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ORIGINAL ARTICLE

# Selective late steroid withdrawal after renal transplantation

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**Abstract** Steroid withdrawal (SW) after paediatric renal transplantation (RTPL) is controversial. Selective late SW has been performed in our unit since 1995. The safety and effects of SW were analysed retrospectively in 47 patients undergoing RTPL between 1995 and 2004. Initial immunosuppression consisted of cyclosporine A, azathioprine or mycophenolate mofetil and steroids. Criteria for SW were: (1) stable renal function, (2) time interval after RTPL ≥ 1 year, (3) no rejection or time interval after last rejection ≥ 1 year and (4) good compliance. SW was performed in 30 patients at an age of 13.5 years (range 4.5–18.5) and 2.2 years (range 1–6.6) after RTPL. After SW, one patient experienced a steroid-sensitive rejection. Follow-up after SW (1.3 year; range 0.25–7.5) showed maintained renal function: glomerular filtration rate at SW and currently was 82 (65–128) and 82 (42–115) ml/min per 1.73 $m^2$, respectively. The number of patients on antihypertensive treatment did not significantly change (at SW: $n$=15; currently: $n$=11). Height and body mass index (BMI) remained stable: Median standard deviation score (SDS) for height/BMI at SW and currently was −1.1/0.2 and −0.8/0.1, respectively. Selective late SW was safe regarding renal function and had no significant effect on blood pressure and growth.

**Keywords** Renal transplantation · Steroid withdrawal · Growth · Renal function · Rejection

## Introduction

Immunosuppressive therapy after paediatric renal transplantation (RTPL) traditionally included glucocorticosteroids. The use of steroids after RTPL is associated with significant morbidity, including body disfigurement, growth retardation and osseous and cardiovascular and metabolic complications [1–3]. Protocols with steroid withdrawal (SW) either early (5 days to 12 months) [4–7] or late (≥12 months) after RTPL [8, 9], or even steroid-free protocols [10, 11] have been proposed. These protocols included induction therapy with thymoglobulin or specific interleukin (IL)-2 receptor blockers [4–8, 11] and/or were tacrolimus (Tac) based [4, 5, 7, 8, 10, 11]. So far, only one study has reported successful SW in paediatric patients receiving cyclosporine A (CyA) maintenance immunosuppression without induction therapy [9].

However, the safety of SW has been questioned in adult [12] and paediatric recipients [13] because of increased risk of acute rejection and graft loss after SW. The benefit of SW on growth (i.e. catch-up growth) and body mass index (BMI) is predominantly observed in prepubertal children [5, 9]. Thus, no consensus has been reached in the paediatric community concerning steroid elimination [14] or preservation [15] after renal RTPL.

Selective late SW after RTPL was introduced at the University Children's Hospital Zurich in 1995. A retrospective study was performed to analyse the safety of SW in a CyA-based immunosuppressive regimen concerning graft function and risk of rejection. In addition, the effect of SW on blood pressure and growth was examined.

## Patients and methods

### Patients

Forty-seven of 56 paediatric patients undergoing their first RTPL in Zurich between 1995 and 2004 could be followed. Eight adolescents had been transferred at or early after RTPL to an adult centre; one patient had died of an

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associated cardiac disease 4 months after RTPL. The underlying diseases were inherited, congenital or acquired in 19, 17 and 11 patients, respectively. This study was part of the regular audit and quality assessment programme of the unit. Written informed consent was obtained from the parents and adolescent patients before RTPL.

### Immunosuppression

Initial immunosuppression consisted of CyA (aiming at trough levels of 180–250 ng/ml for the first 6 months and 80–120 ng/ml thereafter), azathioprine ($n$=7; 1 mg/kg per day) until 1997 or mycophenolate mofetil (MMF) ($n$=40; 1200 mg/m$^2$ body surface area per day) since 1998, and prednisone (initial dosage of 1 mg/kg per day). Six patients had induction treatment with basiliximab 2 h before and 4 days after RTPL (body weight <35 kg: 10 mg per dose; body weight >35 kg: 20 mg per dose) as part of a multicenter trial [16]. Other T-lymphocyte-depleting agents were not used.

