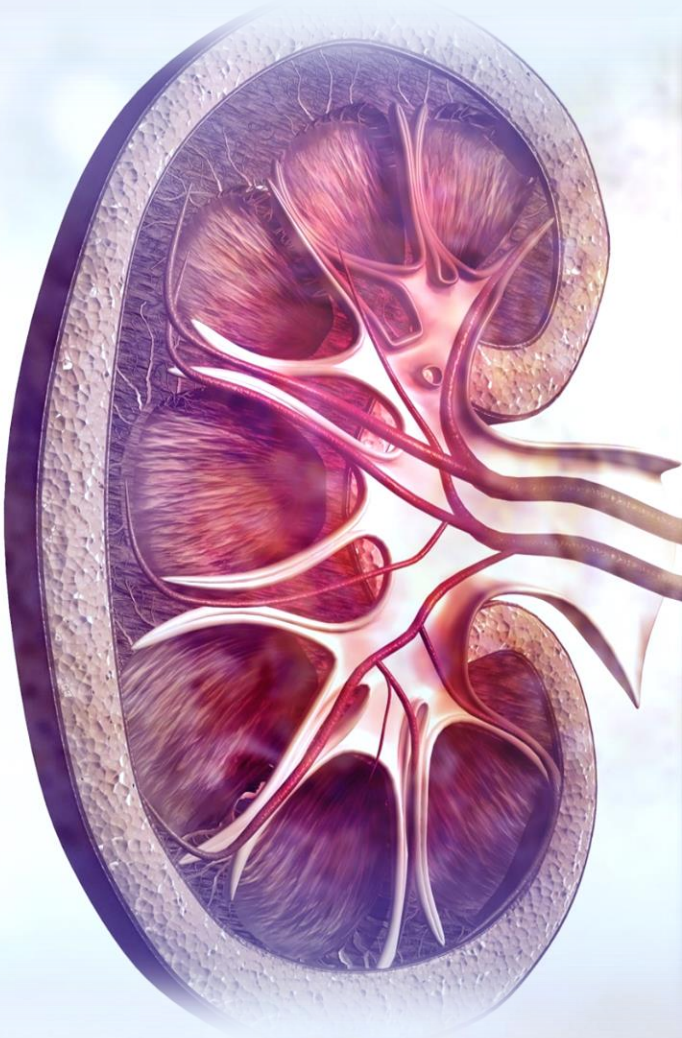
Role of Everolimus as Immunosuppressant in Kidney Transplant



Content

Background and Objective of the Survey

Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, plays a crucial role as an immunosuppressant in kidney transplantation. Its mechanism of action involves inhibiting the proliferation of T and B lymphocytes, as well as the production of pro-inflammatory cytokines, thereby suppressing the immune response and preventing allograft rejection.

In kidney transplantation, everolimus is commonly used in combination with other immunosuppressive agents, such as calcineurin inhibitors (e.g., tacrolimus) and corticosteroids, to form a multidrug regimen aimed at minimizing rejection while reducing the risk of drug-related toxicity.

One of the key advantages of everolimus is its ability to offer nephroprotective effects, which is particularly beneficial in kidney transplant recipients. By reducing the nephrotoxic effects associated with calcineurin inhibitors, such as tacrolimus or cyclosporine, everolimus-based regimens help preserve renal function over the long term, potentially delaying the onset of chronic allograft nephropathy and improving graft survival rates.

Furthermore, everolimus offers flexibility in immunosuppressive therapy, allowing for individualized treatment regimens tailored to the specific needs and characteristics of kidney transplant recipients. Its once-daily oral dosing regimen and lack of significant interactions with other medications make it a convenient option for long-term maintenance therapy. Additionally, everolimus has been shown to have anti-proliferative and anti-angiogenic effects, which may be beneficial in preventing the development of transplant-associated malignancies, such as post-transplant lymphoproliferative disorders and certain skin cancers.

The objective of the survey is:

To evaluate the role of Everolimus as immunosuppressant in kidney transplant

Methodology of the Survey

A survey was conducted to evaluate the role of Everolimus as immunosuppressant in kidney transplant. A total of 150 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Everolimus in renal transplantation – efficacy
- Everolimus with full- or reduced-exposure CNIs
- Everolimus with reduced-exposure CsA
- CNI elimination
- Additional benefits and clinical considerations
- Pharmacokinetics: safety considerations
- Maintenance renal-transplant recipients
- Graft function
- Rejection
- Malignancies
- ABO- incompatible kidney transplantation

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Although advances in immunosuppressive therapy have improved the control of acute allograft rejection, long-term renal-transplantation outcomes have not significantly improved over the last decade. In renal-transplant patients, chronic allograft nephropathy (CAN; specifically interstitial fibrosis and tubular atrophy) is the main cause of graft failure. A number of factors have been implicated in the development of CAN, including donor age, acute rejection, vascular remodeling and calcineurin inhibitor (CNI)-induced nephrotoxicity. The CNIs cyclosporine (CsA) and tacrolimus have been the cornerstone of immunosuppressive therapy for many years, due to their efficacy in preventing acute rejection. However, CNIs have nephrotoxic side effects that can directly contribute to renal dysfunction and compromise long-term outcomes. Consequently, there has been strong interest in developing immunosuppressive regimens that maintain efficacy for the prevention of acute rejection, whilst minimizing risk factors for chronic allograft dysfunction and late graft loss.

Everolimus is a proliferation signal inhibitor (PSI) with potent immunosuppressant effects. In the setting of renal transplantation, everolimus has displayed comparable efficacy to mycophenolate mofetil (MMF) when used with corticosteroids and standard-dose CsA for prevention of acute rejection., Moreover, Phase III studies in *de novo* renal-transplant patients have shown that everolimus allows for the early halving of CNI treatment whilst maintaining renal function, compared with full-dose CsA studies.

In addition to its immunosuppressive efficacy, everolimus possesses other desirable attributes. For example, the antiproliferative mechanism of action of everolimus may help to prevent the main causes of long-term graft loss by inhibiting the underlying processes that contribute to chronic allograft dysfunction.

Everolimus in renal transplantation – efficacy[1]

Mechanism of action

Everolimus belongs to a class of immunosuppressive agents, the PSIs (also known as mammalian target of rapamycin [mTOR] inhibitors), that inhibit the progression of T cells from G1 into the S phase of the cell cycle. By interfering with DNA replication at an early stage, PSIs exert an antiproliferative effect. The immunosuppressive action of everolimus has been demonstrated in preclinical studies in animal models of renal transplantation. Importantly, everolimus has a mechanism of action that is distinct from CNIs. Whereas CNIs prevent T-cell proliferation by blocking transcriptional activation of early T-cell-specific genes, inhibiting the production of T-cell growth factors (eg, IL-2), everolimus acts on a later stage of the T-cell response, by blocking the transduction of signals generated by such growth factors. A synergistic immunosuppressive effect has been demonstrated between everolimus and CsA in preclinical studies, which could be due to their complementary modes of action. These studies showed that, when used concomitantly, the equivalent efficacy of either agent alone could be achieved using 10% to 20% of the everolimus dose and 20% to 40% of the CsA dose, providing a rationale for investigating whether everolimus could allow CsA dose reduction in patients receiving organ transplants.

Since everolimus inhibits growth factor-driven cell proliferation in general, its antiproliferative effects are not limited to the immune system. PSIs have been shown to inhibit smooth muscle cell proliferation and prevent vascular remodeling., Animal studies have demonstrated that the antiproliferative effects of everolimus reduce long-term graft-specific histological changes, delaying the progression of CAN, even when already at an advanced stage. Therefore, the mechanism of action of everolimus appears to target the key cause of CAN.

Clinical efficacy studies[2]

Everolimus versus MMF with full-dose CsA

Two similarly designed Phase III studies (B201 and B251) compared the efficacy of everolimus *versus* MMF in *de novo* renal-transplant recipients. Both were 36-month, parallel-group studies in which patients were randomized to fixed everolimus doses (1.5 or 3 mg/day) or MMF (2 g/day) as part of a triple immunosuppressive therapy regimen with full-dose CsA and corticosteroids., Treatment was blinded for the first year, followed by 2 years of open-label

therapy. The primary endpoint was efficacy failure, a composite endpoint defined as the incidence of biopsy-proven acute refection (BPAR), graft loss, death, or loss to follow-up. In both studies, incidences of composite efficacy failure were similar between the MMF and everolimus 1.5 or 3.0 mg/day cohorts, with therapeutic equivalence maintained over 36 months., In study B201, the incidence of graft loss at 36 months was higher in the everolimus 3 mg/day group (16.7%) compared with the everolimus 1.5 mg/day group (7.2%, p = 0.0048) and the MMF group (10.7%, p = 0.1067). In Study B251, the rate of antibody-treated acute rejection was significantly lower with everolimus 1.5 mg than with MMF at 12 months (7.8% vs 16.3%; p = 0.01) and at 36 months (9.8% vs 18.4%; p = 0.014).

