# Effect of Age on Conversion to Everolimus with Calcineurin Inhibitor Minimization at A Late Post-Transplant Stage

Junji Uchida[1]*, Shunji Nishide[1], Kazuya Kabei[1], Hisao Shimada[1], Akihiro Kosoku[1], Tomoaki Iwai[1], Nobuyuki Kuwabara[1], Toshihide Naganuma[1], Norihiko Kumada[2], Yoshiaki Takemoto[1], Tatsuya Nakatani[1]

**Purpose:** The purpose of this study was to identify the risk factors for everolimus discontinuation in kidney transplant recipients converted to everolimus with calcineurin inhibitor (CNI) minimization at a late post-transplant stage.

**Materials and Methods:** An observational retrospective cohort study was conducted on a total of 38 recipients of kidney transplantation at our institution from June 2012 to March 2015 who were converted from antimetabolites to everolimus at a late post-transplant stage and followed for 1 year. We divided the patients into two groups to evaluate the factors affecting everolimus discontinuation after conversion: everolimus continuation group (n = 23), patients in whom everolimus maintained, and everolimus discontinuation group (n = 15), patients in whom everolimus were stopped within 1 year after conversion.

**Results:** Age at conversion was significantly older in the everolimus discontinuation group compared to the everolimus continuation group (57.9 ± 12.0 years in the everolimus discontinuation group vs 45.7 ± 11.2 years in the everolimus continuous group; $P = .0062$). Multivariate cox proportional hazard regression analysis revealed that age at conversion significantly correlated with everolimus discontinuation ($P = .012$). Receiver operating characteristic curve of age at conversion showed that the cut-off value was 55 years old for the everolimus discontinuation group [area under curve 0.804, 95% confidence interval (0.654-0.954), sensitivity 86.7%, specificity 65.2%].

**Conclusion:** Our results indicated that late conversion to everolimus with CNI minimization in elderly recipients older than 55 years of age may be associated with more frequent adverse events and discontinuations.

**Keywords:** age; calcineurin inhibitor minimization; everolimus; immunosuppressive agent; kidney transplantation

## INTRODUCTION

Kidney transplantation is the most preferable renal replacement therapy in improving life expectancy and quality of life for patients with end-stage renal disease. The central issue in kidney transplantation remains to be the suppression of allograft rejection. The aim of immunosuppression therapy is to reduce the risk of rejection and to prolong patient and graft survival. Current immunosuppressive protocols, consisting of calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF), and steroid, have appreciably improved short- and medium-term graft survival[1]. However, improvements in long-term graft survival are restricted by nephrotoxicity associated with CNI administration[2]. Immunosuppressive regimens that minimize exposure to CNIs following kidney transplantation have been widely investigated in order to reduce the burden of CNI-related complications[3]. Among them, there have been several published clinical studies on conversion to everolimus in maintenance transplants. The ACERTAIN study revealed that conversion to everolimus with CNI minimization or elimination at a late post-transplant stage was associated with more frequent adverse effects and discontinuation[4]. Our previous pilot study showed that recipients with good graft function may benefit from conversion to everolimus with CNI minimization at a late post-transplant stage, as an improvement in graft function compared to baseline was observed in everolimus maintenance patients[5]. Everolimus plus CNI minimization may provide some advantage to the renal function of recipients in whom everolimus could be maintained. The aim of this study was to identify the risk factors for everolimus discontinuation after conversion to everolimus with CNI minimization at a late post-transplant stage.

