Steroid avoidance with early intensified dosing of enteric-coated mycophenolate sodium: a randomized multicentre trial in kidney transplant recipients

Antoine Thierry1,2, Georges Mourad3, Matthias Büchler4, Nassim Kamar5, Florence Villemain6, Anne-Elisabeth Heng7, Yannick Le Meur8, Gabriel Choukroun9,10, Olivier Toupane11, Christophe Legendre12, Patrick Lepogamp13, Michele Kessler14, Pierre Merville15, Bruno Moulin16, Stéphane Quéré17, Arara Terpereau17, Kamel Chaouche-Teyara17 and Guy Touchard1,2

1Service de Néphrologie et Transplantation Rénale, Hôpital La Milétrie, Poitiers, France, 2INSERM U1082, CHU, Poitiers, France, 3Service de Néphrologie et Transplantation Rénale, Hôpital Lapeyronie, Montpellier, France, 4Service de Néphrologie-Transplantation Rénale, Hôpital Bretonneau, Tours, France, 5Service de Néphrologie-Transplantation, Hôpital de Rangueil, Toulouse, France, 6Service Néphrologie, Dialyse et Transplantation, CHU d’Angers, Angers, France, 7Service de Néphrologie et Transplantation Rénale, Hôpital Gabriel Montpied Clermont, Ferrand, France, 8Service de Néphrologie et Transplantation Rénale, Hôpital La Cavale Blanche, Brest, France, 9Service de Néphrologie, Médecine Interne, Dialyse, Transplantation Rénale et Réanimation, Hôpital Sud, CHU Amiens, Amiens, France, 10INSERM ERI-12, Université Jules Verne Picardie, France, 11Service de Néphrologie et Transplantation Rénale, Hôpital Maisonneuve, Reims, France, 12Service de Néphrologie et Transplantation Rénale, Hôpital Necker, Paris, France, 13Service de Néphrologie et Transplantation Rénale, Hôpital Pontchaillou, Rennes, France, 14Service de Néphrologie et Transplantation Rénale, CHU de Nancy, Vandoeuvre les Nancy, France, 15Service de Néphrologie et Transplantation Rénale, Hôpital Pellegrin, Bordeaux, France, 16Service de Néphrologie et Transplantation Rénale, Hôpital Civil, Strasbourg, France and 17Unité Immuno-Transplantation, Novartis Pharma SAS, Rueil-Malmaison, France

Correspondence and offprint requests to: Guy Touchard; E-mail: g.touchard@chu-poitiers.fr

Abstract

Background. Short-term intensified dosing using enteric-coated mycophenolate sodium (EC-MPS) reduces rejection after kidney transplantation without compromising safety and may facilitate steroid avoidance.

Methods. In a 6-month, multicentre open-label trial, 222 de novo kidney transplant recipients at low-immunological risk were randomized to steroid avoidance or maintenance steroids with interleukin (IL)-2 receptor antibody (IL-2RA) induction, EC-MPS (2160 mg/day to Week 6, 1440 mg/day thereafter) and cyclosporine.

Results. The primary end point; treatment failure at Month 6 [biopsy-proven acute rejection (BPAR), graft loss, death or loss to follow-up], occurred in 17.9% (20/112) of steroid-avoidance patients and 14.5% (16/110) of controls (difference 3.4%, 95% confidence interval −6.3 to 13.1, P = 0.47 for superiority testing). BPAR occurred in 11.6 and 7.3% of patients in the steroid-avoidance and control arms, respectively (P = 0.27). Creatinine clearance was similar at Month 6 (steroid-avoidance 56 ± 18 mL/min/1.73m², controls 60 ± 22 mL/min/1.73m², P = 0.34). Cytomegalovirus infection, as reported by investigators, occurred in 12.5% of steroid-avoidance patients and 22.7% of controls (P = 0.045).

Conclusions. A regimen of early intensified EC-MPS dosing with calcineurin inhibitor and IL-2RA induction permits oral steroid avoidance in adult kidney transplant patients at low-immunological risk without compromising efficacy at 6 months’ follow-up.

Keywords: EC-MPS; enteric-coated mycophenolate sodium; MMF; mycophenolic acid; myfortic

Introduction

Steroid-free immunosuppression is a long-standing goal for immunosuppression following kidney transplantation.
Although the advent of calcineurin inhibitors (CNIs) permitted a marked reduction in steroid doses, steroid-induced morbidity—particularly hypertension, hyperlipidaemia and diabetes mellitus [2]—continue to be a major source of concern [3, 4] and steroid withdrawal or avoidance reduces the risk of cardiovascular events and cardiovascular mortality [5, 6] and steroid-related complications, such as cataracts and osteoporosis [5].

