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What is the calcineurin inhibitor of choice for pediatric renal transplantation?

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Abstract: Cyclosporine microemulsion (CyA) and tacrolimus (Tac) are the principal immunosuppressants prescribed for adult and pediatric renal transplantation. In the majority of patients, these calcineurin inhibitors have been used in combination with other immunosuppressive drugs, such as azathioprine or mycophenolate mofetil (MMF). In this review we will address the question of what calcineurin inhibitor we should use in an individual pediatric renal transplant patient. Well-designed randomized studies in children showed no difference in short-term patient and graft survival with cyclosporine microemulsion and tacrolimus. However Tac is significantly more effective than CyA microemulsion in preventing acute rejection after renal transplantation in a pediatric population when used in conjunction with azathioprine and corticosteroids. This difference disappears when calcineurin inhibitors are used in combination with MMF as both Tac and CyA produce similar rejection rates and graft survival. However, Tac is associated with improved graft function at 1 and 2 yr post-transplant. Adverse events of hypomagnesaemia and diarrhea seem to be higher in Tac group whereas hypertrichosis, flu syndrome and gum hyperplasia occurs more frequently in the CyA group. The incidence of post-transplant diabetes mellitus was almost identical between Tac and CyA treated patients. The recommendation drawn from the available data is that both CyA and Tac can be used safely and effectively in children. However Tac may be preferable to CyA because of steroid sparing effect and less hirsutism. We recommend that cyclosporine should be chosen when patients experience Tac-related adverse events. Nevertheless, the best calcineurin inhibitor should be decided on individual patients according to variable risk factors, such as risk of rejection in sensitized patient or delayed graft function. The possibility of adverse events should also be considered.

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Renal transplantation is now established as the best form of renal replacement therapy in children. Since its introduction in the early 1970s, the success rate has been gradually improving (1, 2). The development of more potent immunosuppressive agents over the last two decades has resulted in a progressive improvement in the 1-yr graft survival rates after transplantation as it contributed to the prevention of acute rejection rate. Much of the success in organ transplantation has been credited to the use of CyA; after its introduction renal graft survival at 1 yr increased from 64 to 78% (3).

The CyA, which works through the inhibition of calcineurin, an enzyme important in the activation of T lymphocytes, was originally discovered and developed in the mid-1970s (4). It revolutionized organ transplantation and had been used since the early 1980s in pediatrics renal transplantation (5). However, its oral form had a limited bioavailability, as it is highly lipophilic.

Abbreviations: CyA, cyclosporin A; Tac, tacrolimus; MMF, mycophenolate mofetil; GFR, glomerular filtration rate; RR, relative risk; NAPRTCS, North American Renal Transplant Cooperative Study; DGF, delayed graft function; PTLD, lymphoproliferative disorder; CMV, cytomegalovirus; HUS, hemolytic uremic syndrome; DM, diabetes mellitus; C2, cyclosporine concentration at 2 h post-dose.

Recently other forms of calcineurin inhibitors such as tacrolimus (Tac) and microemulsion cyclosporine have been used as the principal immunosuppressant in adult and pediatric renal transplantation (6). The microemulsion formulation of CyA has much better predictable absorption and pharmacokinetic (7). Immunosuppression in infants and toddlers is complicated by the increased metabolism and variable absorption of cyclosporine (8), in addition to their heightened immunologic responsiveness, which may in turn represent an increased propensity for allograft rejection (9).

Tac was isolated in 1985 from the fermentation of streptomyces stukubaensis (10). It has potent inhibitory effects on T lymphocyte activation by binding specifically to FK-506 binding protein in the cytoplasm and inhibits transcription of the early T cell activation genes for interleukin 2 and other cytokines (6). It was first used in clinical transplantation in 1989 (11).

Both acute dose-dependent and chronic non-dose-dependent nephrotoxicity has been reported with CyA and Tac. Although the exact mechanism of nephrotoxicity is not fully understood, several factors have been implicated in the pathogenesis of immunosuppressive-induced nephrotoxicity. Renal and systemic vasoconstriction, increased release of endothelin-1, decreased production of nitric acid and increased expression of TGF-beta are the major adverse pathophysiologic abnormalities of calcineurin inhibitors (12).