## MATERIALS AND METHODS

### *Study Population*

We began to convert patients on MMF to everolimus with CNI minimization at our institution in June 2012. We have also applied everolimus to ABO-incompatible kidney transplant recipients[6] and patients with relatively good graft function[5]. For this study, a total of 38 recipients of kidney transplantation at our institution from June 2012 to March 2015 who were converted from antimetabolites to everolimus for 1 year ending in March 2016 were investigated. The inclusion criteria for conversion were as follows:[1] at least 3 months after transplantation,[2] renal function defined as a serum creatinine (S-Cr) value < 2.5 mg/dl,[3] no acute rejection episodes for more than 3 months, and[4] normal or slightly increased albuminuria defined as a urinary al-

[1]Department of Urology, Osaka City University Graduate School of Medicine, Osaka, Japan.
[2]Department of Urology, Suita Municipal Hospital, Suita, Japan.
*Correspondence: Department of Urology, Osaka City University Graduate School of Medicine 1-4-3, Asahi-machi, Abeno-ku, Osaka, 545-8585, Japan. Phone: +81-6-6645-3857, Fax: +81-6-6647-4426. E-mail: m9492120@msic.med.osaka-cu.ac.jp.
Received December 2017 & Accepted July 2018

**Table1.** Number of patients

| Postconversion | Everolimus continuation group | Everolimus discontinuation group |
|---|---|---|
| month 1 | 36 | 2 |
| month3 | 34 | 4 |
| month 6 | 27 | 11 |
| month 12 | 23 | 15 |

bumin excretion rate (the ratio of spot urine albumin to Cr)< 300 mg/g Cr. Treatment with everolimus was stopped due to adverse events in 15 patients (39.5%). Seven patients with general fatigue, 2 with interstitial pneumonia, 2 with peripheral edema, 1 with menoxenia, 1 with redness and itching of face, 1 with colon diverticulitis, and 1 with cholecystitis were led to discontinuation of everolimus. Median time from conversion to discontinuation was 119 days, with a range between 17 and 271 days. There were no graft failures or apparent clinical rejection during the observation period. This study analyzed retrospectively the risk factors for everolimus discontinuation after late conversion of stable kidney transplant recipients from antimetabolites with standard exposure CNIs to everolimus with very low exposure CNIs as a 1-year pilot study. We retrospectively compared the clinical parameters such as age at conversion, gender, estimated glomerular filtration rate at conversion, urinary albumin excretion at conversion, type of calcineurin inhibitors, dialysis duration, and period from transplantation to conversion between the two groups to analyze the risk factors for everolimus discontinuation. We divided the patients into two groups to evaluate the factors leading to everolimus discontinuation: the everolimus continuation group (n = 23), patients in whom everolimus was maintained for 1 year after conversion, and the everolimus discontinuation group (n = 15), patients in whom everolimus was stopped within 1 year after conversion. The number of patients at month 1, 3, 6, and 12 in the everolimus continuation group and the everolimus discontinuation group is shown in **Table 1**.

Protocols of conversion to CNI minimization

On the day of conversion, MMF or mizoribine was discontinued and everolimus was started at a dose of 1.5 mg/day (0.75 mg, twice a day) in the patients who received cyclosporine (CsA group) or 3.0 mg/day (1.5 mg, twice a day) in the patients who received tacrolimus (Tac group). The CNI dose was simultaneously reduced to 40-60% below baseline values. Dose adjustments started from 1 week onward to target an everolimus trough level of 3 to 8 ng/ml and a CsA trough level of 25-50 ng/ml or a Tac trough level of 2-4 ng/ml. Everolimus trough levels were assessed at 1 week and every month until 1 year after conversion. Baseline doses of methylprednisolone were continued unaltered in all patients.

Clinical and biochemical measurement and concentration of CNIs and everolimus

At baseline, clinical parameters including age, gender, cause of end-stage renal disease, duration of dialysis, time to transplantation, donor type, and ABO-compatibility were collected. At baseline and at 1, 3, 6, and 12 months after conversion, fasting blood samples were obtained in the early morning for biochemical studies, including total cholesterol, triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and trough levels of CNI and everolimus. Estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease equation using the new Japanese coefficient[7]. Urinary albumin excretion rate (the ratio of spot urine concentrations of albumin to creatinine) was measured at baseline and at 1, 3, 6, and 12 months after conversion. We evaluated these clinical parameters at baseline compared to 12 months after conversion between the two groups. All subjects provided informed consent prior to enrollment in this study, which was approved by the Human Ethics Committee of Osaka City University Hospital. All procedures were in accordance with the Helsinki Declaration of 1975.

