A randomized exploratory trial of steroid avoidance in renal transplant patients treated with everolimus and low-dose cyclosporine

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Abstract

Background. Everolimus and cyclosporine exhibit synergistic immunosuppressive activity when given in combination. In this randomized trial, we explored whether the use of everolimus associated with low-dose cyclosporine could allow an early avoidance of steroids in de novo renal transplant recipients.

Methods. In this exploratory multicenter trial, 65 out of 133 patients treated with basiliximab (days 0 and 4), everolimus 3 mg/day and cyclosporine were randomized to stop steroids on the seventh post-transplant day (group A), whereas the remaining 68 continued low-dose steroid treatment (group B).

Results. During the follow-up, 30 patients of group A (46%) resumed steroids. According to the intention-to-treat analysis, the 3-year graft survival rate was 95% in group A and 87% in group B ($P=\text{ns}$). There were more biopsy-proven rejections in group A, the difference being of borderline significance (32% vs 18%; $P=0.059$). After 3 years, mean creatinine clearance was $52.3 \pm 17.1$ ml/min in group A and $52.2 \pm 21.5$ ml/min in group B. It was similar in the group A patients who experienced rejection ($49.8 \pm 14.7$ ml/min) and those who did not ($53.6 \pm 18.3$ ml/min; $P=0.319$). Mean serum cholesterol and triglyceride levels were, respectively, less than 250 mg/dl and less than 200 mg/dl in both groups, without any significant difference. Vascular thrombosis ($0$ vs $11.7%$; $P=0.0043$) was more frequent in group B.

Conclusions. Treatment based on everolimus and low-dose cyclosporine allowed excellent renal graft survival and stable graft function at 3 years. An early discontinuation of steroids increased the risk of acute rejection, but was associated with a better graft survival in the long-term. However, it was well tolerated only by 54% of patients.

Keywords: basiliximab everolimus and cyclosporine immunosuppression; cyclosporine; early steroid withdrawal; everolimus; kidney transplant; steroid free

Introduction

Everolimus is a macrocyclic lactone that, like sirolimus, inhibits the cell proliferation stimulated by cytokine-driven signal transduction in response to alloantigens by arresting the cell cycle at G1 [1,2]. This mechanism of action is completely different from that of cyclosporine, which inhibits the synthesis of interleukin-2 and other cytokines by T cells after their contact with antigen-presenting cells and thus interrupts cell cycle progression from G0 to G1 [3]. As the two agents interfere with the alloimmune response at different stages of the cell cycle, their combination may have synergistic effects [4].

A paper reporting the results at 12 months of two trials showed that such a combination could achieve good protection from rejection but could increase the nephrotoxicity of cyclosporine, as demonstrated by elevated levels of serum creatinine [5]. However, a retrospective analysis of that study showed that the risk of rejection was mainly related to the low blood levels of everolimus, while the blood levels of cyclosporine had little impact on rejection. Conversely,
the risk of nephrotoxicity was related to the blood levels of cyclosporine, while the blood concentrations of everolimus did not influence the risk of nephrotoxicity [6]. Actually, a randomized trial showed that the association of everolimus with low-dose cyclosporine could significantly reduce the efficacy failure and improve the creatinine clearance when compared with a combination of everolimus and full-dose cyclosporine in renal transplant recipients [7]. A more recent trial confirmed that the combination of everolimus and low-dose cyclosporine could obtain therapeutic efficacy while preserving renal graft function at 12 months [8].

Two important pieces of information are still lacking, whether such an association may maintain stable graft function in the long term and whether it may allow to minimize or even avoid the use of steroids. In this randomized controlled trial, we report the follow-up at 3 years of a cohort of cadaver transplant patients assigned to receive low-dose cyclosporine in combination with everolimus and either minimal doses of prednisone or no prednisone.