Maintenance immunosuppression was switched from CyA to Tac in 12 out of 47 patients due to biopsy-proven steroid-resistant acute rejection ($n$=10 on MMF; $n$=2 on azathioprine) and in one girl with hypertrichosis. MMF dosage was reduced in children on Tac to 900 mg/m$^2$ body surface area per day. MMF was replaced by azathioprine in six children (chronic diarrhoea: $n$=4; recurring leucopenia: $n$=1; chronic abdominal pain: $n$=1) without effect on graft function. Biopsy-proven acute rejection was treated with intravenous methylprednisone pulses (1 g/1.73 m$^2$ body surface per day) on days 1–3. If plasma creatinine did not decrease, steroid pulses were repeated on days 5–7. If plasma creatinine still remained elevated, the rejection was defined as steroid resistant, and maintenance immunosuppression was switched from CyA to Tac aiming at a trough level of 10–15 μg/l for 1 month and 4–8 μg/l thereafter.

### Selective late steroid withdrawal

The selective late SW protocol is summarised in Table 1. Criteria for SW were (1) stable renal function, (2) time interval after RTPL ≥ 1 year, (3) no rejection or time interval since last rejection episode ≥ 1 year and (4) good compliance based on stable drug concentrations and reliable clinic attendance. SW was independent of prevailing steroid side effects (e.g. cushingoid habitus, acne, arterial hypertension, growth retardation or hyperlipidemia). If steroid dosage reduction or SW resulted in an increase of plasma creatinine of more than 20% of baseline, renal biopsy was performed.

### Clinical evaluation

Renal function was assessed as creatinine and glomerular filtration rate (GFR: ml/min per 1.73 m$^2$ body surface area) calculated by the Schwartz formula with a $k$-factor of 40 based on local comparison with Cr-ethylenediaminetetraacetate (EDTA) clearance measurements [17]. Casual blood pressure was measured in the sitting position aiming at <95th centile of systolic blood pressure [18] and was indexed to the 95th centile (i.e. measured systolic/diastolic blood pressure divided by the age-, sex- and height-specific 95th centile for systolic/diastolic blood pressure) [19]. Antihypertensive treatment included β-blockers (atenolol), calcium-channel blockers (nifedipine) and angiotensin-converting enzyme (ACE) inhibitors (enalapril). Height, weight and BMI (BMI; kg/m$^2$) were correlated to normative Swiss data [20]. Serum cholesterol was measured before and after SW.

### Statistical analysis

Statistical analysis was performed using the SPSS 11.0 for windows. Analysis of variance (ANOVA) on repeated measurements was used to detect changes of clinical and laboratory parameters over time. Proportions between groups were compared by Fisher's exact test. A $p$ value<0.05 was considered statistically significant.

## Results

### Steroid withdrawal

Patient and graft survival was 100%. Criteria for SW were fulfilled by 31 (66%) of 47 patients. SW was performed in 30 patients at the median age of 13.5 years (range 4.5–18.5) and 2.2 years (range 1–6.6) after RTPL. Before SW, nine patients experienced 11 biopsy-proven acute rejections, all within 2 months after RTPL; five patients were switched to Tac due to steroid-resistant rejection ($n$=3 on MMF; $n$=2 on azathioprine).

SW was successful in 29 out of 30 children (Table 2). Only one girl developed an acute rejection episode 2 weeks after SW; steroids were restarted and plasma creatinine returned to baseline. Follow-up between SW and the most recent evaluation was median 1.3 year (range 0.25–7.5). An adolescent boy experienced an acute steroid-sensitive rejection 3.3 years after SW due to noncompliance. CyA and Tac trough levels were 125±20.5 ng/ml and 8.5±3.3 μg/l, respectively 1 year after RTPL and 100±22.5 ng/ml and 5.8±0.9 μg/l, respectively 1 year after SW.

