Transplantation Reviews 33 (2019) 191–199

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Review article

Evidence-based practice: Guidance for using everolimus in combination with low-exposure calcineurin inhibitors as initial immunosuppression in kidney transplant patients

Julio Pascual [a,*,1], Stefan P. Berger [b,1], Steven J. Chadban [c], Franco Citterio [d], Nassim Kamar [e], Dennis A. Hesselink [f], Christophe Legendre [g], Ute Eisenberger [h], Federico Oppenheimer [i], Graeme R. Russ [j], Claudia Sommerer [k], Paolo Rigotti [l], Titte R. Srinivas [m], Yoshihiko Watarai [n], Mitchell L. Henry [o], Flavio Vincenti [p], Helio Tedesco-Silva [q,**]

[a] Department of Nephrology, Hospital del Mar, Barcelona, Spain
[b] Division of Nephrology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[c] Renal Medicine, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia
[d] Department of Surgery, Renal Transplantation, Catholic University, Rome 00168, Italy
[e] Department of Nephrology, Dialysis and Organ Transplantation, CHU Rangueil, INSERM U1043, IFR–BMT, University Paul Sabatier, Toulouse, France
[f] Erasmus MC, University Medical Center Rotterdam, Department of Internal Medicine, Division of Nephrology and Transplantation, Rotterdam, the Netherlands
[g] Paris Translational Research Center for Organ Transplantation, INSERM U970, Necker Hospital University Paris Descartes, Paris, France
[h] Department of Nephrology, University Duisburg-Essen, University Hospital Essen, Essen, Germany
[i] Department of Nephrology, Hospital Clinic, Barcelona, Spain
[j] Central and Northern Adelaide Renal and Transplantation Service, Royal Adelaide Hospital, Adelaide, Australia
[k] Department of Nephrology, University Hospital Heidelberg, Heidelberg, Germany
[l] Kidney and Pancreas Transplant Unit, Padua University Hospital, Padua, Italy
[m] Division of Nephrology, Intermountain Healthcare, Salt Lake City, UT, USA
[n] Department of Transplant Nephrology and Surgery, Kidney Disease Center, Nagoya Daini Red Cross Hospital, Nagoya, Japan
[o] Department of Surgery, The Comprehensive Transplant Center, The Ohio State University, Wexner Medical Center, Columbus, OH, USA
[p] Department of Surgery, Kidney Transplant Service, University of California, San Francisco, CA, USA
[q] Division of Nephrology, Hospital do Rim, Universidade Federal de São Paulo, São Paulo 04038-002, Brazil

ARTICLE INFO

Keywords:
Everolimus
mTOR inhibitor/mTORi
Transplantation
Guidelines
Kidney

ABSTRACT

The mammalian target of rapamycin (mTOR) inhibitor, everolimus, in combination with reduced-exposure calcineurin inhibitor (CNI), has been demonstrated in clinical trials to have comparable efficacy in low-to-moderate immunological risk kidney transplant recipients to the Standard of Care, mycophenolic acid (MPA) in combination with standard-exposure CNI. Current treatment guidelines consider mTOR inhibitors to be a second-line therapy in the majority of cases; however, given that everolimus-based regimens are associated with a reduced rate of viral infections after transplantation, their wider use could have great benefits for kidney transplant patients. In this evidence-based practice guideline, we consider the *de novo* use of everolimus in kidney transplant recipients. The main outcomes of our consideration of the available evidence are that: 1. Everolimus, in combination with reduced-exposure CNI and low dose steroids, is a suitable regimen for the prophylaxis of kidney transplant rejection in the majority of low-to-moderate immunological risk adult patients, with individualized management; 2. Induction with either basiliximab or rabbit anti-thymocyte globulin is an effective therapy for kidney transplant recipients when initiating an everolimus-based, reduced-exposure CNI regimen; and 3. An individualized approach should be adopted when managing kidney transplant recipients on everolimus-based therapy.

© 2019 Published by Elsevier Inc.

Abbreviations: AMR, antibody-mediated rejection; BKV, BK virus; BMI, body mass index; BPAR, biopsy-proven acute rejection; C_0, pre-dose concentration; CMV, cytomegalovirus; CsA, ciclosporin/cyclosporine A; CNI, calcineurin inhibitor; CT, computed tomography; DSA, donor-specific antibodies; eGFR, estimated glomerular filtration rate; EVR, everolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; mTORi, mammalian target of rapamycin inhibitor; NMSC, non-melanoma skin cancer; PRA, panel-reactive antibodies; rATG, rabbit antithymocyte globulin; TAC, tacrolimus; tBPAR, treated biopsy-proven acute rejection.

* Corresponding author at: Department of Nephrology, Hospital del Mar, Passeig Maritim 25-29-08003, Barcelona, Spain.
** Corresponding author at: Division of Nephrology, Hospital do Rim-UNIFESP, Rua Borges Lagoa, 960, 11° andar, São Paulo 04038-002, Brasil.
E-mail addresses: jpascual@psmar.cat (J. Pascual), heliotedesco@medfarm.com.br (H. Tedesco-Silva).
[1] Joint first authors.

https://doi.org/10.1016/j.trre.2019.07.001
0955-470X/© 2019 Published by Elsevier Inc.

Contents

1. Introduction

Everolimus (EVR) is a mammalian target of rapamycin inhibitor (mTORi) that can be used to achieve immunosuppression in patients following solid organ transplantation. EVR is approved in over 90 countries to prevent organ rejection, and is currently approved in combination with ciclosporin (CsA) for kidney or heart transplant patients, or in combination with tacrolimus (TAC) for liver transplant patients.

Due to the synergistic immunosuppressive effects of EVR and calcineurin inhibitors (CNI), use of a combination of these drugs post transplant permits a reduction in the dose of CNI. For example, a previous 24-month open-label clinical study in 833 *de novo* renal transplant recipients demonstrated that combination with EVR permitted a 60% reduced dose of CsA while maintaining efficacy, renal function and safety compared with a mycophenolic acid (MPA) + standard dose CsA regimen [1]. Indeed, a reduction in CNI exposure alongside mTORi is necessitated by the potential for nephrotoxicity when these agents are combined with standard CNI doses [2]. The proposed long-term benefits of such a reduction include reduced risk of CNI-associated nephrotoxicity, neurotoxicity, and other adverse events; however, this remains to be demonstrated, potentially due to a lack of standardized and sensitive methods for collecting and analyzing these adverse advents, and insufficient follow-up duration in the clinical studies performed to date.

A number of trials have demonstrated the efficacy of EVR, in conjunction with reduced exposure to either CsA or TAC, in preventing organ loss or dysfunction in kidney transplant recipients [3–5]. The most recent studies to be completed are TRANSFORM (NCT01950819) and ATHENA (NCT01843348), of which TRANSFORM is the stronger study based on its higher patient numbers and longer duration of follow-up.

TRANSFORM was a 24-month, multicenter, randomized, open-label safety and efficacy study in 2037 *de novo* kidney transplant recipients [6]. In line with the 12-month results from this study, the 24-month data from TRANSFORM show that an EVR + reduced-exposure CNI regimen (EVR + rCNI) is non-inferior to a mycophenolic acid + standard exposure CNI regimen (MPA + sCNI) when considering a binary endpoint of treated biopsy-proven acute rejection (tBPAR) or estimated glomerular filtration rate (eGFR) <50 mL/min/1.73m^2 [7,8]. Benefits of the EVR-based regimen in the TRANSFORM trial included a significantly reduced incidence of viral infections, particularly BK virus (BKV) and cytomegalovirus (CMV) [9], and evidence of improved kidney function in the early post-transplant period in EVR-treated patients whose CNI exposure levels were consistently within the lower CNI target range, though this was not deemed clinically or statistically relevant [8].

