Comparison of the Efficacy and Safety of Sirolimus, Everolimus or Mycophenolate in Renal Transplant Recipients Receiving Induction with Anti-thymocyte Globulin, Tacrolimus and Prednisone

Date of document: 03/november/2020, amendment 7

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1. Introduction

1.1 Cytomegalovirus infection

Induction therapy with an anti-interleukin monoclonal antibody (anti-IL2Ra) followed by maintenance therapy with tacrolimus (TAC), mycophenolate (MPA) and prednisone is currently considered the standard immunosuppressive regimen by most transplant centers and regulatory agencies. (1). Use of this regimen is associated with a low incidence of acute rejection and superior renal function at one year (2). However, recent data suggest that the use of anti-IL2Ra in kidney transplant recipients using TAC and MPA does not produce a significant additional reduction in the incidence of acute rejection. With this triple maintenance therapy, the addition of anti-IL2Ra induction can achieve an absolute risk reduction for acute rejection of only 1-4% in standard risk patients without improving graft or patient survival (3). A recent meta-analysis including 71 studies showed that the use of anti-thymocyte globulin (r-ATG) is associated with a 30% reduction in the incidence of biopsy-confirmed acute rejection, but with a 75% increase in malignancy and a 32% increase in increased incidence of CMV disease compared to anti-IL2Ra (4). In patients at high immunological risk, induction of r-ATG reduces the relative risk of acute rejection by almost 50% compared with anti-IL2Ra (3).

Cytomegalovirus (CMV) infection in solid organ transplant recipients is associated with “direct” and “indirect” effects that include graft rejection, predisposition to opportunistic fungal and bacterial infections, and higher incidence of malignancies, increasing morbidity and decreasing graft and patient survival. Risk factors associated with the development of CMV infection are the serological profile of recipients and donors, the type of immunosuppressive regimen, and the treatment of acute rejection (5). A recent review of 29 studies suggested that MPA-containing immunosuppression regimens are associated with an increased likelihood of developing CMV infection (6).

Universal prophylaxis and preemptive therapies are strategies used after solid organ transplantation to control CMV infection. The major advantage of prophylaxis is the inhibition of virus replication, preventing the direct and indirect effects of CMV infection. On the other hand, the antiviral drugs used can cause adverse reactions, are expensive, and a significant proportion of patients end up developing CMV infection after stopping prophylaxis. Preemptive therapy allows treatment to be indicated only

for patients with virus replication. Both strategies have advantages and disadvantages in terms of effectiveness, safety and costs to the health system (5).

Experimental and clinical data suggest that mTOR (mammalian target of rapamycin) inhibitors sirolimus (SRL) and everolimus (EVR) may limit CMV replication. A recent meta-analysis concluded that treatment with an mTOR inhibitor (imTOR), alone or in combination with calcineurin inhibitors, significantly reduces the incidence of CMV after organ transplantation, suggesting that with the use of an imTOR, prophylaxis for CMV infection could be expendable (7).

In a recent study we compared the incidence of CMV infection/disease in kidney transplant recipients receiving EVR or MPA and no pharmacological prophylaxis for CMV infection. 288 patients were randomized to receive a single 3 mg/kg dose of r-ATG, TAC, EVR and prednisone (r-ATG/EVR, n=85), basiliximab (BAS), TAC, EVR and prednisone (BAS/EVR , n=102) or BAS, TAC, MPA and prednisone (BAS/MPS, n=101). The incidence of CMV infection/disease was significantly lower in the everolimus-treated patient groups (r-ATG/EVR 4.7% vs. BAS/EVR 10.8% vs. BAS/MPS 37.6%, $p<0.001$). There were no differences in the incidence of acute rejection (9.4 vs. 18.6 vs. 15.8%, $p=0.403$), wound healing complications, delayed graft function and proteinuria. The estimated mean glomerular filtration rate was lower in BAS/EVR (65.7 ± 21.8 vs. 60.6 ± 20.9 vs. 69.5 ± 21.5 ml/min, $p=0.021$). The reduced incidence of CMV infection observed in this study suggests that even preemptive treatment may be restricted to only those patients at highest risk for CMV infection, further reducing the costs of transplant center management (8).