Table 1. Summary of clinical studies of everolimus in renal-transplant patients

Study	**Design**	**Number of patients**	**Treatments**	**Summary of main findings**
B201	36-month, Phase III, multicenter, randomized, parallel-group, double-blind (12 months), then open-label (24 months)	588 *de novo* Renal-amendment population: 236 patients	Everolimus (1.5 or 3 mg/day) vs MMF (2 g/day), in addition to CsA and steroids	• At 36 months, efficacy failure rates were similar for all groups (p = NS) • At 36 months, patient survival, graft survival and rejection rates were similar for everolimus 1.5 mg/day vs MMF; everolimus 3 mg/day demonstrated inferior graft survival (p = 0.0048 for

				everolimus 1.5 vs 3 mg/day)
B251	36-month, Phase III, multicenter, randomized, parallel-group, double-blind for ≥12 months, then open-label	583 *de novo*	Everolimus (1.5 or 3 mg/day) vs MMF (2 g/day), in addition to CsA and steroids	• At 36 months, efficacy failure rates were similar for all groups (p = NS) • At 36 months, antibody-treated acute rejection was significantly lower for everolimus 1.5 mg/day vs MMF (p = 0.014)
B156	36-month, Phase II, multicenter, randomized, open-label, parallel-group	111 *de novo*	Everolimus 3 mg/day in combination with basiliximab, steroids and either full-dose or reduced-dose CsA	• Efficacy failure was significantly lower in the reduced-dose vs full-dose CsA group at 6, 12 and 36 months (p < 0.05 for all) • Mean creatinine clearance was higher in the reduced-dose vs full-dose CsA group at 6 months (p = 0.009), 12 months (p = 0.007)

				and 36 months (p = 0.436)
US09	6-month, exploratory, multicenter, randomized, open-label	92 *de novo*	Everolimus in combination with steroids, basiliximab and either low- or standard-exposure tacrolimus	• Efficacy was similar between groups, with BPAR occurring in 14% of patients in each group • Renal function (mean serum creatinine level and estimated GFR) was similar between groups (p = NS)
A2306	12-month, Phase III, randomized, open-label, parallel-group	237 *de novo*	Everolimus 1.5 vs 3 mg/day, in combination with steroids and low-exposure CsA (C2 monitoring)	• After 6 months, median serum creatinine levels were 133 and 132 µmol/L in the everolimus 1.5 and 3 mg/day groups, respectively • After 6 months, there were no significant differences between groups for any efficacy parameter

A2307	12-month, Phase III, randomized, open-label, parallel-group	256 *de novo*	Everolimus 1.5 vs 3 mg/day, in combination with steroids, low-exposure CsA (C2 monitoring) and basiliximab induction therapy (Days 0 and 4)	• After 6 months, median serum creatinine levels were 130 µmol/L in both everolimus groups • After 6 months, there were no significant differences between groups for any efficacy parameter
CENTRAL	6-month, single-center, pilot	20 recipients of a first or second single renal transplant from a deceased or living donor	Patients were converted from CsA to everolimus 7 weeks post-transplant; all received basiliximab induction therapy with maintenance EC-MPS and steroids	• Calculated GFR improved significantly following conversion from CsA to everolimus ($p = 0.001$) • BPAR occurred in 3/20 (15.0%) patients during the 7 weeks post-conversion to everolimus, but all episodes were mild and reversible, with subsequent recovery of renal function

				• Abrupt conversion from CsA to everolimus was well tolerated

Abbreviations: BPAR, biopsy-proven acute refection; CsA, cyclosporine; CNI, calcineurin inhibitor; EC-MPS, enteric-coated mycophenolate sodium; GFR, glomerular filtration rate; IL-2, interleukin-2; MMF, mycophenolate mofetil; NS, not significant.

Subsequent analysis of data from these studies demonstrated that patients with everolimus trough blood levels ≥3 ng/mL had a significantly reduced incidence of BPAR after 6 months of treatment, compared with those with trough blood levels <3 ng/mL ($p < 0.0001$). In addition, patients receiving everolimus had higher mean serum creatinine levels than those receiving MMF. After 12 months, protocol amendments were introduced, permitting lower CsA trough levels (50 to 75 ng/mL) in the everolimus groups, provided that everolimus blood trough levels were maintained above 3 ng/mL. After the protocol amendments, mean serum creatinine levels decreased slightly, or remained stable, with no increase in BPAR. The finding that everolimus trough blood levels ≥3 ng/mL were necessary to gain the most clinical benefit highlighted that therapeutic drug monitoring might be useful in optimizing dosing for patients receiving everolimus and CsA.

Everolimus with full- or reduced-exposure CNIs[1]

CNI therapy is associated with nephrotoxicity, which can complicate otherwise successful therapy. Therefore, exploring drug combinations that allow for a reduction in CNI exposure might help to improve long-term outcomes.

Study B156 was a Phase II, 3-year, multicenter, randomized, open-label, parallel-group, CsA dose-finding study of everolimus in *de novo* renal-transplant recipients. After transplantation, patients were randomized to either full-dose (trough blood level 125 to 250 ng/mL from 3 to 36 months) or reduced-dose (trough blood level 50 to 100 ng/mL from 3 to 36 months) CsA, in addition to identical dose regimens of everolimus (3 mg/day), basiliximab (20 mg prior to transplantation and on Day 4) and corticosteroids. Following a protocol amendment, CsA dosing was adjusted to achieve trough blood levels of 50 to 75 ng/mL and everolimus dosing

was adjusted to ensure trough blood levels ≥3 ng/mL in all patients continuing treatment from 12 months onwards. The incidence of efficacy failure (BPAR, graft loss, death, or loss to follow-up) was significantly lower in the reduced-dose CsA group compared with the full-dose CsA group at 6 months ($p = 0.046$), 12 months ($p = 0.012$) and 36 months ($p = 0.032$), mainly as a result of the lower incidence of BPAR in the reduced-dose CsA group, compared with the full-dose group (3.4% vs 15.1% at 6 months; 6.9% vs 17.0% at 12 months; 12.1% vs 18.9% at 36 months). In addition, mean serum creatinine levels were numerically lower in patients receiving reduced-dose CsA compared with full-dose CsA, and mean creatinine clearance rates were significantly higher in reduced-dose *versus* full-dose patients at 6 months ($p = 0.009$) and 12 months ($p = 0.007$). Following transition to the amended protocol after 12 months, mean serum creatinine levels fell in the full-dose CsA group, whilst mean serum creatinine and creatinine clearance values remained stable in the reduced-dose CsA group, reflecting the smaller reduction in CsA dose in these patients. Study B156 therefore demonstrated that using everolimus with reduced-dose CsA resulted in preserved renal function without loss of efficacy, when compared with standard-dose CsA regimens.

Similar results were found with low-exposure tacrolimus and everolimus in Study US09, which was a prospective, 6-month, multicenter, open-label, exploratory study. *De novo* renal-transplant recipients (n = 92) were randomized to everolimus, steroids and basiliximab with low or standard tacrolimus exposure. Lower tacrolimus exposure was not associated with loss of efficacy compared with a standard tacrolimus regimen, with BPAR occurring in 14% of patients in both the low and standard tacrolimus exposure groups at 6 months. Moreover, there were no significant differences in renal function between groups at 6 months: mean serum creatinine levels were 112 ± 31 and 127 ± 50 μmol/L, and mean estimated glomerular filtration rates (GFRs) were 75.3 ± 16.6 and 72.5 ± 15.2 mL/min, in the low and standard tacrolimus exposure groups, respectively. Overall, the study found that treatment with everolimus, in combination with low-exposure tacrolimus, steroids and basiliximab, was effective and well tolerated, resulting in good efficacy with excellent renal function at 6 months.

Given that clinical data are lacking concerning therapeutic action and systemic exposure of a combined regimen of tacrolimus and everolimus in renal transplantation, EVEROTAC, an investigator-driven, prospective, open-label, randomized Phase II pharmacokinetic (PK) study was undertaken in five Spanish centers randomly comparing two fixed everolimus dosages (0.75 mg bid, Group A, or 1.5 mg bid, Group B) in combination with tacrolimus (Pascual unpublished data). Antibody induction was not permitted and all patients received steroid

therapy. Complete 12-hour PK curves of both drugs (high performance liquid chromatography) were performed at Days 4, 14 and 42 post-transplant. After Day 42, everolimus trough levels were adjusted to 3 to 8 ng/mL and tacrolimus to 5 to 8 ng/mL. Higher tacrolimus trough blood levels were observed with everolimus dose of 0.75 mg bid. Accordingly, the exposure to tacrolimus was lower in the group receiving 3 mg/day everolimus despite this combination requiring higher tacrolimus doses to maintain target concentrations. Everolimus minimum concentration (C_{min}), maximum concentration (C_{max}) and area under the curve (AUC) were very low with the initial dose of 0.75 mg bid when combined with tacrolimus and everolimus 1.5 mg bid seems to be the minimal initial advisable dose for Phase III trials. Higher doses would probably be needed for tacrolimus minimization strategies, as 3 mg/day appears insufficient to achieve >3 ng/mL during the first 2 weeks. Acute rejection incidence was 17%, good graft function was consistently achieved, wound healing was uneventful in all patients and lymphocele was diagnosed in only two cases (6%) (Pascual, unpublished data).