ATHENA was a 12-month, multicenter, open-label, prospective, randomized, parallel group study comparing three treatments in 612 *de novo* kidney transplant patients: EVR + TAC, EVR + CsA, and MPA + TAC [10]. In this study, non-inferiority of the primary endpoint (12-month eGFR), as assessed in the per-protocol population (n = 338), was not shown for EVR + TAC or EVR + CsA *vs* MPA + TAC ($p = 0.239$ and $p = 0.151$ for non-inferiority, respectively) [11].The incidence of the key secondary end-point in ATHENA, treatment failure (a composite end-point of tBPAR, graft loss or death), was significantly increased in the EVR + CsA arm, but not the EVR + TAC arm, compared with MPA + TAC (24.6%, 13.0%, 9.8%, respectively) [11]. This was attributable to an increased rate of BPAR in the EVR + CsA group (19.1% compared with 7.2% in the EVR + TAC group and 4.9% in the MPA + TAC group; log rank $p = 0.291$ for EVR + TAC *versus* MPA + TAC and $p < 0.001$ for EVR/CsA *versus* MPA/TAC). Whilst the non-inferiority endpoint with respect to eGFR was not reached in the ATHENA study, the CNI levels were consistently higher than those outlined in the protocol, and higher than those in the TRANSFORM study, which could help to explain this finding. Indeed, in a *post-hoc* analysis considering only patients whose TAC levels were consistently within the target range, there was no significant difference between treatment arms with respect to the increase in eGFR over 12 months ($p = 0.080$) [11].There were also some demographic imbalances, for example the EVR + CsA arm had a higher number of kidneys from deceased donors aged ≥65 years, which is known to be associated with reduced graft function. In addition, there was no control group for the EVR + CsA arm in this study; however, a previous study, A2309, compared EVR + CsA and MPA + CsA and did show non-inferiority for EVR with regard to a composite efficacy failure primary endpoint, or eGFR at 12 months [4]. As in TRANSFORM and other studies, the ATHENA study found a significantly lower rate of viral infections, including CMV and BKV infections, in the EVR arms compared with the MPA + TAC arm [11].

As with any immunosuppressive regimen, there are a number of safety and tolerability considerations that need to be taken into account when initiating an EVR-based regimen. Both the TRANSFORM and ATHENA studies reported a higher rate of adverse events (AE) leading to drug discontinuation in EVR arms compared with MPA arms (23% *vs* 12% in TRANSFORM; 31–35% *vs* 14% in ATHENA) [9,11]. The particular AE underlying discontinuation varied depending on treatment arm, for example in the TRANSFORM study, discontinuation of the study drug was more frequently due to rejection or impaired healing with EVR, and more often due to BKV infection or BKV nephropathy with MPA [9]. One of the aims of this guidance is to assist with the anticipation and management of adverse events that may arise, and guide physicians in balancing the advantages and disadvantages of the available treatment approaches depending on their patient's individual circumstances.

1.1. Existing guidelines

There are a number of post-transplant immunosuppressive treatment options currently available for kidney transplant recipients – including biologics, CNI, antimetabolites, immunomodulators, and mTORi – and guidelines have been published by a number of groups to support physicians in choosing the best options for their individual patients. The most recent global guidelines to be published by Kidney Disease: Improving Global Outcomes (KDIGO) were the 2009 Clinical Practice Guidelines on the Monitoring, Management, and Treatment of Kidney Transplant Recipients [12]. Local modifications and commentaries were subsequently published by groups from around the world; the Canadian Society of Transplantation and Canadian Society of

Nephrology [13], the US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) [14], European Renal Best Practice (ERBP) [15], and Kidney Health Australia – Caring for Australasians with Renal Impairment (KHA-CARI) [16]. Additional guidelines have been published by the European Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group in 2017 [17] and the UK-based Renal Association, also in 2017 [18].

None of these existing guidelines provide a high level of detail on the use of mTORi, and EVR in particular, in kidney transplant patients. In all cases, their advice relates to mTORi as a class, rather than taking into account the individual characteristics of sirolimus and EVR that result from differences in their pharmacokinetic profiles and biochemical properties. In almost all cases, these guidelines suggest mTORi as second line therapy or as an alternative option in patients who are unable to tolerate standard regimens based on MPA + CNI, with the exception of specific patient groups such as patients with Kaposi's sarcoma or those at a high risk of neoplasm. None of these guidelines detail the use of mTORi (or EVR in particular) as a first line, *de novo* therapy in kidney transplant recipients.

In light of the recent availability of the new data from ATHENA and TRANSFORM, it was decided to convene a group of expert transplant specialists, including surgeons and nephrologists, to synthesize the available clinical data and collective experience of *de novo* use of EVR + rCNI regimens in kidney transplant recipients, with the aim of providing guidance on the optimal use of this approach to improve outcomes following kidney transplantation.

We have considered evidence and experience relating to three aspects of the *de novo* use of EVR + rCNI regimens in adult kidney transplant recipients: defining the everolimus patient; initiating patients on everolimus; and patient management. The resulting evidence-based consensus statements are designed to provide guidance based on expert evaluation of the ATHENA and TRANSFORM findings, with additional advice and considerations from other trials and real-world experience of using EVR *de novo* in combination with reduced exposure CNI.

2. Evidence-based practice guidance

2.1. Defining the everolimus patient

1. **Everolimus, in combination with reduced-exposure calcineurin inhibitor and low dose steroids, is a suitable regimen for the prophylaxis of kidney transplant rejection in the majority of low-to-moderate immunological risk adult patients, with individualized management**

Relative considerations and advice:

I. **Low-to-moderate risk**: A patient at low-to-moderate risk for experiencing efficacy or safety concerns on an EVR-based regimen would fulfil the following criteria: first or second transplant, on the condition that the first transplant was not lost due to immunological reasons; low-to-moderate immunological risk based on clinical judgement, low panel-reactive antibodies (PRA) and absence of preformed donor-specific antibodies (DSA); low risk of recurrence of primary kidney disease; and without high risk for wound healing problems.
   - Although patients with focal segmental glomerulosclerosis (FSGS) were not excluded from either the ATHENA or TRANSFORM trials, mTORi-based regimens are often avoided in patients with previous graft loss attributed to primary FSGS as a precaution, since mTORi-related proteinuria may interfere with the detection of recurrent disease.

II. **Donor types**: EVR-based regimens have been used successfully in patients receiving kidneys from a range of donor types.

The TRANSFORM and ATHENA trials included patients receiving a graft from a living donor or a donor deceased after brain death (DBD), based on standard or expanded criteria. Expanded criteria donors included patients aged > 60 years, or > 50 years with two of the following: history of hypertension, terminal serum creatinine ≥ 1.5 mg/dL (132 μmol/L), or death resulting from a cerebrovascular accident [6,10]. In both trials, patients were stratified by donor type prior to randomization to ensure an even distribution between treatment arms. In TRANSFORM, when efficacy endpoints were evaluated by donor, between-arm differences were largely comparable. However, the incidences of primary endpoint and eGFR < 50 mL/min/1.73 m^2 were significantly higher in the EVR + rCNI vs MPA + sCNI arm among recipients of kidneys from standard criteria donors (Efficacy failure: EVR + rCNI, 48.3%; MPA + sCNI, 39.4%; P = 0.022; eGFR: EVR + rCNI, 46.6%; MPA + sCNI, 38.0%) [8].

III. **Viral infection risk**: EVR + rCNI may provide long-term benefit by reducing the risk of viral infection, and should especially be considered in kidney transplant recipients at a high risk of viral infection.

Clinical studies have consistently demonstrated a reduction in the rate of viral infections in patients on an EVR + rCNI regimen vs MPA + sCNI [3–5,19]. In the TRANSFORM study, the 24-month incidences of infection were significantly reduced in EVR + rCNI vs MPA + sCNI patients for overall viral infections (17.2% vs 29.2%, P < 0.001), BKV infection (4.3% vs 8.0%, P < 0.001) and CMV infection (3.6% vs 13.3%, P < 0.001) [9]. Incidence of CMV in the TRANSFORM trial was lower for all serology status pairs except D−/R-, significantly so for high-risk donor-seropositive pairs, and irrespective of prophylaxis [9]. In the ATHENA study, both CMV infection (6.2% EVR + TAC, 2.5% EVR + CsA, 20.6% MPA + TAC) and BKV infection (17.1%, 9.1%, 22.5%, respectively) were significantly more frequent with MPA + TAC [11].

