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Calcineurin inhibitors in paediatric renal transplantation

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GUIDELINES

In children who are treated with azathioprine, tacrolimus should be used rather than cyclosporin because of the reduced incidence of biopsy-proven acute rejection and reduced incidence of graft loss. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **In children treated with cyclosporin, 2 h peak cyclosporin level (C_2) monitoring should be used in the initial post-transplant period, as the C_2 level is a better predictor of cyclosporin exposure than C_0 monitoring (Level III evidence). Limited data suggest that the C_2 level should be maintained above 1500 ng/mL in the early post-transplant period (Level III evidence) to minimize the risks of acute rejection.**
- **Tacrolimus may be preferable in some children and in adolescents because of the decreased incidence of hirsutism and gum hyperplasia in comparison with cyclosporin (Level I evidence, adult studies).**

BACKGROUND

Renal transplantation is established as the best form of renal replacement therapy in children and is followed by improved linear growth, improved cognitive performance, enhanced psychosocial development and improved quality of life for the child and family.[1] As with adults, outcomes of transplantation have steadily improved since the early 1960s[2] and much of this improvement has been attributed to the introduction and widespread use of calcineurin inhibitors (CNI). Cyclosporin microemulsion was the most widely used CNI until the mid-1990s.[3] However, the use of tacrolimus as an alternative immunosuppressant to cyclosporin has increased in recent years with a number of reports in adults about its safety and efficacy in reducing rejection and short-term graft survival. The objective of this guideline is to appraise studies of CNI that compare the safety and efficacy of cyclosporin microemulsion with tacrolimus in renal allograft recipients aged 18 years or younger.

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SEARCH STRATEGY

Databases searched: MeSH terms and text words for kidney or renal transplantation were combined with MeSH terms and text words for cyclosporin, sandimmune, Neoral, tacrolimus, FK506 and growth, lymphoproliferative disease and drug administration schedule. Searches were limited to infant (1–23 months), preschool child (2–5 years), child (6–12 years) or adolescent (13–18 years). The search was carried out in EMBASE, Medline (1996 to March Week 4, 2006) and PubMed. The Cochrane Clinical Trials Register was also searched for trials not indexed in Medline.
Date of searches: 31 March 2006.

WHAT IS THE EVIDENCE?

Dosage and monitoring

As with adult organ transplant patients, cyclosporin dosing in children is guided by therapeutic drug monitoring and while similar trough target levels have been used for both age groups,[4] higher doses of cyclosporin (on a mg/kg basis) may be required in paediatric patients.[5] The current focus in adult transplantation on cyclosporin absorption profiling has led to the increasing use of the 2 h peak cyclosporin level (C_2) for cyclosporin monitoring (see adult guideline titled 'Therapeutic drug monitoring'). However, few data exist on the use of C_2 monitoring in paediatric renal transplant recipients. While significant variability has been demonstrated in the time to peak cyclosporin concentrations in children,[6] in keeping with adult studies, C_2 ($r^2 = 0.99$) was a far better single point predictor of AUC(0–4) than the trough level ($r^2 = 0.56$).[7]

Similar results were reported in a further study of both de novo paediatric renal transplant recipients (C_2: $r^2 = 0.900$; C_0: $r^2 = 0.054$) and maintenance patients (C_2: $r^2 = 0.861$; C_0: $r^2 = 0.522$).[5] However, data on the appropriate C_2 target level for paediatric patients are scarce and there are no prospective randomized controlled trials (RCT) that compare outcomes between C_0- and C_2-monitored paediatric renal transplant recipients.

In a prospective cohort study, Trompeter *et al.*[8] reported that patients achieving $C_2 > 1500$ ng/mL (EMIT assay) by the 5th postoperative day experienced no acute rejection in the first 6 months, compared with a 50% rejection rate among patients with $C_2 < 1500$ ng/mL ($P < 0.05$). Further analysis of their data using binary logistic regression analysis showed that $C_2 > 1700$ ng/mL was associated with ~90% probability of freedom from acute rejection.[8] In this study, there were no adverse effects of higher cyclosporin levels on creatinine or calculated glomerular filtration rate. A further prospective study of 64 paediatric kidney transplant recipients also reported significantly lower C_2 levels (mean C_2: 915 ± 210 ng/mL) in patients with an early rejection episode (within 6 months post transplant), compared with the C_2 level in those without rejection (mean C_2: 1340 ± 470 ng/mL; $P = 0.002$).[9]

There are little data on the pharmacokinetics of tacrolimus in children undergoing renal transplantation. Studies in limited numbers of children (57 patients) have found a daily dose of 0.15–0.19 mg/kg per day produced trough levels within the range of 5–10 ng/mL.[10,11] In one paediatric pharmacokinetic study ($n = 14$), there was very good correlation between AUC and trough levels ($r^2 = 0.73$, $P < 0.001$).[11]