Everolimus with reduced-exposure CsA[1]

A2306 and A2307 were similarly designed Phase III, 1-year, parallel-group studies in which *de novo* renal-transplant patients were randomized to everolimus at an initial dose of 1.5 or 3 mg/day (with subsequent dosing adjusted to maintain trough levels of ≥3 ng/mL for both groups), in combination with reduced-exposure CsA and steroids; patients in A2307 also received induction therapy with basiliximab on the day of transplantation and after 4 days. In Study A2306, CsA C2 (the 2-hour post-dose blood CsA concentration) target ranges were 1000 to 1400 ng/mL for Weeks 0 to 4, 700 to 900 ng/mL for Weeks 5 to 8, 550 to 650 ng/mL for Weeks 9 to 12 and 350 to 450 ng/mL thereafter, but in Study A2307, the ranges were lower, owing to the use of basiliximab induction therapy: 500 to 700 ng/mL for Weeks 0 to 8 and 350 to 450 ng/mL thereafter. The primary efficacy endpoint in both studies was renal function at 12 months. Secondary endpoints included the incidence of efficacy failure and its individual components at 12 months. Serum creatinine levels were stable from Month 2 or 3 onwards. When data from Study A2306 were compared with data from the B251 and B201 studies, concentration-controlled everolimus with reduced-exposure CsA was shown to result in an improvement in serum creatinine, creatinine clearance and GFR, compared with everolimus plus full-exposure CsA., There were no significant differences between the everolimus 1.5 and 3 mg/day groups in either study for any efficacy parameter, and the incidences of efficacy

failure and BPAR were comparable to those observed in the B251 and B201 studies. However, BPAR occurred more frequently with everolimus 1.5 mg/day in Study A2306 (25.0%) than in Study A2307 (13.7%), suggesting that anti-IL-2 receptor induction therapy is probably beneficial in reducing the risk of early BPAR when used with a lower dose of everolimus. Importantly, a comparison of data from Studies B201 (full-exposure CsA) and A2306 (reduced-exposure CsA) demonstrated that CsA blood levels can be reduced by at least 57% at 12 months when used in combination with everolimus, without adversely affecting either efficacy or safety. Consistent with data from studies B201 and B251, in which full-dose CsA was used, a *post hoc* analysis of data from Study A2306 demonstrated that optimal efficacy and safety are achieved in patients receiving reduced-exposure CsA if everolimus trough blood levels are between 3 and 8 ng/mL. Ongoing studies are continuing to investigate the use of therapeutic drug monitoring to optimize everolimus levels in combination with reduced-exposure CsA.–

CNI elimination[1]

The use of CNIs during the initial post-transplant period to prevent acute rejection and the subsequent elimination of CNIs from the treatment regimen may provide a means of preventing long-term nephrotoxicity.

The CENTRAL (CErtican Nordic Trial in RenAL transplantation) study evaluated whether early conversion to everolimus from CsA might improve long-term renal function and slow down the progression of CAN. In this single-center pilot study, 20 renal-transplant patients without prior rejection were converted from CsA to everolimus at Week 7 post-transplantation. All patients received basiliximab induction therapy with maintenance enteric-coated mycophenolate sodium (EC-MPS) and corticosteroids. Patients were monitored for 7 weeks, with a follow-up visit after 6 months. After conversion to everolimus and CsA elimination, calculated GFR improved significantly, from 51 ± 11 mL/min at the time of conversion to 58 ± 12 mL/min at Week 7 post-conversion and 57 ± 17 mL/min at the 6-month follow-up visit ($p = 0.001$). BPAR occurred in 3/20 (15.0%) patients during the 7 weeks post-conversion, but all episodes were mild and reversible, with subsequent recovery of renal function. In this pilot study, abrupt conversion from CsA to everolimus at Week 7 post-transplant was well tolerated. Consequently the trial has been extended and is currently ongoing with planned enrollment of 300 patients and a follow-up of 3 years.

Additional benefits and clinical considerations[1]

Antiproliferative effects

As described earlier, the antiproliferative effects of everolimus are not limited to the immune system. PSIs have been shown to inhibit smooth muscle cell proliferation and prevent vascular remodeling. This attribute may represent an additional benefit of everolimus as these proliferative processes are implicated in the development of CAN in renal-transplant recipients and cardiac allograft vasculopathy in cardiac-transplant recipients, which are key causes of allograft dysfunction, Furthermore, animal studies have demonstrated that the antiproliferative effects of everolimus reduce long-term graft-specific histological changes, delaying the progression of CAN, even when already at an advanced stage. Studies of sirolimus and everolimus drug-eluting stents further support the ability of this class of drugs to inhibit pathological vascular remodeling., Taken together, these data suggest that the mechanism of action of everolimus appears to target the key cause of CAN.

Reduced CMV infection

A number of other factors aside from vascular remodelling have also been implicated in the development of CAN, including acute rejection episodes, CNI-induced nephrotoxicity, and complications of immunodeficiency such as opportunistic CMV infection. CMV is a leading cause of infectious complications in patients who have undergone solid organ transplantation. CMV infection is associated with allograft rejection, decreased graft and patient survival, and predisposition to malignancies. In the B201 study, the incidence of viral infection, particularly CMV infection, was significantly higher after treatment with MMF compared with everolimus. Similarly, earlier studies have suggested a reduced CMV infection rate with sirolimus.

Anti-neoplastic effects

PSIs have been associated with anti-neoplastic effects as a result of their inhibition of cellular signaling pathways involved in critical functions such as cell division, T-cell activation, invasion and growth factor production. A lower incidence of malignancies has been observed in patients receiving PSIs in clinical trials, compared with those receiving CNI-based

immunosuppression. In renal carcinoma, everolimus has been shown to significantly prolong progression-free survival after failure of the approved therapies sunitinib or sorafenib in patients with advanced renal cell carcinoma and is currently being investigated in multiple tumor types.

Adverse events

Renal-transplant recipients frequently experience adverse events as a result of surgery, immunosuppressant side effects and over-immunosuppression. The adverse events most frequently associated with everolimus treatment are similar to those associated with other immunosuppressive therapies, but PSIs, as a class, are associated with a number of specific adverse events.

Proteinuria

Many studies have confirmed that patients with CAN and, to a certain extent, patients without pre-existing CAN, are at risk of high-range urinary protein excretion after conversion to sirolimus., Moreover, proteinuria may occur in patients who receive *de novo* sirolimus. Less data are available about everolimus, but in the A2306 and A2307 studies, conducted in *de novo* renal-transplant recipients, proteinuria (determined by a spot urine protein/creatinine ratio) was detected in <5% of patients. The onset of abundant urinary protein excretion is of importance because proteinuria is a marker for the risk of progressive decline in renal function and is an important predictor of renal dysfunction following conversion from a CNI- to a PSI-based regimen. However, the mechanisms of PSI-induced proteinuria continues to be debated.

Patients with pre-existing proteinuria at levels >800 mg/day should not undergo CNI elimination with conversion to a PSI. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be used for the management of both hypertension and proteinuria in patients receiving everolimus., If massive proteinuria occurs after conversion, (re)introduction of CNI may partially reverse urinary protein excretion and seems a reasonable option.

Dyslipidemia

Dyslipidemia is common in solid organ transplant recipients. PSIs have been linked to hyperlipidemia, with increased serum cholesterol and triglyceride levels occurring in 30% to 50% of patients.,

In renal-transplant recipients, sirolimus induces dose-dependent hyperlipidemia, including hypertriglyceridemia, increased low-density lipoprotein (LDL)-cholesterol and increased apolipoprotein B-100 and apolipoprotein C-III circulating levels. A similar increase in serum cholesterol and triglyceride levels has also been reported in renal transplant recipients receiving everolimus. However, when compared with MMF in *de novo* cardiac transplantation, everolimus did not induce clinically meaningful changes in triglyceride, LDL-cholesterol, or high-density lipoprotein-cholesterol levels. Dyslipidemia should be managed in accordance with guidelines, using lifestyle changes and drug therapy (eg, statins, fibrates). A crossover study conducted in healthy individuals found that single-dose administrations of everolimus with either atorvastatin or pravastatin did not influence the pharmacokinetics of everolimus or the statins to a clinically relevant extent.

Hypercholesterolemia and hypertriglyceridemia are major risk factors for atherosclerosis and associated cardiovascular disease. Recent pre-clinical studies with sirolimus have demonstrated protection from atheroma progression in hyperlipidemic apolipoprotein E-deficient mice.– As this may be a class effect of PSIs, studies are required to investigate if everolimus has any beneficial effects on the development on atherosclerosis.

Wound healing

Due to the antiproliferative action of PSIs, concerns have been raised over possible effects on tissue-regeneration processes. For example, the antiproliferative action of everolimus can reduce the healing of lymphatic channels that are divided during transplant surgery, which may lead to lymphatic leakage and the formation of a lymphocele. The potential impact on wound healing is most relevant in the immediate post-transplant period. Increased incidence of wound-healing complications associated with sirolimus treatment has been observed in renal transplantation. However, data pooled from the B201, B251, A2306 and A2307 everolimus studies showed that the overall incidence and severity of wound-healing-associated

complications following renal transplantation were comparable for MMF- and everolimus-based immunosuppressive regimens.

Edema

Limb edema and bilateral eyelid edema have been observed in transplant recipients receiving sirolimus and everolimus.,, Although edema appears to be a class effect, in a study of 56 cardiac-transplant patients undergoing CNI reduction or elimination, fewer patients experienced edema with everolimus (14.3%) than with sirolimus (64.3%; p = 0.001). When edema does occur with everolimus treatment, dose reduction may be required, but it is generally still possible to maintain everolimus trough blood levels within the optimal therapeutic window (3 to 8 ng/mL).

Pharmacokinetics: safety considerations[1]

Although everolimus and sirolimus are PSIs with similar chemical structures (everolimus is a derivative of rapamycin bearing a hydroxyethyl chain at position 40), there are pharmacokinetic and pharmacodynamic differences between the molecules. For example, the half-life of everolimus (28 hours) is shorter than that of sirolimus (62 hours). Consequently steady-state is achieved more quickly with everolimus (4 days) than with sirolimus (6 days), due to differences in their treatment regimens. These differences may explain certain variations in the safety profiles of the two agents. For example, sirolimus has been associated with the development of pneumonitis following renal transplantation,– which may be a cause of pulmonary fibrosis in later stages of the disease. By contrast, no cases of pneumonitis have been reported in renal-transplant patients receiving everolimus with low-dose CsA. Indeed, there have been case reports of the successful resolution of sirolimus-associated pneumonitis following switching from sirolimus to everolimus in renal-transplant patients and recipients of other solid-organ transplants.