1.2 Objective

This study was designed to assess the influence of using SRL or EVR (controlled for their residual blood concentrations) with TAC (reduced residual blood concentrations) compared to MPA (fixed doses) with TAC (standard residual blood concentrations) with regard to to efficacy and safety in de novo kidney transplant recipients.

The primary outcome is the incidence of CMV infection/disease, a relevant medical need in the absence of pharmacological prophylaxis due to its morbidity and costs incurred by the public health system. This outcome represents an attempt to reduce the negative influence of this infection on the outcome of the transplant and on the

management of health resources, provided that the other key variables of efficacy and safety of these immunosuppression regimens are not inferior to those demonstrated by standard treatment.

2. Research plan

2.1 Study design:

This prospective, randomized, single-center clinical study was designed to compare the safety and efficacy of three immunosuppressive regimens (Group 1, SRL) single-dose r-ATG, TAC, SRL, and prednisone; (Group 2, EVR) single dose of r-ATG, TAC, EVR and prednisone; (Group 3, MCF) single dose of r-ATG, TAC, MPA and prednisone.

The study was submitted to the local research ethics committee for approval and an informed consent form will be obtained from all patients. The study will be conducted within good clinical practice in accordance with the Declaration of Helsinki. Patients who meet the inclusion and exclusion criteria will be randomized within the first 24 hours after transplantation, in a 1:1:1 ratio and stratified according to the type of donor (deceased or living). All patients will be followed for 12 months or until graft loss.

2.2 Treatment Groups

Grupo 1, SRL: r-ATG/SRL/TAC/Prednisone

Patients will receive an initial dose of 0.05 mg/kg BID of TAC adjusted from day 3 to maintain a total blood concentration of TAC between 3-5 ng/mL. Patients will receive an initial dose of 3 mg QD sirolimus adjusted from day 3 to maintain a concentration between 4-8 ng/mL.

Grupo 2, EVR: r-ATG/ EVR /TAC/Prednisone

Patients will receive an initial dose of 0.05 mg/kg BID of TAC adjusted from day 3 to maintain a total blood concentration of TAC between 3-5 ng/mL. Patients will receive an initial dose of 1.5mg BID everolimus adjusted from day 3 to maintain a concentration between 4-8 ng/mL.

Grupo 3, MCF: r-ATG/Mycophenolate/TAC/Prednisone

Patients will receive an initial dose of 0.1 mg/kg BID of TAC adjusted from day 4 to maintain a total blood concentration of TAC between 5-10 ng/mL. Patients will receive fixed doses of mycophenolate (MMF, 1 g BID; MPS, 720 mg BID).

2.3 Induction therapy

All patients will receive 1 g of methylprednisolone before graft revascularization. All patients will receive a single dose of 3 mg/kg body weight of anti-thymocyte globulin administered intravenously over 6-8 hours, starting within the first 24 hours after graft revascularization. Pre-treatment will be performed with hydrocortisone and dipyrone, according to local practice.

2.4 Maintenance therapy

The first dose of all immunosuppressive drugs will be administered within the first 24 hours after graft revascularization.

Treatment group	**Drug**	**Initial dose**	**Concentration (ng/ml)**
Group 1, SRL (n=50)	r-ATG	3 mg/Kg IV day 1	NA
	TAC	0,05 mg/kg BID	3-5
	Sirolimus	3 mg QD	4-8
Group 2, EVR (n=50)	r-ATG	3 mg/Kg IV day 1	NA
	TAC	0,05 mg/kg BID	3-5
	EVR	1,5 mg BID	4-8
Group 3, MCF (n=50)	r-ATG	3 mg/Kg IV day 1	NA
	TAC	0,1 mg/kg BID	5-10
	MMF ou MPS	1000 mg BID 720 mg BID	NA NA

The primary use of other immunosuppressive drugs is prohibited. However, switching to another immunosuppressive drug is permitted both due to lack of efficacy (documented episodes of acute rejection) and the occurrence of adverse events.
At the 6 month visit, all patients who are eligible, according to pre-established criteria, will simplify the TAC and EVR dosing schedule of BID for QD, maintaining the same daily dose in a single dose to achieve blood concentrations between 3 and 5 ng/ ml.

