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# Early Steroid Withdrawal in Pediatric Renal Transplantation

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## Abstract

***Steroid minimization in pediatric renal transplantation is aimed at reducing the risk and severity of relevant adverse events, including retardation of growth, specific for this population. Early steroid withdrawal or complete avoidance was described in 20 reports and, in the vast majority, mono- or polyclonal induction was used followed by variable maintenance protocols, mainly including tacrolimus and mycophenolate mofetil. The growth benefit was proven in pre-pubertal children, whilst the remaining clinical benefits were not age-dependent. Overall efficacy and safety of these protocols was satisfactory.*** **(Trends in Transplant. 2011;5:115-20)**

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## Key words

***Early steroid minimization. Pediatric renal transplantation.***

## Introduction

The expected benefits from early steroid withdrawal in children after renal transplantation include improved glucose metabolism with no use of insulin or oral hypoglycemic medications, better lipid profile with no exposure to statins, improved blood pressure control with less or no use of hypotensives, better growth velocity with no use of growth hormone, improved or preserved bone mineral density with no use of vitamin D analogs, and absence of steroid-related cosmetic defects. Potential disadvantages of early steroid withdrawal include a presumed higher risk of acute rejection and inferior long-term graft function and survival, renal fibrosis and additional risk of specific adverse events due to use of antibody induction. In contrast to late steroid withdrawal (beyond one week posttransplantation), when stable clinical course (absence of acute rejection) and/or protocol biopsy is used to identify the optimal candidates for steroid minimization, in early withdrawal (≤ 7 days after transplantation) and complete avoidance protocols, detailed criteria defined before transplantation are used to enroll the patients to the minimization procedure. In all but one published trials, low-to-moderate immunological risk was one of the major entry criteria.

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## Major Relevant Clinical Pediatric Trials and Reports

Current immunosuppression protocols aiming to facilitate steroid avoidance or early

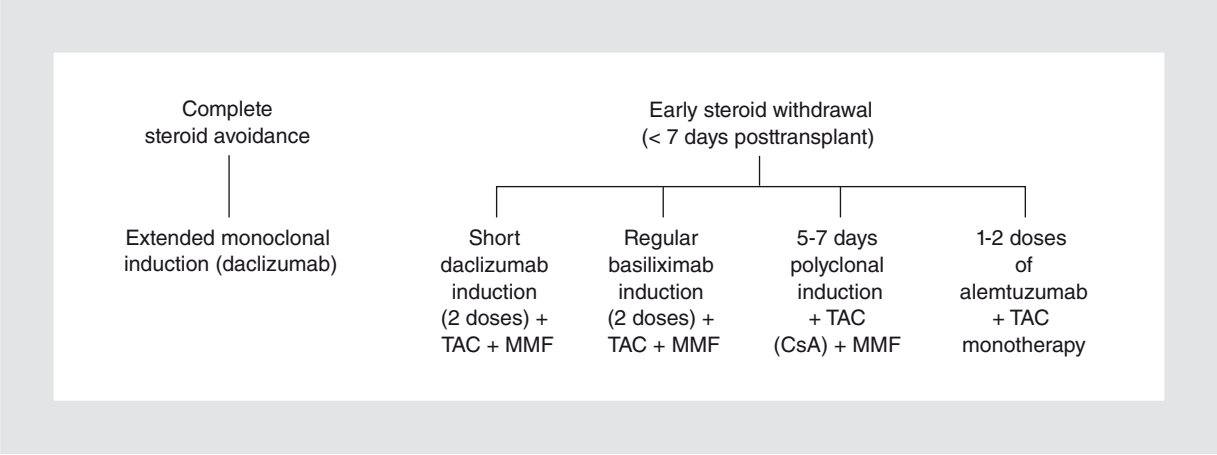


**Figure 1.** *Immunosuppression protocols used for steroid avoidance or early withdrawal in children after renal transplantation. TAC: tacrolimus; MMF: mycophenolate mofetil; CsA: cyclosporin A.*

steroid withdrawal in children predominantly used monoclonal antibody induction with anti-IL2R-α inhibitors (daclizumab or basiliximab), in two anti-CD52 antibody (alemtuzumab), and in the remaining polyclonal induction with thymoglobulin.