De novo renal transplantation[1]

The open-label Mycophenolate sodium vs Everolimus or Cyclosporine with Allograft Nephropathy as Outcome (MECANO) study is investigating an initial 6-month regimen of

basiliximab, CsA, EC-MPS and prednisolone, followed by randomization to 18 months of treatment with either CsA plus prednisolone, EC-MPS plus prednisolone, or everolimus plus prednisolone. The aim of the study is to achieve optimal immune suppression with maximal reduction of side effects, especially of vascular injury. The primary outcome is the degree of inflammation, fibrosis and arteriolar hyalinosis in renal biopsies taken 6 and 24 months post-transplantation.

Immediate (de novo) versus delayed everolimus administration[1]

Delaying the administration of everolimus in *de novo* renal-transplant patients allows a shift of the anti-proliferative effect at the early post-transplantation period. CALLISTO is a multicenter, open-label, 12-month study, being conducted in patients who are deceased-donor renal-transplant recipients at risk of delayed graft function (DGF). Patients are randomized to receive immediate everolimus (within 48 hours post-transplantation) or delayed everolimus after 4 weeks of EC-MPS treatment. All patients received anti-IL-2 receptor induction therapy and steroids. The primary endpoint is a composite of BPAR, graft loss, death, DGF, wound-healing events, or loss to follow-up.

CNI reduction or elimination[1]

The use of therapeutic drug monitoring to optimize everolimus levels in combination with reduced-exposure CsA is being investigated further in the EVEREST (the upper target EVErolimus RandomisEd STudy) AIT02 study. This is a 6-month, multicenter, randomized, open-label study that is comparing two immunosuppressive regimens in *de novo* renal-transplant recipients: (a) higher everolimus target trough levels (C0 8 to 12 ng/mL) with very low-dose CsA (C2 600 ng/mL, tapered to 300 ng/mL at Month 3) and (b) standard everolimus target trough levels (C0 3 to 8 ng/mL) with low-dose CsA (C2 600 ng/mL, tapered to 500 ng/mL at Month 3). The primary objectives are to assess if the optimized new regimen with higher everolimus target trough levels and very low-dose CsA allows improvement in 6-month creatinine clearance, in comparison with the standard everolimus regimen with low-dose CsA and to assess if the optimized new regimen is equally effective in preventing acute rejection, in comparison with the standard regimen.

A2309 is a Phase III, 24-month, multicenter, randomized, open-label, non-inferiority study that will assess two doses of everolimus in combination with reduced-exposure CsA, compared with everolimus/EC-MPS administered with standard-exposure CsA. A2309 has enrolled 833 *de novo* renal-transplant patients at 83 centers worldwide. The primary objective of the study is to demonstrate that at least one of the everolimus treatment regimens is not inferior to the EC-MPS treatment regimen within 12 months of the initial dose of study medication with respect to primary efficacy failure, namely, the composite efficacy endpoint of treated BPAR episodes, graft loss, death or loss to follow-up.

The ERIC study is a Spanish multicenter, randomized, open-label trial, to assess the effect of CNI withdrawal and early (at 3 months) introduction of everolimus on renal allograft function. The primary end-point will be calculated GFR at 2 years, and the first functional and histological results will be available in 2010.

The ZEUS A2418 study has been conducted in *de novo* renal-transplant patients in order to assess whether an EC-MPS plus everolimus regimen after CNI withdrawal was as safe and well-tolerated as the CsA plus EC-MPS regimen, and to determine whether this regimen resulted in improved renal function After induction therapy with basiliximab, all patients were treated with CsA, EC-MPS and corticosteroids for the first 4.5 months post-transplantation. Subsequently, patients were randomized 1:1 to either continue the current regimen of CsA and EC-MPS or to convert from CsA to everolimus. The primary objective of this trial was to show superiority of a CNI-free regimen with respect to the renal function at Month 12 post transplant assessed by GFR (Nankivell method) compared with the standard CNI-based regimen. The results have recently been submitted for publication.

Several other studies are investigating the use of everolimus treatment as a means of reducing or eliminating CNI therapy in *de novo* renal-transplant patients.

Maintenance renal-transplant recipients[1]

The Assessment of everolimuS in addition to Calcineurin inhibitor reduction in the maintEnance of Renal TrAnsplant RecipIeNts (ASCERTAIN; A2413) study is a pivotal Phase IV trial that will assess the feasibility of CNI reduction/elimination in maintenance renal-transplant patients suffering from renal impairment, and its impact on renal function and cardiovascular risk. Patients are randomized to one of three parallel treatment groups:

continuation of the current immunosuppressive regimen without everolimus; initiation of everolimus with discontinuation of CNI; or initiation of everolimus with reduction of CNI blood levels by 70% to 90%. The study is designed to evaluate whether the initiation of everolimus, together with the reduction or discontinuation of CNIs, will improve graft function and reduce the progression of CAN in maintenance renal-transplant recipients. The development of atherosclerosis in the native arteries of the patients will also be explored.

It is noteworthy that the effect of conversion from sirolimus to everolimus has been assessed in a 6-month, pilot study. Eleven maintenance renal-transplant patients receiving sirolimus, mycophenolic acid and corticosteroids without CNI therapy were converted to everolimus 8 mg/day (8 to 15 ng/mL). Mean GFR and mean renal-phosphate threshold remained stable throughout the study and no patient died, lost their graft or experienced BPAR after conversion.

Graft function[2]

Only two major clinical trials are available for the introduction of EVL in kidney transplant recipients at a late posttransplant stage, namely the ASCERTAIN and APOLLO trials. In the open-label multicenter ASCERTAIN study, kidney transplant recipients receiving CNI were randomized to EVL with CNI elimination (n = 127), CNI minimization (n = 144) and continuation of CNI unchanged (controls, n = 123) at a mean of 5.4 years after transplantation. The eGFR at 24 mo was not significantly different among the three groups. However, recipients with baseline creatinine clearance higher than 50 mL/min had a greater increase in measured GFR after CNI elimination.

In the open-label multicenter APOLLO study, kidney transplant recipients were randomized to EVL with CNI elimination (n = 46) or for remaining on standard CNI-based immunosuppression (controls; n = 47) at a mean of 7 years after transplantation. Within the on-treatment population, adjusted eGFR was significantly higher in the EVL continuation group than in the CNI continuation group at 12 mo after conversion. In addition, the 5-year follow-up results showed that eGFR in the EVL continuation group was significantly higher, by 11 mL/min·1.73 m^2 (P = 0.031), in recipients who remained on their randomized study regimen until 60 mo.

Other studies have shown that favorable graft function was sustained by EVL late-induction with CNI elimination or reduction. Our previous study demonstrated that eGFR was

significantly improved in stable kidney transplant recipients already having favorable renal function, after remaining on EVL treatment for 12 mo after conversion. As a histological assessment, Chow et al demonstrated that EVL rescue therapy and CNI inhibitor minimization strategy slowed down the disease progression by reducing the tubular atrophy and interstitial fibrosis score in renal transplant recipients with biopsy-confirmed chronic allograft nephropathy. Miura et al reported that Tac reduction with EVL addition histologically improved CNI arteriolopathy in 5 out of 9 selected recipients, whose alternate quantitative scoring for hyaline arteriolar thickening (aah scores) was under 3.

Rejection[2]

There was no significant difference in the number of BPAR episodes between the intervention group and the control group in both the ASCERTAIN and APOLLO studies. It was reported that EVL-based immunosuppression in early conversion from CNI was associated with an increased risk of developing donor-specific HLA antibodies (DSA) and antibody-mediated rejection. In contrast, late conversion to CNI-free therapy with mTORi did not appear to affect the risk of *de novo* DSA, but there is concern about the development of DSA and antibody-mediated rejection because CNI level variability is a strong risk factor for *de novo* DSA development and death-censored graft loss.

Adverse events[2]

Generally, mTORi administration has been associated with several adverse events, such as gastrointestinal disorders, hyperlipidemia, interstitial pneumonitis, edema, mouth ulcers, proteinuria, impaired wound healing, hematotoxicity and so on. It was reported that adverse events of mTORi accounted for 20%-40% of the drop-out rate in a clinical phase III trial. In the late conversion to EVL studies, the discontinuation of EVL treatment due to adverse events occurred at about the same rate (approximately 30%). In our report, the discontinuation rate of EVL treatment was relatively high, at 42.3%.

The common adverse events leading to discontinuation have been aphthous stomatitis, pneumonitis, progressive renal deterioration and proteinuria. Proteinuria is a well-known prognostic factor for graft and patient survival rates in kidney transplantation. Sanchez-Fructuoso et al reported that risk factors for the development of proteinuria ≥ 900 mg/d at 1

year after late conversion were creatinine clearance of < 60 mL/min, serum triglycerides of ≥ 150 mg/d, no treatment with steroid, baseline proteinuria of ≥ 550 mg/d and conversion at ≥ 3 years after transplantation. An interaction was observed between baseline proteinuria and time to conversion, and the authors concluded that the success of EVL conversion with CNI elimination depended on not making so late conversions and not converting recipients with high baseline proteinuria. On the other hand, Nojima et al demonstrated that late immunosuppression conversion, at > 3 years after kidney transplantation, using EVL in addition to a reduction in CNI dose safely and significantly improved graft function.

