Improved growth and cardiovascular risk after late steroid withdrawal: 2-year results of a prospective, randomised trial in paediatric renal transplantation

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Abstract

Background. Long-term corticosteroid treatment impairs growth and increases cardiovascular risk factors. Hence, steroid withdrawal constitutes a major topic in paediatric renal transplantation and maintenance immunosuppression.

Methods. The lack of data from randomised controlled trials caused us to conduct the first prospective, randomised, multicentre study on late steroid withdrawal among paediatric kidney allograft recipients treated with standard-dose cyclosporine microemulsion (CsA) and mycophenolate mofetil (MMF) for 2 years. Forty-two low- or regular-immunologic risk patients were randomly assigned, ≥1 year post-transplant, to continue taking or to withdraw steroids over 3 months.

Results. Two years after steroid withdrawal, they showed a longitudinal growth superior to controls [mean height standard deviation score (SDS) gain, 0.6 ± 0.1 SDS versus −0.2 ± 0.1 SDS (P < 0.001)]. The prevalence of the metabolic syndrome declined significantly (P < 0.05), 2 years after steroid withdrawal, from 39% (9/23) to 6% (1/16). Steroid-free patients had less frequent arterial hypertension (50% versus 93% (P < 0.05)) and required fewer antihypertensive drugs [0.6 ± 0.2 versus 1.5 ± 0.3 (P < 0.05 versus control)]. Additionally, they had a significantly improved carbohydrate and lipid metabolism with fewer hypercholesterolaemia and hyperglycemia (P < 0.05 versus control). Patient and graft survival amounted to 100%. Allograft function remained stable 2 years after steroid withdrawal. The incidence of acute rejections was similar in the steroid-withdrawal group (1/23, 4%) and controls (2/19, 11%).

Conclusion. Late steroid withdrawal in selected CsA- and MMF-treated paediatric kidney transplant recipients improves growth, mitigates cardiovascular risk factors and reduces the prevalence of the metabolic syndrome, at no increased risk of acute rejection or unstable graft function.

Keywords: cardiovascular; metabolic syndrome; mycophenolate mofetil; paediatric renal transplantation; steroid withdrawal

Introduction

Glucocorticoids (steroids) still form a cornerstone of immunosuppressive regimens for paediatric renal transplant recipients. However, their numerous well-known systemic side effects such as arterial hypertension, diabetes mellitus and dyslipidaemia not only increase the risk of cardiovascular morbidity but also constitute non-immunologic triggers of chronic allograft failure [1–3]. The growing prevalence of the metabolic syndrome in children and adolescents also affects renal allograft patients and is enhanced by continuous steroid treatment [4,5]. Past studies on late steroid withdrawal among paediatric kidney transplant patients receiving cyclosporine microemulsion (CsA) monotherapy or dual therapy with CsA and azathioprine have revealed an increased risk of acute transplant rejection, which, according to a meta-analysis of published paediatric trials, amounts to ~39% on average [6]. However, after the introduction of the more potent mycophenolate mofetil (MMF) instead of azathioprine, the option of steroid withdrawal had to be reconsidered [7].

We have recently published the 1-year results of the first multicentre, randomised, open-label study on late steroid withdrawal (≥1 year post-transplant) in paediatric renal transplantation. The aim of the present study was to determine the medium-term results of the steroid-withdrawal group (S-csA/MMF) and controls (S-csA/MMF + S), to compare with the outcomes of the acute rejection rate of the S-csA/MMF group in the first year of the study [7].

Statistical analysis

The data were evaluated for all patients evaluable for the primary end point (P < 0.05). Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Comparisons between continuous variables were performed by unpaired t-tests. The differences between groups were assessed by paired t-tests. The non-parametric Wilcoxon test was used to compare the results of the two populations. The censored time to the primary outcome was calculated by the Kaplan-Meier estimator with competing risks. The cumulative incidence of the primary endpoint was calculated as the sum of the probability of the primary endpoint and the probability of death or rejection, and the related cumulative incidence curves were estimated by the competing-risk methodology.