Materials and methods

Study design

This exploratory randomized trial was designed to compare the efficacy, safety and effect on graft function of an immunosuppressive regimen consisting of basiliximab, everolimus, cyclosporine and corticosteroids, the last of which were withdrawn after 1 week (group A) or continued at low doses (group B). The study lasted for 3 years after randomization and evaluated all the enrolled patients who completed the study.

The study was sponsored by Novartis Italy and approved by the Ethics Committees of the trial centers. All the patients gave written informed consent.

Patients

Patients of both genders aged 18–65 years, who had received a first or a second cadaveric or non-HLA-identical living donor kidney transplant and given their informed consent, were considered eligible for the trial. The patients receiving a kidney after more than 40 h of cold ischemia were excluded, as were those who had a panel reactive antibody titer ≥50%, transaminase levels more than three times above the upper normal limit, serum cholesterol ≥350 mg/dl or triglycerides ≥500 mg/dl and those carrying HbsAg or HIV. Patients were assigned to randomized blocks, four patients per block, stratified by the center. The data were collected by an external agency and elaborated by the coordinating center with the support of a Novartis statistician.

Treatments

Everolimus. Everolimus 1.5 mg bid was started within 24 h of the completion of the transplantation and was given together with cyclosporine 1 h before breakfast and 1 h before or after dinner. A dose reduction was recommended if serum cholesterol levels remained ≥250 mg/dl despite dietary measures and statin administration or if triglyceride levels were ≥500 mg/dl or the platelet count <75 000/mm³. The drug had to be discontinued if cholesterol levels exceeded 350 mg/dl, triglycerides exceeded 500 mg/dl or platelet numbers fell below 50 000/mm³.

Cyclosporine. Cyclosporine Neoral was administered together with everolimus at a starting dose of 3–5 mg/kg bid. Blood cyclosporine levels were measured using the fluorescence polarization immunoassay method in 87% of the cases, and the enzyme-multiplied immunoassay method in the remaining 13% [9]. Initially, the trough blood levels of cyclosporine had to be 150–350 ng/ml in the first 4 weeks, 100–250 ng/ml until the sixth month and 100–200 ng/ml thereafter. A few months after starting the study, after a retrospective analysis showed that in combination with everolimus, low-dose cyclosporine was sufficient to prevent graft rejection and dysfunction [6], a protocol amendment was introduced that recommended an initial cyclosporine dose of no more than 3–5 mg/kg/day and trough blood levels of no more than 100 ng/ml.

Basiliximab. Basiliximab 20 mg was given intravenously 2 h before the transplantation, with a second 20 mg dose being administered in the morning of day 4.

Corticosteroids. The patients assigned to steroid-free immunosuppression (group A) were given oral prednisone as a single morning dose of 20 mg for 5 days, 10 mg on day 6 and 5 mg on day 7, after which the treatment was discontinued. Steroids could be reintroduced at the discretion of the investigator.

The patients assigned to continue steroids (group B) were given prednisone as a single morning dose of 20 mg for the first 2 weeks, 15 mg/day for the second 2 weeks, 10 mg/day for the third 2 weeks, 5–10 mg/day until the end of the first year and then 2.5–5 mg/day until the end of the third year.

Treatment of acute rejection

A core graft biopsy had to be performed in the case of suspected rejection, i.e. a double-checked increase in serum creatinine of 20% or more over baseline without any other identifiable cause. A biopsy-proven rejection had to be treated with at least two intravenous methylprednisolone pulses (MPP) for a minimum total dose of 750 mg. In the case of a Banff class III rejection [10], the administration of antithymocyte globulins (ATG) or OKT3 monoclonal antibody was permitted as first-line treatment. ATG and OKT3 could also be used if serum creatinine did not decrease within 4–5 days of starting MPP therapy.

Treatment of hyperlipidemia

As per protocol, whenever serum cholesterol levels exceeded 250 mg/dl or triglyceride levels exceeded 300 mg/l, dietary instruction was recommended and statins or gemfibrozil had to be considered.
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Prophylaxis

Cytomegalovirus (CMV) prophylaxis was mandatory in the case of a CMV-negative patient receiving a kidney from a CMV-positive donor and was administered according to local practice (intravenous or oral ganciclovir or acyclovir).

