ANNALS OF TRANSPLANTATION

ORIGINAL PAPER

e-ISSN 2329-0358
© Ann Transplant, 2021; 26: e932434
DOI: 10.12659/AOT.932434

Received: 2021.03.27
Accepted: 2021.07.13
Available online: 2021.08.02
Published: 2021.09.17

Immunological Results of Long-Term Use of Mammalian Target of Rapamycin (mTOR) Inhibitors and Its Effects on Renal Graft Functions

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Mehmet Tanrısev
CD 2 Tülay Ayna Kılıçaslan
BFG 1 Hülya Çolak
BD 1 Sibel Ersan
BFG 1 Banu Yılmaz
B 3 Alper Alp
BC 4 Cem Tuğmen
E 5 Bahar Engin Sevgili

1 Department of Nephrology, SBU İzmir Tepecik Training and Research Hospital, İzmir, Turkey
2 Department of Medical Biology and Tissue Typing Laboratory, SBU İzmir Tepecik Training and Research Hospital, Medical Faculty, İzmir Katip Çelebi University, İzmir, Turkey
3 Department of Nephrology, Medical Faculty, Muğla Sıtkı Koçman University, Muğla, Turkey
4 Department of General Surgery, SBU İzmir Tepecik Training and Research Hospital, İzmir, Turkey
5 Department of Internal Medicine, SBU İzmir Tepecik Training and Research Hospital, İzmir, Turkey

Corresponding Author: Mehmet Tanrısev, e-mail: mehmettanrisev@gmail.com
Financial support: Departmental sources

Background: Calcineurin inhibitor drugs (CNI), which are the basis of immunosuppression in kidney transplantation, contribute to renal graft loss, with increased morbidity and mortality due to their potentially harmful effects on the renal graft, cardiovascular system, and tumor pathology. For this reason, the mammalian target of rapamycin inhibitors (mTORi) such as sirolimus (SRL) and everolimus (EVE) has been preferred more frequently, as they are associated with fewer complications and longer graft function.

Material/Methods: We enrolled 89 adult renal transplant patients (37 patients on mTORi and 52 on CNI) who had similar age, sex, primary renal disease, dialysis type, post-transplant follow-up period, and donor type. We analyzed and compared the data between patients using mTORi for longer than 5 years and those using CNI regarding pre- and post-transplant panel reactive antibody (PRA), and donor-specific antibody (DSA), as well as post-transplantation and current graft functions.

Results: Although those using mTORi for more than 5 years had significantly higher mismatch rates (P=0.024) than those using CNI, there was no significant change in PRA and DSA levels. Transplant time was longer in mTORi users (P=0.025). The switch time to mTORi in patients ranged from 0 to 19 years, but the average was 4 years. As expected, actual spot urine protein/creatinine was significantly higher in those using mTORi (P=0.009). Diabetes mellitus (DM) and BK virus nephropathy (BKVN) rates were significantly higher due to switching the regimen from CNI to mTORi.

Conclusions: Long-term use of mTORi does not appear to be an immunological problem.

Keywords: Calcineurin Inhibitors • Everolimus • Kidney Transplantation • Sirolimus • Transplantation Immunology

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/932434

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Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

CNI-based regimens are switched to mTORi-based regimens due to some indications and adverse effects such as chronic allograft nephropathy, diabetes mellitus, malignancies, and cardiovascular system toxicity. The SYMPHONY trial showed that de novo SRL use without CNI was associated with higher rates of acute graft rejection and poor kidney function compared to full-dose or reduced-dose addition of CNI to the regimen [1]. KDIGO clinical practice guidelines have prevented these drugs from being used as the first-line therapy for immunosuppression in kidney transplants [2]. Instead, as the SMART clinical trial showed, randomized switching from cyclosporin A (CsA) to SRL in the second to the third week was associated with marked improvement of renal function compared to maintenance with CsA [3].

Early conversion from CNI to SRL or EVE can keep a stable kidney function, but it is questionable that this prevents graft dysfunction [4]. EVE added to reduced doses of tacrolimus may cause antifibrotic effects in renal allografts by the inhibition of mTOR [5]. By taking advantage of the antiviral effect of SRL, it has been shown that, the renal allograft is protected and HIV replication is prevented [6].