IV. **Patients at high immunological risk of rejection**: There are no data to support or refute the use of an EVR + rCNI regimen in these patients.
   - The TRANSFORM and ATHENA protocols excluded patients at high immunological risk of rejection, including those who had high anti-donor reactivity (*e.g.* high panel reactive antibodies or presence of pre-existing donor-specific antibody), and those who had lost a previous graft due to immunological reasons.

The TRANSFORM and ATHENA trials did not exclude patients undergoing re-transplantation, provided that the reason for loss of the first graft was non-immunological. Only a small number of patients of this type were enrolled in ATHENA or TRANSFORM, therefore no conclusions can be drawn regarding this specific subpopulation.

V. **Patients receiving ABO-incompatible (ABOi) kidney transplants**: No recommendation can be made on the use of EVR + rCNI regimens in this subset of patients, as they were excluded from the ATHENA and TRANSFORM studies and other pivotal trials.

Nevertheless, the results from a single center case series of 25 ABOi transplantations suggests that a de novo EVR + rCNI regimen does not result in severe surgical or immunological complications, while maintaining a low rate of viral infections [20]. It should be noted that the majority of patients in this case series commenced EVR + rCNI plus immune adsorption or plasmapheresis two weeks prior to transplantation, and received rituximab alongside induction with basiliximab (and in some cases dual induction with basiliximab and rATG) [20].

VI. **Male patients who wish to maintain fertility**: There are no data relating to male infertility, however caution is advised in male patients who wish to have a child, as per the label.

An uncontrolled study in 256 male kidney transplant patients showed changes in testosterone, follicle stimulating hormone and luteinizing hormone with EVR [21]. However, given that these changes were comparable to those described with conventional immunosuppressive regimens, and only three patients reported erectile dysfunction, the authors concluded that EVR should only have a minor, if any, effect on testosterone production [21].

There are literature reports of reversible azoospermia and oligospermia in patients treated with sirolimus [22–25], although the concentrations of sirolimus used in the majority of these instances were higher than contemporary EVR-based regimens. Nevertheless, as detailed in the label, preclinical toxicology studies showed that EVR can reduce spermatogenesis; therefore, male infertility must be considered to be a potential risk of long-term use [26,27].

VII. **Female patients who wish to become pregnant**: Caution is advised when considering the optimal regimen for these patients. As per the label [27]:
- Female patients should be advised to use effective contraception methods during, and for 8 weeks after cessation of, EVR treatment.
- EVR should only be administered to pregnant women when the potential benefit outweighs the potential risk for the fetus.
- EVR should not be administered to patients who are breastfeeding

A previous report found that menstrual irregularity may affect a proportion of patients taking EVR, however this analysis was conducted in patients with tuberous sclerosis complex, whose pre-dose concentration (C_0) levels of EVR were twice the target range for immunosuppression following kidney transplantation (5–15 ng/mL, compared with the 3–8 ng/mL target in transplant recipients in the TRANSFORM trial, among others) [28].
There are very limited data suggesting that female fertility and pregnancy outcomes may not be adversely affected by EVR therapy; a number of case reports have been published relating to pregnancies in kidney transplant recipients taking EVR, with a successful maternal and fetal outcome [29–32].

VIII. **Previous history of solid organ neoplasia**: Clinical trials typically exclude patients with a history of malignancy during the 5 years prior to kidney transplantation. Yet, a previous history of neoplasia is not considered to be a contraindication for EVR therapy in kidney transplant recipients.
- Both the TRANSFORM and ATHENA studies excluded patients with a history of malignancy during the 5 years prior to kidney transplantation, therefore there are no data from these studies to inform on the risk of neoplasia in kidney transplant recipients.
- The TRANSFORM protocol did not exclude patients with a history of localized basal cell carcinoma of the skin, and the ATHENA trial did not exclude patients with a history of squamous or basal cell carcinoma of the skin, renal cell carcinoma ≤T1N0M0, prostate adenocarcinoma ≤T1N0M0, or adenocarcinoma of the thyroid.
- Patients should be monitored regularly for skin neoplasms and advised to minimize exposure to ultraviolet light and sunlight, and to use appropriate sunscreen, in line with both the license for EVR and the advice given to all patients post transplant.

As an antiproliferative agent, and having been approved (albeit at higher doses) for treatment of a variety of solid organ malignancies, including breast cancers and neuroendocrine tumors, EVR might be expected to reduce the risk of de novo or recurrent malignancy in kidney transplant recipients. While there is a strong indication from some trials in kidney transplant patients that early conversion to EVR/mTORi is associated with a reduced rate of overall post-transplant malignancy, the data are not yet strong enough to support the use of mTORi to protect against malignancy except in particular instances, e.g. Kaposi's sarcoma [33,34]. For example, a recent study compared the 9-year risk of incident cancer, non-melanoma skin cancer (NMSC), and death attributed to cancer among participants in four randomized controlled trials comparing de novo or early conversion to an EVR-containing regimen with CNI-based triple therapy. This analysis showed that de novo or early switch to EVR did not alter the 9-year risk of incident cancer or cancer-related death, however in a sub-analysis restricted to NMSC, EVR with reduced-exposure CNI provided significant protection against the long-term risk of NMSC [35].

IX. **Obese patients and patients with pre-transplant diabetes**: It is advisable to exercise caution and conduct a risk-benefit assessment for EVR in obese patients or patients with pre-transplant diabetes mellitus.

Univariate analysis of the 12-month safety analysis of the TRANSFORM study showed that BMI ≥ 30 kg/m^2 or the presence of diabetes at baseline was associated with a significant increase in wound dehiscence (compared with BMI < 30 kg/m^2 or absence of baseline diabetes, respectively) [36], which should be borne in mind when considering EVR treatment in these populations. However, the overall numbers of patients affected remained low. It is important to note that a considerable proportion of patients who had diabetes mellitus at baseline were also obese, therefore the association between wound healing complications and diabetes mellitus reported in TRANSFORM is not definitive.

The available clinical evidence supports the notion that EVR is a safe and effective post-transplant immunosuppressive regimen for the majority of adult kidney transplant patients at low-to-moderate immunological risk. There are limited data relating to the use of EVR in kidney transplant patients at high immunological risk, therefore clinical judgement should be used when considering an EVR-based regimen in these patients, based on the possibility of managing side effects and minimizing existing risk factors.

2.2. Initiating patients on everolimus

2. **Induction with either basiliximab or rabbit anti-thymocyte globulin is an effective therapy for kidney transplant recipients when initiating an everolimus-based, reduced-exposure CNI regimen; at present, there is limited clinical experience of use of this regimen without induction therapy in kidney transplantation**

Relative considerations and advice:

I. **Induction therapy**: The TRANSFORM protocol included induction therapy with basiliximab or rabbit anti-thymocyte globulin (rATG). The ATHENA protocol specified induction with basiliximab.
- There are no concerns regarding efficacy and safety for the use of either induction therapy when initiating EVR.
- There is a potential risk that omission of induction therapy increases the risk of acute rejection, because the majority of the patients do not achieve EVR >3 ng/ml during the first week.
- Nevertheless, clinical study data are available for the use of EVR + rCNI regimen without induction therapy, although no direct comparisons of induction *vs* non-induction exist for this regimen.

Clinical study data on the use of EVR + rCNI without induction demonstrate comparable efficacy to MMF + sCNI without induction [2,3]. However, no clinical studies have yet been performed to compare induction vs non-induction in kidney transplant recipients initiating EVR-based therapy. Notably, data from two prospective, randomized clinical studies investigating the use of de novo EVR in kidney transplant recipients suggest that induction therapy (in this case basiliximab) allows for the use of lower doses of EVR in combination with reduced CsA [37,38]. In addition, the use of basiliximab induction appears to have a protective effect against

Table 1
Recommended pre-dose concentrations (C_0) for CsA and TAC following commencement of EVR in kidney transplant patients.