All the patients received prophylaxis against *Pneumocystis carinii*: one tablet of trimethoprim 80 mg plus sulfamethoxazole 400 mg had to be given every 24 or 48 h for at least 6 months.

Objectives

The primary end point of the study was the graft survival. Secondary end points were patient survival, incidence of biopsy-proven acute rejection, serum creatinine, median dose of prednisone and incidence of serious adverse events.

Randomization

At the time of transplantation, the patients who met the study entry criteria and gave written informed consent were assigned a unique identification number that could not be reused and were then allocated to group A (the steroid-free regimen) or group B (the continuous steroid regimen) by a randomization list, stratified within centers.

Randomization was centralized using an interactive voice-response system. The sequence was concealed until interventions were assigned.

The participants were enrolled and assigned to either group by the surgeons or nephrologists of the center where the transplantation was performed.

Statistical methods

All the analyses considered all the randomized patients, grouped originally by randomized treatment, as per intention-to-treat (ITT) concept. Patient or graft survival was analysed using the product limit method and compared between groups by means of the log-rank test. The same analysis was made in relation to the time to the first biopsy-proven acute rejection. Descriptive statistics and frequency distributions were produced as applicable. All the analyses considered all the randomized patients, grouped originally by randomized treatment, as per intention-to-treat (ITT) concept.

Results

Demographics

Of 133 patients who accepted to enter the study, 65 were randomly assigned to group A and 68 to group B. Ninety-five percent of the patients received a kidney from a cadaveric donor; only three patients in group A and four in group B received a kidney from an HLA-mismatched living donor. The main demographic characteristics at transplantation were similar in the two groups (Table 1).

<table>
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<tr>
<th>Table 1. Baseline demographic characteristics</th>
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<td>Steroid free (65)</td>
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<tr>
<td>Age, years (SD)</td>
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<tr>
<td>Male/female</td>
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<tr>
<td>Causes of renal disease (%)</td>
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<td>Glomerulonephritis</td>
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<td>Interstitial nephritis/pyelonephritis</td>
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<td>Polycystic kidney</td>
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<td>Hypertensive nephrosclerosis</td>
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<td>Diabetics</td>
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<td>Obstructive disorder/reflux</td>
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<td>Unknown origin</td>
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<td>Total time on renal dialysis, months (SD)</td>
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<td>Current dialysis (%)</td>
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<tr>
<td>Hemodialysis</td>
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<td>Peritoneal dialysis</td>
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<td>HLA mismatches (SD)</td>
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<td>Panel reactive antibodies (%)</td>
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<td>Delayed graft function (need for dialysis)</td>
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Exposure

During the follow-up, 35 patients in group A (54%) never resumed steroids, although 7 with delayed graft function discontinued them after day 7. Of the 30 patients who resumed prednisone, 17 did so because of acute rejection, even if rejection was completely reversible in most cases, with serum creatinine returning to the pre-rejection levels. The other 13 patients reintroduced or never stopped steroids because of the slower and lower recovery of graft function or late graft dysfunction. There were no significant differences between the 35 patients who remained steroid free and the 30 patients who resumed steroids with regard to age, sex, causes of renal disease, time of dialysis, type of dialysis, HLA mismatches and PRA. Also, the donor’s age, sex, type and the number of severely hypotensive donors were not different (data not shown). The median total dose of oral prednisone multiplied by the median time of assumption was 420 mg (75–16,768) in group A and 5729 mg (20–11,905) in group B. The median duration of administration was 30 (5–1129) and 1085 days (1–1174), respectively. The mean daily dose of everolimus tended to be higher in the subgroup of the 35 steroid-free patients (4.5±1.8 mg) than in the 30 patients who resumed steroids (2.4±2.2 mg) (P = 0.0001). The average daily dose of cyclosporine also tended to be higher in steroid-free patients (159.0±63.8 mg) than in patients who resumed prednisone (139.0±76.1 mg), although to a lesser extent, but the difference was not significant (P = ns). The mean trough blood everolimus levels (Figure 1) were similar in groups A and B. Cyclosporine C₀ levels
were also similar in the two groups at all time points: the data refer to all the patients at risk (Figure 2).