Chronic antibody-mediated rejection is one of the major causes of graft loss today and the cause is insufficient immunosuppression. Although the immunologic effects of the mTORi in the literature are based on the short-term uses, it was not known what the result would be if it was used longer than 5 years.

In chronic graft dysfunction, the contribution of antibody-mediated rejection (AMR) is highly appreciated. AMR is triggered by the action of humoral immunity against various antibodies, especially human leukocyte antigens (HLA). Several reports demonstrated that the presence of DSA is related to poor graft function in long-term follow-up [7-10].

Croze et al reported that DSA levels were increased in patients who switched from CNI to mTORi-based regimens, but this increase did not reflect any clinical follow-up or graft function [11]. In that study, a clinical outcome of DSA in the first year was not shown. For this reason, we wanted to investigate whether DSA positivity has a clinically significant long-term effect.

Material and Methods

This single-center retrospective cohort study compared clinical and immunological outcomes of kidney transplant recipients receiving a CNI-based immunosuppressive regimens versus a cohort of patients converted from CNI to mTORi-based immunosuppressive therapy due to CNI-associated adverse events.

We included adult renal transplant patients receiving mTORi-based therapy for more than 5 years or CNI-based regimen, with functional graft function higher than 25 ml/min/1.73 m^2, followed at the Izmir Tepecik Training and Research Hospital. Patients with incomplete information in their files and those who lost their graft or died were excluded. Thus, a total of 89 patient files, 37 of whom were using mTORi and 52 using CNI, were examined with the approval of the Ethics Committee.

Age, sex, dialysis duration, donor type, transplant times, transplant number, mismatch number, diabetes mellitus (DM), history of cardiovascular disease (CVD) and hypertension (HT), delayed graft function (DGF), and induction treatments were recorded in both groups. Serum CNI and mTOR levels have been tried to be kept at therapeutic levels since the transplantation of the patients. Patients whose drug levels could not be provided were switched to a different drug. Serum drug levels in the patients included in the study were at therapeutic levels (EVE: 3-8 ng/ml, SRL: 8-12 ng/ml, TAC: 3-8 ng/ml as c0, CsA: -800 ng/ml as c2).

We recorded PRA levels before transplantation and the latest PRA and DSA results for post-transplant immunological monitoring, as well as the lowest creatinine level reached by the patients after transplantation and data showing the graft function at the last visit. We also recorded the reason for switching to mTORi, as well as the duration of mTORi and CNI use before conversion. Acute rejection, malignancy, and BKVN were noted in both groups.

Sequence-specific Oligonucleotides Method

Sequence-specific oligonucleotides (SSO) method was performed according to the manufacturer's instructions (Lifecodes HLA SSO Typing Kit Immucor, USA). For the first amplification step, 16 µl of a mix containing master mix, H_2O, and Taq polymerase was added to 4 microliters of DNA (15-200 ng) in an Eppendorf tube (200 µl). The total volume of 20 µl sample was placed in the thermal cycler and the program was run. For the second hybridization step, the probe mix was warmed at 56°C for 7 minutes. The probe mix was sonicated and vortexed before use. Then, 15 µl of probe mix was added to 5 microliters of amplicon in 96-well plates, and the samples were placed in the thermal cycler and the hybridization program was run for 20 minutes. During this run, the Luminex fluoroanalyzer instrument was prepared for the analysis. When the hybridization program ended at 56°C, 170 µl diluted streptavidin was added on the samples in the wells, and the well was placed in the Luminex instrument. The results were analyzed by MatchIt software program.

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Panel Reactive Antibody method

Lifecodes LifeScreen Class I and II ID Kits (Immucorgamma, USA) were used for Class I and Class II identification, respectively. After the 96-well plates were moisturized, and washed with buffer, patient/control sera and HLA Class I or II ID beads were added into the wells. The plate was incubated at room temperature for 30 minutes in the dark. After incubation, the wells were washed with 200 µl buffer 3 times. Then, the conjugate was prepared in appropriate concentration and added into the wells. After incubation at room temperature for 30 minutes in the dark, 150 µl wash buffer was added into the wells. The plate was gently mixed in the Luminex Fluoroanalyzer instrument, and the results were analyzed by MatchIt Software program.