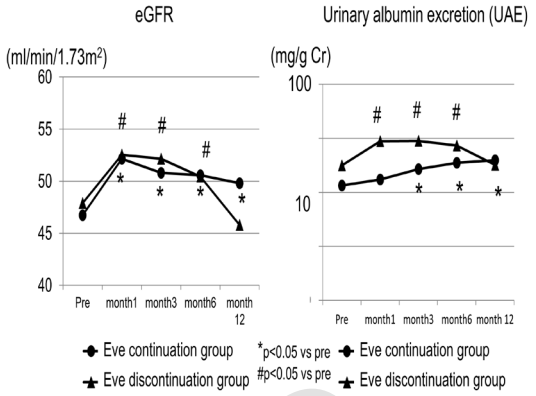


**Figure 1.** Changes in estimated glomerular filtration rate and urinary albumin excretion before and after conversion. Recipients in whom everolimus was maintained for 1 year after conversion (everolimus continuation group) or recipients in whom everolimus was stopped (everolimus discontinuation group). NS=not significant

### *Statistical analysis*

Statistical analysis was conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Australia). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[8]. The results are expressed as mean ± standard deviation or median with ranges and as proportions for categorical variables. Changes were evaluated with the paired t test or Wilcoxon test. Differences between the two groups were analyzed by Student's t-test or Mann-Whitney U-test. Categorical variables were compared using chi-squared analysis or Fisher's exact test. Univariate association between variables was assessed by cox proportional hazard regression analysis, and multivariate cox proportional hazard regression analysis was performed to determine the factors related to everolimus discontinuation. Cut-off values of the factors related to everolimus discontinuation were calculated by the receiver operating characteristics curve (ROC curve). Statistical significance was set as $p < 0.05$.

**Table 2.** Comparison of clinical parameters between Everolimus continuous and discontinuous group

| | Everolimus continuation group | Everolimus discontinuation group | *P*-value |
|---|---|---|---|
| n | 23 | 15 | |
| Age at transplant (year) | 45.7 ± 11.2 | 57.9 ± 12.0 | .00622 |
| Gender (male: female) | 13:10 | 10:5 | .736 |
| HD duration (months) 7 | 7.2 ± 100 | 67.6 ± 73.8 | .786 |
| Calcineurin inhibitor (Cyclosporin: Tacrolimus) | 14:9 | 9:6 | 1.0 |
| Cause of end stage renal disease | CGN; 5, IgA N; 6, DM N; 2, Renal sclerosis; 1, ADPKD; 2, Unknown; 5, Others; 2 | CGN; 3, IgA N; 1, DM N; 3, Renal sclerosis; 2, ADPKD; 0, Unknown; 5, Others; 1 | .415 |
| Donor age (year) | 55.0 ± 11.8 | 56.9 ± 9.7 | .634 |
| Donor type (living: deceased) | 19:4 | 14:1 | .63 |
| Donor relation | Spouses; 10, Parent/Child; 8, Sister;1 | Spouses; 11, Parent/Child; 3, Sister;0 | .344 |
| HLA mismatch (antigen) | 3.5 ± 1.1 | 4.1±1.6 | .0675 |
| ABO-compatibility | compatible; 13, incompatible; 10 | compatible; 4, incompatible; 11 | 1.0 |
| Period from transplant to conversion (months) | 41.7 ± 54.5 | 44.8 ± 32.1 | .848 |
| Age at conversion (year) | 48.9 ± 12.0 | 61.9 ± 11.5 | .00563 |
| eGFR (ml/min/1.73m$^2$) | 46.7 ± 12.6 | 47.9 ± 12.6 | .786 |
| Urinary albumin excretion (mg/g Cr) | 13.8 ± 7.4 | 20.9 ± 13.4 | .0776 |
| Total cholesterol (mg/dL) | 201.8 ± 26.9 | 198.8 ± 34.5 | .779 |
| Triglyceride (mg/dL) | 121.5 ± 52.2 | 108.8 ± 42.9 | .464 |
| Low density lipoprotein (mg/dL) | 103.3 ± 26.0 | 106.4 ± 17.0 | .692 |
| High density lipoprotein (mg/dL) | 65.8 ± 16.0 | 68.1 ± 20.6 | .734 |