Novel immunosuppressant agents have provided a new impetus to attempt aggressive steroid minimization, and increasingly, very early steroid discontinuation or complete steroid avoidance is being sought [7]. Results have been conflicting for using a steroid-free regimen comprising a proliferation signal inhibitor (everolimus or sirolimus) with CNI therapy and interleukin (IL)-2 receptor antibody (IL-2RA) induction [8–11]. Using mycophenolic acid (MPA) and CNI therapy, complete steroid avoidance appears problematic [12] but steroid withdrawal within the first week post-transplantation may be feasible in patients who are not at high-immunological risk, if induction therapy is used [12–15]. In the large CARMEN study, mycophenolate mofetil (MMF), tacrolimus and daclizumab induction with up to 500 mg bolus dose of methylprednisolone on the day of surgery for all patients and a 125 mg bolus on the second day for patients randomized to tacrolimus, MMF and steroids was associated with the same rate of biopsy-proven acute rejection (BPAR) at Month 6 as a regimen of MMF, tacrolimus and maintenance steroids with no induction (16.5% in both groups) [14]. The FREEDOM study, however, in which all 224 patients received IL-2RA induction, cyclosporine (CsA) and enteric-coated mycophenolate sodium (EC-MPS), reported a non-significantly higher 12-month rate of BPAR following steroid withdrawal at Day 7 versus maintenance steroids (29.6 versus 19.3%) [12], although two smaller studies found no loss of efficacy following steroid withdrawal during Week 1 [13, 15].

These results raise the question of whether more intensive MPA exposure in the immediate post-transplant period would be beneficial in the absence of maintenance steroid therapy. Early intensive EC-MPS dosing has been investigated within a steroid-containing regimen in the recent Optimize trial, in which the 6-month incidence of BPAR was significantly lower in the intensified group versus standard EC-MPS dosing [16]. In that study, MPA exposure was significantly higher during Days 3–10 post-transplantation in patients receiving intensified dosing, with a corresponding lower level of inosine monophosphate dehydrogenase activity [17]. Elsewhere, the CLEAR study has shown that a higher proportion of patients given an increased dose of MMF (3 g/day instead of the conventional 2 g/day in combination with tacrolimus and prednisone) achieved higher MPA exposure at Day 5, with a trend to reduced acute rejection (suspected and treated) at Month 6 [18]. Short-term intensified MPA dosing within a steroid-free regimen may be a promising strategy following kidney transplantation. We report here the results of the DOMINOS (Intensified Dose of Myfortic INvestigation Open Study for Steroids avoidance) trial, which was undertaken with the objective of comparing the efficacy and tolerability of a steroid avoidance regimen versus maintenance steroid therapy in de novo kidney transplant patients receiving CsA and early intensified EC-MPS dosing.

Materials and methods

Study design and conduct

DOMINOS was a multicentre, randomized, parallel group, open-label 6-month trial conducted at 14 transplant centres in France between April 2007 and March 2009. The objective was to evaluate whether steroid avoidance with an intensified EC-MPS dosing regimen would preserve efficacy compared to full-dose maintenance steroids while providing a benefit in terms of tolerability. The study was undertaken in accordance with the Declaration of Helsinki and the ICH Harmonised Tripartite Guidelines for Good Clinical Practice. All patients provided written informed consent following ethical approval from the Comité de Protection des Personnes (Poitiers).

Participants

Male or female patients aged 18–70 years were eligible to enter the study if they received a first or second kidney transplant from a deceased, living-related or living-unrelated donor and were scheduled to receive IL-2RA induction with CsA maintenance therapy. Patients were required to have panel-reactive antibodies (PRA) ≤20% at the last pre-transplant assessment. The key criteria for non-inclusion were receipt of a multi-organ transplant (including two kidneys) or a previous non-renal transplant, graft donation after cardiac death and cold ischaemia time >36 h.

Study medication

Patients were randomized in a 1:1 ratio on Day 1 using a block size of 4 with no stratification by the contract research organization using a validated automated system, with sealed envelopes distributed to participating centres. After providing informed consent, patients were allocated a randomization number and the investigator opened the corresponding envelope. EC-MPS was administered at a dose of 2160 mg/day in two divided doses to Week 6 post-transplantation, after which the dose was reduced to the standard 1440 mg/day.