The protocols aimed at complete steroid avoidance universally used long-term daclizumab induction. The Stanford trial was the largest single-centre study based on an extended (up to six doses) daclizumab induction, administered until month 6 posttransplantation in patients on tacrolimus and mycophenolate mofetil maintenance immunosuppression (or sirolimus given in cases when mycophenolate mofetil was not well tolerated). The results were compared to historical controls[1,2]. A similar protocol was used in smaller study[3]. A prospective study described by the UCLA group with complete steroid avoidance used nine doses of daclizumab (up to 22 weeks posttransplantation), tacrolimus, and mycophenolate mofetil[4]. Protocols based on early steroid withdrawal (< 7 days posttransplantation) used shorter courses of monoclonal induction. The European TWIST (Tacrolimus and Withdrawal of Steroids) study was a multicentre randomized trial, evaluating tacrolimus combined with mycophenolate mofetil and early steroid withdrawal (at day 5) and with two doses of daclizumab versus standard triple therapy[5]. A prospective study described by Delucchi, et al. used two doses of basiliximab, tacrolimus, and mycophenolate mofetil for early (< 7 days) steroid withdrawal in 23 children[6]. The protocols with early steroid withdrawal followed by tacrolimus monotherapy used alemtuzumab in short induction. The study described by the Pittsburgh group used, in one of the study arms, single dose of 0.4-0.5 mg/kg alemtuzumab together with tacrolimus monotherapy and rapid steroid withdrawal (1-5 days after transplantation). The same protocol was then used electively in living donor-related renal transplantation[7,8]. Polyclonal induction was used in another study conducted by the Stanford group. Patients were given six doses of thymoglobulin (cumulative dose of 9 mg/kg), tacrolimus, and mycophenolate mofetil and steroids were withdrawn at day 7 after transplantation[9]. Polyclonal induction (5-7 doses; 1.5 mg/kg) was also used in combination with cyclosporine, mycophenolate mofetil, and a five-day course of steroids, immediately withdrawn at day 6 posttransplantation[10]. Polyclonal induction for early steroid withdrawal was also used in other smaller pediatric trials[11-13].

Different protocols are presented in figure 1.

**Table 1. Incidence of acute rejection and one-year graft survival in major pediatric trials aimed at steroid avoidance or early withdrawal, compared to registry data (NAPRTCS)**

| Report | Acute rejection rate (%) | One-year graft survival (%) |
|---|---|---|
| NAPRTCS Annual Report 2008 | DD 17.7 ± 1.5<br>LRD 8.7 ± 1.3 | DD 94.4<br>LRD 96.1 |
| Stanford study<br>Sarwal, et al. 2003[1] | 8 | 100 |
| Pittsburgh studies<br>Shapiro, et al. 2006[7]<br>Tan, et al. 2008[8] | Alemtuzumab arm 0<br>Thymoglobulin arm 14<br>LRD, alemtuzumab 0 | Alemtuzumab arm 100<br>Thymoglobulin arm 94<br>LRD alemtuzumab 97.6 |
| UCLA study<br>Bhakta, et al. 2008[4] | 5 | 100 |
| Minnesota study<br>Chavers, et al. 2009[10] | 14 | 90 |
| TWIST study<br>Grenda, et al. 2010[5] | 10.2 | 99 (6 months) |
| Stanford study (thymoglobulin)<br>Li, et al. 2010[8] | 0 | 100 |

DD: deceased donor transplantation; LRD: living-related transplantation.

## Efficacy and Safety

Both steroid avoidance and early withdrawal were effective protocols in terms of acute rejection and graft survival, compared to steroid-treated patients. The incidence of acute rejection was reported as 0-14% and one-year graft survival from 100 to 90% (Table 1). These data are comparable with the "standard care" results, as reported by NAPRTCS[14].

Steroid avoidance and early steroid withdrawal have no detrimental effect on long-term graft function. In none of the reports was the glomerular filtration rate (GFR) in children being off steroids described as inferior to steroid-treated controls, and in some reports GFR was significantly higher in steroid-free patients, as in the Stanford study (eGFR 95.8 ± 24.9 vs. 72.2 ± 25.6 ml/min/1.73 $m^2$; p = 0.004, at two years posttransplantation) and the UCLA study (significantly better at six months posttransplantation)[1,4]. One of the concerns of the long-term effects of steroid withdrawal is a risk of late humoral rejection and occurrence of anti-HLA antibodies. There is no evidence so far that the long-term absence of steroids is a significant risk factor for late chronic humoral rejection. Overall, 246 protocol biopsies were performed in the steroid-free Stanford patients at 0, 3, 6, 12, and 24 months posttransplantation, showing a cumulative tacrolimus toxicity incidence of 48%. All patients beyond one year posttransplantation showed mild tacrolimus toxicity with no chronic rejection[1]. The significant impact of steroid withdrawal on the development of donor-specific antibodies in adult patients was not confirmed[15].

There was no report of the detrimental effect of protocols aimed at steroid avoidance or early withdrawal on the higher risk of infection or malignancy. The incidence of post-transplant lymphoproliferative disease (PTLD) was reported as 0-2%, regardless of the use of variable induction protocols[1,5,7,9]. The only exception was the US multicentre study, where patients received two doses of basiliximab, sirolimus, tacrolimus or cyclosporine and steroids and after six months, upon result of the protocol biopsy, were randomized to steroid withdrawal. During the first phase of the trial

(prior to randomization; being on steroids) 6.9% of patients developed PTLD. It was mainly seen in young Epstein-Barr virus (EBV)-naive children, receiving an EBV-seropositive renal allograft[16,17]. This study was not designed as an early steroid withdrawal trial; however, the message coming from this experience about the need for very close PTLD surveillance in young children given monoclonal induction should be extrapolated to the common medical practice. Some reports showed a higher incidence of bone marrow suppression, including anemia, in children being off steroids[1,5], probably due to the lack of steroid-driven cellular proliferation. Leucopenia was responding to dose reduction of mycophenolate mofetil in some cases[1,5,10]; however, up to 52% of patients treated with thymoglobulin and presenting with leucopenia required administration of bone marrow stimulating agents (GCSF)[10].