In this study, we performed a bead-based PRA specific test. Since we know the patient-donor HLA typing results, we interpreted whether patients had DSA according to the PRA results; in other words, we can express this as a virtual cross-match.

The main tests used to investigate the presence of DSA are cell-based cross-match tests such as CDCXM and FCXM. We need living cells to perform these tests. However, some of our patients included in the study had cadaveric transplants. There are transplants from living donors, but our study covers the late post-transplant period and it was difficult to reach the donors. In recent years, it has been used to support the determination of DSA in solid-phase cross-match tests. Since solid-phase cross-match tests were not performed in our laboratory during the years covering the study, we evaluated our results according to Luminex-PRA specific test results.

Additionally, DSA can be interpreted with single-antigen brad tests. However, due to high cost of soap kits, it could not be performed by us.

Statical Analysis

Statistical analyzes were performed using IBM® SPSS® 25 (NY, USA) software. The suitability of variables to normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics were done by giving the mean±standard deviation, median and IQR, minimum-maximum value. In categorical variables, frequency and percentage values were given and Pearson's or Fisher's Exact Chi-Square test were used for comparison of categorical variables. In comparison of independent groups between continuous variables, the *t* test was used for variables that conformed to normal distribution, and the Mann-Whitney U test was used for non-normal distribution. In comparison of more than 2 groups, Kruskal-Wallis test was used and then post hoc Bonferroni correction was used. $p<0.05$ was considered significant.

Results

Primary etiologies of kidney diseases, dialysis type, donor type, history of hypertension, cardiovascular disease, rate of DGF, and induction therapy were similar in both groups. Additional immunosuppressive drugs given to both groups were MMF/MPA and prednisolone. The switch time to mTORi in patients ranged from 0 to 19 years, but the average was 4 years.

In the mTORi group, all the individuals were initiated with CNI and 75% of them were switched to mTORi regimen due to adverse reactions with CNI. These adverse reactions were diabetes mellitus (18.9%), gingival hyperplasia (16.2%), BK and CMV infections (10.8%), malignancy (8.1%), dermatological effects (8.1%) in decreasing frequency. Therapeutic transition was made in 35% of the patients because the desired drug blood level was not achieved and nephrotoxicity needed to be avoided. In 4 patients with acute rejection, kidney biopsy was performed in 1 steroid-resistant patient and chronic antibody-mediated rejection was detected. No finding related to CNI toxicity was detected in the biopsy.

The demographic information and comorbid diseases of the patients are shown in **Table 1** and the biochemical data are shown in **Table 2**. Tables revealed that mismatch (MM), transplant time, DM, BKVN, and actual spot urine protein/creatinine ratios were significantly different between the 2 groups.

The increased prevalence of MM in the CNI group might be related to targeting more potent immunosuppression. The higher rates of DM and BKVN in the mTORi group may be attributed to the use of CNIs before conversion to mTORi. Proteinuria, which is a specific adverse effect of mTORi, was significantly increased in our study. Acute rejection was increased in the CNI group, whereas malignancy rates were increased in mTORi group, although the differences were not statistically significant.

As seen in **Table 3**, no difference was found between the groups in immunological tests such as PRA and DSA.

Discussion

DSAs that occurs against a graft's antigens cause AMR and subsequent chronic graft dysfunction [12]. Use of solid-phase single-antigen bead technology to detect HLA antibodies has started a new research phase in this field. Solid-phase immunity analysis, especially LUMINEX®, is more sensitive than complement-dependent lymphocytotoxicity (CDC) analysis that has been used before; thus, it is recommended for use in high-risk patients [13]. In our center, therapy is managed based on immunologic analysis and pathological data when necessary, by performing these follow-ups at regular intervals.

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Table 1. Comparing demographic and comorbidity variables between groups.