A number of investigators have shown that Tac in adults is more powerful in preventing severe and refractory rejection, even when compared with the new cyclosporine microemulsion formulation (13–18). A similar result was reported in children in a prospective, randomized study (19) as it showed that tacrolimus based triple therapy (in combination with azathioprine and corticosteroids) resulted in a significantly lower rate of acute rejection as well as steroid resistant rejection, compared with microemulsion cyclosporine based triple therapy. The use of Tac therapy was not associated with a higher rate of infection; post-transplant lymphoproliferative disease or diabetes mellitus, when compared with CyA therapy. Long-term outcome of using Tac or CyA in pediatric renal transplant recipients is not yet available. However, recently published data in adults demonstrated that Tac based immunosuppression is associated with a superior long-term renal function and more favorable cardiovascular risk profile than CyA microemulsion based immunosuppression which translates into improved long-term renal allograft survival (20). This may be different in children who do not usually suffer from cardiovascular diseases or diabetes, which may have a major effect on renal function.

However, the increasing frequency of using of MMF in pediatric renal transplantation (21) was associated with a better outcome and continuing improvement in graft survival was observed over the recent years (12, 22, 23). Many randomized trials have been reported in adults to compare the immunosuppression effect and the complications of CyA and Tac. Only a few studies in children have been reported to date. We will address the question: what is the calcineurin inhibitor of choice for pediatric renal transplantation?

Cyclosporine or tacrolimus in combination with azathioprine

Using the triple therapy (prednisone, azathioprine, and CyA or Tac) remains the principal practice in most pediatric renal transplantation centers (19). However, since the mid-1990s, MMF is used more frequently particularly in North America (21). Cyclosporine was the most widely used as the most important immunosuppressive agent in pediatric renal transplantation until the mid-1990s. The use of tacrolimus as an alternative immunosuppressant to cyclosporine has increased in recent years with a number of reports about its effect in reducing the incidence of rejections and improved short-term renal graft survival.

Recently, a multiple-center trial studied 196 pediatric patients who were randomly assigned to receive either Tac or CyA microemulsion administered concomitantly with azathioprine and corticosteroids (19). Tac therapy resulted in a significantly lower incidence of acute rejection (36.9%) compared with CyA therapy (59.1%) ($p = 0.003$). The incidence of corticosteroid-resistant rejection was also significantly lower in the Tac group compared with the CyA group (7.8% vs. 25.8%, $p = 0.001$). The difference was also significant for biopsy-confirmed acute rejection (16.5% vs. 39.8%, $p < 0.001$). At 1 yr, patient survival was similar (96.1% vs. 96.6%); ten grafts were lost in the Tac group compared with 17 graft losses in the CyA group ($p = 0.06$). At 1 yr, the Tac group had a significantly better GFR calculated according to Schwartz formula and the study concluded that Tac is significantly more effective than CyA microemulsion in preventing acute rejection after renal transplantation in pediatric population. The efficacy of both drugs were monitored by measuring 12 h trough level which seems appropriate for Tac,

while cyclosporine concentration at 2 h post-dose (C2) level provides more reliable marker for CyA exposure than C0 in pediatric renal transplant recipients, and is more closely predictive of acute rejection risk (23). This might bias the study in favor of Tac, however 2 yr follow up demonstrates that Tac-treated patients continued to enjoy higher GFR at 2 yr (64.9 vs. 51.7 mL/min/1.73 m^2, $p = 0.0002$) and they had better graft survival (90.3% vs. 79.6%, $p = 0.0367$) (24). Furthermore, previous studies had shown a decreased risk of chronic rejection graft failure in transplanted children associated with a minimization of acute rejection episodes (25). Patients with two or more acute rejections have a 12-fold increased RR of chronic rejection graft loss (26).

With the introduction of cyclosporine microemulsion with its better pharmacokinetics properties, further studies were conducted to compare it with Tac. A large, multicenter trial studied 560 adult patients at 50 European centers who were randomized to receive a triple regimen consisting either of Tac ($n = 287$) or cyclosporine microemulsion ($n = 273$) concomitantly with azathioprine and corticosteroids (16, 27, 28). There was no difference between the two groups in patient survival (99.3 vs. 98.5%) or graft survival (94.8 vs. 91.9%) at 6 month after transplantation. However, the incidence of biopsy-proven acute rejection was significantly lower in Tac group than in the cyclosporine microemulsion group (32.5 vs. 51.3%; $p < 0.001$) as well as the incidence of biopsy-proven corticosteroids-resistant rejection (0.4 vs. 21%; $p < 0.001$). The conclusion of this study was that Tac therapy proved to be superior to cyclosporine microemulsion-based therapy in preventing acute allograft rejection with less adverse events such as hypertension and hypercholesterolemia (27, 28). In other large, prospective, randomized, multicenter trials in adults and children receiving solid organ transplants, tacrolimus was found to be at least as effective or provided better efficacy than cyclosporine microemulsion treatment in terms of patient and graft survival, treatment failure and the incidence of acute and corticosteroid-resistant rejection episodes. The reduced incidence of rejection episodes in renal transplant recipients receiving tacrolimus translated into a better-cost effectiveness relative to cyclosporine microemulsion treatment (29).