Results

The overall incidence of rejection in the steroid-withdrawal group (1/23, 4%) was significantly lower versus controls (2/19, 11%) (P < 0.05). The analysis of the primary endpoint showed a significant difference between the two groups (P < 0.05). The Kaplan-Meier estimates for the incidence of rejection were 100% versus 100% in the steroid-withdrawal group and controls, respectively (P < 0.05). No early graft losses were observed. The overall patient and graft survival rates were 100% versus 100% in the steroid-withdrawal group and controls, respectively (P < 0.05).

Discussion

The long-term adverse effects of glucocorticoids in children and adolescents have been well documented recently. The metabolic syndrome, which includes insulin resistance, obesity, hypercholesterolaemia and hypertension, is highly prevalent in children with chronic diseases and is associated with increased cardiovascular morbidity and mortality [1–3]. Chronic corticosteroid treatment is clearly a risk factor for the metabolic syndrome and its high prevalence in kidney transplant recipients is at least partly due to the use of immunosuppressive drugs [4,5]. Glucocorticoids increase insulin resistance, increase plasma glucose levels, induce protein catabolism, affect adipose tissue distribution and increase blood pressure [4,5]. The incidence of arterial hypertension and diabetes mellitus is significantly higher in kidney transplant recipients than in the general population [4,5]. A long-term effect of glucocorticoids on the cardiovascular system has been reported previously [4,5]. Aortic root dilatation and increased cardiovascular morbidity and mortality have been shown in patients on long-term corticosteroid treatment [4,5]. The finding of this study is consistent with this observation and provides evidence of the long-term effects of glucocorticoids on cardiovascular risk factors in paediatric kidney transplant recipients.

Conclusion

Late steroid withdrawal is safe and feasible and improves growth and cardiovascular risk factors in selected paediatric kidney transplant recipients.
allograft recipients with stable allograft function and low or regular immunological risk, undergoing CsA- and MMF-based concomitant immunosuppression [8]. This paper reports on the final 2-year data obtained from this trial.

Subjects and methods

Patients and study design

This is the final study report on a multicentre, randomised, open-label study (study number: NCT00309218; https://register.clinicaltrials.gov), which compared late steroid withdrawal (≥ 1 year post-transplant) with continuous steroid treatment under CsA- and MMF-based concomitant immunosuppression in paediatric kidney allograft recipients with stable allograft function. This report meets all CONSORT criteria for the publication of randomised trials [9,10]. Allocation was performed as central randomisation by the principal investigator of the study (University Children’s Hospital of Heidelberg) using numbered containers that were concealed until intervention assignment. After block stratification by pubertal status and randomisation, patients in the steroid-withdrawal group withdrew steroids over a 12-week period, whereas those in the control cohort underwent daily steroid treatment. This final analysis was undertaken at study Month 27, which corresponds to a 2-year time period of steroid-free immunosuppression.

Eligible study subjects were kidney allograft recipients of a first or second transplant, aged < 18 years with a bone age ≥ 15 years in boys and ≤ 13 years in girls, who were administered a triple immunosuppression consisting of CsA, MMF and steroids and had a calculated creatinine clearance (CrCl) of ≥ 40 ml/min/1.73 m² (Schwartz formula) [11]. Time post-transplant was 12–24 months. Exclusion criteria were a panel-reactive antibody (PRA) titre > 80% within 12 months, diabetes and transplantation, an irreversible acute rejection episode (according to the Banff’97 classification) of a former graft or any previous steroid-resistant acute rejection episode, more than two acute rejection episodes prior to study entry or more than one acute rejection episode over the last 6 months before study entry, and an increase in serum creatinine of > 20% during the last 6 months prior to study entry, biopsy-proven chronic rejection, non-compliance, growth hormone therapy, and use of immunosuppressants other than CsA, MMF and steroids [12].