Variables	mTOR group (n=37) mean±SD	CNI group (n=52) mean±SD	p
Age (year)	45.2±12.5	46.4±12.1	0.500
Transplant year	11.2±4.5	9.1±3.9	**0.025**
Transplant number	1.03±0.1	1.02±0.1	0.800
Mismatch	3.27±0.6	3.56±0.6	**0.024**
	n (%)	n (%)	
Sex (F/M)	19/18 (51.4/48.6)	21/31 (40.6/59.4)	0.300
Presence of DM	8 (21.6)	2 (3.8)	**0.015**
Presence of HT	17 (45.9)	31 (59.6)	0.200
Presence of CVD	2 (5.4)	1 (1.9)	0.568
Post-transplant BKVN	4 (10)	0 (0)	**0.020**
Post-transplant AR	4 (10.8)	7 (13.5)	0.700
Post-transplant malignancy	3 (8.1)	1 (1.9)	0.300
Delayed graft function	4 (10.8)	10 (19.2)	0.282
Cadaveric donor	15 (40.5)	22 (42.3)	0.867
Live donor	22 (59.5)	30 (57.7)	0.867
Induction therapy	29 (78.4)	42 (80.8)	0.781
Used ATG	8 (21.6)	21 (40.4)	0.236
Used IL-2 antagonist	21 (56.8)	21 (40.4)	0.693

Independent t test was used for comparing age parameter. Pearson's or Fisher's exact chi-square tests were used for categorical data. P<0.05 was considered significant. DM – diabetes mellitus; HT – hypertension; CVD – cardiovascular disease' BKVN – BK virus nephropathy; AR – acute rejection.

Table 2. Biochemical analysis features of the study groups.

Variables	mTOR group (n=37) mean±SD	CNI group (n=52) mean±SD	p
Post-transplant creatinine (mg/dl)	1.20±0.3	1.30±0.3	0.060
Actual creatinine (mg/dl)	1.32±0.5	1.43±0.5	0.330
Post-transplant eGFR (ml/min per/1.73 m^2)	67.4±16	63±12.8	0.230
Actual eGFR (ml/min per/1.73 m^2)	59.7±20	57±17	0.520
Post-transplant spot urine protein/creatinine	0.1±0.2	0.14±0.3	0.110
Actual spot urine protein/creatinine	0.3±0.5	0.28±1.0	**0.009**

Independent t test was used and P<0.05 was considered significant.

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Table 3. Comparing pre- and post-transplant immunological variables between study groups.

Variables	mTOR group (n=37) n (%)	CNI group (n=52) n (%)	p
Pretransplant PRA positivities	4 (11.1)	10 (20)	0.240
Pretransplant PRA I positivities	4 (11)	7 (14)	0.260
Pretransplant PRA II positivities	3 (8.7)	7 (14)	0.260
Post-transplant PRA positivities	12 (33)	13 (27)	0.390
Post-transplant PRA I positivities	3 (8.3)	7 (14.6)	0.670
Post-transplant PRA II positivities	8 (22)	9 (18)	0.900
Post-transplant PRA-A positivities	0 (0)	3 (6.3)	0.160
Post-transplant PRA-B positivities	4 (11.1)	5 (10.4)	0.500
Post-transplant PRA-DR positivities	2 (5.6)	1 (2.1)	0.570
Post-transplant PRA-DQ positivities	7 (19.4)	9 (18.8)	0.500
Post-transplant DSA positivities	6 (16.7)	6 (12.5)	0.290
Post-transplant non-DSA positivities	7 (19.4)	10 (20)	0.720

Pearson's or Fisher's exact chi-square tests were used. P<0.05 was considered significant.

The emerging information regarding the effect of DSA on graft results and the ability to evaluate DSA levels under specific immunosuppressive regimens highlighted the question of which classes of drugs may affect the risk of DSA occurrence [14]. The SPIESSER and CENTRAL trials showed that no significant effect was found after discontinuation of CsA then switching to SRL or EVE [15,16]. We observed no significant increase of DSA levels after using these drugs for a longer period.

In another trial it was reported that switching therapy from CNI to mTORi in the 2nd year after transplantation, HLA class I levels were higher in the group that was switched to EVE than in the control group, whereas HLA class II levels were similar [17].