All patients received IL-2RA induction according to the local centre protocol. CsA was initiated within 24 h of transplantation at a dose of 8 mg/kg/day in two divided doses, subsequently adjusted according to the CsA concentration at 2 h post-dose (C2) based on the following targets: Month 1, 1200 ng/mL (range 1100–1300 ng/mL); Months 2–3, 900ng/mL (800–1000 ng/mL) and Months 4–6, 700 ng/mL (600–800 ng/mL). CsA C2 concentration was measured locally.

Patients in both treatment arms received a total perioperative dose of 500 mg intravenous methylprednisolone, given as a bolus dose of 250 mg on Day −1 and Day 0 (the day of transplantation). Patients in the steroid-avoidance group then received no further steroids unless clinically mandated. Patients in the control group also received a bolus dose of 250 mg on Day −1 and Day 0, then received oral prednisone from Day 1 as follows: 1 mg/kg/day (maximum 80 mg/day) for 1 week, then 0.5 mg/kg/day (maximum 40 mg/day) for 1 week, which was then decreased by 0.5 mg/week until the dose was 10 mg/day and then decreased by 2.5 mg/week until the dose was 10 mg/day. The dose was maintained at 10 mg/day for 4 weeks and at least until Month 3 post-transplantation. Subsequently, if protocol biopsy findings at Month 3 were negative (local reading), the dose was decreased by 2.5 mg/15 days until steroids were stopped. If biopsy at Month 3 showed signs of subclinical rejection, steroid therapy was continued at a dose of 10 mg/day.

A kidney biopsy was performed in the event of suspected rejection, using the updated Banff 1997 classification [19, 20]. Protocol biopsy was performed at Month 3. A blinded central review of all biopsy samples was performed at the end of study.

Cytomegalovirus (CMV) prophylaxis consisting of valganciclovir or valaciclovir was mandatory for at least the first 3 months post-transplantation if the donor was positive and the recipient negative for anti-CMV IgG. The decision to administer CMV prophylaxis to other patients was made according to centre practice. The same regimen was to be administered to all patients from a single centre. All patients received Pneumocystis jiroveci prophylaxis.

Materials and methods

Study design and conduct
Primary and secondary end points
The primary end point was the incidence of treatment failure at Month 6, defined as clinical BPAR (central review), graft loss, death or loss to follow-up. Subclinical BPAR from the protocol-defined biopsies at Month 3 were excluded. Secondary efficacy end points were the incidence and severity of clinical BPAR at Months 3 and 6, graft histology on the 3-month protocol biopsy (central review), treatment failure at Month 3, graft and patient survival at Months 3 and 6, renal function at Months 3 and 6 estimated by serum creatinine and calculated creatinine clearance (Cockcroft–Gault formula [21], adjusted for body surface area) and estimated glomerular filtration rate (eGFR; Nankivell formula [22]) and renal function at Months 3 and 6 in patients with delayed graft function (DGF, defined as requirement for dialysis during the first post-transplant week) or immediate graft function. Safety end points were all adverse events, considered to be related to EC-MPS or steroid therapy by the investigator, laboratory results, dose reduction or discontinuation of EC-MPS and cumulative steroid dose.

Evaluation
Study visits took place on Days 1, 3, 5 and 7, Weeks 2 and 4 and Months 3 and 6. Laboratory tests (including haematology and viral serology) were performed at all visits other than Day 3. CsA C2 level was measured at all visits from Day 3 onwards.

Statistical methods
The primary analysis was to demonstrate non-inferiority of the steroid-avoidance group versus the control group for the primary efficacy variable, i.e. treatment failure at Month 6. The sample size calculation was based on a non-inferiority margin of 20%, which was considered indicative of comparable efficacy in this setting. It was assumed that the control group would show a treatment failure rate of 20%, based on published data [23–25], while the steroid-avoidance group would have a slightly higher rate of treatment failure (23%) largely due to BPAR. The calculation showed that 105 patients per treatment arm would provide 85% power to demonstrate non-inferiority using a two-sided alpha level of 0.05 (nQuery Advisor V4.0; Statistical Solutions Ltd, Cork, Ireland).