**Efficacy**

According to the ITT analysis, all patients were considered as grouped by the original assigned treatment. The 3-year patient survival was 100% in group A and 97% in the low-dose steroid group, in which two deaths occurred: one patient died in the third post-transplantation month because of disseminated aspergillosis and the other died 32 months after transplantation because of an accident while working. At the end of 3 years, 62 patients (95.4%) were alive with a functioning graft in group A and 58 (85.2%) in group B ($P=\text{ns}$). Three graft losses occurred in group A, respectively, caused by primary graft non-function, progressive graft dysfunction in a patient with severe peripheral obliterative arteriopathy and chronic rejection. Only the last patient resumed prednisone. There were 10 graft losses in group B: in addition to the two patients who died, the other causes were recurrent hemolytic uremic syndrome in a young woman, renal vascular thrombosis not caused by technical errors in two patients, primary non-function in one, chronic rejection in three and the discontinuation of immunosuppressive therapy in an elderly patient with severe cardiopulmonary failure, diabetes and poor graft function. Therefore, the graft survival was 94.2% in patients of group A, who remained without steroids, 96.6% in those of group A, who resumed steroids and 85.2% in patients of group B. Most of the events occurred during the first 100 post-transplantation days (Figure 3).

There were more biopsy-proven acute rejections in group A (21/65, 32%) than in group B (12/68, 18%); this difference was of borderline significance ($P=0.059$). All but one of the events occurred in the first year.

The mean levels of creatinine clearance were similar in the two groups at all time points and remained stable over time. The mean 3-year values were $52.3 \pm 17.08$ ml/min (serum creatinine $1.80 \pm 0.55$ mg/dl) in group A and $52.2 \pm 21.52$ ml/min (serum creatinine $1.95 \pm 1.09$ mg/dl) in group B (Figure 4). In group A, mean creatinine clearance after 3 years was $49.8 \pm 14.7$ ml/min in the patients experiencing a rejection and $53.6 \pm 18.3$ ml/min in those who did not ($P=0.409$). The corresponding figures in group B were $42.8 \pm 21.3$ ml/min and $54.3 \pm 21.3$ ml/min ($P=0.094$). Between-group differences were $7.0$ ml/min ($P=0.273$) in patients who experienced rejection and $-0.7$ ml/min ($P=0.863$) in those who did not. In the 35 group A patients who never resumed steroids, mean creatinine clearance was $58.7$ ml/min at 6 months and $58.6 \pm 1$
8.35 ml/min at 3 years. The mean creatinine clearance in patients who resumed steroids was, respectively, 47.0 ml/min and 46.2 ± 13.52 ml/min, which was not different from that of patients of group B who experienced rejection. Only one patient in each group had proteinuria levels of more than 0.5 g/day.

Safety

Discontinuation. The rate of premature transient discontinuation of study medications at 3-years was similar in the two arms (30 in group A and 31 in group B). Adverse events were the main reason for discontinuation (21 and 15, respectively). In most cases (89%), treatment was resumed after resolution of the causative adverse event (mostly infection or drug toxicity).

Adverse events. Almost all the patients reported at least one adverse event during the study; 64/65 in group A and 68/68 in group B. The most important serious adverse events are listed in Table 2. There were more thrombotic events (three cases of thrombophlebitis, two of retinal vein thrombosis, two of graft thrombosis and one pulmonary embolism) in low-dose steroid patients. It is worth noting that there were three cases of CMV disease in the study population as a whole.