In a study of 232 adult patients who were randomized to receive a Tac ($n = 115$) or cyclosporine microemulsion ($n = 117$), in addition to azathioprine and corticosteroids, the 6-yr outcome was reported (20). Renal function determined by GFR was significantly better in tacrolimus-treated patients from month three post-transplant. Furthermore, normal renal function was maintained throughout a 5-yr follow-up in a significantly higher proportion of non-rejecting patients treated with tacrolimus than with cyclosporine microemulsion (58 vs. 10%, respectively, at 5 yr; $p = 0.002$). Morphometric analysis of protocol biopsies revealed that the degree of interstitial fibrosis, similar in both treatment groups at baseline, was significantly greater in the cyclosporine microemulsion group over 12 months. Patients receiving tacrolimus had significantly greater 6 yr graft survival (81 vs. 60%, $p = 0.0496$) and a higher projected graft half-life (15 vs. 10 yr) than those receiving cyclosporine microemulsion. The conclusion of the study was that tacrolimus treatment is associated with a significantly better cardiovascular risk profile and superior renal function compared with cyclosporine microemulsion treatment, which appears to translate into improved long-term graft survival. Murphy et al. (30) also demonstrated in a prospective randomized trial that cyclosporine emulsion was associated with increased allograft fibrosis and significantly higher serum low-density lipoprotein cholesterol levels compared with tacrolimus. One hundred and two patients were randomized to receive Tac or cyclosporine microemulsion at higher dose, in conjunction with steroids, or at a lower dose with the addition of azathioprine for non-heart-beating renal transplant recipients. Renal transplant interstitial fibrosis was quantified using computerized histomorphometric measurement and there was a significant increase in allograft interstitial fibrosis in the patients treated with CyA compared with those given tacrolimus. There was no significant difference in the demographic characteristics between the patient groups or in the incidence of acute rejection (CyA 36% vs. tacrolimus 35%) or steroid-resistant rejection (both 10%) between the two drugs. There was a higher incidence of insulin resistance in the tacrolimus group (post-transplant diabetes mellitus, glucose tolerance testing) but this was not statistically significant. CyA was associated with a significant increase in total cholesterol ($p = 0.030$) and low-density lipoprotein ($p = 0.021$) levels, which persisted throughout the study period.

There is therefore evidence that Tac is superior to cyclosporine (conventional or microemulsion form) in preventing acute rejection after renal transplantation in adults and pediatric populations when used as part of triple therapy in conjunction with azathioprine and corticoster-

oids. It also seems more effective in improving long-term graft survival in adults. Further follow up studies are required to see if Tac improves long-term survival of kidney grafts in children.

Cyclosporine or tacrolimus with MMF

MMF had been used with increasing frequency in the last few years in pediatric renal transplantation (21). It inhibits inosine monophosphate dehydrogenase, the key enzyme in the *de novo* purine biosynthesis of proliferating T and B-lymphocytes. MMF acts as a highly specific inhibitor of human lymphocyte proliferation. MMF is more effective than azathioprine in combination with cyclosporine and corticosteroids and reduces the incidence of acute rejection episodes in the first year post-transplant in adults as well as in children (13, 31–34). A recent study showed superiority of MMF at 3 yr post-transplant (98% vs. 80%; $p < 0.001$) with a less episodes of acute rejection as acumulative acute rejection episodes occurred in 47% of patients in the MMF group vs. 61% in the azathioprine group ($p < 0.05$) (35).

A retrospective study of the NAPRTCS (36) database of 986 pediatric renal transplant recipients who were treated either with CyA, MMF and steroids ($n = 766$) or TAC, MMF and steroids ($n = 220$) revealed that Tac and CyA, in combination with MMF and steroids, produce similar rejection rates and graft survival in pediatric renal transplant recipients. However, Tac was associated with improved graft function at 1 and 2 yr post-transplant. There was no difference in time to first rejection, risk for rejection, and risk for graft failure or graft survival at the first year post-transplant or at 2 yr post-transplant. Tac-treated patients were significantly less likely to require antihypertensive medication at 1 and 2 yr post-transplant. At 1 yr post-transplant, Tac-treated patients enjoyed a higher mean GFR at both 1 yr (98.6 mL/min/1.73 m^2 vs. 78.0 mL/min/1.73 m^2, $p = 0.0003$) and 2 yr post-transplant (96.7 mL/min/1.73 m^2 vs. 73.2 mL/min/1.73 m^2, $p < 0.0001$).