Two-sided 95% confidence intervals (CIs) were calculated for the difference in treatment rate between the steroid-avoidance and control groups using the Wald method, a simple asymptotic method without continuity correction. Non-inferiority was demonstrated if the upper limit of the CI for this difference was <20% for both the intent-to-treat (ITT) and per protocol (PP) analysis sets. The ITT analysis set was defined as all randomized patients who received at least one dose of study medication. The PP analysis set comprised all ITT patients who completed the 6-month study without any major protocol violations. Major protocol deviations constituted not being treated as randomized, not receiving IL-2RA induction, PRA >20%, stopping steroids before Month 3 or temporary discontinuation of steroids for >5 days in the control group or taking oral steroids without any reason or clinical event in the steroid-avoidance group. The safety analysis set was defined as all randomized patients who received one or more doses of study medication and then provided at least one safety assessment.

Comparisons between treatment groups were made using the Fisher’s exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Event rates at Months 3 and 6 were compared by Fisher’s exact and chi-square tests. No procedure was used to control the overall Type 1 error rate for secondary end points since these were non-primary analyses. Missing data were not imputed. No interim analyses were planned or performed and no stopping criteria were pre-defined. All statistical analyses were performed using SAS 8.2 software (SAS Institute, Cary, NC).

Results
Patient population
In total, 222 patients were randomized and formed the ITT and safety analysis sets. One patient in the steroid-avoidance group was excluded from the PP analysis set for taking oral steroids without any reason or clinical event and two control patients were excluded because they were not treated as randomized. Fifty-six patients discontinued the 6-month study prematurely (25.2%), most frequently due to adverse events (n = 20) or unsatisfactory therapeutic effect as defined by the investigator (n = 20), such that 166 patients completed the study (74.8%) (Figure 1).

Demographics and baseline characteristics were similar between treatment groups (Table 1). Over 90% of patients were white, and more than half were male. Mean age was 51 years. All but one patient in each group had PRA ≤10%. An ‘old-for-old’ transplant (recipient and donor ≥60 years) was performed in 14.4% of patients. Mean

![Fig. 1. Patient disposition during the 6-month study. ITT, intent-to-treat, PP, per protocol.](https://academic.oup.com/ndt/article-abstract/27/9/3651/1860423)
cold ischaemia time was 16 h and 48 min. Approximately, a quarter of transplants (24%) involved a CMV− recipient and a CMV+ donor.

**Immunosuppression**

Mean EC-MPS dose was similar in the steroid-avoidance and control groups throughout the study (Table 2). Excluding protocol-stipulated dose changes, the proportion of patients requiring one or more EC-MPS dose decrease was 38.4% (43/112) and 43.6% (48/110) among patients randomized to the steroid-avoidance or control groups, respectively. Of these 91 non-protocol dose decreases, 74 (81.3%) were due to adverse events or laboratory abnormalities. EC-MPS was discontinued for ≥7 days in 4.5% of steroid-avoidance patients (n = 5) versus 9.1% of control patients (n = 10) and for ≥3 days in 6.3% of steroid-avoidance patients versus 13.6% of controls (P = 0.066). In total, there were eight discontinuations of EC-MPS of any duration in the steroid-avoidance group compared to 36 discontinuations in the control arm (P = 0.066). Among patients with at least one momentary discontinuation, the mean duration of discontinuation was 13.9 ± 17.3 days in the steroid-avoidance group versus 32.7 ± 53.5 days in controls. Mean CsA C2 concentration was similar between groups (Table 2). At Months 1 and 3, mean C2 concentration was towards the upper end of the 1100–1300 ng/mL target range in both groups and slightly exceeded the target range (600–800 ng/mL) in both groups at Month 6.

The proportion of patients assigned to the steroid-avoidance group who received oral steroids was 23.8% (24/101) at Month 1, 30.8% (28/91) at Month 3 and 38.1% (32/84) at Month 6. The mean (SD) cumulative oral dose of steroids was 516 (761) mg in the steroid-avoidance group and 2234 (692) mg in the control arm.

Of the 52 patients in the steroid-avoidance group who received steroids at any point after randomization, the reason was treatment of BPAR rejection in 25 patients, suspected rejection (not confirmed) in 20 patients, response to an adverse event or laboratory abnormality in 6 patients (for example, to compensate for a decrease in the dose of another immunosuppressant) and 4 other reasons in the steroid-avoidance cohort, including protocol-stipulated dose changes.