Treatment	Month 1	Month 6	Month 6+
Ciclosporin	100–150 ng/mL	50–100 ng/mL (following a gradual reduction from Month 2 onwards)	25–50 ng/mL
Tacrolimus	4–7 ng/mL	3–6 ng/mL (following a gradual reduction from Month 2 onwards)	3–5 ng/mL

CsA, ciclosporin; EVR, everolimus; TAC, tacrolimus.

BPAR in patients with EVR C_0 below the target therapeutic range (<3 ng/mL). No data have been published regarding the use of EVR in combination with TAC without induction.

There are no previous publications comparing basiliximab vs rATG induction prior to the initiation of a de novo EVR + rCNI regimen. A Cochrane Collaboration review including studies in kidney transplant recipients receiving CNI in combination with MPA or azathioprine (AZA) found that there were some differences between outcomes when using interleukin-2 receptor (IL-2R) antagonists or rATG; while there was no difference in clinically diagnosed acute rejection, induction with rATG (albeit at higher doses than are currently used) was associated with an increased risk of CMV disease, malignancy, and side effects, but a lower rate of BPAR at one year [39].

Results from TRANSFORM showed that there were no significant differences in efficacy outcomes between treatment arms for either basiliximab or rATG induction [40].

II. **CNI exposure**: CNI C_0 should be maintained within the following ranges (Table 1):

- Ciclosporin:
  - 100–150 ng/mL during Month 1
  - 50–100 ng/mL by Month 6, following a gradual reduction from Month 2 onwards
  - 25–50 ng/mL from Month 6 onwards
- Tacrolimus:
  - 4–7 ng/mL during Month 1
  - 3–6 ng/mL by Month 6, following a gradual reduction from Month 2 onwards
  - 3–5 ng/mL from Month 6 onwards

It should be noted that the target C_0 levels for TAC recommended in this guidance are based on the true C_0 levels as measured during the TRANSFORM study, rather than the target ranges as defined in the TRANSFORM protocol.

The TRANSFORM results show comparable efficacy results within treatment arms regardless of the concurrent CNI used. However, while no significant differences were found, CsA was associated with a higher incidence of composite efficacy failure and eGFR <50 mL/min/1.73m^2 compared with TAC [8].

The results from the ATHENA study more strongly caution against the combination of EVR + CsA in favor of EVR + TAC; patients in the EVR + CsA arm in this trial experienced a higher treatment failure rate (BPAR, graft loss or death; P < .001 vs MPA + TAC), which was attributable to an increased rate of BPAR in the EVR + CsA arm (although the majority of these incidences were mild) [11].

III. **Everolimus exposure**: The starting dose of EVR is dependent upon the CNI used, due to pharmacokinetic interactions (see Fig. 1).
- With concomitant TAC, the starting dose is 3.0 mg/day (administered as 1.5 mg b.i.d.), compared with 1.5 mg/day (administered as 0.75 mg b.i.d.) in patients receiving concomitant CsA. The dose must then be adjusted to achieve an EVR C_0 of 3–8 ng/mL.
- EVR blood C_0 should be measured at 3–5 days post transplantation. If the result is <3 ng/ml, a 50% increase in the dose (2.25 mg b.i.d.) is advised.
- Certain medications and health conditions may alter the clearance of EVR; careful monitoring of EVR levels is advised in these patients, with adjustments made as necessary.
  - For example, special care should be taken in patients with impaired hepatic function; the dose should be adjusted according to Child-Pugh class and C_0 concentrations closely monitored [27].

Clinical studies have demonstrated a significantly higher incidence of BPAR in patients with EVR C_0 <3 ng/mL, irrespective of the use of induction therapy [37,41,42]. However, the use of basiliximab induction therapy does appear to reduce the overall rate of BPAR in these patients [37].

It is equally important not to exceed the target EVR C_0 concentration range, as higher exposure to EVR, especially at C_0 > 8 ng/mL, has been associated with higher levels of proteinuria, wound healing events, peripheral edema and hypercholesterolemia [27,43–45].

IV. **Monitoring**: Having achieved adequate target C_0 for EVR and the concomitant CNI, monitoring of both drugs should proceed as per the center treatment protocol. If the dose of EVR requires adjustment, or any additional changes are made to concomitant medication, further therapeutic drug monitoring is recommended.

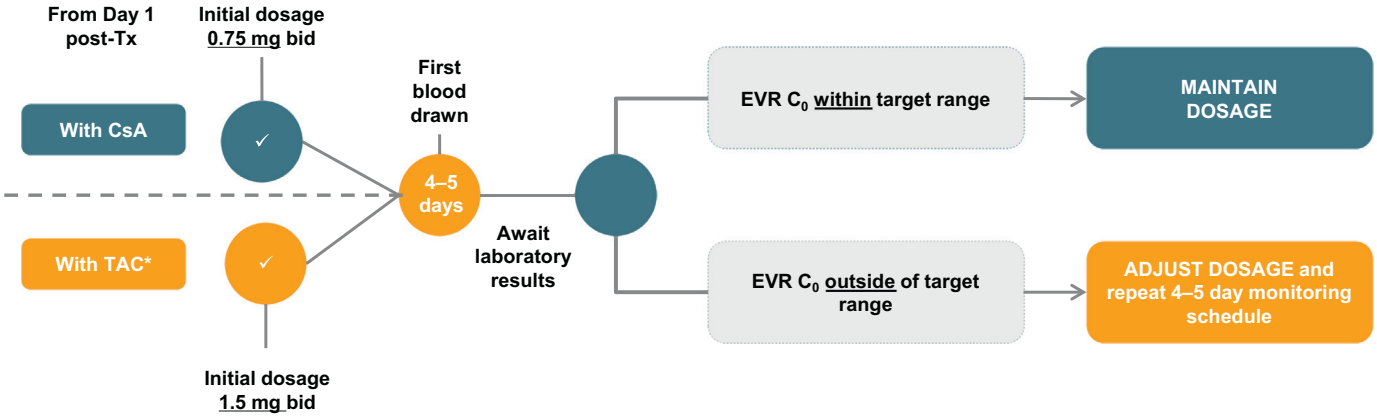

Fig. 1. Recommended protocol for initiating and therapeutic dose monitoring of everolimus in kidney transplant patients [6]. *EVR in combination with TAC is not approved for use in kidney transplantation patients. Example induction therapy: 2 × 20 mg basiliximab IV; first dose within 2 hours prior to surgery, second dose 4 days post-transplant. bid, twice daily; C0, pre-dose concentration; CsA, ciclosporin; EVR, everolimus; IV, intravenous; TAC, tacrolimus; Tx, transplantation.

2.3. Patient management

3. **An individualized approach should be adopted when managing kidney transplant recipients on everolimus-based therapy**

Relative considerations and advice:

I. **Wound healing events**: Certain patients may be at increased risk of experiencing wound healing complications, due to factors such as obesity. Patients with a BMI >35 kg/m^2 were excluded from TRANSFORM due to safety concerns. Downward adjustment of steroid dose should be considered in patients experiencing wound healing problems.

- If you consider your patient to be at high risk of experiencing wound healing events, an alternative immunosuppressive treatment should be considered in the immediate post-operative period.
  - o Commencement of an EVR-based regimen with a reduced initial dose is not advised, as the patient would be at increased risk of acute rejection [46,47].
  - o It is advisable to use an alternative treatment to EVR in the early post-transplant period and then switch to EVR at a later time point, *e.g.*, 3 months.

- If a patient experiences wound healing events following commencement of an EVR-based regimen, the approach should depend on the severity:
  - o In case of lymphoceles, they may not require discontinuation of EVR, but can be monitored or treated for example by drainage.
  - o For wound dehiscence, or for patients undergoing major surgery (*e.g.* bowel resection, joint replacement), it is advisable to temporarily discontinue EVR until resolution, and to increase the dose of CNI, if required, depending upon the immunological risk of the patient.