Similarly in adults a multicenter, randomized trial of Tac plus MMF, Tac plus azathioprine and cyclosporine microemulsion plus MMF, patient and graft survival rates were almost the same in all groups; the incidence of rejection were 15, 17 and 20%, respectively and the incidence of steroid-resistant rejection were 4, 12 and 11, respectively. These data suggest that Tac plus MMF immunosuppression is quite effective (37). The same three immunosuppressive regimens were studied in another randomized trial by Ahsan et al. (38) who reported that the best results were achieved with Tac plus MMF. Patients with delayed graft function/acute tubular necrosis had a 23% increase in graft survival in the group of Tac plus MMF. At 2 yr post-transplant the tacrolimus group had a better renal function than the cyclosporine group.

Recently, Gonwa et al. reported 3 yr follow up 223 transplant adult recipients who were randomized to receive any of the three regimens (39). They found that patients with DGF who were treated with Tac + MMF experienced an increase in 3-yr allograft survival compared with patients receiving CyA + MMF (84.1% vs. 49.9%, $p = 0.02$). Patients randomized to either treatment arm containing Tac exhibited numerically superior kidney function when compared with CyA. The authors concluded that the combination of Tac and MMF might provide a particular benefit to kidney allograft recipients with DGF. In patients who experienced DGF, graft survival was better at 3 yr in those patients receiving Tac in combination with either MMF or azathioprine as compared with the patients receiving CyA with MMF. However, another study reported a better 2-yr renal allograft survival in living-donor recipients receiving CyA compared with Tac as initial immunosuppression in combination with MMF (40).

MMF is a very potent immunosuppressant and was reported to be associated with increase in gastrointestinal, hematological and infectious adverse events (13, 33, 41–43). There is a particularly increased risk of CMV infection (13, 33). PTLD was reported to be higher with the use of MMF in adults (13), however, this does not appear to be the case in the children as shown by the NAPRTC study of 197 patients who received both tacrolimus and MMF and none of them developed PTLD at day 30 post-transplantation (44).

MMF is particularly useful as initial therapy in patients with a special risk such as patients who had a typical HUS where the use of calcineurin inhibitor increases the risk of the post-transplant recurrence of HUS particularly in patients with factor H or von Willebrand factor-cleaving protease deficiency (45). It is also used as a rescue agent in the setting of chronic transplant nephropathy, where calcineurin inhibitors reduced slowly with the introduction of MMF (46).

Sirolimus and calcineurin inhibitor

Sirolimus (rapamycin or rapamune) is a new antiproliferative immunosuppressant. It is a

macrolide immunosuppressant that blocks the growth factor-driven transduction signals in the T-cell response to alloantigen. Sirolimus acts at a later stage in the T-cell mediated response than cyclosporine and other calcineurin inhibitors. It blocks the growth factor-driven proliferation of both hematopoietic and non-hematopoietic cells. These activities are complementary to those of cyclosporine and provide a rationale for the addition of sirolimus to cyclosporine-based immunosuppression, with the potential for minimizing calcineurin nephrotoxicity, reducing the incidence of acute rejection, and favoring long-term graft survival (47).

There is currently little published data on the use of sirolimus in the pediatric population (48–51). Early reports suggested that sirolimus might hold promise as a primary immunosuppressive agent in children under defined protocol conditions (51), with a particular advantage of enabling rapid withdrawal of calcineurin inhibitors (52).

In adults, large scale randomized studies showed that sirolimus in combination with cyclosporine is much more potent than azathioprine in renal transplantation (53, 54). While, only a limited experience is available on the combination of sirolimus with Tac, with reports of its efficiency in reducing rejection episodes (55). No large, randomized studies comparing cyclosporine plus sirolimus and Tac plus sirolimus immunosuppression have been performed and no conclusion could be drawn on the superiority of either of calcineurin inhibitors when used in combination with sirolimus (13).

Adverse events

Malignancy

There is no difference in the incidence of PTLD between Tac and cyclosporine microemulsion treated recipients when used in combination with azathioprine/steroids [1% (1/103) vs. 2.1% (2/93)] (19) or when used in conjunction with MMF/steroids (1.4% vs. 2%) (32). This is similar to adults, recent large, randomized studies could not show any difference in the incidence of malignancy between patients treated with Tac or cyclosporine (13, 14, 16).