**Efficacy**

The incidence of the primary efficacy variable, treatment failure at Month 6, was 17.9% (20/112) in the steroid-avoidance arm and 14.5% (16/110) in the control arm. These incidences were not statistically different (P = 0.50). The between-group difference was 3.4% (95% CI –6.3 to 13.1), such that the steroid-avoidance group was
Steroid avoidance with intensified early EC-MPS

**Table 3. Efficacy end points at Months 3 and 6 (ITT analysis set)**

<table>
<thead>
<tr>
<th></th>
<th>Month 3</th>
<th></th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without steroids</td>
<td>With steroids</td>
<td>P-value⁴</td>
</tr>
<tr>
<td>Treatment failure⁵</td>
<td>17 (15.2%)</td>
<td>8 (7.3%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Acute rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPAR³</td>
<td>10 (8.9%)</td>
<td>5 (4.5%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Antibody-mediated</td>
<td>0</td>
<td>1 (0.9%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Cellular</td>
<td>10 (8.9%)</td>
<td>5 (4.5%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Grade IA</td>
<td>4 (3.6%)</td>
<td>2 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Grade IB</td>
<td>2 (1.8%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Grade IIA</td>
<td>4 (3.6%)</td>
<td>3 (2.7%)</td>
<td></td>
</tr>
<tr>
<td>Grade IIB</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Graft loss</td>
<td>5 (4.5%)</td>
<td>1 (0.9%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Death</td>
<td>2 (1.8%)</td>
<td>2 (1.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

⁴Chi-squared test.

⁵Treatment failure was defined as BPAR (central review), graft loss, death or loss to follow-up. BPAR detected on the 3-month protocol biopsy was excluded.

Two patients experienced both cellular and humoral acute rejection lesions.

Non-inferior to the control group for the primary end point (P = 0.47 for superiority testing). Similar results were obtained in the PP analysis set [18.0% (20/111) versus 15/108 (13.9%), difference 4.1% (95% CI 6.3 – 13.1%)]. There were no significant differences in the incidence of individual end points [i.e. treatment failure, BPAR (central review), graft loss or death] at Month 3 or Month 6, although the rate of BPAR was numerically higher in the steroid-avoidance group at both time points (Table 3). No patient in the steroid-avoidance arm experienced BPAR greater than Grade IIA; one patient in the control arm had an episode of Grade IIB rejection.

A 3-month protocol biopsy was performed in 59 patients in the steroid-avoidance group and 66 patients in the control arm, with adequate samples available in 52 and 60 patients, respectively. Subclinical rejection was observed in 12/52 (23.1%) and 17/60 (28.3%) samples in the steroid-avoidance and control groups, with borderline lesions in 2/52 (3.8%) and 5/60 (8.3%) cases, respectively. Kaplan–Meier estimates indicated the probability of remaining free from both BPAR and subclinical rejection to be 75.6% in the steroid-avoidance group versus 80.0% in the control arm at Month 6 (P = 0.392, log-rank test).

No graft was lost due to rejection. There were five graft losses in the steroid-avoidance arm (three renal artery thrombosis, one renal vein thrombosis and one infarcted kidney) and three in the control arm (one renal artery thrombosis, one renal artery aneurysm and one false aneurysm (myotic)). Two patients died in the steroid-avoidance group (cardiac arrest and mesenteric ischaemia) while receiving study treatment, and a third patient died due to renal vein thrombosis 2 days after discontinuing study medication. Five patients died in the control group due to inhalation after vomiting, pulmonary embolism, sudden death (one possibly due to cardiac causes, the other of unknown causes) and death of unknown origin at home.

DGF occurred in 25 steroid-avoidance patients (22.3%) and 24 controls (21.8%) (P = 0.93). Immediate graft function was reported in 87 steroid-avoidance patients (77.6%) and 86 controls (78.2%).

Mean creatinine clearance (Cockcroft–Gault) at Month 1 was 46 ± 15 mL/min/1.73m² in the steroid-avoidance arm and 55 ± 23 mL/min/1.73m² in controls (P = 0.007) but was similar between groups at Months 3 and 6 (Table 4). eGFR using the Nankivell formula was also significantly different between groups only at Month 1 (53 ± 16 versus 59 ± 22 mL/min/1.73m², P = 0.042). No difference was observed in patients with immediate graft function or DGF between the two groups in terms of creatinine clearance or eGFR at Months 3 and 6 (Table 4).