**Abbrebiations:** HD, hemodialysis; CGN, chronic glomeronephritis; IgA N, IgA nephropathy; DM N, Diabetic nephropathy; ADPKD, autosomal dominant polycystic kidney disease; HLA, human leukocyte antigen; eGFR, estimated glomerular filtration rate.
[a]Differences between the two groups were analyzed by Student's t-test or Mann-Whitney U-test. bCategorical variables were compared using chi-squared analysis or Fisher's exact test.

## RESULTS

### *Baseline patient characteristics*

The demographic and clinical characteristics at baseline of the everolimus continuation and discontinuation groups are presented in Table 2. Age at transplant and conversion was significantly older in the everolimus discontinuation group compared to the everolimus continuation group. No significant differences were observed between the two groups with regard to the other clinical parameters.

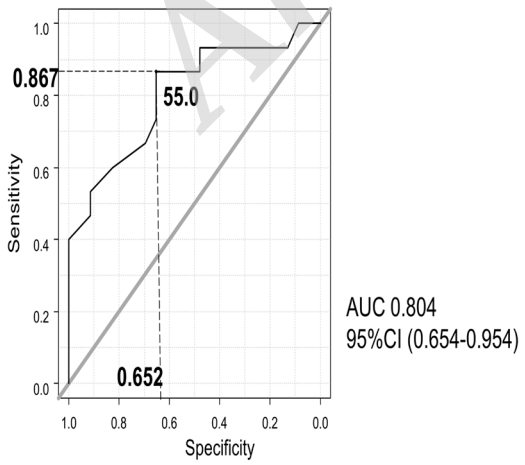


**Figure 2.** A threshold of age at conversion associated with discontinuation of everolimus by use of receiver operating characteristic curve analysis.

### Renal function and urinary albumin excretion (**Figure 1**)

There were no significant differences in eGFR and urinary albumin excretion at baseline between the two groups (**Table 2**). In the everolimus continuation group, the mean eGFR value was significantly elevated from 46.7±12.6 ml/min/1.73m2 at baseline to 49.8 ± 14.3 ml/min/1.73m2 at 12 months after conversion. In the everolimus discontinuation group, there was no significant difference in the mean eGFR between baseline and 12 months after conversion. Furthermore, there was a significant difference in the change of eGFR between the two groups. In the everolimus continuation group, the log [urinary albumin excretion] was significantly increased from 1.06 ± 0.29 at baseline to 1.29 ± 0.44 at 12 months after conversion. In the everolimus discontinuation group, there was no change in the log [urinary albumin excretion] between baseline and 12 months after conversion.

### *Lipid profile*

There were no significant differences in total cholesterol and low-density lipoprotein at baseline between the two groups. There were no significant differences in total cholesterol and low-density lipoprotein between baseline and 12 months after conversion in both groups.

Relationship between everolimus discontinuation and clinical parameters

Univariate cox proportional hazard regression analysis revealed that discontinuation of everolimus correlated with urinary albumin excretion and age at conversion. We selected age at conversion, urinary albumin excretion, and eGFR as variables associated with everolimus discontinuation for the multivariate analysis. Age