### Renal function, blood pressure and growth

Renal function remained stable throughout the entire observation period (Table 3; Fig. 1). There was no significant difference in blood pressure before and after SW (Table 3), but antihypertensive medication could be

**Table 1** Protocol of selective late steroid withdrawal

| Months after renal transplantation | Prednisone dosage |
|---|---|
| 1 | 1 mg/kg per day (maximal dose 75 mg)<br>→ continuous, weekly tapering |
| 2 | 0.5 mg/kg per day<br>→ continuous, weekly tapering |
| 3 | 0.1 mg/kg per day<br>→ continuous tapering to minimal dose of 5 mg |
| 7–12 | 10 mg/m$^2$ on alternate day (minimal 10 mg; maximal 20 mg)<br>→ continuous slow tapering to minimal dose of 2.5 mg |
| 12 | Steroid withdrawal if:<br>- stable renal function<br>- RTPL ≥1 year<br>- last rejection episode ≥ 1 year<br>- good compliance |
| Early follow-up after SW | Outpatient consultations: 1, 3, 5 and 9 weeks after SW |

stopped in four out of 15 patients. Height increased slightly but not significantly during the first year after RTPL and remained stable thereafter. BMI did not change throughout the entire period (Table 3). At the most recent examination, there was no significant difference between the height, assessed as standard deviation score (SDS), of prepubertal children <13 years ($n$=13; median SDS −1.1; range −2.1 to +1.2) and children >13 years ($n$=16; median SDS −0.75; range −2.9 to +1.8). Three patients in the SW group had significant proteinuria (IgA nephropathy $n$=2, cystinosis $n$=1), but all patients had good graft function.

**Table 2** Clinical data of 29 patients with successful steroid withdrawal (SW)

| Parameter | Data |
|---|---|
| Sex: male/female | 21/8 |
| Renal transplantation (RTPL) | |
| Recipient age (years) | 11.2 (2–16)[a] |
| HLA mismatch ($n$) | 3 (2–6)[a] |
| Living donor/cadaveric donor ($n$) | 17/12 |
| Donor age (years) | 39 (2–56)[a] |
| Steroid withdrawal | |
| Age (years) | 13.5 (4.5–18.5)[a] |
| Follow-up after steroid withdrawal | |
| Age at evaluation (years) | 14.9 (5.2–23)[a] |
| Time after RTPL (years) | 4.7 (1.0–8.7)[a] |
| Time after SW (years) | 1.3 (0.25–7.5)[a] |
| Current immunosuppression | |
| Cyclosporine A (CyA) and mycophenolate mofetil (MMF) | 11 |
| CyA and azathioprine | 10 |
| Tacrolimus (Tac) and MMF | 6 |
| Tac and azathioprine | 2 |
| Induction with basiliximab | 4 |

[a] Median (range)

## Extrarenal complications

No patient suffered from bone disease (i.e. fracture, epiphysiolysis, aseptic necrosis), and there was no clinical evidence of eye disease (i.e. cataract, visual acuity). There was no significant difference in serum cholesterol levels 1 year before SW (4.7±1.5 mmol/l) and 2 years after SW (4.6±1.0 mmol/l). One boy suffered from Hodgkin's disease at the age of 12 years and 3.3 years after RTPL; his immunosuppression therapy consisted of CyA, MMF and low-dose alternate-day prednisone. After successful cytostatic therapy, the boy is in remission with good graft function off steroids.

## Patients maintained on steroids

Seventeen patients were maintained on steroids. Only one patient, fulfilling all criteria and eligible for SW, was maintained on steroids, as parents did not give consent for SW. This patient was the brother of the above-mentioned girl with acute rejection after SW. Eight patients had so far not yet fulfilled the criteria for SW (time interval after RTPL ≤1 year: $n$=4; time interval since last rejection ≤1 year: $n$=4). Eight further patients were still on steroids for the following reasons: repeated urinary tract infections with transient rise of plasma creatinine ($n$=3), colitis ($n$=1) and recurrence of focal segmental glomerulosclerosis ($n$=1); one patient each had side effects of Tac (biopsy-proven calcineurin-inhibitor toxicity) or MMF (leucopenia) necessitating dose reduction and maintenance of low-dose alternate-day prednisone; one 17-year-old patient developed B-cell lymphoma 5 years after RTPL, but after successful cytostatic therapy, was in remission with impaired graft function (plasma creatinine 220 μmol/) on low-dose alternate-day steroids.

