Pediatr Nephrol (2010) 25:747–752
DOI 10.1007/s00467-009-1318-3

REVIEW

Effects of steroid avoidance and novel protocols on growth in paediatric renal transplant patients

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Received: 9 June 2009 / Revised: 28 July 2009 / Accepted: 17 August 2009 / Published online: 21 October 2009

Abstract The vast majority of kidney transplant recipients undergo triple maintenance immunosuppression that includes the use of steroids. Irrespective of their long history in organ transplantation and proven efficacy in preventing acute graft rejection, steroids exhibit an unfavourable toxicity profile, including growth retardation in children. Given these negative effects, therapeutic approaches that will substantially decrease patients' exposure to steroids have been considered. The planned approaches included alternate day administration, rapid or late steroid withdrawal at the pre-scheduled time after transplantation and complete steroid avoidance. All three of these strategies have been tested in single- or multicentre studies and shown to have distinct clinical advantages in terms of decreasing the incidence and severity of specific adverse events. However, the safety of these protocols could not be universally proven. The Stanford study showed that a complete steroid avoidance under the "cover" of tacrolimus, mycophenolate mofetil and extended daclizumab induction is a very effective regimen for obtaining an improvement in post-transplantation growth. The recently reported international randomized TWIST trial demonstrated growth improvement as early as 6 months post-transplantation. These protocols may potentially enable paediatric renal graft recipients to safely avoid steroid exposure.

Keywords Growth · Induction · Renal transplant · Steroid avoidance

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Since the very beginnings of transplantation medicine, corticosteroids have been considered to be the basic immunosuppressants. They have been routinely included in various protocols, such as double, triple, quadruple and sequential therapy, as well as administered as the first-line therapy in acute graft rejection. Specific steroid-related adverse events include post-transplantation glucose metabolism disorders (including diabetes mellitus) and lipid disorders, hypertension and cardiovascular sequelae, growth retardation in children, cosmetic-type adverse effects (such as body disfigurement, acne) and peripheral bone fracture and avascular necrosis. The main aim of steroid exposure minimization is to reduce or preclude specific drug-related adverse events—without increasing the incidence of acute graft rejection and late graft loss. Paediatric patients represent a unique target group in view of the beneficial effects of steroid minimization on growth in prepubertal individuals and on decreasing the risk of non-adherence in adolescents.

The two main factors impacting on the safety of steroid withdrawal are the concomitant immunosuppression and the timing of withdrawal. In adult patients, the impacts of these two factors have been summarized in two meta-analyses, published in 2000 and 2009, respectively. The first one, by Kasiske and colleagues, included trials conducted between 1987 and 1997, the majority of which used azathioprine and cyclosporin A, with the latter used as the main calcineurin inhibitor [1]. The analysis showed that the risk of acute graft rejection was significantly higher after a late steroid withdrawal, which was also unfavourable in terms of an increased incidence of late graft failure. Data from the last decade are presented in the recent meta-analysis by Pascual and colleagues, covering 30 randomized controlled trials involving 5949 adult participants. These authors showed that a change in the maintenance

immnosuppression regimen, including the use of mycophenolic acid precursors and tacrolimus, decreased the risk of acute graft rejection in steroid withdrawal patients. Overall, this latter review has confirmed that steroid avoidance and withdrawal strategies in kidney transplantation are not associated with an increased graft loss in adult patients despite an increase in the acute graft rejection rate, and that the correct choice of withdrawal strategy can significantly decrease the incidence of steroid-related metabolic adverse events [2]. It should be noted that one of the more important factors influencing the success of late steroid withdrawal protocols is the racial factor. As indicated by Matas, most of the studies reporting a success of late steroid withdrawal have been performed in Europe, while those demonstrating the failure of this strategy have usually been conducted in the USA and involved a significant participation of African-American patients [3]. The majority of trials reporting a rapid (<7 days post-transplantation) steroid withdrawal or total avoidance in adult patients have used induction protocols with monoclonal or polyclonal antibodies [3–7].