2.5 Corticosteroids

All patients will receive 0.5 mg/kg/day of prednisone with a maximum dose of 30 mg starting on day 1. Doses of prednisone will be reduced to 20 mg/day on day 7, 15 mg/day on day 14, 10 mg /day on day 21 and 5 mg/day on day 30, which will be maintained for at least 12 months.

2.6 Study rationale

The use of a single dose of 3 mg/kg of anti-thymocyte globulin in induction therapy is currently standard in our institution, consistently providing an incidence of acute rejection of less than 10% at the end of the first year of transplantation. However, patients receiving this therapy and induction combined with standard maintenance therapy (TAC, mycophenolate, and prednisone) have a high incidence (60%) of CMV infection/disease. Using sirolimus or everolimus instead of mycophenolate may maintain efficacy for preventing acute rejection while reducing the incidence of CMV infection/disease.

Adherence to immunosuppressive treatment is one of the factors with an important influence on long-term renal graft survival (9). The incidence of non-adherence to treatment varies among different populations of kidney transplant recipients, reaching 60% in some cases. Constant education, technological facilities to alert the patient and simplification of medication dosage are strategies that can improve treatment adherence (10).

Among the maintenance immunosuppressive regimens currently available to kidney transplant recipients, none offers the possibility of once-daily administration of all drugs to facilitate adherence to treatment.

2.7 Rationale of drug doses and concentrations

Doses and concentrations of TAC combined with sirolimus or everolimus were based on prospective multicenter studies and also on the experience of our transplant center. Sirolimus was used in these studies as a loading dose because of its longer half-life. Recent evidence suggests an association of this loading dose with a higher incidence of wound complications. The effectiveness of using r-ATG induction therapy may justify not using this loading dose. Sirolimus and everolimus belong to the same therapeutic class of immunosuppressants (mTOR inhibitors). A comparative analysis of published works suggests that the target concentrations of these two drugs are very close. Thus, the initial dose chosen for sirolimus and everolimus was 3 mg QD and the target residual blood concentrations will be similar, between 4-8 ng/ml.

Although it is assumed that the use of SRL or EVR can provide similar results, some uncertainties justify the performance of this study. Due to its prolonged elimination half-life, SRL is administered as a single daily dose, usually after a loading dose (11). Recent studies suggest that this loading dose may be associated with the higher incidence of wound complications observed in the initial studies (12). Another important point is that the therapeutic concentration of SRL has not been clearly determined through prospective studies using current immunosuppression regimens (13). The evaluation of this regimen is therefore essential for its wider use, when indicated, especially considering the ease of dosage.

Doses and concentrations of TAC and MPA correspond to those obtained in the largest prospective study in kidney transplant recipients and accepted as “standard of care” by regulatory agencies (14).

Blood concentrations of SRL and EVR will be determined by HPLC and blood concentrations of TAC will be determined by chemiluminescence microparticle immunoassay (CMIA).

2.8 Risks/benefits

Sirolimus or everolimus regimens may reduce the incidence of viral infections, including CMV, herpes, and polyomavirus infection. In addition, there may be a reduction in the incidence of fungal and bacterial infections, a lower incidence of

diarrhea and myelotoxicity associated with the use of MPA. On the other hand, these regimens are associated with slow recovery of renal function, higher incidence of wound complications, edema, nephrotoxicity, proteinuria, and dyslipidemia. All of these adverse reactions are associated with disproportionately high concentrations of TAC and sirolimus or everolimus.

3. Population

A sample calculation was performed for each outcome to be analyzed in this study. The complete description is in section 10. “Statistical planning”.

A total of 319 patients were included in the study.