Malignancies[2]

Kidney transplant recipients late-converted to sirolimus-based, CNI-free immunotherapy had a lower risk of malignancies at 2 years postconversion, with a high degree of heterogeneity attributed in the CONVERT trial. The reduction was driven by a significant reduction in nonmelanoma skin carcinoma rate ($P < 0.001$), while the rate of all other malignancies was numerically lower, although without statistical significance ($P = 0.058$). It has been reported that switching from CNIs to sirolimus had an antitumoral effect among kidney transplant recipients with previous nonmelanoma skin carcinoma. In the cases of late EVL conversion, however, the ASCERTAIN study showed that the incidence rates of malignancies were 7.1%, 7.6% and 5.7%, respectively in the CNI elimination, CNI minimization and control groups at 2 years after EVL conversion.

Cause of late conversion to EVL[2]

Chronic allograft nephropathy, CNI nephrotoxicity and CNI arteriolopathy may be good indications for late conversion to EVL. Furthermore, cancer is one of the main indications for late conversion to EVL. As mentioned in the above section on “malignancies”, there is no evidence to date for the superiority of EVL in suppressing malignancies at late conversion. However, Lim et al published that *de novo* use of EVL with reduced exposure to CNIs may enable a reduction in malignancy burden after transplantation.

Viral infection is also an indication for late conversion to EVL. It is well known that kidney transplant recipients receiving mTORi have a lower risk of developing cytomegalovirus (CMV) infection. Furthermore, cases with ganciclovir-resistant cytomegalovirus infection

have been reported to be cured after switching to mTORi. Kidney transplant recipients who have BK virus infection may benefit from conversion to mTOR. Polanco et al reported a recent prospective study of 15 recipients with BK virus-associated nephropathy. As a result, MMF elimination and conversion from Tac to EVL occurred in 9 recipients (60%), and 6 (67%) of the 9 recipients had improvement and 3 maintained stable renal function. In addition, BK viremia cleared in 5 (56%) of the recipients and decreased more than 95% in the remaining 4. With respect to Epstein-Barr virus infection, there is lack of evidence on whether the use of mTORi reduces the risk of infection in solid organ transplant recipients.

ABO-incompatible kidney transplantation[2]

Only two short-term pilot studies have been published about the introduction of EVL in ABO-incompatible kidney transplant recipients at a late posttransplant stage. In our study, 16 stable ABO-incompatible kidney transplant recipients were switched from MMF to EVL with CNI minimization. Our results showed that conversion to EVL with CNI minimization for 3 mo did not induce acute rejection and C4d deposition in all recipients, and the mean eGFR value significantly increased at 3 mo after conversion compared to baseline. In another study, 7 stable ABO-incompatible kidney transplant recipients were converted from mycophenolate acid to EVL at a late posttransplant phase because of active BK virus replication, and then compared with a reference group of 14 ABO-incompatible patients receiving standard Tac and mycophenolate acid. Conversion from mycophenolate acid to EVL decreased the BK viral load in 5 patients. Thus, this study demonstrated that ABO-incompatible kidney transplant recipients with an active BK virus infection may benefit from conversion to EVL.

References:

1. Pascual J. The use of everolimus in renal-transplant patients. *Int J Nephrol Renovasc Dis*. 2009;2:9-21.
2. Uchida J, Iwai T, Nakatani T. Introduction of everolimus in kidney transplant recipients at a late posttransplant stage. *World J Transplant*. 2018;8(5):150-155.

Survey Form

1) Which of the following are common primary reasons of renal failure in your patients?

A. Diabetes mellitus
B. Glomerulonephritis
C. Hypertension, renovascular disease
D. Polycystic kidney disease

2) Which of the following mammalian target of rapamycin (mTOR) inhibitors do you use in your clinical practice?

A. Everolimus
B. Sirolimus
C. Both
D. None

3) According to you, what could be probable reasons of prescribing Everolimus as a first-line treatment or switching patients from calcineurin inhibitors (CNI) to everolimus?

A. Nephrotoxicity associated with CNIs
B. Neurotoxicity associated with CNIs
C. Cardiovascular (CV) disease
D. Metabolic abnormalities
E. Malignancy

4) To what percentage of your renal transplant patient do you prescribe Everolimus as a firstline immunosuppresssant?

A. <10%
B. 10-20%
C. 21-30%
D. 31-40%
E. 41-50%
F. >50%
G. None

5) What percentage of your transplant patient do you switch from calcineurin inhibitors (CNIs) to Everolimus?

A. <10%
B. 10-20%
C. 21-30%
D. 31-40%
E. 41-50%
F. >50%
G. None

6) What is the preferred dose for everolimus in your patients who had renal transplant?

A. 0.25 mg twice daily
B. 0.5 mg twice daily
C. 0.75 mg twice daily
D. 1 mg twice daily

7) According to you, what are the important advantages of everolimus over CNIs?

A. Reduce or withdraw CNI therapy
B. Preserve renal function
C. Amelioration of CV events
D. A reduced incidence of viral infections
E. Fewer de novo malignancies

8) What are the common side effects that you observe in your patients taking Everolimus?

A. Peripheral edema
B. Constipation
C. Hypertension
D. Nausea
E. Anemia
F. Hyperlipidemia
G. UTI

9) Which one of the following is the most commonly observed side effect in your patients taking Everolimus?

A. Peripheral edema
B. Constipation
C. Hypertension
D. Nausea
E. Anemia
F. Hyperlipidemia
G. UTI
H. Mouth sores
I. Insomnia

10) In which of the following settings do you prescribe everolimus in kidney transplant?

A. Initiation immunosuppression
B. Maintenance immunosuppression
C. Both
D. None

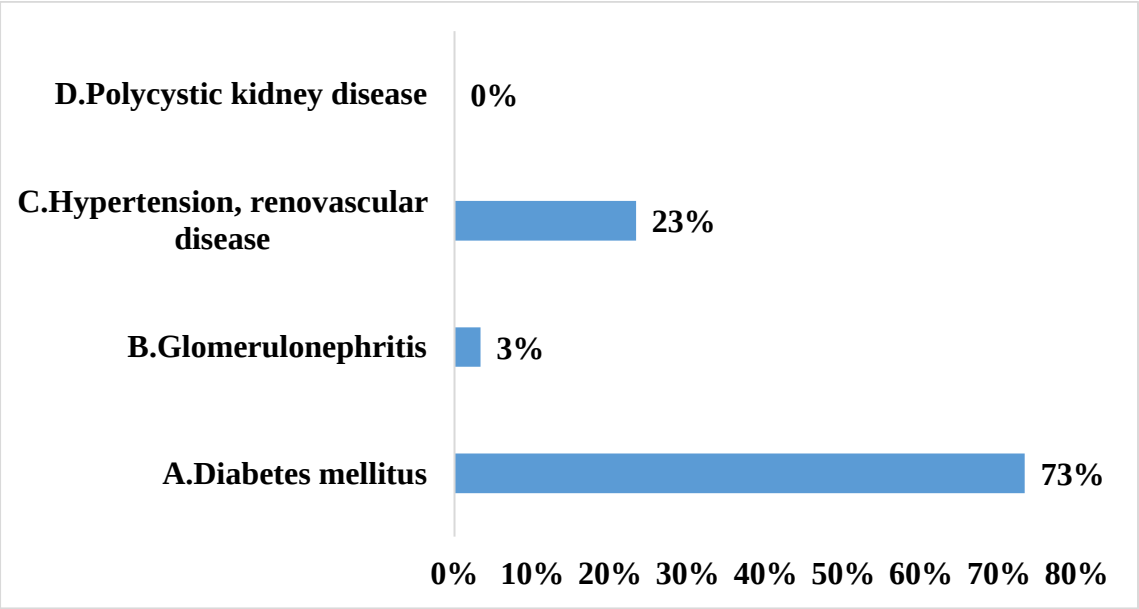
11) Have you ever observed Hypersensitivity in your patients taking everolimus?

A. Very Rarely
B. Rarely
C. Never
D. Often

Survey Findings

1) Which of the following are common primary reasons of renal failure in your patients?

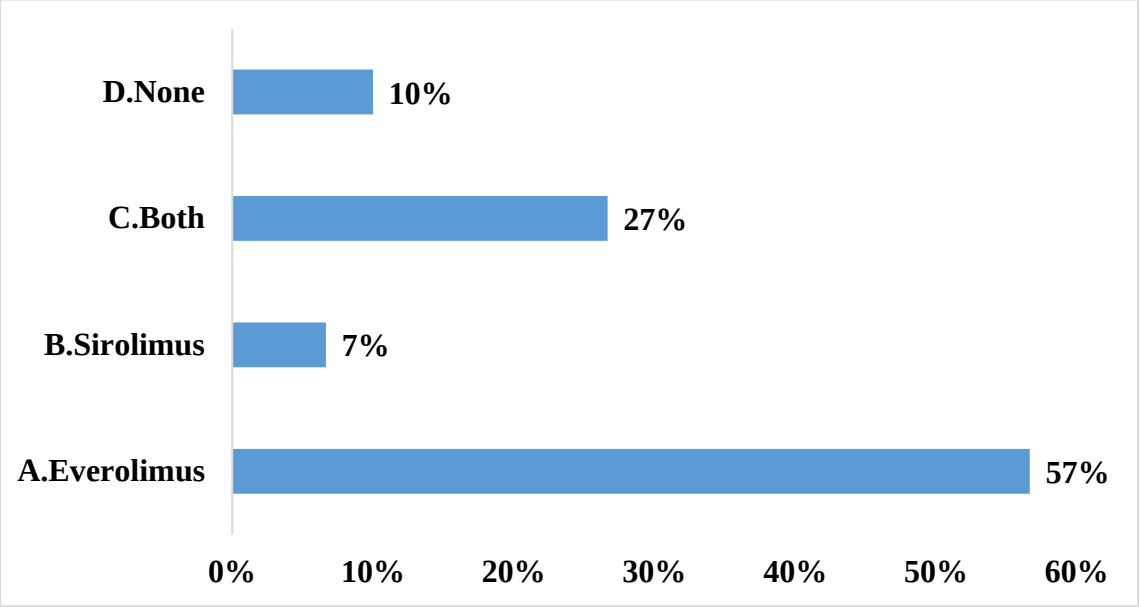
A. Diabetes mellitus
B. Glomerulonephritis
C. Hypertension, renovascular disease
D. Polycystic kidney disease



As per 73% of doctors, diabetes mellitus is the common primary reasons of renal failure in their patients.