According to ITT, mean serum cholesterol and triglyceride levels were lower in the steroid-free group, but the differences were not statistically significant: mean cholesterol levels in group A were 214 ± 0.88 mg/dl at 1 year, 206 ± 83.3 at 2 years and 204 ± 85.8 at 3 years. The corresponding figures in group B were 247.4 ± 85.1, 226 ± 77.2 and 218 ± 85.7 mg/dl (P = ns). Mean triglyceride levels at 3 years were 167 ± 95.6 mg/dl in group A and 191 ± 127.1 mg/dl in group B (P = ns). Twenty-one (60%) of the 35 group A patients who never resumed steroids had received statins, as against 22 (73%) of the 30 who did and 48 (71%) of the 68 patients in group B. None of the patients had received statins before undergoing transplantation. All but two of the group A patients who started statins in the second post-transplant year did so between the third and eighth month.

Mean arterial blood pressure was also similar in the two groups (data not shown). Forty patients in group A and 49 in group B were given antihypertensive agents: the mean number of antihypertensive agents per patient was, respectively, 1.8 and 1.7.

Discussion

A meta-analysis of randomized controlled trials (RCT) found that patients treated with the old formulation of cyclosporine A (CsA), who stopped taking corticosteroids had a significantly higher rate of acute rejection and graft failure than patients who did not [11]. A more recent meta-analysis of studies in which

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<th>Table 2. Serious adverse events</th>
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<td><strong>Steroid-free (65)</strong></td>
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<tr>
<td>No. of pts with SAEs</td>
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<tr>
<td>Urinary tract infection</td>
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<td>Pneumonia</td>
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<td>Thrombosis</td>
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<td>Arthralgia</td>
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<td>Leucopenia</td>
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<td>Lymphocele</td>
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<td>Anemia</td>
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<td>HUS</td>
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<td>New onset diabetes</td>
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<td>Solid tumour/(skin ca.)</td>
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<td>Kaposi’s sarcoma</td>
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<td>Thrombocytopenia</td>
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transplant recipients were treated with tacrolimus or the microemulsion of CsA confirmed a significantly higher incidence of rejection, but a reduced risk of hypercholesterolemia in the patients who stopped taking steroids [12]. Reviewing the data of Collaborative Transplant Study, Opelz et al. [13] reported significantly better 7-year patient and pure graft survivals with significantly improved risk factors among patients who stopped steroids than in those who continued them. In another RCT, 150 kidney recipients treated with basiliximab calcineurin inhibitors and mycophenolate mofetil or sirolimus stopped steroids on the second day while 150 continued steroid treatment: 3-year graft survival was 78% in steroid-free group and 79% in control. The acute rejection rate and serum creatinine levels were similar in the two groups [14]. The feasibility of avoiding steroids in the early post-operative days has been also confirmed by recent randomized trials with short follow-up [15,16].

To the best of our knowledge, this is the first randomized trial of steroid avoidance in renal transplant patients treated with a mammalian target of rapamycin (mTOR) inhibitor in association with cyclosporine. Retrospective studies have reported that steroid-free immunosuppression is feasible in renal transplant recipients treated with the other mTOR inhibitor sirolimus in combination with calcineurin inhibitors [17,18], and a pilot study of 77 patients given basiliximab, sirolimus, calcineurin inhibitors and steroids for 4 days (74% of whom received a living donor kidney) recorded 100% graft survival and excellent graft function after 12 months [19].