12-month safety analysis of the TRANSFORM data showed an increased risk of wound healing events in patients in the EVR + rCNI arm compared with MPA + sCNI (19.8% vs 16.2%; Relative Risk [RR] 1.22; 95% Confidence Interval [CI] 1.02, 1.47) [9]. In the ATHENA study, rates of wound healing complications were comparable between groups, affecting 30.5%, 28.3% and 33.3% of patients in the EVR + TAC, EVR + CsA and MPA + TAC arms, respectively [11].

II. **Proteinuria**: Proteinuria is a known side effect of mTORi, although less frequent with *de novo* use compared with post-transplant switch, especially late conversion (>12 months post transplant) [48,49]. Overall, proteinuria is uncommon in *de novo* kidney transplant recipients. As is the case for all kidney transplant recipients, patients receiving EVR should be monitored for proteinuria in line with the label. The cause of any significant proteinuria should be thoroughly investigated, and other causes should be ruled out before attributing proteinuria to EVR treatment. A proposed management algorithm for proteinuria is shown in Table 2.
  - ▪ The use of concomitant medication such as angiotensin receptor antagonists should be considered before switching immunosuppressive regimens [50].
  - ▪ If proteinuria persists in the nephrotic range, a biopsy is necessary; a switch to MPA may be appropriate if the biopsy reveals glomerular pathology or if the nephrotic syndrome develops.
  - ▪ It should be noted that there is no defined level that distinguishes acceptable or unacceptable proteinuria. In patients where persistent proteinuria is observed, a biopsy would be appropriate to assess glomerulopathy.

In the TRANSFORM study, proteinuria was assessed at scheduled visits by spot analysis of urinary protein/creatinine and categorized by levels of clinical relevance [6]. 12.6% of patients in the EVR + rCNI arm had proteinuria reported as an adverse event, compared with 5.6% in the MPA + sCNI arm [9]. The vast majority of patients in both arms had proteinuria in the

Table 2
Suggested management algorithms for selected adverse events following commencement of everolimus in kidney transplant patients.

Condition	Management	Follow-up
Proteinuria [50]		
Mild (<1 g/day)	• Continue administration of EVR (3–8 ng/mL)	Improvement or stabilization: Continue treatment with EVR
	• Administer an ACEI/ARB	Constantly monitor proteinuria
Moderate, non-nephrotic (1–3 g/day)	• Continue administration of EVR, aiming for the lower end of the range (*e.g.* 4 ng/mL) • Administer an ACEI/ARB	Improvement (proteinuria reduced to ≤1 g/day): • Continue treatment No improvement (persistent proteinuria > 1 g/day): Kidney biopsy • Glomerulonephritis: interrupt EVR, reintroduce CNI • Rejection: start antirejection treatment based on the center's standard procedures
Severe, nephrotic (>2 g/day despite ACEI/ARB)	• Kidney biopsy • Administer an ACEI/ARB	Kidney biopsy • Glomerulonephritis: interrupt EVR, reintroduce CNI
	• It may be necessary to interrupt or discontinue EVR (see biopsy)	• Rejection: start antirejection treatment based on the protocol
Peripheral edema [50]		
Mild to moderate	• Continue administration of EVR, consider decreasing dose to aim for 4–5 ng/mL	Improvement or resolution Continue treatment with EVR
	• Consider loop diuretics (furosemide/torsemide)	Inadequate response Consider reducing/withdrawing EVR
Severe/periorbital edema	• Discontinue EVR • Consider replacing with MPA or reintroducing CNI • Consider loop diuretics (furosemide/torsemide)	
Hyperlipidemia		
LDL cholesterol ≥100 mg/dL and/or total cholesterol ≥200 mg/dL	• Treat with statins • Consider treatment with ezetimibe if hyperlipidemia is persistent	Clinical improvement • Continue treatment with EVR Inadequate response to hypolipidemic therapy • Reduce blood levels of EVR
Triglycerides ≥170 mg/dL	• Treat with low-dose fibrates	• Gradually reduce or interrupt steroids; consider introducing or increasing the doses of azathioprine or MPA
Both LDL cholesterol and triglycerides are high (most common situation in clinical practice)	• Treat with statins	• Gradually reduce CsA or suspend it; consider increasing doses of MPA • If necessary, interrupt treatment with EVR and adjust immunosuppressive therapy

ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CNI, calcineurin inhibitor; CsA, ciclosporin; EVR, everolimus; LDL, low-density lipoprotein; MPA, mycophenolic acid.
Algorithms were based on the cited publication and internal Novartis documents.

non-nephrotic range; only 3.1% of patients in the EVR + rCNI arm and 1.4% of patients in the MPA + sCNI arm had proteinuria in the nephrotic range (≥3000 mg/g) at 12 months [9].

In the ATHENA study, urinalysis was performed at Months 1, 3, 6, 9 and 12. Proteinuria was reported as an adverse event in 4.3%, 15.2% and 11.8% in the EVR + TAC, EVR + CsA and MPA + TAC groups, respectively [11]. Over half of patients with proteinuria were in the mild category (<3.39 mg/mmol); nephrotic proteinuria (>339 mg/mmol) was rare, affecting <4% in any treatment arm [11].

III. **Edema**: In patients with edema, rule out other medical reasons for the appearance of edema and the concomitant use of other drugs known to produce edema, for example calcium channel blockers. Edema is more common in females with poor renal function, in patients with hypertension, and in those using concomitant drugs [51]. A proposed management algorithm for edema is shown in Table 2.
   - For patients experiencing discomfort from edema, conservative measures such as switching/discontinuing calcium channel blockers and/or introducing diuretics may be considered as a means to control edema in these patients.
   - Exclude significant proteinuria as a cause of edema
   - If edema remains poorly controlled, if the patient has the nephrotic syndrome, or in case of lymphedema, treatment may be discontinued, and the patient switched to an alternative regimen. Careful and periodic physical examination and early and prompt discontinuation can be recommended in the case of lymphedema.

In the 24-month TRANSFORM study data, peripheral edema was reported as an adverse event in 36.8% of patients within the EVR + rCNI arm, compared with 25.9% of patients in the MPA + sCNI arm (P < .001) [9]. In the ATHENA study, peripheral edema was reported in 40.5%, 50.5% and 30.4% of patients in the EVR + TAC, EVR + CsA and MPA + TAC arms, respectively [11].

IV. **Pneumonitis**: Pneumonitis is a severe adverse reaction that has been associated with EVR treatment, and in some instances may be life threatening or associated with long lasting sequelae. Patients should be carefully monitored for the development of pneumonitis. In patients with EVR-associated pneumonitis, EVR should be discontinued.
   - As noted in the label, cases of interstitial lung disease/pneumonitis generally resolve on drug interruption, with or without steroid therapy [27].
   - Workup should include high resolution CT, right and left heart catheterization as appropriate to exclude cardiogenic causes and if necessary, bronchoscopy with bronchoalveolar lavage or transbronchial biopsy. Appropriate testing for *Pneumocystis jirovecii* should be applied and all patients on mTORi should receive *P. jirovecii* prophylaxis for a recommended duration of 6 months.

24-month data from TRANSFORM show that the incidence of interstitial lung disease (pneumonitis) in the EVR + rCNI arm was 1.1%, compared with 0.3% in the MPA + sCNI arm (RR 3.66; 95% CI 1.02, 13.08; P = .032) [9].

V. **Lipids**: Discontinuation of EVR should only be considered in patients who are refractory to anti-hyperlipidemia drugs. Statins or other alternative treatments, *e.g.* ezetimibe, may be considered. Statin therapy is typically sufficient to achieve control of hypercholesterolemia. In refractory patients, switching from EVR treatment may be appropriate. A proposed management algorithm for hyperlipidemia is shown in Table 2.
   - Hypertriglyceridemia is more difficult to manage than hypercholesterolemia, due to safety concerns with the available therapies.
   - The clinical relevance of hypertriglyceridemia is limited to rare severe cases.