The investigations were conducted in accordance with the Good Clinical Practice Guidelines and the 1983 Helsinki Declaration and approved by the ethics committee of each contributing centre. Written informed consent of patients’ parents or guardians was obtained prior to initiation of any study-related procedure.

Immunosuppression was composed of standard-dose CsA (5–10 mg/kg/day) divided into two or three single doses, target trough level of 70–140 µg/l (EMIT immunoassay, Dade-Behring, Germany) and MMF [1200 mg/m² body surface area (BSA) per day, divided into two single doses]. Before study entry, patients received 5 mg/m² BSA prednisone per day (or the equivalent of 4 mg/m² BSA methylprednisolone per day). In the steroid-withdrawal group, the corticosteroid dose was slowly tapered over a 12-week period (i.e. 0.35 mg/m² BSA/week or 0.7 mg/m² BSA/2 weeks) until cessation, whereas in the control cohort daily steroid administration continued.

Patients’ medical histories, vital signs, anthropometric data, laboratory parameters of renal transplant function, lipid metabolism and haematology, CsA trough concentrations in whole blood, rejection episodes, medication and any adverse events were recorded regularly at scheduled visits (every 3 months during the first year and every 6 months thereafter). The stage of puberty was assessed using Tanner’s method [13]. Height and body mass index (BMI) were converted to standard deviation score (SDS) values related to age- and gender-specific means and SD of European reference populations [14]. Systolic and diastolic blood pressures were derived from casual blood pressure measurements (average of three measurements taken within 5 min) by sphygmomanometer and converted to SDS values based on reference data from a multicentre trial [15]. The prevalence of metabolic syndrome was defined as a combination of three out of five criteria (modified version of the criteria used by Weiss et al.): (1) BMI > 97th percentile, (2) blood pressure > 95th percentile or on anti-hypertensive medication, (3) high-density lipoprotein (HD) cholesterol < 5th percentile, (4) triglycerides > 95th percentile or on lipid-modifying therapy and (5) fasting glucose > 100 mg/dl or on hypoglycaemic treatment [4,16]. In place of oral glucose tolerance test values, which were not determined in the study protocol (Weiss criterion), we used fasting glucose concentrations as described by Wilson et al. [16].

The primary endpoint was defined as standardized longitudinal growth, i.e. change in height SDS. Secondary endpoints were patient and graft survival, rate and severity of biopsy-proven acute rejection episodes (BPARs), classified according to the revised International Society of Heart and Lung Transplantation criteria and clinical parent episodes of acute rejection, renal transplant function (CₕRO), BMI SDS relative to height age, arterial hypertension, need of antihypertensive drugs, and carbohydrate (fasting glucose and HbA₁c concentrations) and lipid metabolism [serum triglyceride as well as total cholesterol, HDL and low-density lipoprotein (LDL) cholesterol concentrations in the fasting state] [11,17]. We registered any adverse event, including opportunistic and other infections.

Statistical analyses

The primary endpoint was defined as standardized longitudinal growth, i.e. change in height SDS. We assumed that height SDS would rise by 0.25 ± 0.3 per year in patients randomised to the steroid-withdrawal group, as compared with the control group. Based on sample size calculation for a two-sided t-test on a power of at least 0.8 and a significance level of 0.05, we obtained a sample size of 34 for either group, i.e. 68 for the whole study population. Recruitment of patients for this study was more difficult than anticipated (only 42 patients enrolled over 6 years from eight centres), so we performed an interim analysis that revealed a significant difference in growth between both groups. Hence, patient recruitment was finished prematurely.