**Table 3** Glomerular filtration rate (GFR), patients on antihypertensive treatment (AT), casual systolic (SBP) and casual diastolic (DBP) blood pressure (also given as indexed blood pressure), height and body mass index (BMI) in 29 patients with steroid withdrawal (SW)

| Time period | GFR[a] ml/min per 1.73 m$^2$ | AT[b] *n* (%) | SBP Casual indexed | DBP Casual indexed | Height[a] Standard deviation score (median, range) | BMI[a] |
|---|---|---|---|---|---|---|
| RTPL+1 month | 86 (71–132) | 21 (72%) | – | – | −1.6 (−3.0[c] to +0.6) | 0.2 (−3.0 to +2.8) |
| | | | – | – | −1.5 (−2.1 to −0.2)[d] | |
| RTPL+1 year | 86 (53–125) | 18 (62%) | 118±9.9 | 72±9.9 | −0.9 (−2.6[c] to +1.5) | 0.14 (−2.8 to +4.0) |
| | | | 0.93±0.08 | 0.87±0.12 | −0.7 (−1.4 to +0.8)[d] | |
| SW | 82 (65–128) | 15 (52%) | 118±10.7 | 71±9.2 | −1.1 (−4.0[c] to +1.8) | 0.2 (−2.2 to +1.7) |
| | | | 0.94±0.07 | 0.86±0.13 | −1.1 (−2.0 to +1.1)[d] | |
| SW+3 months | 86 (56–127) | 13 (45%) | 117±11.2 | 70±10.6 | −1.0 (−3.9[c] to +1.8) | 0.2 (−2.0 to +1.9) |
| | | | 0.93±0.08 | 0.86±0.14 | – | |
| SW+12 months | 85 (52–122) | 12 (41%) | 117±12.3 | 68±9.3 | −1.0 (−4.3[d] to +1.6) | 0.1 (−1.5 to +1.6) |
| | | | 0.92±0.02 | 0.84±0.12 | – | |
| Most recent follow-up | 82 (42–115) | 11 (38%) | 115±11.7 | 68±9.7 | −0.8 (−4.6[c] to +1.8) | 0.1 (−1.7 to +1.8) |
| | | | 0.91±0.08 | 0.82±0.12 | −1.1 (−2.1 to +1.2)[d] | |

[a] No significant difference over time, [b] no significant difference between blood pressure at SW and follow-up, [c] patient with multicentric osteolysis type III, [d] prebubertal children only ($n$=13)

## Discussion

Late selective SW was safe in children undergoing their first RTPL on a CyA-based immunosuppressive regimen. Two thirds of the patients fulfilled the restrictive criteria for SW, and all eligible patients except one underwent SW. Slow steroid tapering and late SW, i.e. >12 months after RTPL, was successful in 29 out of 30 children, with maintained graft function. Only one patient experienced a steroid-sensitive acute rejection episode immediately after SW. As safety was the main concern, both parents (and patients) and physicians were rather cautious, and steroid tapering was often delayed compared with the protocol, with subsequent postponement of SW. Thus, the observation period after SW was limited, with a range of 0.25–7.7 years.

There was no significant effect of SW on blood pressure, height and BMI. The lower immunosuppression following SW might have been compensated in part in patients on MMF, as steroids interfere with MMF bioavailability and SW results in higher MMF exposure [21]. However, one third of our patients with successful SW were on azathioprine.

These findings are consistent with a recent report by Höcker al. of successful late SW after RTPL in 20 children receiving a CyA-based regimen, with an observation period of 2.1–6.3 years [9]. However, there was a major methodological difference compared with our protocol: indications for SW were limited to steroid side effects, and the decision for SW was made on an individual basis by the covering physician or on patient demand [9]. In contrast, SW in our unit followed criteria applicable to all patients. In fact, all