In the TRANSFORM study, an increased rate of hyperlipidemia was observed in the EVR + rCNI arm despite more frequent use of statin therapy: EVR + rCNI 34.5%, MPA + sCNI 18.6% (RR 1.86; 95% CI 1.59, 2.17; P < .001) [9].

VI. ***de novo* Donor-Specific Antibodies (DSA)**: No recommendations can be made in patients who develop *de novo* DSA due to lack of clinical study experience.

- Centers should follow their usual protocols for treating patients who develop *de novo* DSA.

A number of previous clinical studies reported that conversion to EVR-based CNI-free regimens might be associated with a higher risk of development of de novo DSA [52,53]. However, the timing of the development of AMR might suggest that it is steroid withdrawal rather than conversion to mTORi that explains the finding in these particular studies [54]. Nevertheless, the combination of EVR alongside reduced exposure CNI, rather than a CNI-free regimen, along with steroids aims to take advantage of the anti-DSA benefits of the CNI whilst also maintaining the benefits of EVR, such as the reduced rate of viral infections.

During two years of follow up in the TRANSFORM study, the incidence of de novo DSA development in patients receiving EVR + rCNI was comparable to the incidence in patients receiving MPA + sCNI, (overall population: 22.4% vs 17.7%, P = 0.5047) but lower when considering the on-treatment population (12.3% vs 17.6%, P = 0.6801) [8]. The incidence of antibody-mediated rejection (AMR) in patients who developed de novo DSA was also comparable between the EVR + rCNI and the MPA + sCNI arms (19.0% vs 19.6%) [55,56].

VII. **Thrombosis, thrombotic events, repeated thrombotic events**: Although thrombotic events are uncommon after kidney transplantation, mTOR inhibitors are known to have a prothrombotic effect.
   - In those patients at risk of thromboembolic events in whom antithrombotic prophylaxis is contraindicated, an alternative to EVR should be considered.

The safety results from TRANSFORM showed an elevated incidence of thrombotic events in the EVR + rCNI arm compared with the MPA + sCNI arm: 1.3% vs 0.5% (P = .059) for thrombotic microangiopathy, 3.2% vs 2.4% (P = .282) for deep vein thrombosis, 1.6% vs 0.5% (P = .016) for pulmonary embolism, 0.2% vs 0.0% (P = .157) for graft thrombosis and 0.4% versus 0.2% (P = .415) for hemolytic uremic syndrome [9].

This might be attributable to prothrombotic effects of EVR: a small, single-center study published in 2013 reported that treatment with EVR was associated with a procoagulant state with elevated levels of von Willebrand factor, prothrombin fragment 1 + 2, thrombin-activatable fibrinolysis inhibitor and plasminogen activator inhibitor-1 as compared with treatment with CNI ± MPA [57].

3. Discussion

The purpose of this evidence-based practice guidance is to support clinicians in initiating and managing their adult kidney transplant patients on *de novo* EVR-based regimens, based on the currently available

evidence. To date, there is a considerable body of evidence supporting the use of *de novo* EVR + rCNI regimens in kidney transplant recipients. The experience and confidence of clinicians in anticipating and managing EVR-related adverse events is also increasing, which will hopefully lead to a greater number of patients benefiting from the advantages offered by such a regimen, in particular the significantly reduced rate of viral infections.

As detailed above, despite the broad experience and high number of patients who have initiated *de novo* EVR + rCNI regimens in the clinic, there remain gaps in our knowledge regarding the use of this regimen in kidney transplant recipients. Most importantly, the potential for a nephroprotective effect of a reduced- *vs* a standard-exposure CNI regimen remains to be demonstrated; although it might be expected that the sustained reduced CNI exposure may be beneficial to the patients in the long term, the absence of long-term data (beyond 2 years) means that this is not evidence-based. Additionally, there are aspects which have yet to be fully investigated, such as potential differences between outcomes for patients taking EVR in combination with TAC *vs* CsA, the importance or differences between types of induction therapy prior to initiating a *de novo* EVR-based regimen, the effects of EVR on male fertility, and steroid withdrawal in the maintenance phase.

Nonetheless, the comparable and good efficacy outcomes with respect to patient and graft survival and renal function, the comparable incidence of *de novo* DSA development and AMR, and the significantly reduced rate of viral infections when comparing EVR + rCNI regimens with MPA + sCNI regimens, supports the *de novo* use of this treatment approach in the majority of adult kidney transplant patients.

Declaration of Competing Interest

Julio Pascual has received consulting honoraria from Novartis and Chiesi, travel grants from Novartis and Chiesi, and his institution has received research grants from Novartis, Astellas, Chiesi and Amgen.

Stefan P. Berger is a member of advisory boards for Astellas, Chiesi and Novartis (all payments made to institution) and has received travel support from Chiesi and Astellas.

Steven J. Chadban has received institutional research funding, travel support or consulting honoraria from Novartis, Astellas and Alexion.

Franco Citterio has received consulting honoraria and travel grants from Novartis and Astellas.

Nassim Kamar has received speaker fees and participated in advisory boards for AbbVie, Amgen, Astellas, Chiesi, Fresenius, Gilead, Medical Care, Merck Sharp & Dohme, Neovii, Novartis, Roche, Sanofi and Shire.

Dennis A. Hesselink has received lecture and consulting fees from Astellas, Chiesi and Novartis, as well as grant support (paid to the Erasmus MC) from Astellas, Bristol-Myers Squibb and Chiesi.

Christophe Legendre has received travel grants from Astellas, Novartis, Chiesi, Genzyme, and CSL Behring, and speaker fees from Astellas, Novartis, Genzyme and Alexion.

Ute Eisenberger has received speaker fees, consulting honoraria or travel support from Astellas, Novartis, Otsuka and Teva.

Federico Oppenheimer has received speaker fees and travel support from Novartis.

Graeme R. Russ has received travel grants and honoraria from Novartis.

Claudia Sommerer has received institutional research grants from Novartis, Chiesi and Astellas.

Paolo Rigotti has participated in advisory boards for Astellas, Novartis, and Sanofi.

Titte R. Srinivas has received study grants and speaker honoraria from Novartis.

Yoshihiko Watarai has received travel support and speaker fees from Novartis.

Mitchell L. Henry has received consulting honoraria from Novartis.

Flavio Vincenti has received consultancy honoraria from Novartis and Sanofi, and research grants from Astellas.

Helio Tedesco-Silva has received consulting honoraria and travel grants from Novartis, Pfizer, Bristol-Myers Squibb and Roche, and his institution has received research grants from Novartis, Pfizer, Bristol-Myers Squibb, Roche, Veloxis and Theraclone.

Acknowledgements

The manuscript was prepared with assistance from a professional medical writer, funded by Novartis.

References

[1] Cibrik D, Tedesco-Silva Jr H, Vathsala A, Lackova E, Cornu-Artis C, Walker RG, et al. Randomized trial of everolimus-facilitated calcineurin inhibitor minimization over 24 months in renal transplantation. Transplantation 2013;95:933Y942. https://doi.org/10.1097/TP.0b013e3182848e03.

[2] Lorber MI, Mulgaonkar S, Butt KMH, Elkhammas E, Mendez R, Rajagopalan PR, et al. Everolimus versus mycophenolate mofetil in the prevention of rejection in *de novo* renal transplant recipients: a 3-year randomized, multicenter, phase III study. Transplantation 2005;80:244–52. https://doi.org/10.1097/01.TP.0000164352.65613.24.

[3] Vitko S, Margreiter R, Weiman W, Dantal J, Kuypers D, Winkler M, et al. Three-year efficacy and safety results from a study of everolimus versus mycophenolate mofetil in *de novo* renal transplant patients. Am J Transplant 2005;5:2521–30. https://doi.org/10.1111/j.1600-6143.2005.01063.x.