Results are expressed as mean ± standard error of the mean (SEM), unless stated otherwise. We analysed the intention-to-treat (ITT) population and likewise performed a per-protocol (PP) analysis. While the ITT analysis included data of all recruited patients until their dropout of the trial, the PP analysis comprised only data of those who were treated according to protocol for the whole 27-month study period. Where not specifically indicated, the results of the ITT and the PP analyses did not differ significantly, so only the former are given. Normal distribution of the data was evaluated using the Shapiro-Wilk test. Any divergences between the control and the withdrawal group were analysed by means of Student’s t-test or, if normality failed, the Mann–Whitney rank-sum test. For repeated measurements, Bonferroni adjustment was carried out. A mixed linear model (analysis of response profiles, including data of drop-outs) served to detect any significant changes in clinical or laboratory data over time in either study group. The rates of adverse events in both groups were compared using Fisher’s exact test. Differences of means or proportions with a two-tailed P < 0.05 were assumed to be statistically significant.

Results

Between January 2000 and April 2006, 42 paediatric kidney allograft recipients from eight German centres were randomly allocated to either steroid withdrawal (n = 23) or continued steroid treatment (n = 19). During the 27-month study period, 21 out of 23 patients (91%) received steroid-free immunosuppression. In the remaining two patients, steroid withdrawal was performed successfully, but they were lost to follow-up at study Months 12 and 15, respectively. In the control group, all patients received daily steroid treatment throughout the entire study period. Figure 1 depicts the trial profile including study drop-outs and treatment failures over the 27-month observation period. Dropouts, occurring within the first year after study entry, have been previously described [8]. In the second year, three additional drop-outs occurred (Figure 1). In the steroid-withdrawal group, one patient’s immunosuppressive regimen was switched from CsA- to tacrolimus-based therapy because of pronounced hypertrichosis and gingival hyperplasia; another patient was lost to follow-up. In the control group, immunosuppressive treatment with MMF was discontinued in one patient because of...
Efficacy of late steroid withdrawal

Longitudinal growth and body mass index

Longitudinal growth in the steroid-withdrawal group was superior to controls. In response to steroid withdrawal, patients exhibited a significant catch-up growth with a mean standardized height gain of 0.6 ± 0.1 SDS over the 27-month study period (P < 0.001 versus control), whereas standardized height in steroid-treated patients decreased by 0.2 ± 0.1 SDS (P < 0.01 versus baseline) (Figure 2A).

Table 1. Anthropometric data, medication and laboratory values at baseline, 15 and 27 months after study entry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Steroid-withdrawal group (n = 23)</th>
<th>Control group (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>15 months</td>
<td>27 months</td>
</tr>
<tr>
<td>ΔBody mass index SDS</td>
<td>n.a.</td>
<td>−0.55 ± 0.15</td>
<td>−0.62 ± 0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.001##</td>
<td>&lt;0.001##</td>
</tr>
<tr>
<td>Systolic blood pressure SDS</td>
<td>1.74 ± 0.21†</td>
<td>1.01 ± 0.19†</td>
<td>0.65 ± 0.19†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.05##, &lt;0.05##</td>
<td>&lt;0.05##</td>
</tr>
<tr>
<td>Diastolic blood pressure SDS</td>
<td>1.54 ± 0.22†</td>
<td>0.59 ± 0.15†</td>
<td>0.74 ± 0.20†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.05##, &lt;0.01*</td>
<td>&lt;0.05##</td>
</tr>
<tr>
<td>Number and percentage of hypertensive patients (%)</td>
<td>21/23 (91%)</td>
<td>9/19 (50)†</td>
<td>8/16 (50)†</td>
</tr>
<tr>
<td>MMF dose (mg/m²/day)</td>
<td>909 ± 39</td>
<td>972 ± 44</td>
<td>825 ± 55</td>
</tr>
<tr>
<td></td>
<td>5.62 ± 0.48</td>
<td>4.88 ± 0.42</td>
<td>4.49 ± 0.39##</td>
</tr>
<tr>
<td></td>
<td>110 ± 9.9</td>
<td>91 ± 9.6</td>
<td>79 ± 7.1</td>
</tr>
<tr>
<td></td>
<td>97.2 ± 5.4</td>
<td>97.1 ± 5.7</td>
<td>95.5 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>204 ± 8.2</td>
<td>162 ± 5.6</td>
<td>169 ± 8.6</td>
</tr>
<tr>
<td></td>
<td>44.9 ± 2.7</td>
<td>41.2 ± 2.5</td>
<td>49.0 ± 2.7</td>
</tr>
<tr>
<td></td>
<td>113 ± 8.1</td>
<td>97 ± 4.7</td>
<td>96 ± 6.5</td>
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<tr>
<td></td>
<td>154 ± 14.4</td>
<td>104 ± 11.0</td>
<td>110 ± 9.0##</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.7 ± 0.27</td>
<td>11.2 ± 0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8043 ± 493</td>
<td>6767 ± 313*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>303 ± 21</td>
<td>281 ± 29</td>
</tr>
</tbody>
</table>