2) Which of the following mammalian target of rapamycin (mTOR) inhibitors do you use in your clinical practice?

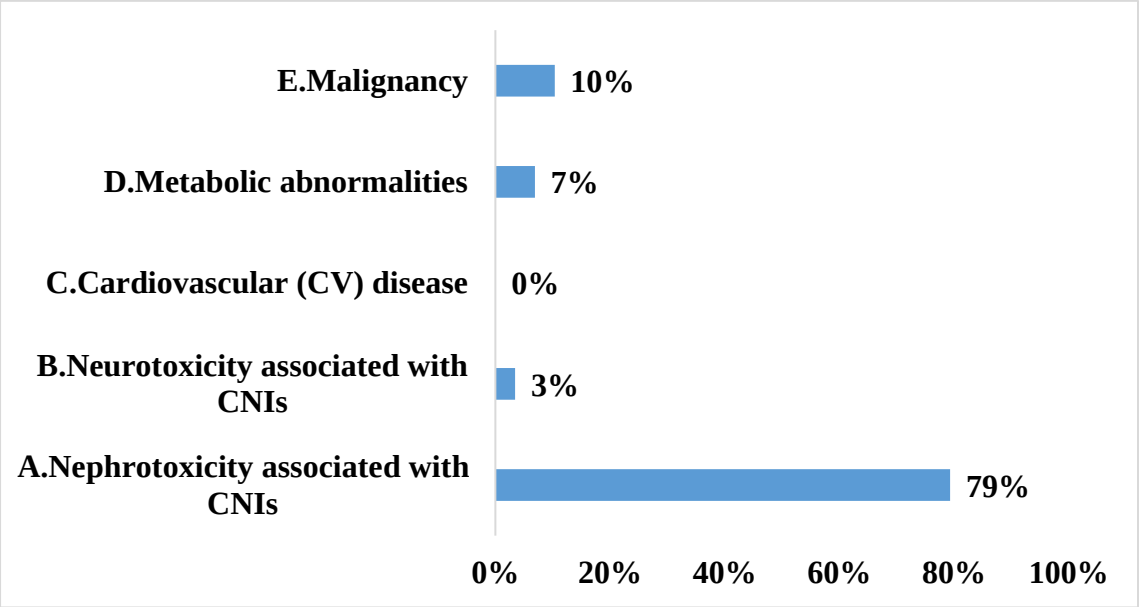
A. Everolimus
B. Sirolimus
C. Both
D. None



According to 57% of doctors, everolimus is the mammalian target of rapamycin (mTOR) inhibitors used in their clinical practice.

3) According to you, what could be probable reasons of prescribing Everolimus as a first-line treatment or switching patients from calcineurin inhibitors (CNI) to everolimus?

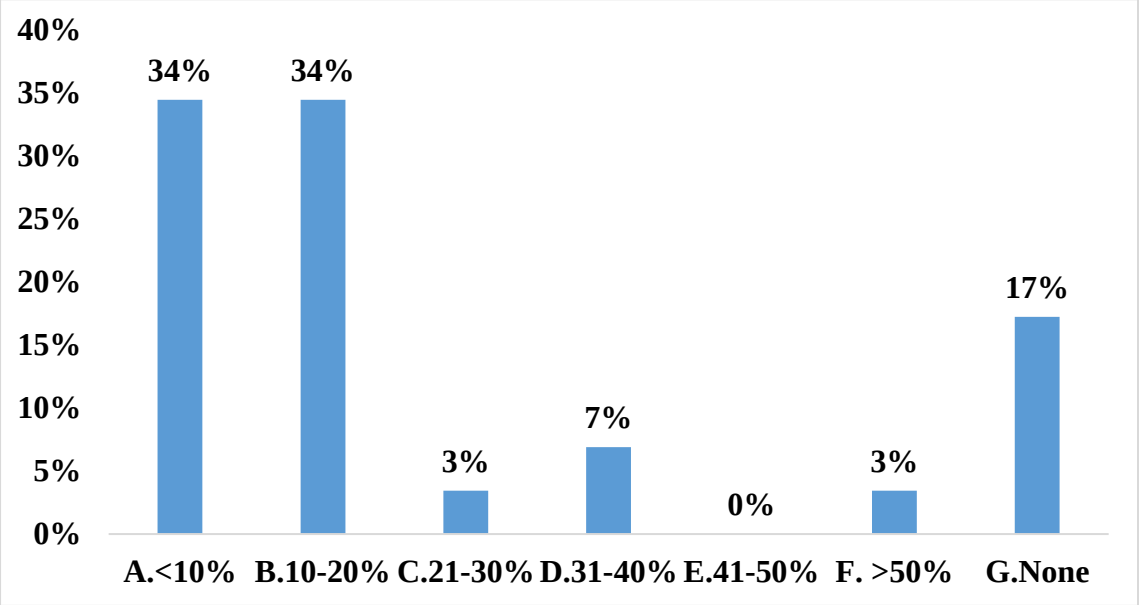
A. Nephrotoxicity associated with CNIs
B. Neurotoxicity associated with CNIs
C. Cardiovascular (CV) disease
D. Metabolic abnormalities
E. Malignancy



According to majority of doctors, nephrotoxicity associated with CNIs is the probable reasons of prescribing everolimus as a first-line treatment or switching patients from calcineurin inhibitors (CNI) to everolimus.

4) To what percentage of your renal transplant patient do you prescribe Everolimus as a firstline immunosuppresssant?

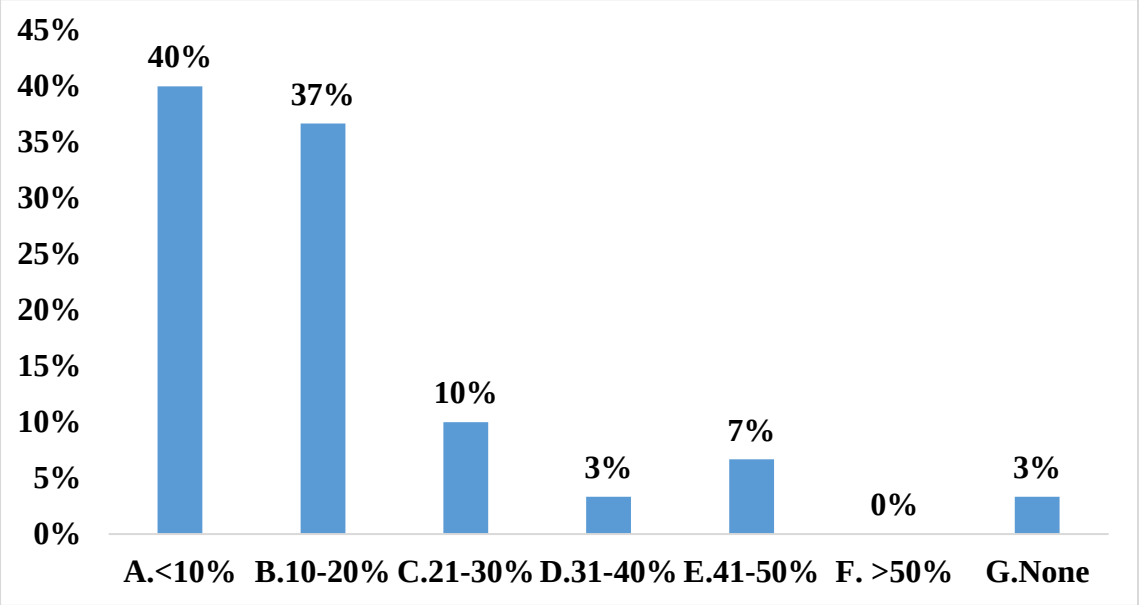
A. <10%
B. 10-20%
C. 21-30%
D. 31-40%
E. 41-50%
F. >50%
G. None



As per 34% of doctors, <10% of their renal transplant patient are prescribed with everolimus as a firstline immunosuppressant. while as per other 34% of doctors, 10-20% of their renal transplant patient are prescribed with everolimus as a first line immunosuppressant.

5) What percentage of your transplant patient do you switch from calcineurin inhibitors (CNIs) to Everolimus?