In paediatric patients, growth acceleration is one of the most important objectives of early steroid withdrawal. Evidence based on a number of late and early withdrawal trials and steroid avoidance trials indicates that a total elimination of steroids is an effective approach for promoting growth improvement. Paediatric studies evaluating growth under the above strategies are summarized in Table 1 [8–19].

The immunosuppression regimens used in these trials did not universally include induction. Those presented by Hodson and colleagues [8], Reisman and colleagues [9], Ellis [11], Höcker and colleagues [12] and Motoyama [15] were based on mono-, double or triple therapy without the use of antibodies. The immunosuppressive agent(s) used in the different maintenance protocols was (were) most likely one of the major factors influencing the reported acute rejection rates, which ranged from 56% in the study using cyclosporin monotherapy [8] to 0% in the German multicentre trial with a combination of cyclosporin and mycophenolate mofetil [12]. All other paediatric steroid withdrawal studies published after 2000, with two exceptions, have been based on an induction with poly- or monoclonal antibodies. In the maintenance immunosuppression regimens reported in these later studies, cyclosporin was replaced by tacrolimus, while azathioprine was replaced by mycophenolate mofetil [13, 14, 16–19]. Almost universally, an overall beneficial effect of steroid withdrawal on growth was reported. In some studies, a more marked benefit was observed in prepubertal children, as reported by Höcker and colleagues [12] for a late steroid withdrawal setting [baseline height standard deviation score (SDS) −2.24±0.38 vs. −0.77±0.42 after 46±2.3 months, $p<0.01$] and by Sarwal and colleagues and Li and colleagues for the Stanford trial [17–19].

The Stanford trial is the largest single-centre study carried out to date based on an extended daclizumab induction, which was administered until month 6 post-transplantation in patients on tacrolimus and mycophenolate mofetil maintenance immunosuppression (with sirolimus given in cases when mycophenolate mofetil was not well tolerated). Linear growth was significantly improved in the steroid-free arm, and this effect was most notable in patients aged <5 years at time points of 6 months, 1 year and 2 years post-transplantation (mean change in height SDS was respectively: 1.32±0.69 vs. −0.15±1.46, $p=0.005$; 1.72±0.83 vs. −0.16±1.21, $p=0.0008$; 1.42±0.64 vs. −0.5±1.23, $p=0.0009$; respectively). Importantly, the acute rejection rate was found to be significantly lower in steroid-free patients (8 vs. 32%, $p<0.001$) [18]. The effect on growth was sustained during the subsequent follow-up period of 4 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. The beneficial effect of steroid avoidance was observed in children aged up to 12 years at the time of transplantation, but in patients older than 12 years the trend in growth improvement was not significant. Late (>1 year post-transplantation) clinical acute rejection episodes occurred in 4% of steroid-free and 12% of steroid-treated patients [19]. We await the final results of the recently completed U.S. multicentre trial, which extend the promising Stanford experience over a larger population of children and adolescents and over other centres. A preliminary report has not confirmed the effects of steroid avoidance on growth at 1 year post-transplantation [delta height SDS 0.6 vs. 0.5 in children aged from 0 to 5 years, and 0.3 vs. 0.34 in patients aged from 6 to 12 years, $p=$ non-significant (NS)]. The incidence of acute rejection was comparable between the arms (28 vs. 34%, NS) [20].

The European study TWIST (Tacrolimus and WIthdrawal of STeroids) is a multicentre randomized trial that evaluates the tacrolimus-based regimen combined with mycophenolate mofetil and early steroid withdrawal (at day 5) under two doses of daclizumab versus triple therapy. The preliminary results showed a significant improvement of the change in height SDS, adjusted for the pubertal status and baseline value, in the steroid withdrawal arm during the 6 months of follow-up (0.17 vs. 0.03, $p=0.005$). At the same time, the acute graft rejection rate (percentage of patients free from biopsy-proven acute rejection; 92.3 vs. 89.2%), graft survival (96.9% in both arms) and renal function (97.1 vs. 98.7 ml/min/1.73 m^2) were comparable in both study arms [21].