ΔSDS, change of standard deviation score; BMI, body mass index; MMF, mycophenolate mofetil; CsA, cyclosporine microemulsion; C_\text{Cr}, calculated creatinine clearance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n.a., not applicable; n.s., not significant.

†P-value versus baseline; ‡P-value versus control.

Based on arterial hypertension is defined as systolic and/or diastolic blood pressure >95th percentile and/or antihypertensive drug requirement.
In response to steroid withdrawal, standardized BMI decreased significantly by 0.6 ± 0.3 SDS ($P < 0.001$ versus controls). In individual patients, the decline of standardized BMI led to a remarkable improvement of their cushingoid appearance. In contrast, there was no change in BMI in the control group ($\Delta$ BMI $0.2 \pm 0.1$ SDS at study Month 27, n.s.) (Table 1).

**Carbohydrate and lipid metabolism**

The mean fasting glucose levels declined significantly by 11% from 94 ± 5.1 mg/dl at baseline to 84 ± 3.6 mg/dl 2 years after steroid withdrawal ($P < 0.05$ versus baseline). In addition, glycosylated haemoglobin A1c (HbA1c) level decreased significantly by 7% from 5.5 ± 0.1% to 5.1 ± 0.1% during the 27-month study period ($P < 0.05$ versus baseline). In the control group, the mean fasting glucose (93 ± 3.3 mg/dl versus 101 ± 9.2 mg/dl) and HbA1c levels (5.4 ± 0.1% versus 5.3 ± 0.2%) did not change significantly.

The mean serum cholesterol and triglyceride values dropped significantly in the 2 years following steroid withdrawal (Table 1). The total serum cholesterol decreased by 17% at study Month 27 in the steroid-withdrawal group ($P < 0.001$ versus baseline); there was also a slight decline of serum cholesterol by 5% in controls (Table 1). While the ITT analysis did not show a significant alteration of serum LDL cholesterol concentrations in both treatment groups, the PP analysis revealed a significant decrease of LDL cholesterol in response to steroid withdrawal from 116 ± 8.4 mmol/l at baseline by 17% to 96 ± 6.5 mmol/l at Month 27 ($P < 0.05$). HDL cholesterol concentrations remained unchanged both in patients off steroids and in controls (Table 1).

**Blood pressure**

Steroid withdrawal was associated with a significant reduction of arterial hypertension over the first steroid-free year (Table 1), and this effect persisted during the second study year. Compared to baseline, mean standardized systolic and diastolic blood pressure in the steroid-withdrawal group declined significantly at Month 27 by 0.78 ± 0.27 SDS and 0.53 ± 0.27 SDS, respectively, while the corresponding values in controls increased by 0.53 ± 0.35 SDS and 0.49 ± 0.29 SDS, respectively (Table 1, Figure 3A and B). In addition, patients off steroids required significantly less antihypertensive medication than controls ($P < 0.05$), who needed increasingly more antihypertensive drugs ($P < 0.01$ versus baseline) (Table 1, Figure 3C). By Month 27, steroid-free patients suffered arterial hypertension (50%) less frequently than controls (93%, $P < 0.05$) (Table 1).