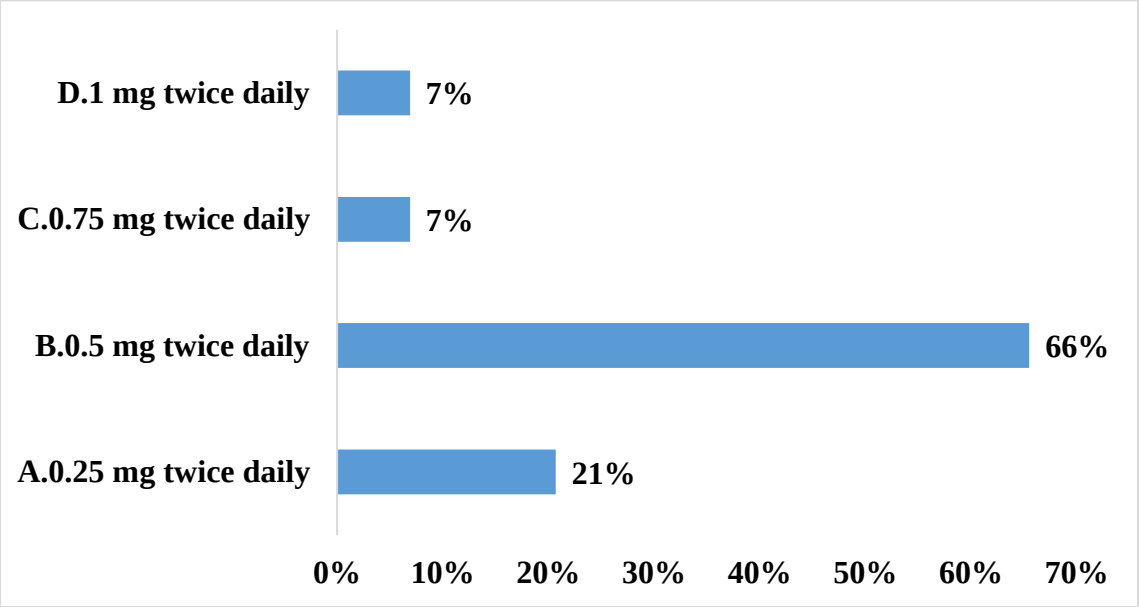
A. <10%
B. 10-20%
C. 21-30%
D. 31-40%
E. 41-50%
F. >50%
G. None



According to 40% of doctors, <10% of their transplant patient are switched from calcineurin inhibitors (CNIs) to everolimus.

6) What is the preferred dose for everolimus in your patients who had renal transplant?

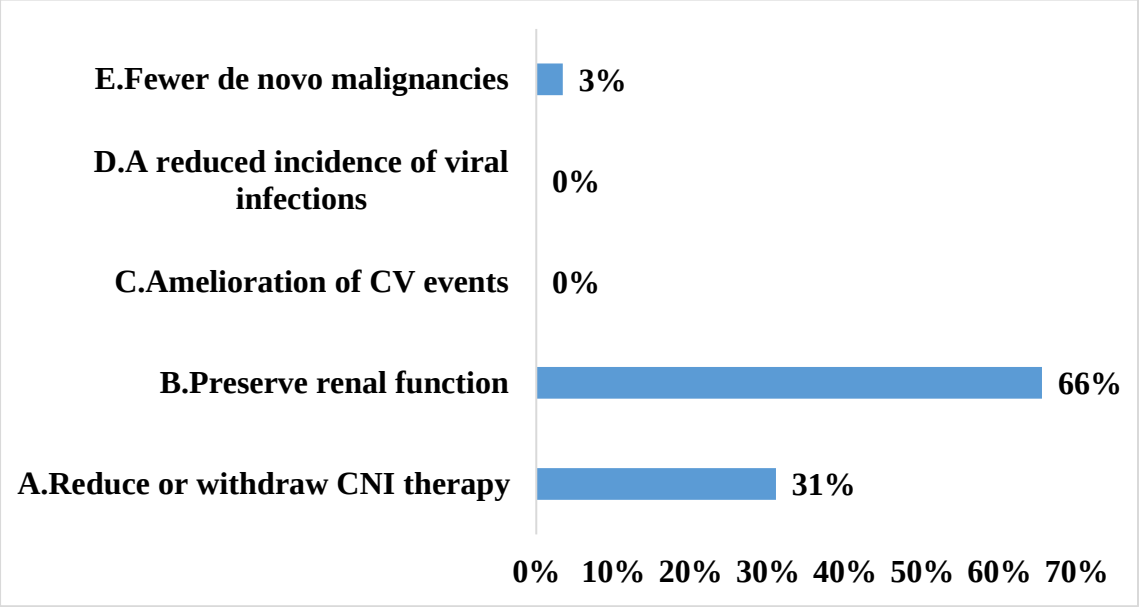
A. 0.25 mg twice daily
B. 0.5 mg twice daily
C. 0.75 mg twice daily
D. 1 mg twice daily



According to 66% of doctors, 0.5 mg twice daily is the preferred dose for everolimus in their patients who had renal transplant.

7) According to you, what are the important advantages of everolimus over CNIs?

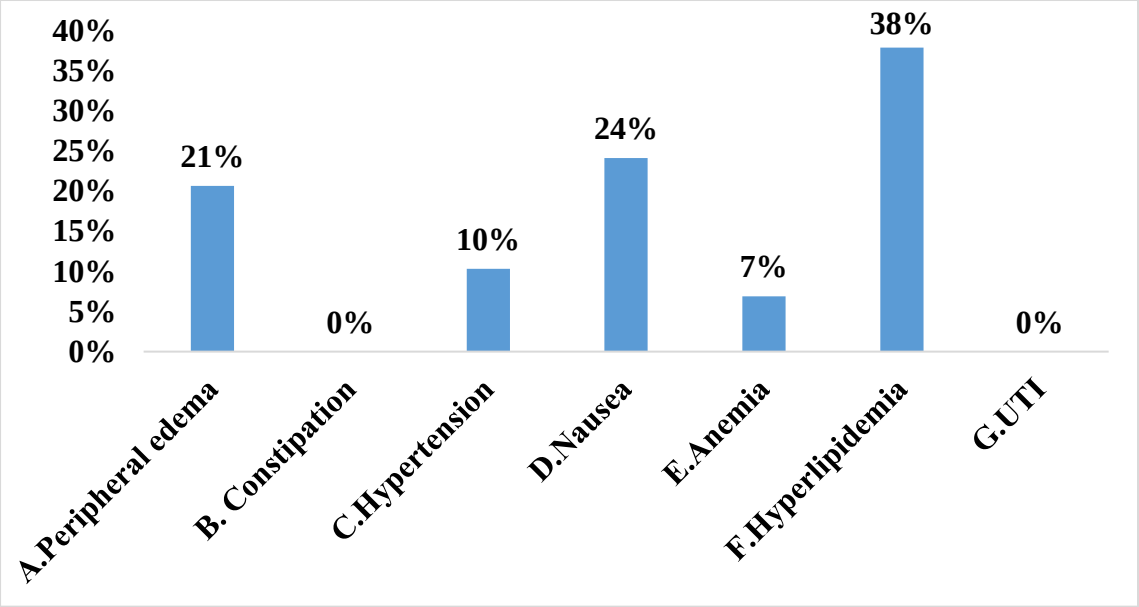
A. Reduce or withdraw CNI therapy
B. Preserve renal function
C. Amelioration of CV events
D. A reduced incidence of viral infections
E. Fewer de novo malignancies



According to 66% of doctors, preserve renal function is the important advantage of everolimus over CNIs.

8) What are the common side effects that you observe in your patients taking Everolimus?

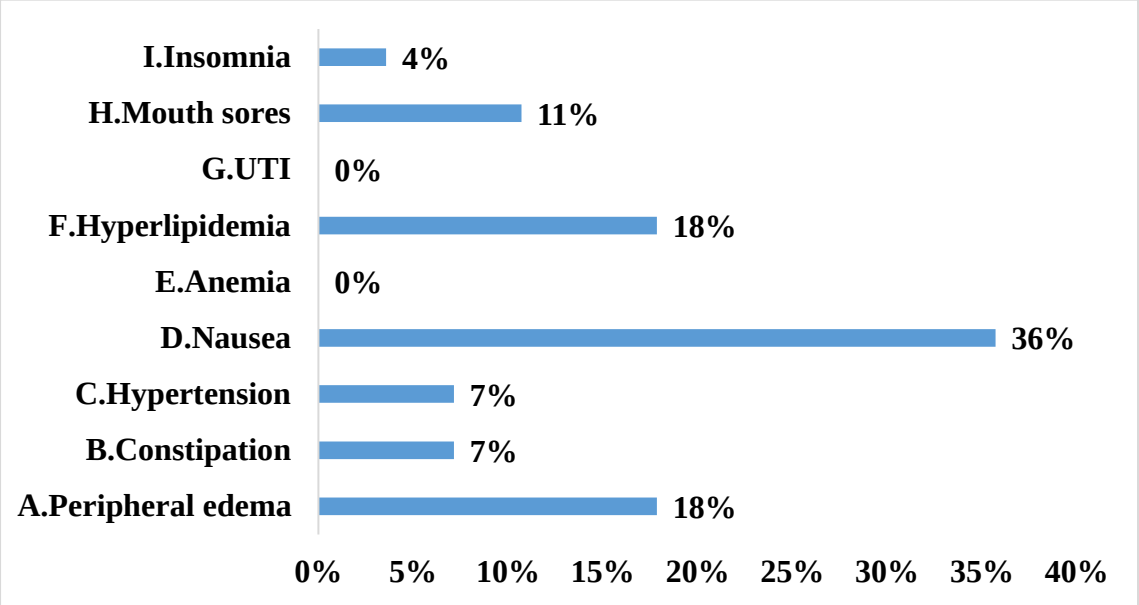
A. Peripheral edema
B. Constipation
C. Hypertension
D. Nausea
E. Anemia
F. Hyperlipidemia
G. UTI



According to 38% of doctors, hyperlipidemia is the common side effect that they observe in their patients taking everolimus.