The clinicians' first mission should be preventing AMR occurrence, as there is no specific salvage therapy. Post-transplant DSA formation risk is determined by the intensity of immunosuppressive therapy and the rate of patient compliance to the therapy. An early switch from CNI to mTORi might increase the risk of DSA formation. To reduce risk, maintaining optimal MMF/MPA and probably continuing steroids seems to be convenient. In case of an early switch to another regimen without CNI, DSA follow-up and protocol biopsies should be performed. The late transformation from CNI treatment to a mTORi after the first year of transplantation has not been shown to affect the risk of developing DSA [18].

In the clinical trial carried out in human cell culture, EVE was found less potent in inhibiting cellular alloimmunity, but equally effective on humoral alloimmunity. This is why EVE might be a suitable alternative if tacrolimus toxicity occurs in the early period of renal transplant patient [19]. In an EVE study aimed at avoiding CNI toxicity, EVE was shown to be no less effective than MPA in patients with low to moderate immunological risk [20]. Improvement in kidney functions was observed when the regimen was switched from CNI to mTORi in liver transplant patients [21].

Randomized controlled studies show that an optimal treatment can be successful in terms of both adverse effects and efficacy with everolimus added with reduced tacrolimus levels [22,23]. The use of mTOR-i instead of antimetabolites may not significantly alter major clinical outcomes. The use of mTOR-i can be a valuable pharmacological tool to minimize complications of CNI and achieve adequate immunosuppression [24].

Complement-based IgG subgroup-DSAs might be more useful in immunological monitoring [25,26]. Immunological responses emerging as either subclinical or clinical rejections critically affect both graft and overall survival [27]. It has also been shown that there is no increase in AMR in short-term results [28].

After 7 years of follow-up, there was no significant difference between the groups in terms of IMT (intima media thickness), actual CV events and mortality, CV risk profile, predicted MACE/Mortality between the mTORi and CNI-based regimen [29].

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This study was retrospective. In both groups, those who died and those who lost their graft were excluded. Unfortunately, these are the shortcomings of the study. This study is prospective and can yield better results in cases where regular immunological monitoring is performed from the beginning and any graft loss is noted by supporting biopsy when necessary. But still, there is no immunological problem in using mTORi instead of or alongside CNI for whatever reason.

Conclusions

Long-term use of mTORi does not appear to be an immunological problem. Further clinical trials with a larger population are needed to optimize the strength of our evidence.

Conflict of Interest

None declare.

References:

1. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007;357:2562-75
2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(Suppl.3):S1-155
3. Guba M, Pratschke J, Hugo C, et al, SMART-Study Group. Renal function, efficacy, and safety of sirolimus and mycophenolate mofetil after short-term calcineurin inhibitor-based quadruple therapy in de novo renal transplant patients: One-year analysis of a randomized multicenter trial. Transplantation. 2010;90:175-83
4. Hernández H, Martínez D, Gutiérrez E, et al. Clinical evidence on the use of anti -mTOR drugs in renal transplantation. Nefrologia. 2011;31(1):27-34
5. Nishioka S, Ishimura T, Endo T, et al. Suppression of allograft fibrosis by regulation of mammalian target of rapamycin-related protein expression in kidney-transplanted recipients treated with everolimus and reduced tacrolimus. Ann Transplant. 2021;26:e926476
6. Alfano G, Fontana F, Mori G, et al. Antiviral activity of sirolimus in an HIV-positive kidney transplant recipient. Int J STD AIDS. 2019;30(9):919-22
7. Colvin RB. Antibody-mediated renal allograft rejection: Diagnosis and pathogenesis. J Am Soc Nephrol. 2007;18:1046-56
8. Worthington JE, Martin S, Al-Husseini DM, et al. Posttransplantation production of donor HLA-specific antibodies as a predictor of renal transplant outcome. Transplantation. 2003;75:1034-40
9. Mao Q, Terasaki PI, Cai J, et al. Extremely high association between appearance of HLA antibodies and failure of kidney grafts in a five-year longitudinal study. Am J Transplant. 2007;7:864-71
10. Lachmann N, Terasaki PI, Budde K, et al. Anti-human leukocyte antigen and donor-specific antibodies detected by luminex posttransplant serve as biomarkers for chronic rejection of renal allografts. Transplantation. 2009;87:1505-13
11. Croze LE, Tetaz R, Roustit M, et al. Conversion to mammalian target of rapamycin inhibitors increases risk of de novo donor-specific antibodies. Transpl Int. 2014;27(8):775-83
12. Loupy A, Hill GS, Jordan SC. The impact of donor-specific anti-HLA antibodies on late kidney allograft failure. Nat Rev Nephrol. 2012;8:348-57
13. Tait BD, Süsal C, Gebel HM, et al. Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. Transplantation. 2013;95:19-47
14. Thaunat O, Koenig A, Leibler C, Grimbert P. Effect of immunosuppressive drugs on humoral allosensitization after kidney transplant. J Am Soc Nephrol. 2016;27:1890-900
15. Gatault P, Bertrand D, Büchler M, et al. Eight-year results of the Spiesser study, a randomized trial comparing de novo sirolimus and cyclosporine in renal transplantation. Transpl Int. 2016;29:41-50
16. Mjörnstedt L, Schwartz Sørensen S, von Zur Mühlen B, et al. Renal function 3 years after early conversion from a calcineurin inhibitor to everolimus: Results from a randomized trial in kidney transplantation. Transplant Int. 2015;28:42-51
17. de Fijter JW, Holdaas H, Øyen O, et al. Early conversion from calcineurin inhibitor- to everolimus-based therapy following kidney transplantation: Results of the randomized ELEVATE trial. Am J Transplant. 2017;17(7):1853-67
18. Grimbert P, Thaunat O. M-TOR inhibitors and risk of chronic antibody-mediated rejection after kidney transplantation: Where are we now? Transpl Int. 2017;30(7):647-57
19. Eleftheriadis T, Pissas G, Sounidaki M, et al. 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(9):1691-97
20. Pascual J, Berger SP, Witzke O, et al; TRANSFORM Investigators. Everolimus with reduced calcineurin inhibitor exposure in renal transplantation. J Am Soc Nephrol. 2018;29(7):1979-91
21. Hüsing A, Schmidt M, Beckebaum S, et al. Long-term renal function in liver transplant recipients after conversion from calcineurin inhibitors to mTOR inhibitors. Ann Transplant. 2015;20:707-13
22. Traitanon O, Mathew JM, Shetty A, et al. Mechanistic analyses in kidney transplant recipients prospectively randomized to two steroid free regimen-Low dose Tacrolimus with Everolimus versus standard dose Tacrolimus with Mycophenolate Mofetil. PLoS One. 2019;14(5):e0216300
23. Sommerer C, Suwelack B, Dragun D, et al, Athena Study Group. An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in de novo kidney transplant patients. Kidney İnt. 2019;96(1):231-44
24. Caletti C, Manuel Ferraro P, Corvo A, et al. Impact of 3 major maintenance immunosuppressive protocols on long-term clinical outcomes: Result of a large multicenter Italian cohort study including 5635 renal transplant recipients. Transplant Proc. 2019;51(1):136-39
25. Cozzi E, Biancone L. C1q-binding donor-specific antibody assays help define risk and prognosis in antibody-mediated rejection. Kidney Int. 2018;94(4):657-59
26. Ponsirenas RVG, Cazarote HB, Araújo SA, et al. Anti-HLA donor-specific IgG subclasses and C1q-binding evolution in posttransplant monitoring. Transplant Direct. 2018;4(9):e385
27. da Silva CK, Meinerz G, Bruno RM, et al. Late impact of preformed anti-HLA antibodies on kidney graft outcome. Transpl Immunol. 2019;55:101212
28. de Sousa MV, Gonçalez AC, de Lima Zollner R, Mazzali M. Effect of preformed or de novo anti-HLA antibodies on function and graft survival in kidney transplant recipients. Ann Transplant. 2018;23:457-66
29. van Dijk M, van Roon AM, Said MY, et al. Long-term cardiovascular outcome of renal transplant recipients after early conversion to everolimus compared to calcineurin inhibition: Results from the randomized controlled MECANO trial. Transpl Int. 2018;31(12):1380-90

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