REVIEW ARTICLE

Immunosuppression in Paediatric Renal Transplant Patients

Rajendra Bhimma

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Introduction:

Renal transplantation is now the optimal treatment for many children with end-stage kidney disease. Effective immunosuppression is quintessential to successful kidney transplantation. Both national and international registries report 1-year graft survival rates of over 85% and this improvement in outcome has largely been dependent on developments in immunosuppressive therapy [1].

Although protocols for kidney transplantation are similar in both adults and children, there are nonetheless distinct differences. Children develop end-stage kidney failure at a much lower frequency than adults do and the diseases that result in kidney failure are substantially different [2]. Infants and young children cannot swallow pills and they metabolize at substantially different rates from adults. As a result, they frequently require special formulations and schedules [3,4,5,6]. Children also have unique medical and surgical requirements both before and following transplantation. Current all available immunosuppressive agents cause non-specific immunosuppression and hence increase the risk of infection and certain types of malignancy (skin cancer and post-transplant-lymphoproliferative disease). The latter has a much higher incidence in children compared to adults [7]. If these issues are specifically and carefully addressed, the outcome of kidney transplantation in children can parallel or even surpass that in adults [2]

Immunosuppressive Agents Used in Kidney Transplantations in Children:

An increasing number of immunosuppressive agents are available for use in both adult and paediatric kidney transplants and these target different steps of the immunological response to an allograft. Table 1 lists the most common immunosuppressive agents used in kidney transplantation.

Currently, the majority of paediatric transplant recipients are treated with some form of induction antibody [8]. Although presently no 'universal' protocol for immunosuppression in paediatric kidney transplant exists, current trends are towards early steroid withdrawal or directed at eliminating either steroids or calcineurin inhibitors, or both [9,10]. Another approach is to use robust induction therapy with alemtuzumab (Campath®), followed by eventual monotherapy with Tacrolimus [11,12].

Thus, although presently there is no clearly defined approach to immunosuppression in kidney transplantation for children, the eventual goal is to permit long-term graft survival and minimize side effects by the use of the fewest possible chronic medications.

A. Induction Therapy

(a) Polyclonal lymphocyte depleting antibodies.

The 2 polyclonal antibodies currently in use are Equine gamma globulin and anti thymocyte globulin. Equine

Table 1. Immunosuppressive agents used in solid organ transplantation

Class of agent	Agent
Corticosteroid	Prednisolone Prednisone Methyl-prednisone
Antiproliferative	Azathioprine Mycophenolate mofetil Mycophenolate sodium
Calcineurin Inhibitor	Cyclosporine Tacrolimus
TOR inhibitor	Sirolimus Everolimus
Polyclonal anti-lymphocyte antibodies	ALG ATG ALS
Monoclonal antibodies	Muromonab-CD3 Basiliximab Daclizumab

gamma globulin has to be given through a central catheter because of the sclerosing nature of the preparation. Calcineurin inhibitors are generally withheld during administration. The dose used is 15mg/kg per day. Thymoglobulin may be given through a peripheral line at a dose of 1.5-2mg/kg per day. A single centre study has shown that recipients of thymoglobulin have decreased incidence of acute rejections [13]. However, this result may be the reflection of the overall improved outcomes of kidney transplants in more recent cohorts of patients [8]. Anti-lymphocyte antibody preparations are still widely used to treat steroid resistant acute rejection episodes and are effective in 70-96% of patients [14,5,16,17]. If a second course of polyclonal antibody therapy is required in a patient, it is advisable to use a preparation obtained from a different species because of reduced efficacy resulting from the development of xeno-specific neutralizing antibodies.

(b) Monoclonal antibodies

(i) Monoclonal lymphocyte depleting antibodies

In comparison to polyclonal antibody preparations, monoclonal antibodies do not contain irrelevant proteins, are more standardised and have a single well-defined specificity. The two most widely used monoclonal lymphocyte-depleting antibodies are OKT3 and Alemtuzumab.

OKT3 is administered as a bolus injection into a peripheral vein daily for 10-14 days at a dose of 5mg per day for children >30kg and 2.5mg per day for children <30kg. Calcineurin inhibitors are withheld during the use of OKT3. Adverse effects include neurological problems [18] reactivation of viral infections such as cytomegalovirus and Epstein-Barr virus as well as 'first-dose reaction' [19,20]. Campath has been used in multiple uncontrolled pilot trials mainly in adult renal transplant recipients. Alemtuzumab was well tolerated, but some children had acute rejection episodes. This agent has been used more extensively in paediatric small bowel transplants [21]. Presently there is no recommended paediatric dosing for children undergoing kidney transplantation.