**Metabolic syndrome**

Steroid withdrawal was associated with a significantly reduced incidence of the metabolic syndrome. While 9 of 23 patients (39%) suffered the metabolic syndrome at baseline, only 1 recipient (6%) still exhibited such syndrome 2 years after steroid withdrawal ($P < 0.05$ versus baseline) (Figure 4). In the control group, 3 out of 17 patients (18%) had the metabolic syndrome at study entry, and 3 of 15 recipients (20%) at Month 27 (n.s.) (Figure 4).
Improved growth and cardiovascular risk after late steroid withdrawal

**Safety aspects**

Patient and graft survival amounted to 100% during the 27-month study period. Also, renal allograft function ($C_{cr}$) remained stable in both treatment arms (Table 1).

While no BPAR was observed in the steroid-withdrawal group, two patients of the control group developed a biopsy-proven borderline rejection at study Months 9 and 21, respectively. One patient in the steroid-withdrawal cohort was treated for presumed acute rejection 12 months after steroid withdrawal; graft function recovered completely after steroid-pulse therapy. Hence, the overall incidence of acute rejections (biopsy-proven and/or treated) amounted to 1/23 (4%) in the steroid-withdrawal group and to 2/19 (10%) in the control cohort (n.s.). The mean urinary protein excretion was $157 \pm 6.7 \text{ mg/m}^2 \text{BSA/day at study entry}$ and $145 \pm 5.6 \text{ mg/m}^2 \text{BSA/day 2 years after steroid withdrawal}$ and was comparable with that observed in the control group ($152 \pm 1.8 \text{ mg/m}^2 \text{BSA/day at baseline versus 152} \pm 2.1 \text{ mg/m}^2 \text{BSA/day at study Month 27}$). Seven of 23 patients (30%) off steroids and 9 of 17 patients (53%) in the control group received angiotensin-converting enzyme inhibitor therapy.

Both treatment groups showed a similar incidence and pattern of adverse events. Upper respiratory tract infections and diarrhoea turned out to be the most common infections in both groups (Table 2).

**Discussion**

This paper presents the final results of the first prospective, randomised, multicentre, controlled trial on late steroid withdrawal in paediatric kidney allograft recipients. Steroid withdrawal was accomplished successfully in 91% of patients and was associated with a marked reduction of cardiovascular risk factors and pronounced catch-up growth at no increased risk of acute rejection or unstable graft function in this selected, low- or regular-immunologic-risk patient population.

In our study, steroid withdrawal led to a marked decrease of the prevalence and severity of arterial hypertension and to an improved carbohydrate and lipid metabolism. Furthermore, the standardized BMI also dropped significantly in response to steroid withdrawal, which, at least in some patients, was associated with a remarkable regression of cushingoid disfigurement. By this mechanism, steroid withdrawal potentially enhances adherence to immunosuppressive drug taking [18].
Cardiovascular events rank among the main causes of death of paediatric and adult kidney allograft patients [19–21]. Arterial hypertension, dyslipidaemia, obesity and diabetes mellitus are common steroid-associated side effects and known to increase the risk of cardiovascular complications. A recent study among 2071 adult renal transplant recipients has shown that arterial hypertension, elevated triglyceride levels and post-transplant diabetes mellitus represent significant risk factors associated with cardiovascular complications and that intake of steroids is one of the most significant detrimental factors [21]. Compared with steroid-treated patients, steroid-free recipients show a significantly lower risk of dying or developing cardiovascular problems [21].