Mean urine protein/creatinine ratio was similar between treatment groups at Months 1, 3 and 6 (Table 4).

Adverse events

All patients reported one or more adverse event within the 6-month study period, with a total of 971 and 1009 adverse events recorded in the steroid-avoidance and control arms, respectively (Table 5). In total, 64.9% of patients (144/222) experienced one or more adverse event with a suspected relation to EC-MPS, of which the most frequent were anaemia [36/222 (16.2%)], leucopenia [32/222 (14.4%)], diarrhoea [30/222 (13.5%)], CMV infection [20/222 (12.6%)], and urinary tract infection [26/222 (11.7%)]. Gastrointestinal adverse events were reported in 125/222 patients (56.3%) overall, the most frequent being diarrhoea (39/222), constipation (34/222) and abdominal pain (25/222). Thirty-five patients (35/222 (15.8%)] had one or more gastrointestinal adverse event with a suspected relation to EC-MPS, most frequently diarrhoea (30/222). Serious adverse events occurred in a similar proportion of patients in both groups (Table 5). Forty-five patients [45/222 (20.3%)] had one or more serious adverse event with a suspected relation to EC-MPS.
### Table 4. Renal function at Months 1, 3 and 6 (ITT analysis set)

<table>
<thead>
<tr>
<th>Month 1</th>
<th>Without steroids (n = 112)</th>
<th>With steroids (n = 110)</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Month 3</th>
<th>Without steroids (n = 112)</th>
<th>With steroids (n = 110)</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Month 6</th>
<th>Without steroids (n = 112)</th>
<th>With steroids (n = 110)</th>
<th>P-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Creatinine clearance, Cockcroft-Gault (mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;)</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All patients</td>
<td>46 ± 15 (n = 95)</td>
<td>55 ± 22 (n = 96)</td>
<td>0.007</td>
<td></td>
<td>52 ± 17 (n = 90)</td>
<td>56 ± 19 (n = 90)</td>
<td>0.17</td>
<td></td>
<td>56 ± 18 (n = 79)</td>
<td>60 ± 22 (n = 81)</td>
<td>0.34</td>
</tr>
<tr>
<td>DGF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>53 ± 15 (n = 14)</td>
<td>53 ± 19 (n = 17)</td>
<td>0.97</td>
<td></td>
<td>53 ± 12 (n = 12)</td>
<td>51 ± 18 (n = 19)</td>
<td>0.48</td>
<td></td>
<td>56 ± 19 (n = 67)</td>
<td>62 ± 23 (n = 62)</td>
<td>0.11</td>
</tr>
<tr>
<td>Immediate function</td>
<td>52 ± 16 (n = 76)</td>
<td>56 ± 19 (n = 73)</td>
<td>0.13</td>
<td></td>
<td>56 ± 19 (n = 73)</td>
<td>60 ± 22 (n = 81)</td>
<td>0.34</td>
<td></td>
<td>56 ± 19 (n = 67)</td>
<td>62 ± 23 (n = 62)</td>
<td>0.11</td>
</tr>
<tr>
<td>eGFR, Nankivell (mL/min/1.73m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>53 ± 16 (n = 94)</td>
<td>59 ± 22 (n = 96)</td>
<td>0.042</td>
<td></td>
<td>59 ± 16 (n = 89)</td>
<td>61 ± 19 (n = 90)</td>
<td>0.41</td>
<td></td>
<td>63 ± 16 (n = 78)</td>
<td>65 ± 19 (n = 80)</td>
<td>0.48</td>
</tr>
<tr>
<td>DGF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>60 ± 14 (n = 14)</td>
<td>58 ± 22 (n = 17)</td>
<td>0.72</td>
<td></td>
<td>61 ± 7 (n = 11)</td>
<td>57 ± 17 (n = 18)</td>
<td>0.47</td>
<td></td>
<td>64 ± 17 (n = 67)</td>
<td>68 ± 19 (n = 62)</td>
<td>0.23</td>
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<tr>
<td>Immediate function</td>
<td>59 ± 16 (n = 75)</td>
<td>62 ± 18 (n = 73)</td>
<td>0.26</td>
<td></td>
<td>64 ± 17 (n = 67)</td>
<td>68 ± 19 (n = 62)</td>
<td>0.23</td>
<td></td>
<td>64 ± 17 (n = 67)</td>
<td>68 ± 19 (n = 62)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Serum creatinine, mean ± SD (μmol/L)</strong></td>
<td>173 ± 75 (n = 101)</td>
<td>156 ± 83 (n = 104)</td>
<td>0.007</td>
<td>147 ± 48 (n = 95)</td>
<td>142 ± 49 (n = 100)</td>
<td>0.55</td>
<td>135 ± 37 (n = 22)</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urine protein: creatinine ratio (g/mmol)</strong></td>
<td>0.1 ± 0.21 (n = 80)</td>
<td>0.1 ± 0.3 (n = 85)</td>
<td>0.29</td>
<td>0.0 ± 0.04 (n = 84)</td>
<td>0.0 ± 0.05 (n = 79)</td>
<td>1.00</td>
<td>0.0 ± 0.03 (n = 70)</td>
<td>0.0 ± 0.05 (n = 69)</td>
<td>0.46</td>
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<sup>a</sup>Data are shown as mean ± SD.