In contrast, there have been recent reports of the incidence of acute rejection being low and not affected by steroid withdrawal [12, 17–21]. One of the concerns about the safety of this strategy pertains to the long-term renal

Table 1 Effects of steroid avoidance or withdrawal on growth in paediatric studies

Author/reference	Design	Number of patients	Immunosuppression[a]	Steroid withdrawal	Effect on growth
Hodson et al. (1989) [8]	Retrospective avoidance	20	CsA	Complete avoidance	Beneficial
Reisman et al. (1990) [9]	Prospective late withdrawal	16	CsA	Between 7 months and 5 years post-transplantation	Beneficial
Birkeland et al. (1998) [10]	Retrospective rapid withdrawal	14	ALG/ATG+CsA+MMF	Day 1	Beneficial
Ellis (2000) [11]	Prospective late withdrawal	52	TAC, Pred	6 months	Beneficial
Höcker et al. (2004) [12]	Case-controlled late withdrawal	20	CsA, MMF, Pred	Mean time: 1.5±1.3 years post-transplantation	Beneficial better growth in prepubertal patients
Silverstein et al. (2005) [13]	Retrospective avoidance	22	Daclizumab (6 doses)+TAC+MMF; no steroids (controls: basiliximab 2 doses+TAC, MMF, steroids)	Complete avoidance	No effect
Oberholzer et al. (2005) [14]	Retrospective early withdrawal	13	ATG/OKT3/basiliximab+TAC/ CsA+MMF/AZA	Day 6 post	Beneficial
Motoyama et al. (2005) [15]	Prospective late withdrawal/alternate-day	27 withdrawal 69 alternate-day	CsA, mizoribine, Pred	3-6 months	Beneficial
Hamiwka et al. (2006) [16]	Retrospective late withdrawal	67	Daclizumab/ATG+TAC, AZA/MMF, Pred	Mean time 9.7±4.5 months post-transplantation	Beneficial
Sarwal et al. (2001, 2003) [17, 18]	Prospective (with historical controls)	10	Daclizumab (6 doses)+TAC+MMF; no steroids (SIR if MMF not tolerated)	Complete avoidance	Beneficial
Li et al. (2009) [19]		57	controls: daclizumab 5 doses until month 2 (65%) or ATG (35%)+AC, MMF, Pred		Better growth in children aged <12
	Avoidance	129			The best growth rate in children aged <6 at transplantation

[a] CsA, cyclosporin A; ALG, antilymphocytoglobulin; ATG, anti-thymocyte globulin; MMF, mycophenolate mofetil; TAC, tacrolimus; Pred, prednisone; OKT3, muromonab-CD3; AZA, azathioprine; SIR, sirolimus

graft function in steroid-free patients, in terms of a possible risk of inflammatory or fibrotic processes that may occur in the renal graft tissue. In a study involving 200 adult patients, protocol renal biopsies at 1, 6, 12, 24, 36, 48 and 60 months post-transplantation were performed in kidney graft recipients subjected to an early (day 2) steroid withdrawal, basiliximab induction and either of the four different maintenance regimens: cyclosporin and mycophenolate mofetil (CsA+MMF), cyclosporin and sirolimus (CsA+SIR), tacrolimus and mycophenolate mofetil (TAC+MMF) or tacrolimus combined with sirolimus (TAC+SIR). The incidence of interstitial fibrosis/tubular atrophy (Banff IF/TA), which is indicative of chronic calcineurin inhibitor nephrotoxicity, increased with time irrespective of the type of maintenance immunosuppression used, and at 5 years it reached 54% in CsA/MMF-, 16% in CsA/SIR-, 38% in TAC/MMF- and 14% in TAC/SIR-treated patients. Despite these differences (in favour of the use of sirolimus in combination with calcineurin inhibitors), the renal graft function and survival at 5 years were comparable between the subgroups [22]. Interestingly, an additional analysis aimed at evaluating the racial impact on late renal fibrosis showed that IF/TA was more common in African-American patients (47 vs. 32%, $p=0.05$) [23].