The emerging prevalence of the metabolic syndrome, especially in paediatric kidney allograft patients, is alarming [5,16]. The occurrence of the metabolic syndrome in childhood predicts an adult metabolic syndrome and is accompanied by an increased risk of developing type II diabetes mellitus [22]. The prevalence of the metabolic syndrome in paediatric kidney allograft recipients ranges between 25% and 37% at 1 year post-transplant, consistent with the observation in this study (30% in the overall patient population at study entry) [5,16]. Recently, an association between the prevalence of the metabolic syndrome and the degree of coronary artery calcification was described, and there is a significantly increased incidence of left ventricular hypertrophy in paediatric renal transplant recipients suffering from the metabolic syndrome [16,23]. Hence, our observation that the prevalence of the metabolic syndrome dropped significantly in response to steroid withdrawal is important for the prevention of cardiovascular complications in this patient population.

In addition to provoking cardiovascular events, arterial hypertension, hyperlipidaemia and obesity contribute to progressive graft failure in both paediatric and adult renal transplant patients [3,24–26]. Well-controlled blood pressure markedly improves long-term allograft survival in adult renal allograft recipients [26]. It is, therefore, likely that the improvement in arterial hypertension, hyperlipidaemia and obesity in response to steroid withdrawal will both reduce the cardiac risk profile and prolong renal graft survival.

We observed a stable graft function within 2 years of steroid withdrawal. While long-term follow-up studies are undoubtedly needed to assess allograft survival, our trial to date represents the longest follow-up period after prospective, controlled steroid withdrawal in paediatric renal allograft recipients. Our findings are supported by the recently published 5-year results of a prospective, randomised, multicentre trial on steroid withdrawal versus low-dose steroid therapy in adult kidney allograft recipients under tacrolimus- and MMF-based immunosuppression [27]. Patients off steroids showed significantly less cardiovascular risk factors than steroid-treated recipients, while the rate of renal allograft loss or reduced kidney function was comparable [27]. Furthermore, Opelz et al. demonstrated a significant benefit of steroid withdrawal versus steroid continuation in a 7-year outcome analysis of 1010 adult renal transplant recipients from the Collaborative Transplant Study registry (94% receiving cyclosporine; 97% Caucasian), in whom steroids were withdrawn no earlier than 6 months post-transplant. Controls were retrospectively matched for graft survival, patient survival and death-censored graft survival [28]. The rates of acute rejection and kidney dysfunction did not differ between steroid-free and steroid-continuation groups [28].

It has been argued that late steroid withdrawal offers negligible benefit, since it takes place when the majority of side effects have already manifested themselves in a patient [29]. However, our data indicate that patients who continue low-dose corticosteroid treatment after the first year post-transplant show further deterioration in growth and persistence or aggravation of cardiovascular risk factors such as arterial hypertension and hyperlipidaemia. This occurred despite the fact that the BSA-adjusted maintenance corticosteroid dose in controls dropped by 15% over the 27-month study period. The differences between the steroid-withdrawal and the control group might, therefore, have been even more pronounced under unchanged steroid exposure administered according to the protocol.

Strategies other than late steroid withdrawal have been developed to ameliorate steroid-specific side effects such as an alternate-day steroid dosing regimen [30,31]. However, an obvious disadvantage of alternating steroid therapy is the unchanged total exposure to steroids with its remaining

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**Table 2. Incidence of infections and other adverse events**

<table>
<thead>
<tr>
<th>Clinical event</th>
<th>Steroid-withdrawal group (n = 23)</th>
<th>Control group (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events per patient (n)</td>
<td>Number of patients (%)</td>
<td>Events per patient (n)</td>
</tr>
<tr>
<td>Opportunistic infections</td>
<td>1.0</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1.4</td>
<td>9 (39)</td>
<td></td>
</tr>
<tr>
<td>Respiratory tract infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>4.3</td>
<td>18 (78)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.0</td>
<td>5 (22)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>3.6</td>
<td>6 (26)</td>
<td></td>
</tr>
<tr>
<td>Other infections</td>
<td>2.4</td>
<td>15 (65)</td>
<td></td>
</tr>
<tr>
<td>Presumed adrenal insufficiency</td>
<td>1.0</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Pseudotumour cerebi</td>
<td>1.0</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>1.0</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>1.0</td>
<td>2 (9)</td>
<td></td>
</tr>
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</table>
Improved growth and cardiovascular risk after late steroid withdrawal cardiovascular side effects. Thus, steroid avoidance seems well suited to completely eliminate steroid-induced complications [32]. However, long-term consequences of the intensified initial immunosuppressive regimen needed for steroid avoidance are still to be evaluated. Compared with steroid avoidance or early withdrawal protocols, late steroid withdrawal offers the opportunity to assess the patient’s individual immunological risk beforehand and to exclude immunologically high-reactive patients from steroid-free immunosuppression.