Hypertension and hyperlipidemia

Hypertension is the most commonly reported adverse event in the European study where calcineurin inhibitors were used in conjunction with azathioprine and steroid. The administration of antihypertensive medication was similar in both groups; 88.3% in Tac group and 86.2% in the CyA group (19). However, in the NAPRTC study where calcineurin inhibitors were used in combination of MMF and steroid, Tac treated patients were significantly less likely to require antihypertensive medications at 1 and 2 yr post-transplant (36). This is similar to adults where a lower systemic blood pressure was reported in the Tac treated patients in several studies (13, 56).

The mean total cholesterol levels were reported to decrease in Tac group and increase in the CyA group at the end of 6 months in the European study (19). Similarly in adults, several studies have showed that lipid levels are much lower in Tac treated recipients than in cyclosporine treated patients (13). The improved lipid profiles, found in Tac treated recipients may contribute to a better long-term outcome.

Infectious complications

In the European, randomized trial comparing Tac and CyA in combination with azathioprine and steroid, there was no significant difference in the incidence of the infections during the first 6 months in both treatment groups with 68.9% (Tac) and 64.5% (CyA) (19). The comparable incidence of infections for patients receiving Tac and CyA was also observed in multicenter, randomized trials in adults (13, 14, 16, 37). Urinary tract infection was the most frequently reported infection in both pediatrics and adults studies (13, 19).

Linear growth and steroid-sparing effects

In the NAPRTC study, at 2 yr post-transplantation, Tac treated patients had a significantly higher delta height SDS; 0.37 in Tac patients vs. 0.11 in CyA patients ($p = 0.019$), although the difference was not statistically difference at 1 yr post-transplantation; 0.14 vs. 0.04 ($p = 0.738$) (36). Furthermore, as Tac exerts a much more potent immunosuppressive effect than CyA, steroid withdrawal seems to be safer in Tac-based than in CyA-based immunosuppression. The Pittsburgh group reported on steroid withdrawal under Tac immunosuppression in both adult and pediatric patients, which was achieved in over 90% of children and long-term steroid withdrawal was feasible in 70%. Five-year patient and graft survival in pediatric patients taken off corticosteroids were 96 and 82%, respectively (57).

Diabetogenicity

In the pediatric multicenter European study there was no difference in the incidence of new onset insulin-dependent DM between the Tac group (3%) and the CyA group (2.2%) (19). Although in early clinical trials of Tac, a significantly higher of DM was reported in Tac-treated adult patients than in CyA-treated recipients, the incidence of DM with Tac immunosuppression has become less frequent in recent randomized trials comparing Tac and CyA (13, 58, 59). Both reduction of corticosteroids dosage and the low target trough Tac concentrations contribute to the recent marked reduction of the incidence of DM under Tac immunosuppression in both adults and children (13).

Other adverse events

The incidence of hypomagnesaemia was significantly higher in Tac group (34%) compared with the CyA group (12.9%) ($p = 0.001$) (19). Similarly diarrhea was more frequent in Tac treated patients (13.6% vs. 3.2%, $p = 0.011$). Hypertrichosis, gum hyperplasia and flue syndrome were reported only in CyA group and tremor was reported only in Tac group (19). Those results are similar to adults where tremor is consistently more common with Tac and hirsutism and gum disease more common in CyA (13, 14, 16).

Conclusion

Tac and cyclosporine microemulsion have almost similar short-term patient and graft survival in the pediatric population. However, the incidence of acute rejection is lower in Tac treated patients when used with Azathioprine. The incidence of acute rejection is similar in CyA or Tac treated patients when used with MMF. Adverse events, such as hypertension, hyperlipidemia, gum hypertrophy and hypertrichosis seem to be less frequent in Tac-treated than CyA-treated patients. While diarrhea, hypomagnesaemia and tremor are reported more with Tac treated patients, no difference in the incidence of DM between Tac and CyA treated patients was observed. Liner growth seems to be better with Tac treated patients.

The recommendation drawn from the available data is that both CyA and Tac can be used safely and effectively in children. However Tac may be preferable to CyA because of steroid sparing effect and less hirsutism. We recommend that cyclosporine should be chosen when patients experience Tac-related adverse events. Nevertheless, clinicians should tailor immunosuppressive protocols to individual patients by optimizing dosages and drugs according to the maturation and clinical status of the child.

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