<sup>b</sup>Chi-squared test.

<sup>c</sup>DGF defined as requirement for dialysis during the first post-transplant week.
adverse event by investigators at Month 6 [steroid-avoidance 8.7% (9/103), controls 13.0% (13/100), P = 0.33]. Mean values for blood glucose concentration and lipid parameters did not vary between groups. Dyslipidaemia was reported by investigators in 14/112 patients (12.5%) and 24/110 patients (21.8%) in the steroid-avoidance and control groups, respectively (P = 0.065). Systolic and diastolic blood pressure were similar between groups at Month 6. Mean body mass index was non-significantly lower in the steroid-avoidance group compared to controls at Month 6: 24.3 ± 3.6 versus 25.8 ± 4.8 kg/m² (P = 0.08). In absolute terms, the steroid-avoidance cohort showed no change in body mass index over the 6-month study period (+0.2 ± 1.6 kg/m², P = 0.20 versus baseline), while the control group experienced an increase (+0.6 ± 2.0 kg/m², P = 0.002 versus baseline).

Haematology and liver function parameters showed no differences between treatment arms other than a non-significant trend to higher haemoglobin in the steroid-avoidance group at Month 6 (mean 12.5 ± 1.6 versus 12.1 ± 1.6 g/dL in the control arm, P = 0.07).

**Discussion**

Results from this multicentre randomized study suggest that oral steroid therapy can be avoided in low-immunological risk kidney transplant patients given a regimen of early intensified EC-MPS dosing, CNI and IL-2RA induction without compromising efficacy compared to a maintenance steroid regimen. However, almost half of the patients (52/110) required steroids at some point during the 6-month study period. The steroid-avoidance group experienced a numerically lower rate of serious infections and fewer CMV infections versus control patients, but it should be noted that intensified EC-MPS therapy with maintenance steroids may have led to overimmunosuppression in the control arm. No cases of BK virus nephropathy were observed.

The incidence of BPAR (9% overall at Month 6) was lower than that reported in previous studies in which standard-dose EC-MPS was administered with CsA and steroids [26, 27], most likely due to the protocol-specifed use of IL-2RA induction and exclusion of patients with high PRA level or an extended cold ischaemia time. Notably, the incidence and severity of BPAR indicated a similar immunosuppressive potency in both treatment groups. Protocol biopsies at Month 3 confirmed that inflammatory lesions suggestive of subclinical rejection occurred with a comparable frequency with or without maintenance steroids. While almost 1 in 10 patients discontinued due to unsatisfactory therapeutic effect, there were no differences between treatment groups. These findings are encouraging in the light of a recent meta-analysis of 34 trials in which steroid avoidance or withdrawal was associated with an increased risk of rejection (relative risk 1.56, P < 0.001) and reduced creatinine clearance versus maintenance steroid regimens [28]. In the current study, no difference in renal function was observed between groups after Month 1. We are not clear why a difference was observed at Month 1 since the rate and severity of BPAR were similar between groups, as well as CsA exposure levels.