(ii) Monoclonal nondepleting antibodies
IL2-receptor antibodies
The two IL2-receptor antibodies presently used are basiliximab and daclizumab. These two high-affinity chimeric or humanized antibodies act on the inducible alpha chain of the interleukin-2 receptor (IL-2r) on the surface of the activated lymphocyte.

Basiliximab is given on day 0 and 4 post-transplant (generally 10mg for children <40kg and 20mg for those >40mg) [22]. One study showed that paediatric patients receiving basiliximab as induction therapy may have elevated cyclosporine levels and therefore would require reduced doses to avoid toxicity [23]. Induction with basiliximab in adult kidney transplant recipients has been induced to allow the successful early withdrawal of steroids [24] and even steroid avoidance albeit with a high incidence of rejection [25].

Daclizumab is generally given in a regimen of 1mg/kg intravenously on the day of transplantation and every 14 days thereafter for 5 doses [26]. Higher doses may be required for saturation of IL-2r in younger children [9].

Unlike OKT3, these antibodies do not produce a first-dose-reaction and have few side effects.

B. Maintenance Immunosuppression
(a) Corticosteroids
Corticosteroids are still widely used as an important component of most immunosuppressive regimens and are almost universally used as first line treatment for acute rejection. The North American Pediatric Renal Transplant Collaborative Study (NAPRTCS) reports shows that until recently, up to 96% of children who underwent kidney transplantation and still have a functioning graft were maintained in prednisone [8,27]. In most steroid based regimens the dosage is usually high in the immediate post-transplant period, approximately 2mg/kg//day (maximum 80mg), with a gradual reduction to approximately 0.2-0.3mg/kg/day within a 6-month to 1-year period.

Corticosteroids have a variety of anti-inflammatory and immunomodulatory effects [28]. These include stabilization of lysosomal membranes, suppression of prostaglandin synthesis, reduction of histamine and bradykinin release and lowering of capillary permeability. Anti-inflammatory effects are mediated mainly through induced production of cytokines, including IL-1, IL-2, IL-6, ILN- beta and TNF–beta and TNF-alpha. Corticosteroids impair monocyte/macrophage function and decrease the number of circulating $CD4^+$ T-cells.

The numerous mechanisms of action of corticosteroids lead to multiple side effects and toxicities. The major concern in children with respect to its long-term use in children is growth retardation. Studies have shown that doses in excess of 8.5mg/day will impair normal growth [29].

Other side effects include increased appetite with weight gain with Cushingoid facies, acne, glucose intolerance, hypertension, increased susceptibility to infection, impaired wound healing, aseptic necrosis of bone, cataracts, psychosis and peptic ulceration [30]. Sometimes there are consequences of the mineralocorticoid activity of these agents leading to fluid retention, hypokalemia and hypertension.

In view of these multiple side effects of maintenance steroid therapy, attempts are focused on early withdrawal or reduction of steroids or steroid avoidance [31]. Unfortunately the majority of these attempts have failed because of the development of acute rejection episodes [32,33,34]. Alternate day steroid therapy reduces its impact on growth inhibition and should be encouraged. IL-2r antibody has been used in steroid avoidance protocols, with low acute rejection rates and striking reduction in post-transplant complications. The Cooperative Clinical Trial in Paediatric Transplantation aimed at corticosteroid withdrawal showed acute rejection rates at 6 months to be very low. However the incidence of post-transplant lymphoproliferative disease was unacceptably high. In comparison, in the control group receiving chronic low-dose corticosteroids there was no higher rate of late rejection and long-term graft survival was similar in both groups [35]

(b) Antiproliferative agents
(i) Azathioprine
This was the first immunosuppressive agent approved for organ transplantation use. Azathioprine is metabolized to 6-mercaptopurine (6-MP) through reduction by glutathiamine, and then converted to 6-thiouric acid, 6-methyl-MP, and 6 thioguanine (6 TG). These compounds are incorporated into replicating DNA, halt DNA replication, and block the de novo pathway of purine synthesis by puration of thio-iosinic acid. This latter effect confers specificity of action on lymphocytes that lack a salvage pathway for purine synthesis.

For paediatric patients the dosage is 1-2mg/kg/day as a single dose. It can be used in combination with all other immunosuppressive agents except mycophenolate mofetil (MMF). The most serious side effects include skin cancers following chronic use, bone marrow suppression that is dose dependent and occasional liver impairment and cholestatic jaundice. Minor effects include hypersensitivity reactions manifesting as a rash [36].