3.1 Inclusion criteria

1. Recipients, adults of both genders, of the first standard living or deceased donor kidney transplant;
2. Patients who agree to participate in the study and sign the informed consent form

3.2 Exclusion criteria

1. Recipients with a medical history of nephrotic syndrome or focal segmental glomerulosclerosis confirmed as the etiology of end-stage renal disease;
2. Recipients with difficulty understanding chronic kidney disease and its treatment alternatives;
3. Recipients with anticipated difficulty in adhering to treatment with immunosuppressive drugs;
4. Retransplant recipients;
5. Multi-organ receptors;
6. Recipients with BMI>30 kg/m2;
7. Deceased donor kidney recipients with KDPI > 80%;
8. Deceased donor kidney recipients with cold ischemia time greater than 24 hours;
9. Patients without specific antibodies against the donor.

10. Women of childbearing age who do not commit to using contraceptive methods (condoms or oral contraceptives).
11. Patients using immunosuppressive therapy before transplantation, except for low-dose prednisone;
12. Patients with severe uncontrolled dyslipidemia;
13. Patients who have a known contraindication for the administration of any of the immunosuppressive drugs provided for in this study;

4. Randomization

At the baseline visit, within 24 hours after vascular anastomosis, all eligible patients will be randomized using a numerical sequence, stratified by type of donor (deceased or living), generated by a computer program and placed in opaque envelopes. The open envelope, designated the treatment allocated to the patient, will be kept in your record.

5. Prophylaxis against infections

No pharmacological prophylaxis will be used against CMV infection. Preventive treatment will be carried out by monitoring virus replication detected by the antigenemia test. All patients will use oral nystatin for at least 30 days as prophylaxis of fungal infections. All patients will receive prophylaxis of parasitic infections with albendazole. All patients will use oral trimethoprim-sulfamethoxazole as prophylaxis of pneumocystis jirovecii or urinary tract infection.

9. Definitions

9.1 Delay Graft Function

Delayed Garft Function will be defined as the need for dialysis during the first week after transplantation (with the exception of a single dialysis in the first 48 hours to treat hypervolemia and/or hyperkalemia after surgery. Patients with graft loss due to vascular thrombosis will be excluded.

9.2 CMV infection and disease

9.2.1 **CMV Infection:** evidence of asymptomatic replication of CMV.

9.2.2 **CMV Disease:** evidence of CMV infection with related symptoms. CMV disease can be categorized as a syndrome (fever, malaise, leukopenia, or thrombocytopenia) or as an invasive disease with histological evidence.

9.2.3 **Recurrent CMV disease/infection:** defined as a new episode of CMV infection after documented effective previous treatment (2 weekly negative antigenemia tests).

9.2.4 **CMV replication:** will be confirmed by detection of CMV pp65 antigen by indirect immunofluorescence in peripheral blood leukocytes. The diagnosis of viral replication is confirmed by the presence of 10 or more positive cells per 200,000 peripheral blood leukocytes in asymptomatic patients or any number of positive cells in the presence of typical symptoms or in recipients with negative serology for CMV.

9.2.5 **Preemptive strategy:** monitoring of CMV replication will be performed every 15 days between the third and 12 weeks after transplantation. Additional monitoring will be performed for 12 weeks after treatment for acute rejection.

9.2.6 **Treatment of CMV disease/infection:** Patients will receive standard intravenous ganciclovir (5 mg/kg every 12 hours) corrected for renal function as per package insert recommendations. Monitoring of CMV replication will be carried out weekly. The duration of treatment will be extended by one week after the first negative antigenemia test. Consequently, the minimum duration of treatment will be 14 days. The duration of treatment for patients with invasive disease will be at least 21 days, being extended in the presence of a positive antigenemia test.

10 Statistical planning

10.1 Sample size - main study

Primary outcome: cytomegalovirus infection or disease

For the primary outcome of cytomegalovirus infection, we calculated the sample required to show superiority of the experimental groups (EVR and SRL) over the control (MPA). For this calculation, we considered an incidence of 72% in the MPA group and an expected reduction of 50% (to 36%) in the experimental groups. For a margin of superiority of 0% and power of 90%, the total number of patients would be 42 in each group, considering 20% drop outs.

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