Overall, 246 protocol biopsies were performed in the steroid-free Stanford patients at 0, 3, 6, 12 and 24 months post-transplantation, with a cumulative tacrolimus toxicity incidence of 48%, manifested primarily by the presence of patchy tubular atrophy and vacuolization involving 15–20% of the sampled core and a 12.5% rate of mild medial hyalinosis. All patients beyond 1 year post-transplantation showed mild tacrolimus toxicity with no chronic rejection, as based on transplant vasculopathy. In four of the steroid-free children, subclinical acute rejection (Banff 1A) was found in protocol biopsies [18]. In addition, the renal graft function at 2 years post-transplantation was better in the steroid-avoidance group of Stanford patients than in children maintained on steroids [estimated glomerular filtration rate (eGFR) 95.8±24.9 vs. 72.2±25.6 mL/min/1.73 m^2, $p=0.004$; historical controls] [18]. Notably, this effect of steroid avoidance was maintained in a longer (4 years) follow-up period [19].

At the same time, there was no difference in the 1-year graft function between the subsets of steroid-free patients maintained on either TAC+MMF or TAC+SIR (eGFR controlled for age 91.9±23.9 vs. 84.3±23.1, $p=0.52$) [18].

An alternative approach to treating the condition of growth retardation in paediatric renal transplant recipients is the use of the recombinant growth hormone. Four 1-year randomized trials and one 6-month crossover study have produced evidence demonstrating the efficacy of growth hormone use in paediatric patients. An annual growth rate of 3.9–10.1 cm was observed, and in all five trials, the growth velocity was significantly higher in the treated children than in the untreated control groups. Moreover, the results from all of the above trials confirmed the safety of growth hormone therapy in terms of the incidence of acute rejection [24–27]. Concerns have been raised about the risk of post-transplantation malignancy in growth hormone-treated patients, as Tyden and colleagues have described two late (7 and 9 years post-transplantation) renal cell carcinoma cases in living-related kidney grafts transplanted to children receiving the growth hormone. It was argued that renal cell carcinoma cells secrete insulin-like growth factor-1 (IGF-1) and express specific IGF-1 receptors on their cell membrane; consequently, thus there exists a potential threat that the administered growth hormone may stimulate their growth [28]. This issue has been exhaustively investigated by Mehls and colleagues who have analysed a number of international databases containing reports of adverse events in children treated with the growth hormone. Apart from the two cases reported by Tyden and colleagues, only one additional case of post-transplantation renal carcinoma was found among 42,000 patients covered by the Pharmacia International Growth Database, with 314 of them having been treated with the growth hormone. Another large database, the United States National Cooperative Genentech Study, covering nearly 43,000 children in total and 1170 patients treated with the growth hormone in the course of renal disease (with 277 of them being graft recipients), did not contain a single report of renal cancer. In addition, other databases maintained by the manufacturers of growth hormones also did not contain any mention of cases of renal carcinoma in relation to growth hormone treatment. It was therefore concluded that growth hormone therapy should not, at this stage, be considered an additional risk factor for post-transplantation renal cancer [29]. This conclusion is supported by the last of any case of renal cell carcinoma in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) registry [30].

Yet another concern about the growth hormone therapy pertains to its potential correlation with the risk of post-transplantation lymphoproliferative disease (PTLD) due to the modulating effect of growth hormone on the development of B-cell precursors. Based on NAPRTCS data and taking into account the confounding factors present, a borderline risk of PTLD development in patients treated with growth hormone prior to the transplantation (odds ratio 1.88, 95% confidence interval 1.00-3.55, $p=0.05$) was found to exist, while the use of growth hormone during the dialysis and post-transplantation periods was not associated with a higher risk of PTLD [31]. Growth hormone has been widely used in patients from different age groups. Notably, as evidenced by the reports of NAPRTCS and the German Study Group for Growth Hormone Treatment in Children Post Renal Transplantation, prepubertal children in whom

the growth hormone therapy was initiated before the age of 10 years and patients with a significant delay of bone age are the best responders to the post-transplantation treatment [30, 32].

Summary points

- The evidence-based trials have proven that steroid avoidance and early steroid withdrawal are effective in terms of growth improvement and safe management in children post-renal transplantation.
- Pre-pubertal children benefit most in terms of growth velocity and final growth under these regimens.
- Growth hormone is an alternative, safe and effective option in patients not qualifying for steroid withdrawal, primarily in prepubertal children with delayed bone age.

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