[4] Tedesco-Silva H, Cibrik D, Johnston T, Lackova E, Mange K, Panis C, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. Am J Transplant 2010;10:1401–13. https://doi.org/10.1111/j.1600-6143.2010.03129.x.

[5] Qazi Y, Shaffer D, Kaplan B, Kim DY, Luan FL, Peddi VR, et al. Efficacy and safety of everolimus plus low-dose tacrolimus versus mycophenolate mofetil plus standard-dose tacrolimus in *de novo* renal transplant recipients: 12-month data. Am J Transplant 2017;17:1358–69. https://doi.org/10.1111/ajt.14090.

[6] Pascual J, Srinivas TR, Chadban S, Citterio F, Oppenheimer F, Tedesco H, et al. TRANSFORM: a novel study design to evaluate the effect of everolimus on long-term outcomes after kidney transplantation. Open Access J Clin Trials 2014;6:45–54. https://doi.org/10.2147/OAJCT.S63058.

[7] Pascual J, Berger SP, Witzke O, Tedesco H, Mulgaonkar S, Qazi Y, et al. Everolimus with reduced calcineurin inhibitor exposure in renal transplantation. J Am Soc Nephrol 2018;29:1979–91. https://doi.org/10.1681/ASN.2018010009.

[8] Berger SP, Sommerer C, Witzke O, Tedesco H, Chadban SJ, Mulgaonkar S, et al. Two-year outcomes in *de novo* renal transplant recipients receiving everolimus-facilitated calcineurin inhibitor reduction regimen from TRANSFORM study. Am J Transplant Jun 1 2019. https://doi.org/10.1111/ajt.15480 (Epub ahead of print).

[9] Tedesco Silva H, Pascual J, Viklicky O, Basic-Jikic N, Cassuto E, Kim DY, et al. Safety of everolimus with reduced calcineurin inhibitor exposure in *de novo* kidney transplants: an analysis from the randomized TRANSFORM study. Transplantation 2019 Feb:19. https://doi.org/10.1097/TP.0000000000002626 https://www.ncbi.nlm.nih.gov/pubmed/30801548. [Epub ahead of print].

[10] Sommerer C, Suwelack B, Dragun D, Schenker P, Hauser IA, Nashan B, et al. Design and rationale of the ATHENA study–a 12-month, multicentre, prospective study evaluating the outcomes of a *de novo* everolimus-based regimen in combination with reduced cyclosporine or tacrolimus versus a standard regimen in kidney transplant patients: study protocol for a randomised controlled trial. Trials 2016;17:92. https://doi.org/10.1186/s13063-016-1220-9.

[11] Sommerer C, Suwelack B, Dragun D, Schenker P, Hauser IA, Witzke O, et al. An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in de novo kidney transplant patients. Kidney Int 2019;96:231–44. https://doi.org/10.1016/j.kint.2019.01.041.

[12] Kasiske BL, Zeier MG, Craig JC, Ekberg H, Garvey CA, Green MD, et al. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guidelines for the care of kidney transplant recipients. Am J Transplant 2009; 9:S1–S155.

[13] Knoll GA, Blydt-Hansen TD, Campbell P, Cantarovich M, Cole E, Fairhead T, et al. Canadian Society of Transplantation and Canadian Society of Nephrology commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Kidney Dis 2010;56:219–46. https://doi.org/10.1053/j.ajkd.2010.05.004.

[14] Bia M, Adey DB, Bloom RD, Chan L, Kulkami S, Tomlanovich S. KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Kidney Dis 2010;56:189–218. https://doi.org/10.1053/j.ajkd.2010.04.010.

[15] Heemann U, Abramowicz D, Spasovski G, Vanholder R. Endorsement of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines on kidney transplantation: a European Renal Best Practice (ERBP) position statement. Nephrol Dial Transplant 2011;26:2099–106. https://doi.org/10.1093/ndt/gfr169.

[16] Chadban SJ, Barraclough KA, Campbell SB, Clark CJ, Coates PT, Cohney SJ, et al. KHA-CARI guideline: KHA-CARI adaptation of the KDIGO clinical practice guideline for the care of kidney transplant recipients. Nephrol Ther 2012;17:204–14. https://doi.org/10.1111/j.1440-1797.2011.01559.x.

[17] Neuberger J, Wolf O, Kuypers DRK, Burra P, Citterio F, de Geest S, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver

transplant recipients: a guidance report and clinical checklist by the consensus on managing modifiable risk in transplantation (COMMIT) group. Transplantation 2017;101:S1–S56. https://doi.org/10.1097/TP.0000000000001651.
[18] Baker RJ, Mark PB, Patel RK, Stevens KK, Palmer N. Renal association clinical practice guideline in post-operative care in the kidney transplant recipient. BMC Nephrol 2017;18:174. https://doi.org/10.1186/s12882-017-0553-2.
[19] ClinicalTrials.gov. 12 Month ATHENA study. Everolimus vs Standard Regimen in *De Novo* Kidney Transplant Patients (ATHENA). Results published. Available online at https://clinicaltrials.gov/ct2/show/results/NCT01843348; 1 May 2017, Accessed date: 22 November 2018.
[20] Koch M, Wiech T, Marget M, Peine S, Thude H, Achilles EG, et al. *De novo* mTOR inhibitor-based immunosuppression in ABO-incompatible kidney transplantation. Clin Transplant 2015;29:1021–8. https://doi.org/10.1111/ctr.12624.
[21] Krämer BK, Neumayer HH, Stahl R, Pietrzyk M, Krüger B, Pfalzer B, et al. Graft function, cardiovascular risk factors, and sex hormones in renal transplant recipients on an immunosuppressive regimen of everolimus, reduced dose of cyclosporine, and basiliximab. Transplant Proc 2005;37:1601–4. https://doi.org/10.1016/j.transproceed.2004.09.026.
[22] Boobes Y, Bernieh B, Saadi H, al Hakim MR, Abouchacra S. Gonadal dysfunction and infertility in kidney transplant patients receiving sirolimus. Int Urol Nephrol 2009;42:493–8. https://doi.org/10.1007/s11255-009-9644-8.
[23] Hussain SS, Farhat S, Wani I. Oligospermia secondary to sirolimus. Indian J Transplant 2015;9:119–21. https://doi.org/10.1016/j.ijt.2015.10.006.
[24] Skrzypek J, Krause W. Azoospermia in a renal transplant recipient during sirolimus (rapamycin) treatment. Andrologia 2007;39:198–9. https://doi.org/10.1111/j.1439-0272.2007.00787.x.
[25] Deutsch MA, Kaczmarek I, Huber S, Schmauss D, Beiras-Fernandez A, Schmoeckel M, et al. Sirolimus-associated infertility: case report and literature review of possible mechanisms. Am J Transplant 2007;7:2414–21. https://doi.org/10.1111/j.1600-6143.2007.01929.x.
[26] Novartis. Data on File: Expert Commentary no. T/P (CH) 99/001; 1999.
[27] Certican Summary of Product Characteristics. Novartis Pharmaceuticals UK Ltd. Available online at https://www.medicines.org.uk/emc/medicine/30306; Updated 21 August 2018, Accessed date: 15 November 2018.
[28] Sparagana S, Franz DN, Krueger DA, Bissler JJ, Berkowitz N, Burock K, et al. Pooled analysis of menstrual irregularities from three major clinical studies evaluating everolimus for the treatment of tuberous sclerosis complex. PLoS One 2017;12:e0186235. https://doi.org/10.1371/journal.pone.0186235.
[29] Margoles HR, Gomez-Lobo V, Veis JH, Sherman MJ, Moore Jr J. Successful maternal and fetal outcome in a kidney transplant patient with everolimus exposure throughout pregnancy: a case report. Transplant Proc 2014;46:281–3. https://doi.org/10.1016/j.transproceed.2013.09.029.
[30] Veroux M, Corona D, Veroux P. Pregnancy under everolimus-based immunosuppression. Transpl Int 2011;24:e115–7. https://doi.org/10.1111/j.1432-2277.2011.01356.x.
[31] Fiocchi R, D'Elia E, Vittori C, Sebastiani R, Strobelt N, Eleftheriou G, et al. First report of a successful pregnancy in an everolimus-treated heart-transplanted patient: neonatal disappearance of immunosuppressive drugs. Am J Transplant 2016;16:1319–22. https://doi.org/10.1111/ajt.13514.
[32] Carta P, Caroti L, Zanazzi M. Pregnancy in a kidney transplant patient treated with everolimus. Am J Kidney Dis 2012;60:329. https://doi.org/10.1053/j.ajkd.2012.05.012.
[33] de Fijter JW. Cancer and mTOR inhibitors in transplant recipients. Transplantation 2017;101:45–55. https://doi.org/10.1097/TP.0000000000001447.
[34] Holdaas H, de Simone P, Zuckermann A. Everolimus and malignancy after solid organ transplantation: a clinical update. J Transplant 2016;2016:4369574. https://doi.org/10.1155/2016/4369574.
[35] Ying T, Wong G, Lim W, Kanellis J, Pilmore H, Campbell S, et al. *De novo* or early conversion to everolimus and long-term cancer outcomes in kidney transplant recipients: a trial-based linkage study. Am J Transplant 2018;18:2977–86. https://doi.org/10.1111/ajt.14948.
[36] Citterio F, et al. Effects of the *de novo* use of everolimus with reduced calcineurin inhibitor on wound healing events in the TRANSFORM study Presented at the 27th international congress of The Transplantation Society; 30 June–5 July 2018 Madrid, Spain; 2018 [Transplantation 102(Supp 7)].
[37] Vitko S, Tedesco-Silva H, Eris J, Pascual J, Whelchel J, Magee JC, et al. Everolimus with optimized cyclosporine dosing in renal transplant recipients: 6-month safety and efficacy results of two randomized studies. Am J Transplant 2004;4:635–6. https://doi.org/10.1111/j.1600-6143.2004.00389.x.
[38] Tedesco-Silva H, Vitko S, Pascual J, Eris J, Magee JC, Whelchel J, et al. 12-month safety and efficacy of everolimus with reduced exposure cyclosporine in *de novo* renal transplant recipients. Transpl Int 2007;20:27–36. https://doi.org/10.1111/j.1432-2277.2006.00414.x.
[39] Webster AC, Playford EG, Higgins G, Chapman JR, Craig J. Interleukin 2 receptor antagonists for kidney transplant recipients. Cochrane Database Syst Rev 2010;1:CD003897. https://doi.org/10.1002/14651858.CD003897.
[40] Oberbauer R, Vincenti F, Viklicky O, Huynh-Do U, Kim D, Cruzado DM, et al. Effect of induction therapy on outcomes of *de novo* renal transplant recipients receiving everolimus with reduced-dose calcineurin inhibitor: 24-month results from the TRANSFORM study, Abstract 557. Presented at Boston, MA, USA: the American Transplant Congress; June 2019 1–5 June 2019.
[41] Shihab F, Qazi Y, Mulgaonkar S, McCague K, Patel D, Peddi VR, et al. Association of clinical events with everolimus exposure in kidney transplant patients receiving low doses of tacrolimus. Am J Transplant 2017;17:2363–71. https://doi.org/10.1111/ajt.14215.
[42] Chan L, Hartmann E, Cibrik D, Cooper M, Shaw LM. Optimal everolimus concentration is associated with risk reduction for acute rejection in *de novo* renal transplant recipients. Transplantation 2010;90:31–7. https://doi.org/10.1097/TP.0b013e3181de1d67.
[43] Loriga G, Ciccarese M, Pala PG, Satta RP, Fanelli V, Manca ML, et al. *De novo* everolimus-based therapy in renal transplant recipients: effect on proteinuria and renal prognosis. Transplant Proc 2010;42:1297–302. https://doi.org/10.1016/j.transproceed.2010.03.120.
[44] Cooper M, Wiseman AC, Zibari G, McCague K, Kim Y, Geissler F, et al. Wound events in kidney transplant patients receiving *de novo* everolimus: a pooled analysis of three randomized controlled trials. Clin Transplant 2013;27:E625–35. https://doi.org/10.1111/ctr.12223.
[45] Shihab FS, Cibrik D, Chan L, Kim YS, Carmellini M, Walker R, et al. Association of clinical events with everolimus exposure in kidney transplant patients receiving reduced cyclosporine. Clin Transplant 2013;27:217–26. https://doi.org/10.1111/ctr.12045.
[46] Kahan BD, Kaplan B, Lorber MI, Winkler M, Cambon N, Boger RS. RAD in *de novo* renal transplantation: comparison of three doses on the incidence and severity of acute rejection. Transplantation 2001;71:1400–6. https://doi.org/10.1097/00007890-200105270-00008.
[47] Pascual J, del Castillo D, Cabello M, Pallardó L, Grinyó JM, Fernández AM, et al. Interaction between everolimus and tacrolimus in renal transplant recipients: a pharmacokinetic controlled trial. Transplantation 2010;89:994–1000. https://doi.org/10.1097/TP.0b013e3181ccd7f2.
[48] Kaplan B, Qazi Y, Wellen JR. Strategies for the management of adverse events associated with mTOR inhibitors. Transplant Rev 2014;28:126–33. https://doi.org/10.1016/j.trre.2014.03.002.
[49] Diekmann F, Andrés A, Oppenheimer F. mTOR inhibitor-associated proteinuria in kidney transplant recipients. Transplant Rev 2012;26:27–9. https://doi.org/10.1016/j.trre.2011.10.003.
[50] Pascual J, Diekmann F, Fernández-Rivera C, Gómez-Marqués G, Guiérrez-Dalmau A, Pérez-Sáez MJ, et al. Recommendations for the use of everolimus in *de novo* kidney transplantation: false beliefs, myths and realities. Nefrologia 2017;37:253–66. https://doi.org/10.1016/j.nefroe.2017.04.016.
[51] Trayes KP, Studdiford JS, Pickle S, Tully AS. Edema: diagnosis and management. Am Fam Physician 2013;88:102–10.
[52] Grimbert P, Thaunat O. mTOR inhibitors and risk of chronic antibody-mediated rejection after kidney transplantation: where are we now? Transpl Int 2017;30:647–57. https://doi.org/10.1111/tri.12975.
[53] Liefeldt L, Brakemeier S, Glander P, Waiser J, Lachmann N, Schönemann C, et al. Donor-specific HLA antibodies in a cohort comparing everolimus with cyclosporine after kidney transplantation. Am J Transplant 2012;12:1192–8. https://doi.org/10.1111/j.1600-6143.2011.03961.x.
[54] Pascual J, Arns W. Does everolimus increase donor-specific HLA antibodies in kidney transplant recipients? Am J Transplant 2012;12:2561–2. https://doi.org/10.1111/j.1600-6143.2012.04159.x.
[55] Mulgaonkar S, Pascual J, Chadban S, Tedesco H, Berger S, Qazi Y, et al. Everolimus with reduced calcineurin inhibitor exposure in *de novo* kidney transplant recipients: efficacy and safety outcomes from the TRANSFORM study. Abstract 597; presented at the American Transplant Congress; 2018 2–6 June 2018; Seattle, WA, USA. Am J Transplant 18(S4).
[56] Pascual J, Chadban S, Tedesco H, Berger S, Qazi Y, Crusado JM, et al. Efficacy and safety of everolimus with reduced-dose calcineurin inhibitor in *de novo* kidney transplant recipients: results from the TRANSFORM study. Abstract 591.9; presented at the 27th international congress of The Transplantation Society; 30 June–5 July 2018. Madrid, Spain: Transplantation; 2018 102(Supp 7).
[57] Baas MC, Gerdes VEA, ten Berge IJM, Heutinck KM, Florguin S, Meijers JCM, et al. Treatment with everolimus is associated with a procoagulant state. Thromb Res 2013;132:307–11. https://doi.org/10.1016/j.thromres.2013.07.004.