The steroid-avoidance regimen exhibited a more favourable safety profile. This is not unexpected since use of intensified EC-MPS therapy with maintenance steroids using conventional dosing represents a relatively high intensity of immunosuppression which would not have been the case if the control arm had received a standard EC-MPS regimen with maintenance steroids. Here, the overall rate of adverse events and serious adverse events was similar between groups, but total incidence of steroid-related adverse events and steroid-related serious events of any type were both significantly lower in the steroid-avoidance patients (Table 5), as might be expected. Common steroid-related adverse events (hypertension, dyslipidaemia, urinary tract infection and diabetes mellitus) were numerically less frequent in the steroid-avoidance group. Steroid-related infections and CMV infection were less frequent in the steroid-avoidance group, although it should be taken into account that use of CMV prophylaxis may not have been homogeneous between centres and that CMV infection was reported as an adverse event without pre-specified definitions and thus vulnerable to bias. It should also be remembered that all patients received the intensified EC-MPS regimen so no comparison versus standard EC-MPS dosing is possible, but a direct effect of steroids on viral replication is suspected. With infection reported to be the second most common cause of death with a functioning graft [29, 30], an immunosuppressive regimen that can reduce infection rates—and particularly CMV infection [31]—without loss of efficacy is an attractive option. The hyperglycaemic effect of long-term steroid therapy is also of concern in view of the impact of new-onset diabetes on mortality after kidney transplantation [32, 33]. In our population, hyperglycaemia and diabetes mellitus were reported less frequently in the steroid-avoidance group despite similar use of anti-diabetic therapy, but the differences were not statistically significant. Reported elsewhere, 1-year [12] and 5-year [10] follow-up data have shown a reduced requirement for hypoglycaemic treatment following very early steroid withdrawal, while a meta-analysis involving 5537 patients found the rate of new-onset diabetes to be significantly reduced with steroid avoidance or withdrawal [28]. A regimen of early intensified EC-MPS dosing with CsA and induction therapy with steroid avoidance may offer a useful alternative to a tacrolimus–steroids–MPA regimen, particularly in patients at high risk of diabetes [34] or BK virus infection [35–37].

As reported previously in the Optimize study [16], the early intensified EC-MPS dosing regimen was associated with a low rate of temporary discontinuations and <2% of patients discontinuing due to adverse events with a suspected relation to EC-MPS. Recent evidence that MMF dose shows a non-linear relationship with MPA bioavailability in CNI-treated patients, with relative bioavailability decreasing at higher doses [38], may help to explain the low requirement for discontinuation despite the increased dosing level. The differences in EC-MPS discontinuations between the two treatment arms most likely reflect greater reluctance of investigators to withdraw MPA therapy in
patients randomized to steroid avoidance and is not regarded as clinically significant.

Certain features of the study may influence the design of future trials. Firstly, the study was open-labelled since the pill burden in the period immediately after transplantation was considered too high to justify administration of the necessary matched placebo. Inevitably, this has the potential to introduce bias. Secondly, the duration of the study (6 months) was relatively short and thus unable to assess the longer-term metabolic effects of steroid therapy. Thirdly, patients at high-immunological risk (i.e. PRA ≥20% or extended cold ischaemia time) were excluded from the study population, but the low rate of rejection in this population suggests that steroid avoidance with early intensified EC-MPS dosing could be explored in higher risk individuals. As in other trials of steroid avoidance using MPA and CNI [8, 12–15, 39], intravenous steroids were administered and appear necessary [12]. In studies of later steroid withdrawal (3–4 months post-transplant) [40, 41] in which IL-2RA induction was not used, the efficacy of MPA and CNI therapy following steroid withdrawal was less convincing and induction therapy would seem advisable. It should also be remembered that at any one time, approximately one quarter of patients randomized to the steroid-avoidance group were receiving steroid therapy. Fourthly, the steroid dosing in the control may not represent current practice in which lower doses may be employed. The doses used here were based on regimens used at the time, the protocol was developed. Lastly, in hindsight, the non-inferiority margin of 20% was too high, but even using the smaller margin of 15%, non-inferiority would still have been demonstrated since the upper limit of the 95% CI for the primary end point was 13.1%. Lastly, future trials could assess a regimen of intensified EC-MPS with steroid avoidance versus standard EC-MPS dosing with a modern regimen of maintenance steroids, a comparison that might more accurately reflect likely strategies in current clinical practice.

In conclusion, a regimen of early intensified EC-MPS dosing with CNI and IL-2RA induction may permit steroid avoidance in adult kidney transplant patients at low-immunological risk without compromising efficacy and is associated with a significant reduction in the risk of CMV infection when compared to intensified EC-MPS dosing with maintenance steroids. A benefit in terms of the metabolic and cardiovascular complications of steroids was not observed, but since these develop progressively, this 6-month study was unlikely to have revealed the differences that have been reported after 5 years of steroid-free immunosuppression [10].

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