**Table 3.** Cox hazard regression analysis of risk factors associated with everolimus discontinuation

| Variable | Univariate Hazard ratio (95% CI) | *P*-value | Multivariate Hazard ratio (95% CI) | *P*-value |
|---|---|---|---|---|
| Gender | 1.478 (0.505-4.327) | .476 | | |
| Age at conversion | 1.080 (1.025-1.136) | .00416 | 1.075 (1.016-1.137) | .012 |
| Period from transplant to conversion (months) | 1.001 (0.992-1.011) | .815 | | |
| HD duration | 0.999 (0.993-1.004) | .626 | | |
| CsA/Tac | 1.023 (0.364-2.877) | .965 | | |
| Donor age | 0.978 (0.921-1.04) | .468 | | |
| HLA mismatch | 1.508 (0.961-2.361) | .074 | | |
| ABO-incompatiblity | 2.808 (0.893-8.84) | .077 | | |
| eGFR at conversion | 1.003 (0.965-1.042) | .252 | 1.017 (0.934-1.062) | .454 |
| Urinary albumin excretion | 1.041 (1.003-1.079) | .0318 | 1.028 (0.988-1.068) | .173 |

**Abbreviations:** HD, hemodialysis; CsA, cyclosporin; Tac, tacrolimus; eGFR, estimated glomerular filtration rate.

at conversion was selected as a variable by the backward model. Previous reports showed that conversion to everolimus was advised in patients with proteinuria or not good graft function[4,9]. Multivariate cox proportional hazard regression analysis indicated that age at conversion was independently associated with discontinuation of everolimus (**Table 3**).

Cut-off value of everolimus discontinuation

The ROC curve of age at conversion for the everolimus discontinuation group showed that the cut-off value was 55 years old [area under curve 0.804, 95 % confidence interval (0.654-0.954), sensitivity 86.7 %, specificity 65.2%] (**Figure 2**).

## DISCUSSION

In this study, the risk factors for everolimus discontinuation after conversion to everolimus with CNI minimization in the kidney transplant recipients with good renal function were analyzed. Age at conversion was significantly older in the everolimus discontinuation group (average age: 61.9 years) compared to the everolimus continuation group and significantly correlated with discontinuation of everolimus by multivariate analysis. Moreover, we revealed that late conversion to everolimus with CNI minimization in elderly recipients older than 55 years of age may be associated with more frequent adverse events and discontinuations by the ROC curve, although the specificity was relatively low because of the small sample size. To our knowledge, there have been no reports on the safety and efficacy of everolimus in elderly recipients, although the cut-off point for elderly patients differs among various countries. Our results may be useful to explore patients who could be converted to everolimus with CNI minimization at a late post-transplant stage.

Increasing age is associated with structural and functional changes in body compartments and tissue that alter absorptive capacity, volume of distribution, hepatic metabolic function, and ultimately drug disposition. Age-related changes may appear in most organs and can alter pharmacodynamics responses to medications[10]. Although no data have been published on elderly changes, elderly recipients may be more susceptible to developing adverse effects related to immunosuppressive drugs, especially everolimus. That is, elderly recipients may not be eligible for conversion from MMF to everolimus at a late post-transplant stage.

The present study showed that eGFR in the everolimus continuation group was significantly improved compared with that at baseline. Moreover, there was a significant difference in the change in eGFR between the two groups. In the post hoc analysis of the Zeus study, the renal benefit increased slightly from year 1 for living donor kidney transplant recipients who remained on everolimus-maintained immunosuppression, and for living donor kidney transplant recipients who discontinued everolimus, the renal benefit was lost[11]. Our study showed that selected recipients with good renal function may acquire renal benefit, if they remained on everolimus-maintained immunosupression.

The nephrotoxic effect of CNIs can limit long-term survival[2]. Recent strategies to avoid or reduce exposure to CNIs have focused on immunosuppressive drugs that are generally considered non-nephrotoxic, such as mTOR inhibitors. Everolimus has shown potent antiproliferative effects and has prevented allograft rejection in preclinical models[12]. In experimental models, everolimus has been shown to ameliorate progression of chronic allograft nephropathy, not only when administered prophylactically from the time of transplantation but also in advanced disease[13,14]. Even conversion to everolimus in maintenance transplants may lead to renal benefit. However, late conversion everolimus in recipients with high baseline proteinuria has been reported to induce a decline in graft function and poor graft prognosis in previous clinical trials[15].