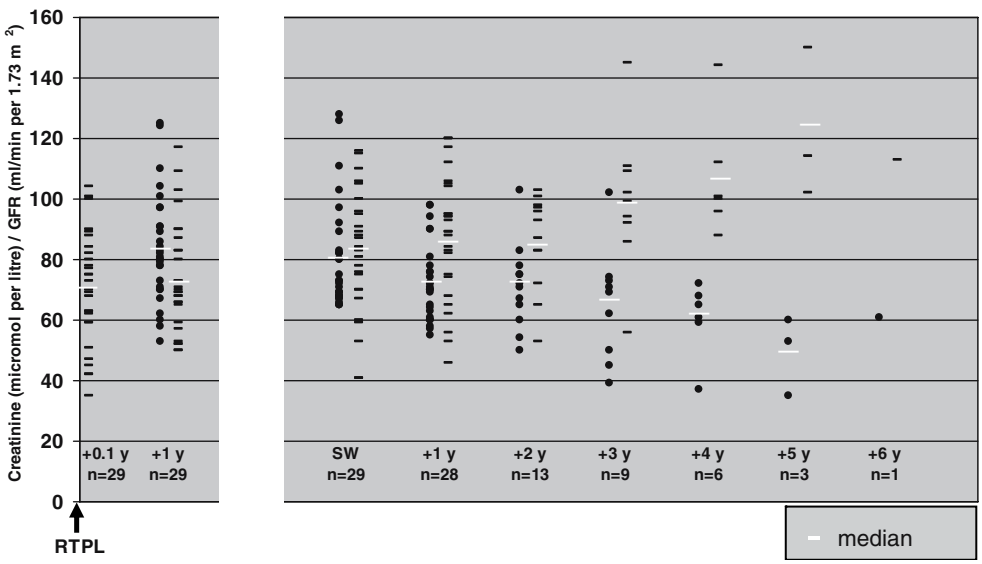


**Fig. 1** Plasma creatinine (−) and glomerular filtration rate (GFR; •) after renal transplantation (RTPL) before and after steroid withdrawal (SW), year (y)

eligible patients except one underwent SW. Successful late SW, approximately 12 months after RTPL, has also been reported by Jensen et al. in 17 children: All patients were on Tac, and almost all received induction therapy [8].

To reduce the steroid burden even more, early SW protocols have been proposed. Oberholzer et al. reported 13 children with 100% graft survival after 12 months: immunosuppression included a 5-day course of steroids, induction therapy (thymoglobulin or basiliximab) and maintenance therapy with Tac [4]. Another centre performed SW between 4 and 12 months after RTPL. Immunosuppression was Tac based without induction therapy. GFR remained stable over 3 years; but graft loss occurred in 5 children after SW [5]. Two paediatric studies used complete steroid avoidance protocols, with an extended course of daclizumab, Tac and MMF demonstrating 100% graft survival and stable renal function after 1 year [10, 11].

Other studies reported less favourable results on SW after RTPL. A study from Japan showed acute rejection in one third of patients after SW [6], and Klaus et al. observed a high risk of acute rejection after SW in children [13]. A meta-analysis in adults undergoing SW after renal transplantation showed a low but significant risk of acute rejection after SW. But there was no increased risk of early graft failure [12].

Taken together, major concerns regarding SW protocols for paediatric RTPL are, firstly, the rather short observation period of prevailing studies, and secondly, the fact that most SW protocols used induction therapy carrying an increased risk of posttransplant lymphoproliferative disorder (PTLD) [8, 22]. Thus, a more individualised and selective approach to immunosuppressive treatment has been proposed [15].

Hypertension after renal RTPL is a risk factor for graft dysfunction [23, 24] and development of end-organ damage including early cardiomyopathy and premature atherosclerosis [24]. SW has been associated with significant reduction in blood pressure [4, 8, 9]. In our study, there was also a trend to achieve better blood pressure control (i.e. <95th centile) with less antihypertensive medication.

Major side effects of steroids after renal RTPL are stunted growth, obesity and body disfigurement [1, 2]. Thus, steroid-induced side effects were the only inclusion criteria in one SW study [9]. Significant catch-up growth after SW was more pronounced in prepubertal compared with pubertal children [5, 9]. In our study, height and BMI did not change after SW. Height SDS increased slightly but not significantly during the first year after RTPL. Aggressive nutrition (via gastrostomy in younger children) and early growth hormone therapy were apparently the main reasons for satisfactory growth before RTPL.

Successful graft survival depends on long-term compliance and drug adherence. Noncompliance is a major issue among adolescent graft recipients [25, 26]. Adolescents are particularly prone to noncompliance of medications, such as steroids, [25] the side effects of which cause visible physical and bodily changes that differentiate them from their peers [26]. SW with consequent reduction of side effects might have a beneficial impact on long-term compliance and therefore favour graft survival.

In summary, selective late SW was safe in children after RTPL but had no significant effect on blood pressure and growth.

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