Efficacy

The single RCT of CNI use in paediatric renal transplant recipients demonstrated a significantly decreased risk of biopsy-proven rejection at 6 months in those patients treated with tacrolimus (18.1%) compared with cyclosporin (43.0%, $P < 0.001$).[12] Cyclosporin was monitored by trough levels and adjuvant immunosuppression was with azathioprine rather than mycophenolate mofetil (MMF) and these factors may have contributed to the observed difference in acute rejection. A subsequent large retrospective cohort study using data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) registry did not demonstrate any difference in rejection rates or graft survival in children when cyclosporin or tacrolimus was combined with MMF and steroids.[13] There are no data in paediatric patients on the efficacy of cyclosporin versus tacrolimus as ‘rescue’ therapy or following a first rejection episode.

Adverse events

Infectious complications

Ellis *et al.*[14] reported a greater incidence of cytomegalovirus (CMV) infection within 6 months post transplant in paediatric patients treated with tacrolimus (4/24) compared with those on cyclosporin (0/24). However, the European multicentre study reported a similar incidence of infections between both treatment groups[12] and the incidence of infection in both groups was also comparable when stratified according to organism (bacterial, viral, fungal). Prospective and retrospective case series have shown no difference in the incidence of BK nephropathy in children treated with tacrolimus compared with cyclosporin.[15–17]

Malignancy

The incidence of post-transplant lymphoproliferative disorder (PTLD) in paediatric series is between 1.2% and 4.5%,[18–20] and is four times higher in paediatric than in adult transplant recipients.[21] Initial data from the NAPRTCS registry[20] suggested a trend towards increasing incidence and earlier occurrence of PTLD in the paediatric renal transplant population. The same study reported a highly significant difference in the prevalence of PTLD between children treated with cyclosporin (prevalence rate 1.1%) and tacrolimus (11.5%, $P < 0.0001$).[20] However, a more recent report from NAPRTCS[19] did not show a relationship between tacrolimus or MMF use and PTLD. Other studies that have also reported no difference in the incidence of PTLD between tacrolimus- and cyclosporin-treated recipients[12,14] are reassuring but have lacked adequate statistical power for assessing this outcome.

Growth

In two studies,[13,14] there was no difference in growth post transplant between children who remained on steroids and were treated with either tacrolimus or cyclosporin.

Diabetogenicity

An initial study in paediatric renal transplant recipients suggested a significant incidence of reversible post-transplant diabetes mellitus (PTDM) in patients treated with tacrolimus.[10] A further study in children with a variety of transplants reported that 2.8% of children had developed permanent diabetes mellitus.[22] More recent studies have shown a lower incidence of PTDM in children and no difference between tacrolimus- and cyclosporin-based regimens.[12] There are no paediatric data that use the more stringent World Health Organization criteria for diabetes.

Cardiovascular complications

In the single RCT, the use of antihypertensive medication was similar when either CNI was combined with azathioprine and steroids (88.3% tacrolimus/86.2% cyclosporine).[12] However, mean total cholesterol levels at 6 months decreased in the tacrolimus group (4.88 ± 2.2 mmol/L to 4.32 ± 1.48 mmol/L), while mean total cholesterol increased in the cyclosporin e group (4.73 ± 2.2 mmol/L to 5.02 ± 1.92 mmol/L).[12] In a large registry study,[13] tacrolimus-treated patients were significantly less likely than cyclosporine-treated patients to require antihypertensive medications at 1 and 2 years post transplant.

Other

The incidence of hypomagnesaemia has been reported to be significantly higher in children treated with tacrolimus

(34%) compared with cyclosporin (12.9%; $P = 0.001$).[12] In the same study, diarrhoea was also more frequent in tacrolimus-treated patients (13.6% *vs* 3.2%, $P = 0.011$) while tremor was only reported in the tacrolimus group. Other neuropsychological and behavioural symptoms have also been reported in children following conversion to tacrolimus.[23] In keeping with other uncontrolled studies[10] and studies in adults,[24] the single RCT comparing tacrolimus with cyclosporin found that hirsutism and gingival hyperplasia were reported more frequently by CyA-treated patients.[12] In contrast, alopecia is reported more frequently by patients on tacrolimus.[24]

SUMMARY OF THE EVIDENCE

Table 1 summarizes the key findings of the few trials that have been carried out in paediatric renal transplant patients. There are no systematic reviews (Level I evidence) on the use of CNI that deal solely with the paediatric population and only one RCT (Level II evidence) that is limited by a significant loss of participants and what many would consider as suboptimal cyclosporin monitoring and adjuvant immunosuppression. Level III evidence suggests that both cyclosporin and tacrolimus are safe and, in combination with MMF, equally effective. The use of tacrolimus in current immunosuppressive protocols does not appear to be associated with an increased risk for PTLD although ongoing surveillance is warranted. Tacrolimus may be preferable to cyclosporin in some paediatric patients (e.g. adolescent girls) because of its lower incidence of cosmetic side-effects. Tacrolimus has shown promise in steroid-sparing immunosuppressive regimens, but further discussion of the role of steroids in paediatric renal transplantation is beyond the scope of this guideline.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney disease outcomes quality initiative: No recommendation.
UK Renal Association:[25]