The introduction of everolimus with CNI minimization at a late post-transplant stage may have some benefits due to its pleiotropic effects. Everolimus exhibits anti-neoplastic, anti-viral, anti-atherosclerotic, and anti-proliferative properties. It is well known that kidney transplant recipients receiving mTOR inhibitors have a lower risk of developing cytomegalovirus infection[16]. The CONVERT trial revealed that mTOR inhibitor-based immunosuppression was associated with a lower rate of malignancy at 2 years postconversion compared with CNI-based immunosuppression[17,18].

Chronic antibody-mediated rejection is considered to play a major role in late allograft loss[2,19]. Although everolimus-based immunosuppression in early conversion from CNI was reported to be associated with an increased risk of developing denovo donor-specific antibodies and antibody-mediated rejection[20], a recent review demonstrated that late conversion to CNI-free immunosuppressive regimen with mTOR inhibitors did not appear to affect the risk of denovo donor-specific

antibodies[21]. Moreover, in human cell cultures, it was reported that everolimus was equally effective as tacrolimus in suppressing humoral alloimmunity[22]. Late conversion to everolimus may be a favorable strategy in the expectation of avoiding MMF toxicity or reducing CNI-associated long-term toxicities, because it may not elicit the development of denovo donor-specific antibodies, if the patient remained on everolimus treatment. The recipients who remained on everolimus in this study showed a significant increase in urinary albumin excretion compared to the recipients in whom everolimus was stopped. mTOR inhibitor use has been associated with proteinuria/albuminuria in kidney transplant recipients[23]. Potential mechanisms for mTOR-associated proteinuria/albuminuria include decreased vascular endothelial growth factor synthesis and inhibition of key podocyte proteins that comprise the glomerular slit diaphragm, including nephrin[23]. In kidney transplant recipients, microalbuminuria predicts graft loss and all-cause mortality[24]. However, the impact of mTOR inhibitor-induced proteinuria/albuminuria on graft outcome has remained unclear. In this study, albuminuria was slightly elevated after late conversion to everolimus in patients in whom everolimus was maintained (median value of urinary albumin excretion: 16 mg/g Cr (6-126 mg/g Cr)). Slightly increased albuminuria may well induce an undesirable effect for long-term graft and patient survival.

The present study might have limitations because of the small sample size and because it is a retrospective study. However, there have been few reports on everolimus in elderly patients receiving kidney transplantation. It is not yet established whether everolimus is safe and effective for elderly recipients. To our knowledge, this is the first demonstration to identify the possible risk factors for discontinuation of everolimus at late conversion by multivariate analysis, although the present study is a pilot. Further prospective well-controlled and long-term follow-up trials with a larger number of patients are needed to confirm our results.

## CONCLUSIONS

In conclusion, the present study identified the possibility that late conversion to everolimus with CNI minimization in elderly recipients older than 55 years of age may be associated with more frequent adverse events and discontinuations. The recipients enrolled in this study had relative good graft function with less albuminuria. Therefore, recipients whose ages are less than 55 years and who have relatively good graft function with little chronic allograft damage may be available for late conversion to everolimus. Our results may be useful to explore patients who could be converted to everolimus with CNI minimization at a late post-transplant stage.

## CONFLICT OF INTEREST

The authors report no conflict of interest.