9) Which one of the following is the most commonly observed side effect in your patients taking Everolimus?

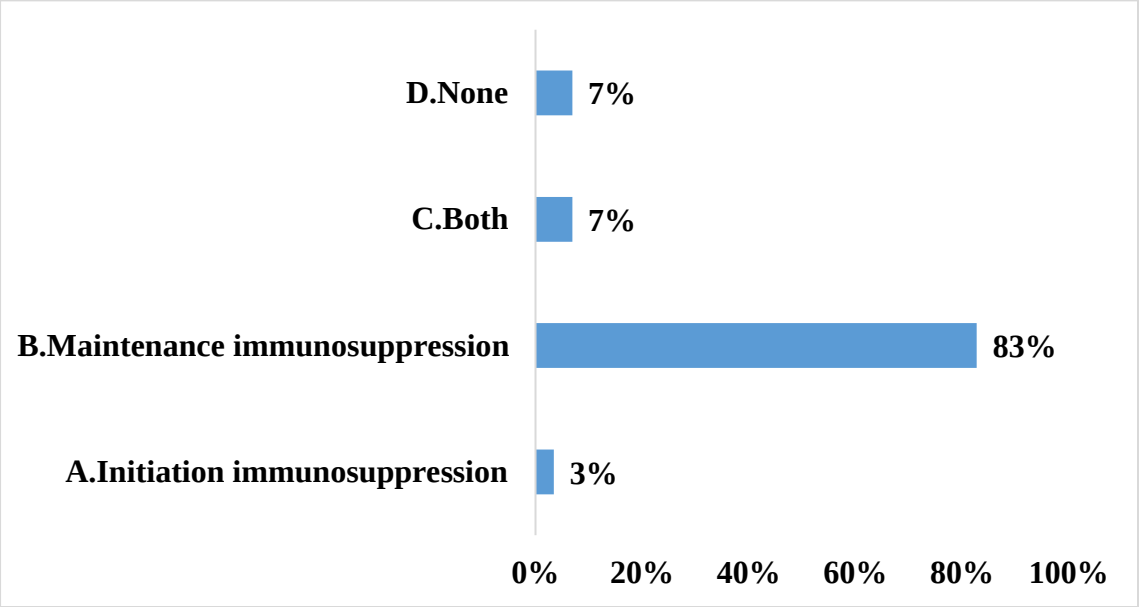
A. Peripheral edema
B. Constipation
C. Hypertension
D. Nausea
E. Anemia
F. Hyperlipidemia
G. UTI
H. Mouth sores
I. Insomnia



According to 36% of doctors, nausea is the most commonly observed side effect in their patients taking everolimus.

10) In which of the following settings do you prescribe everolimus in kidney transplant?

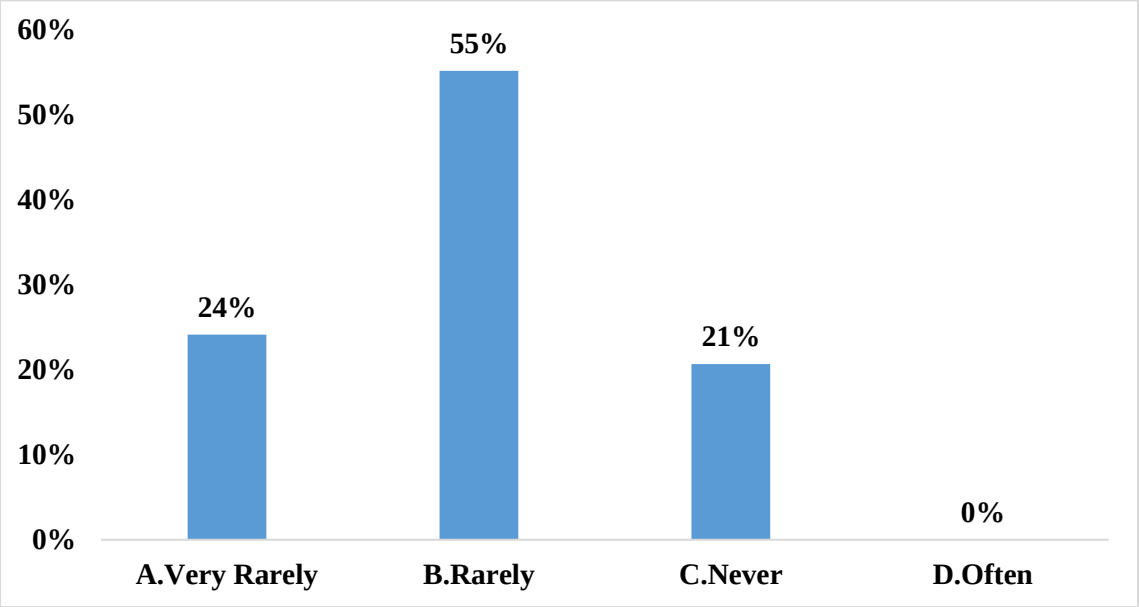
A. Initiation immunosuppression
B. Maintenance immunosuppression
C. Both
D. None



According to majority of doctors, 83%, maintenance immunosuppression is the following setting in which they prescribe everolimus in kidney transplant.

11) Have you ever observed Hypersensitivity in your patients taking everolimus?

A. Very Rarely
B. Rarely
C. Never
D. Often



As per 55% of doctors, they have rarely observed hypersensitivity in their patients taking everolimus.

Summary

- As per 73% of doctors, diabetes mellitus is the common primary reasons of renal failure in their patients.
- According to 57% of doctors, everolimus is the mammalian target of rapamycin (mTOR) inhibitors used in their clinical practice.
- According to majority of doctors, nephrotoxicity associated with CNIs is the probable reasons of prescribing everolimus as a first-line treatment or switching patients from calcineurin inhibitors (CNI) to everolimus.
- As per 34% of doctors, <10% of their renal transplant patient are prescribed with everolimus as a firstline immunosuppressant. while as per other 34% of doctors, 10-20% of their renal transplant patient are prescribed with everolimus as a first line immunosuppressant.
- According to 40% of doctors, <10% of their transplant patient are switched from calcineurin inhibitors (CNIs) to everolimus.
- According to 66% of doctors, 0.5 mg twice daily is the preferred dose for everolimus in their patients who had renal transplant.
- According to 66% of doctors, preserve renal function is the important advantage of everolimus over CNIs.
- According to 38% of doctors, hyperlipidemia is the common side effect that they observe in their patients taking everolimus.
- According to 36% of doctors, nausea is the most commonly observed side effect in their patients taking everolimus.
- According to majority of doctors, 83%, maintenance immunosuppression is the following setting in which they prescribe everolimus in kidney transplant.
- As per 55% of doctors, they have rarely observed hypersensitivity in their patients taking everolimus.

Consultant Opinion

Primary Causes of Renal Failure:

A significant majority of doctors identified diabetes mellitus as the most common primary cause of renal failure among their patients. This underscores the critical role of diabetes management in preventing kidney disease progression.

Use of Everolimus (mTOR Inhibitor):

Over half of the doctors reported utilizing everolimus, a mammalian target of rapamycin (mTOR) inhibitor, in their clinical practice. This suggests that everolimus is recognized as a valuable immunosuppressant option in renal transplant patients.

Reasons for Prescribing Everolimus:

Nephrotoxicity associated with calcineurin inhibitors (CNIs) emerged as the primary reason for prescribing everolimus as a first-line treatment or for switching patients from CNIs to everolimus. This highlights the desire to mitigate renal toxicity while maintaining effective immunosuppression.

Prevalence of Everolimus Usage:

A significant proportion of doctors reported prescribing everolimus as a first-line immunosuppressant for renal transplant patients, with varying percentages ranging from less than 10% to 10-20%. This indicates the growing acceptance of everolimus as an initial treatment option.

Dosage Preference:

Doctors commonly preferred a dosage of 0.5 mg twice daily for everolimus in renal transplant patients, suggesting a standardized dosing regimen based on clinical experience and efficacy.

Advantages of Everolimus:

Preserving renal function was identified as the most important advantage of everolimus over CNIs by a significant majority of doctors. This highlights the therapeutic benefit of everolimus in maintaining kidney function post-transplantation.

Common Side Effects:

Hyperlipidemia and nausea were reported as the most commonly observed side effects in patients taking everolimus. Monitoring and managing these side effects are crucial for optimizing patient outcomes and adherence to treatment.

Clinical Setting for Everolimus Prescriptions:

Maintenance immunosuppression following kidney transplant was identified as the most common clinical setting for prescribing everolimus. This suggests that everolimus is primarily utilized to maintain long-term graft function and prevent rejection.

Rarely Observed Side Effects:

Hypersensitivity reactions were rarely observed by the majority of doctors in patients taking everolimus, indicating a generally favorable safety profile for this immunosuppressant.

In summary, everolimus is increasingly recognized as an important immunosuppressant option in renal transplant patients, particularly due to its potential to preserve renal function and mitigate nephrotoxicity associated with CNIs. However, careful monitoring for common side effects such as hyperlipidemia and nausea is essential to optimize patient outcomes and ensure long-term graft success.

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