One limitation of our study consists in the relatively low number of patients (42) enrolled over 6 years from eight paediatric transplant centres. Recruitment of patients proved more difficult than anticipated, as some covering physicians and patients or their guardians had a strong bias either pro or con steroid withdrawal. In addition, it is generally difficult to perform studies altering the maintenance immunosuppressive regimen in stable transplant patients beyond 1 year post-transplant; hence, most trials among kidney allograft recipients are conducted as de novo studies. Furthermore, the implementation of convincing clinical trials in paediatric patients is complicated by the fact that the incidence of end-stage renal failure in children and adolescents is rare compared to adults; only 5% of kidney transplants are performed in paediatric patients. Other reasons for the relatively low patient number in our study are the stringent inclusion and exclusion criteria applied.

In conclusion, this first prospective, randomised, multicentre, controlled trial has shown that late steroid withdrawal in European paediatric kidney allograft recipients with low or regular immunological risk constitutes an encouraging approach to improve growth and ameliorate cardiovascular risk factors without the burden of increased rejection rates or unstable graft function.

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Long-term renal function after allogenic haematopoietic stem cell transplantation in adult patients: a single-centre study

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Abstract

Background. Reported data regarding chronic kidney disease (CKD) in haematopoietic stem cells transplantation (HSCT) recipients are highly discrepant.

Materials and methods. We undertook a retrospective single-centre study in order to assess the rate, risk factors and outcome of HSCT-associated CKD in 123 allogeneic HSCT patients.

Results. Twenty-four months after HSCT, CKD [e.g. glomerular filtration rate (GFR) estimated using the MDRD formula <60 ml/min/1.73 m²] was noted in 49 patients (40%). Age ≥ 45 years, early acute kidney injury and a baseline GFR < 90 ml/min/1.73 m² predicted the occurrence of CKD at 24 months after HSCT. One hundred and six patients (45 with and 61 without CKD at 24 months) were followed up for more than 36 months (range 36–142). Among the 45 patients with CKD at 24 months after HSCT, CKD persisted in 30 (67%), 10 patients (22%) showed a transient improvement in GFR but retained CKD and 10 patients (22%) had a sustained improvement of GFR. Among 61 patients without CKD at 24 months after HSCT, 3 (5%) developed CKD during the follow-up. Our data indicate that HSCT-related CKD probably includes two subsets: a frequent early-onset CKD, a consequence of ARF in older patients with pre-existent renal impairment, and a rare late-onset CKD occurring more than 2 years following HSCT.

Conclusions. Careful monitoring of renal function is mandatory in patients undergoing HSCT, especially old patients with pre-existent renal impairment.

Keywords: chronic kidney diseases; haematopoietic stem cell transplantation

Introduction

Haematopoietic stem cell transplantation (HSCT) is an established and increasingly used treatment for a wide range of haematological malignancies. Improved supportive care and transplantation procedures have translated into a dramatic improvement of overall survival of patients undergoing HSCT. However, long-term organ damage has emerged as an increasingly identified cause of morbidity and mortality in patients who have undergone HSCT [1].

In the last decade, chronic kidney disease (CKD) arising after HSCT has been increasingly reported. However, published studies have yielded discrepant results with an