## REFERENCES


1. Xie X, Jiang Y, Lai X, Xiang S, Shou Z, Chen J. mTOR inhibitor versus mycophenolic acid as the primary immunosuppression regime combined with calcineurin inhibitor for kidney transplant recipients: a meta-analysis. BMC Nephrol. 2015;16:91.
2. Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. N Engl J Med. 2003;349:2326-33.
3. Golshayan D, Pascual M. Minimization of calcineurin inhibitors to improve long-term outcomes in kidney transplantation. Transpl Immunol. 2008;20:21-8.
4. Holdaas H, Rostaing L, Serón D, et al. Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. Transplantation. 2011;92:410-8.
5. Uchida J, Iwai T, Kuwabara N, et al. Clinical Experience of Late Conversion From Antimetabolites With Standard Exposure Calcineurin Inhibitors to Everolimus With Calcineurin Inhibitor Minimization in Stable Kidney Transplant Recipients With Good Renal Function. Transplant Proc. 2016;48:775-80.
6. Uchida J, Machida Y, Iwai T, Kuwabara N, et al. Conversion of stable ABO-incompatible kidney transplant recipients from mycophenolate mofetil with standard exposure calcineurin inhibitors (CNIs) to everolimus with very low exposure CNIs-a short-term pilot study. Clin Transplant. 2014;28:80-7.
7. Imai E, Horio M, Nitta K, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol. 2007;11:41-50.
8. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452-8.
9. Sánchez-Fructuoso AI, Ruiz JC, Calvo N, et al. Everolimus as primary immunosuppression in kidney transplantation: experience in conversion from calcineurin inhibitors. Transplantation. 2012 27;93:398-405.
10. Kuypers DR. Immunotherapy in elderly transplant recipients: a guide to clinically significant drug interactions. Drugs Aging. 2009;26:715-37.
11. Sommerer C, Budde K, Zeier M, et al. Early conversion from cyclosporine to everolimus following living-donor kidney transplantation: outcomes at 5 years posttransplant in the randomized ZEUS trial. Clin Nephrol. 2016;85:215-25.
12. Schuler W, Sedrani R, Cottens S, et al. SDZ RAD, a new rapamycin derivative: pharmacological properties in vitro and in vivo. Transplantation. 1997;64:36-42.
13. Viklický O, Zou H, Müller V, Lacha J, Szabó A, Heemann U. SDZ-RAD prevents manifestation of chronic rejection in rat renal

allografts. Transplantation. 2000;69:497-502.

14. Lutz J, Zou H, Liu S, Antus B, Heemann U. Apoptosis and treatment of chronic allograft nephropathy with everolimus. Transplantation. 2003;76:508-15.
15. Sánchez-Fructuoso AI, Ruiz JC, Calvo N, et al. Everolimus as primary immunosuppression in kidney transplantation: experience in conversion from calcineurin inhibitors. Transplantation. 2012;93:398-405.
16. Tedesco-Silva H, Felipe C, Ferreira A, et al. Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses. Am J Transplant. 2015;15:2655-64.
17. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med. 2012;367:329-39.
18. Alberu J, Pascoe MD, Campistol JM, et al. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. Transplantation. 2011;92:303-10.
19. Gaston RS, Cecka JM, Kasiske BL,et al. Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. Transplantation. 2010;90:68-74.
20. Liefeldt L, Brakemeier S, Glander P, et al. Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. Am J Transplant. 2012;12:1192-8.
21. Grimbert P, Thaunat O. mTOR inhibitors and risk of chronic antibody-mediated rejection after kidney transplantation: where are we now? Transpl Int. 2017;30:647-657.
22. Eleftheriadis T, Pissas G, Sounidaki M, Antoniadi G, Antoniadis N, Liakopoulos V, Stefanidis I. In human cell cultures, everolimus is inferior to tacrolimus in inhibiting cellular alloimmunity, but equally effective as regards humoral alloimmunity. Int Urol Nephrol. 2017;49:1691-1697.
23. Biancone L, Bussolati B, Mazzucco G, et al. Loss of nephrin expression in glomeruli of kidney-transplanted patients under m-TOR inhibitor therapy. Am J Transplant. 2010;10:2270-8.
24. Halimi JM, Buchler M, Al-Najjar A, et ak. Urinary albumin excretion and the risk of graft loss and death in proteinuric and non-proteinuric renal transplant recipients. Am J Transplant. 2007;7:618-25.