## Clinical Benefits

Specifically for the pediatric population, clinical benefit in terms of improvement of linear growth was universally proven by all major reports in pre-pubertal children. In the Stanford study (long daclizumab induction) this effect was most notable in patients aged under five at time points of six months, one year, and two years posttransplantation The effect on growth was sustained during the subsequent follow-up period of four years, while in the youngest children maintained on the steroid-free therapeutic regimen the catch-up growth rates were even higher than in the normal, healthy, age- and gender-matched controls[1,2]. In the TWIST study (short daclizumab induction), a significant improvement of the change in height standard deviation score (SDS), adjusted for the pubertal status and baseline value, was seen in the steroid-withdrawal arm during the six months of follow-up (0.17 vs. 0.03; $p = 0.005$)[5]. Mean gain of height expressed as delta Z-score 0.79 ± 0.67 was reported by Shapiro, et al. (alemtuzumab induction)[7]. Significant difference of height SDS in steroid-free children versus controls (–0.6 ± 1.1 vs. –2.0 ± 1.6) was reported by Chavers, et al. (thymoglobulin induction)[10]. The same reports confirmed better glycemic control (expressed as normal glucose, lower incidence of posttransplant new-onset diabetes, less patients requiring antidiabetic treatment), lipid control (expressed as lower cholesterolemia and triglyceridemia) and blood pressure control (lower incidence of hypertension; lower number of hypotensives). All these favorable effects of steroid withdrawal were independent of age[1,2,4,5,7,8,10]. The impact of steroid withdrawal on cosmetic side effects was evaluated in one randomized trial and there was significant difference in terms of Cushingoid facies in patients maintained on daily steroids compared to those who were withdrawn[16]. The impact of the early steroid withdrawal on long-term bone mineralization status was evaluated in the single-centre study. Patients with no steroids (treated according to the TWIST trial protocol) and not receiving specific prophylaxis were compared with two groups of patients on steroids, receiving or 0.25 μg of 1α(OH)D3 analog daily or two doses of oral 50 mg bondronate, given < 7 days posttransplantation and then 30 days thereafter. Steroid minimization by itself appeared to be not effective in terms of complete prevention of bone mineral loss during two-year follow-up[18].

## Who is Viable?

In all but one pediatric report on steroid avoidance and early withdrawal, patients were at low-to-moderate immunological risk. Only one report recently published by the Stanford group included high-risk patients, as defined by significantly lower incidence of PRA < 20% vs. controls (69 vs. 92%; $p = 0.04$), higher incidence of zero HLA match (38.5 vs. 7.6%; $p = 0.06$, no case of living-related donor transplantation (0 vs. 46%; $p = 0.005$) and higher presence

of African American patients (15 vs. 0%; NS). High-risk patients were given thymoglobulin induction, followed by maintenance tacrolimus and mycophenolate mofetil and early steroid withdrawal (< 7 days posttransplantation)[9]. There was no rejection episode in this group, and therefore one can conclude that polyclonal induction is the protocol of choice for early steroid withdrawal in the higher-risk patients.

## Is Type of Monoclonal Anti-IL2Rα Antibody Important?

Daclizumab, used in several pediatric minimization trials and universally in all complete steroid avoidance protocols, currently is not commercially available. Basiliximab, as two-dose induction, was used in several adult and pediatric trials aimed at steroid withdrawal; however, there is no data on direct (randomized) comparison to daclizumab efficacy in pediatric renal transplantation. There are conflicting data from adult studies relevant to this subject[19-21], so the results from pediatric daclizumab-based trials cannot be directly extrapolated to basiliximab-related practice, especially in terms of prolonged induction, as used in the complete steroid avoidance protocols.

## Reasons for Breaking Steroid-Free Regimen

The incidence of introducing or re-introducing steroids to the maintenance immunosuppression at long-term follow-up was reported from 0% (Pittsburgh group) to 13.2% (Stanford group). The most common reason was refractory acute rejection (52.9%) and recurrence of primary glomerulonephritis (35.3% of steroid-free patients, as reported by the Stanford group). The role of steroid absence in increasing the risk of recurrence of primary glomerulonephritis was denied by the report, describing no significant difference in incidence of posttransplant recurrence in adult patients, given steroids or not in the maintenance immunosuppression[22,23]. These conflicting data need verification in further investigations. This difference may be related to the age-related specificity of posttransplant recurrence of glomerulonephritis in children and adults.

## Summary

- Efficacy and safety of steroid avoidance and early withdrawal were proven in relevant pediatric clinical trials.
- Expected clinical benefits were documented; pre-puberty determines improvement of growth, but not the remaining benefits, which appear regardless of age.
- There is no clear superiority of any specific protocol in low-risk patients.
- Polyclonal induction should be considered in high-risk patients.

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