transplantation cyclosporine had an important effect on bone remodelling there is no negative effect in nephrotic syndrome. This situation was interpreted to be caused because of the bone mineral deformation before the transplantation.

**Cosmetic Side Effects**

Gingival hypertroplasia and hipertrichosis are cosmetics side effects of cyclosporine. It causes problems, especially in the adolescent patients that leads to incompliance of the treatment. When hypertrichosis and gingival hyperplasia is detected in the patient, cyclosporine should be changed with tacrolimus which has fewer side effects.

**Posttransplant Lymphoproliferative Disease**

Long-term use of the immunosuppressive drugs can cause an increase in malignancies risk. Especially, posttransplant lenhoproliferative disease related to Ebstein Barr virus is the most common of them. Using with the other calcineurin inhibitor should be avoided in the children with posttransplant lenhoproliferative disease.
development risk.  

**Neurologic Side Effects**

Tremor, convulsion, and posterior reversible encephalopathy syndrome are the most common neurologic side effects. Side effects such as dyspnea, pruritus, pancreatitis, liver failure, burning in the tips of fingers, peptic ulcer, nausea, and depression are also reported.

**Teratogenicity**

Kidney damage and delay in the hematopoietic organ development were shown in the infant rats as a result of giving cyclosporine to pregnant rats. Permanent loss of nephrons due to the exposure to cyclosporine in antenatal period was found to be glomerular, tubular, and intrarenal hemodynamic dysregulation, renal enlargement, and endothelin-dependent systemic hypertension. In our study done on the rats, we determined that there was a functional change in the kidneys and their uses as a result of cyclosporine exposure through the milk of their mothers who received cyclosporine treatment, and this may cause permanent damage. Although nephrotoxicity and other side effects were not shown in the infants breastfed by their mothers who received cyclosporine treatment in some studies, American Pediatric Academy stated that cyclosporine is transmitted into breast milk and its long-term effects are not known. Cyclosporine exposure in the infancy period with lactation may cause permanent damage.  

**CONCLUSIONS**

Although cyclosporine is a frequently used agent in organ transplantation and in autoimmune diseases, its side effects limit its usage. Preference for cyclosporine and tacrolimus as a calcineurin inhibitor is left for the choice of the department. There are still countries with preferred-cyclosporine use because of economic reasons. Cyclosporine is currently using in the treatment of nephrotic syndrome, but due to its high relapse rates in a short-term use, and nephrotoxicity in long-term use, searches for new drugs with fewer side effects keeps continuing. As long as its use is indispensable, it will be necessary to keep track of kidney function and drug level of this drug closely to protect patients from toxicity.

**CONFLICT OF INTEREST**

None to be declared.

**REFERENCES**


70. Mengel M, Mihatsch M, Halloran PF. Histological characteristics of calcineurin inhibitor toxicity—there is no such thing as specificity Am J Transplant. 2011;11:2549-50.


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