> There are insufficient data to permit specific recommendations to be made with regard to immunosuppressive therapy. Cyclosporin-based triple therapy remains the most widely used combination of agents. Data from the North American Pediatric Renal Transplant Cooperative Study show an increasing tendency in North American centre to use newer immunosuppressive agents. It is essential that the efficacy, safety and tolerability of these agents are fully assessed in prospective randomised paediatric trials and all centres should be encouraged to enter patients into such trials. Given the improved results obtained with the use of well-matched cadaveric transplants, the widespread adoption of intensive immunosuppressive regimens may not be justified. More potent immunosuppressive therapies may be associated with an increased lifetime risk of malignancy, which is particularly important with paediatric patients who have many years of renal replacement therapy ahead of them. Immunosuppressive regimens need to be tailored to paediatric patients. It is not acceptable to extrapolate the findings of adult-based studies to the childhood population.

Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

IMPLEMENTATION AND AUDIT

No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

1 Perform trials determining clinical outcomes in trough- versus C_2-monitored paediatric patients.
2 Conduct an RCT of cyclosporin versus tacrolimus in combination with mycophenolate and steroids in paediatric patients.

CONFLICT OF INTEREST

Steven McTaggart has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDIX

Table 1 Summary of characteristics and outcomes for included paediatric trials and reports

				Outcomes								
Study ID (author, year)	Study design	Population	Intervention	Acute rejection	Biopsy-proven acute rejection	Graft survival			Infection	Post-transplant diabetes mellitus	Post-transplant lympho-proliferative disease	Comments
Trompeter *et al.* 2002[12]	Multicentre RCT	<18 years	CyA/Aza/Pred ($n = 93$) *vs* Tac/Aza/Pred ($n = 103$)	59.1% 36.9% $P = 0.003$	43.0% 18.1% $P < 0.001$	1 year 81.7% 90.3% $P = 0.06$	2 years 79.6% 90.3% $P = 0.028$	4 years 69% 86% $P = 0.025$	64.5% 68.9% P = ns	2.2% 3% P = ns	2.1% 1.0% P = ns	• Biopsies optional and were only performed by 13/18 centres • 57 patients withdrawn (77% follow up in Tac and 63% in CyA) • C_0 monitoring
Neu *et al.* 2003[13]	Retrospective cohort (registry) analysis	<18 years	CyA/MMF/Pred ($n = 766$) *vs* Tac/MMF/Pred ($n = 220$)	29% 29.1% $P = 0.84$		1 year 97.9% 96.8% $P = 0.607$	2 years 95.1% 91.4% $P = 0.151$		Not reported	Not reported	1.4% 2.0% P = ns	• No significant difference between Tac and CyA groups in mean delta height SDS[†] at 1 year and 2 years
Ellis *et al.* 1994[14]	Case–control (retrospective controls)	1.2–16 years	CyA/Aza/Pred ($n = 24$) *vs* Tac/Aza/Pred ($n = 24$)	0.21 episodes/ patient 0.58 episodes/ patient	1 year 92% 92% P = ns				3/24 (0 CMV) 5/24 (4 CMV)	Not reported	2/24 (8.3%) 3/24 (12.5%) P = ns	• Tac serum levels measured by mouse monoclonal antibody assay • Steroid withdrawal undertaken in Tac group (59% successful)
Ellis 1995[10]	Case series (unselected series of high- and low-risk transplants)		Tac/Pred (withdrawn 3–6 months) ($n = 43$)	53%		1 year 96%	3 years 85%		CMV (14%) EBV (9%)	11%	14%	
McKee *et al.* 1997[26]	Case series (incident transplant patients and conversion from CyA)	8–20 years	Tac/MMF or Aza/Pred ($n = 11$ incident; $n = 9$ conversion)	45% (incident group) 44% (conversion group)		15.5 months 91%				10%	0%	• 25% incidence of neurological side-effects

[†]Delta height SDS = change in height standard deviation score. Ht SDS = $\frac{\text{Actual Height} - \text{50th percentile Height for Age}}{\text{standard deviation}}$; Acute Rejection/Biopsy-proven Acute Rejection = within 6 months post transplant; Post-transplant Diabetes Mellitus, defined as new insulin use for more than 30 consecutive days in previously non-diabetic patients. Aza, azathioprine; CMV, cytomegalovirus; CyA, cyclosporin (Neoral, unless otherwise specified); EBV, Epstein Barr virus; MMF, mycophenolate mofetil; Pred, prednisolone; RCT, randomized controlled trial; Tac, tacrolimus.