(ii) Mycophenolate mofetil (MMF)
MMF and mycophenolate sodium (MPS) are rapidly converted in the liver to mycophenolic acid, which is the active compound. The target of mycophenolic acid is inosine monophosphate dehydrogenase (IMDPH). This is the rate-limiting enzyme in the de-novo synthesis of guanosine nucleotides, themselves essential for DNA synthesis. The majority of cells generate guanosine nucleotides by two pathways, the IMPDH pathway, and a salvage pathway; hence blockade of the IMPDH pathway results in relatively selective blockage of lymphocyte proliferation [37].

The recommended dose for paediatric patients is $1200mg/m^2$/day, divided in two, three, or four doses [38]. Although therapeutic monitoring is available, current standards in paediatric patients are not yet available to guide treatment [39,40,41,42,43,44]. MMF must not be used in combination with azathioprine.

The most common dose limiting adverse effects is diarrhoea. Other gastrointestinal side effects include nausea, vomiting and abdominal pain. Bone marrow suppression also occurs. Some clinical trials have shown an increased incidence of viral infections (CMV, herpes simplex) and candida [45].

Analysis of large databases of renal transplant recipients have shown decreased incidence of chronic allograft nephropathy with improved long-term renal graft function in patients on MMF [46,47].

(c) Calcineurin inhibitors
(i) Cyclosporine

The mechanism of inhibiting T-cell activation by calcineurin inhibitors (CNI) is well-understood [48]. After entering the cytoplasm, CNIs form complexes with their immunophilins. Cyclosporine binds to cyclophilin and Tacrolimus and Pimecrolimus bind to the 12 kDa FK 506-binding protein (FKBP-12). The CNI-immunophilin complexes inhibit calcineurin activity, and hence prevent nuclear translocation of NF-AT and cytokine gene transcription. The net result is that CNIs block the production of cytokines and as IL-2 and inhibit T cell activation and proliferation.

For induction purposes, cyclosporine is given intravenously in a dosage of 165mg/m^2/day in children over 6 years of age, and 145mg/m^2/day should be given as a continuous infusion over a 24-hour period starting intraoperatively. Induction therapy should be continued only for 48 hours and then converted to oral cyclosporine. The recommended starting oral dose for children less than 6 years old is 500mg/m^2/day, administered in three divided doses. The doses given in children are much higher than in adults as the drug is metabolized more rapidly in children [5]. Calcium channel blockers are used concomitantly to reduce nephrotoxicity [49]. The irregular absorption and inherent nephrotoxicity of the drug makes drug monitoring and adjustment essential. In the first three months whole blood trough levels measured by high-pressure liquid chromatography should be maintained between 200-250 mcg/ml, then between 100-200 mcg/ml in patients after 3 months. More recent data suggest that measuring the level 2 hours after receiving the dose may lead to more accurate dosing, assessing the true area under the curve and avoiding toxicity [50,51,52].

Many of the side effects of CNIs are dose dependent and relate to the sites where calcineurin concentrations are highest, notably the brain and kidney [53]. Nephrotoxicity is mainly due to severe vasoconstriction of the afferent arteriole, with concomitant reduction in renal blood flow and glomerular filtration rate [54,55,56]. Long-term use of CNIs leads to interstitial fibrosis and obliterative arteriolar changes due to fibrosis intimal thickening in the kidneys; changes that are non-reversible [57]. Because of its renal effects, hypertension is a common side effect of CNIs [58]. The neurotoxicity of CNIs are more common with tacrolimus than cyclosporine and are exacerbated by hypomagnesaemia [59]. Neurotoxic effects include headaches, tremors, agitation, convulsion, psychosis, hallucinations, encephalopathy, and impaired consciousness [60].CNIs also have metabolic effects that include hyperglycemia, hyperkalemia, hyperuricemia, and hyperlipidemia. Hyperglycaemia is two to four times more common with Tacrolimus than cyclosporine, and may also reflect different sensitivity to the diabetogenic effects of corticosteroids [61,62]. Other side effects of CNIs include hyperplasia and hypertrichosis that are drug specific side effects of cyclosporin. Alopecia on the other hand may accompany Tacrolimus use [63].

Cyclosporin has been used in combination with all other immunosuppressive agents except tacrolimus. However, because of the potential increased risk of post transplant lymphoproliferative disease (PTLD), the use of a combination of a calcineurin inhibitor, rapamycin and corticosteroids should probably be avoided, particularly in high-risk children [64].

(ii) Tacrolimus

Tacrolimus is presently being increasingly used in paediatric renal transplant [65]. When compared to cyclosporin, patient and graft survival at 2 years using tacrolimus are equivalent [66]. Tacrolimus use is associated with a lower incidence of acute rejection and improved graft function. Children treated with tacrolimus had a lower incidence of rejection (9.7% vs. 18.3%) at 2 years.