In this randomized trial, according to the ITT, our basiliximab, everolimus and low-dose cyclosporine regimen allowed excellent 3-year graft survival in the patients assigned to either steroid-free or low-dose prednisone treatment. There were more biopsy-proven acute rejections in the patients assigned to stop corticosteroids than in those who continued taking low-steroid doses. In the group assigned to stop steroids, most of the rejections developed during the first 100 post-transplantation days and most were completely reversible, with serum creatinine levels returning to their pre-rejection values. However, because of the fear that rejection may affect the long-term results [20], many of our investigators preferred to resume steroids temporarily or permanently even after a single and completely reversible rejection; so, only 54% of the patients in group A never resumed corticosteroids. At the end of the 3-year follow-up, none of the 65 patients assigned to steroid-free immunosuppression had died and only 3 had lost their grafts, as against 12 failures in the control group. Taking together the results of the two arms, it was observed that none of the graft losses was due to acute rejection, while three were due to progressive graft dysfunction. Many failures were caused by renal graft thrombosis, primary non-function in marginal kidneys or the discontinuation of therapy due to the poor clinical condition of the patient. These data emphasize the role played by the ‘quality’ of the donor and the recipient in influencing the results of renal transplantation. According to the ITT analysis, the mean creatinine clearance values in the two groups were similar at any time point considered and remained stable over time. Previous studies indicated that early rejection is easily detectable in patients undergoing steroid-free immunosuppression [21] and that, when reversible, it does not affect long-term outcome [22,23]. Our data would confirm that an early rejection in steroid-free patients does not carry severe consequences in the long term. It should be noted however that most patients reintroduced steroids after rejection and this may have contributed in preventing long-term graft dysfunction.

Considering the results of the ITT, it appears that patients assigned to rapidly eliminate steroids were not disadvantaged in comparison to patients assigned to continue steroids either in terms of graft survival or graft function. But what about those 30 patients assigned to steroid-free immunosuppression, who had to reintroduce steroids? None of those patients died and only one lost his graft because of chronic rejection. The mean creatinine clearance was lower than that observed in patients who could remain without steroids. The difference was expected as a number of patients reintroduced steroids because of an unsatisfying graft function. However, the mean values remained stable up to 3 years, showing that this subset of patients who probably had received kidneys with functional impairment from the beginning were not handicapped by randomization.

This study was not sized to detect between-group differences in side effects. Furthermore, the already low scheduled doses of oral prednisone in the control group were progressively reduced to a minimum of 2.5 mg/day. Nevertheless, the patients assigned to stop corticosteroids had lower serum cholesterol levels, which remained at approximately the recommended level of 200 mg/dl after 3 years. The mean triglyceride levels were less than 200 mg/dl in both arms after 3 years despite the hyperlipidemic effect of everolimus. New onset diabetes was observed with comparable frequency in both groups. The patients in group A had a lower incidence of thrombotic events and severe pneumonia.

It is worth noting that, regardless of steroid administration, there were only three cases of CMV disease among the 133 transplant recipients followed up for 3 years. This confirms the finding of a recent randomized study of heart transplant patients in which treatment with everolimus and cyclosporine was associated with a significantly lower incidence of CMV infections than treatment with cyclosporine and azathioprine [24]. Furthermore, a report of two large-scale trials comparing different doses of everolimus in association with cyclosporine and corticosteroids in renal transplant recipients also reported a low incidence of CMV infection: 11 cases out of 493 patients [5]. Finally, a meta-analysis of randomized controlled trials comparing the effects of mTOR inhibitors and inhibitors of purine synthesis in renal transplant
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In summary, this exploratory study shows that at least 50% of renal transplant recipients given a basiliximab, everolimus, cyclosporine regimen may avoid the use of corticosteroids. According to the ITT analysis, in spite of a higher incidence of rejection in patients randomized to steroid-free immunosuppression, the 3-year graft survival was better in patients assigned to an early withdrawal of steroids than in patients assigned to continue steroids. Those patients who had to resume steroids did not show a worse outcome when compared with patients who were given steroids from the beginning. The potential advantages of steroid avoidance are a reduced risk of hyperlipidemia, a well-known side effect of anti-mTOR agents [30], a reduced risk of vascular thrombosis and, probably, greater adherence to prescriptions. Larger randomized studies are needed in order to verify whether steroid-free immunosuppression in everolimus- and cyclosporine-treated transplant patients also reduces the risk of cardiovascular disease, diabetes and osteoporosis while improving compliance.

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