Induction therapy is given as a continuous infusion using a dose of 0.1mg/kg/24 hours, with a switch to oral therapy within 2-3 days. Sometimes the drug is commenced via nasogastric tube using the oral preparation because it has very good absorption. Initial oral doses should not exceed 0.15mg/kg twice daily and should not exceed 0.1mg/kg as maintenance dose. Monitoring trough blood levels is essential because of its nephrotoxicity. Recommended trough levels are between 10-20 mcg/l in the first 3 months and therefore between 7-12 mcg/l up to 12 months and then maintained at 5-7 mcg/l.

In view of the similar mechanism of action with cyclosporine, the side-effect profile of tacrolimus is similar to that seen with cyclosporine [67]. Hypertrichosis and the dysmorphic features like gum hypertrophy seen with cyclosporine use are not seen with tacrolimus [68].

Nephrotoxicity is seen similar to cyclosporin use [69]. Neurological side effects are common and may be seen more frequently than with cyclosporine [59,70]. Tacrolimus treated patients have a higher incidence of post transplant lymphoproliferative disease and hyperglycaemia [71,72]. However, with lower doses the incidence of post transplant lymphoproliferative disease has significantly decreased [73].

Tacrolimus can be used in combination with all other immunosuppressants except cyclosporine. Combination with rapamycin and corticosteroids should be used with caution in children with a higher risk of developing post transplant lymphoproliferative disease [64].

(d) Mammalian target of rapamycin (mTOR) inhibitors

Sirolimus and everolimus are the newest immunosuppressive agents being used for kidney transplant. Both are macrocyclic lactones, with sirolimus being a naturally occurring fermentation product of the actinomycete *streptomyces hygroscopicus,* while everolimus represents a chemical modification of sirolimus to improve

absorption.
TOR is a cytoscolic enzyme that regulated differentiation and proliferation of lymphocytes. Inhibition of mTOR has a profound effect on the cell signaling pathway required for cell-cycle progression and cellular proliferation. The net effect is blockade of T-cell activation by preventing progression of the cell cycle from the GI to the S phase. The TOR inhibitors bind to the immunophillin
FKBPI2 inhibits the actions of TOR [74,75,76,77,78,79]. TOR inhibitors may be particular important in long-term immunosuppression since they stimulate T-cell apoptosis. They inhibit mesenchymal proliferation, an important factor in graft vascular disease [80,81]. mTOR also inhibits fibroblast growth factors required for tissue repair thus resulting in impaired wound healing.

Rapamycin is available as either a solid or a liquid oral preparation. Although in adults a single dose may suffice to maintain therapeutic levels, in children it has a much shorter half-life and thus necessitates twice-daily dosaging [6]. Recommended therapeutic levels in children remain speculative and range from 12-25ng/ml in the early post-transplant period without calcineurin inhibitors and 4-12ng/ml with calcineurin inhibitors [6,82]. After the early post-transplant period (>3-6months), levels are maintained between 5-10ng/ml. Lower therapeutic levels are desired when used with calcineurin inhibitors because of enhanced nephrotoxicity.

Side effects of mTOR inhibitors include metabolic, haematological, dermatological effects and effects related to growth factor inhibition [83,84]. The most common side effects of rapamycin include hyperlipidaemia, thrombocytopenia, leucopenia and delayed wound healing [85]. Dermatological side effects include acne and mouth ulcers. Another side effect that is being increasingly seen is interstitial pneumonitis, which appear to be dose related and resolves with drug withdrawal [89]. Peripheral oedema, diarrhoea and lymphocele formation post renal transplant are also well recognized complications [87]

Rapamycin has been found to be effective in combination with calcineurin inhibitors [88,89,85,90,91] in a calcineurin-inhibitor sparing protocol [83] and in a steroid-free protocol [92].

C. Novel Immunosuppressant Agents

Several new biological agents are in various stages of development for the purposes of replacing maintenance therapy with calcineurin inhibitors and steroids [7]. Table 2 shows the list of some of these new agents and their status in transplantation.

Currently, only LEA29YT (belatacept) is in phase III trials. Whilst the co-stimulatory pathway is emerging as an important therapeutic area for immunosuppression therapy, other promising targets include interleukin-15 and adhesion molecules [3].

Costimulation signal is provided by engagement of one or more T-cell surface receptors with their specific ligands on antigen presenting cells. Signaling through the T-cell receptor alone without a costimulatory signal can lead to a prolonged state of T-cell energy [93]. Presently the only agent used in clinical trials in adult kidney transplant recipients, which blocks co-stimulation is belatacept [94]. This agent is typically administered intravenously on a once-per-month schedule. The results showed decreased incidence of acute rejection at 6 months (6-8%), improved glomerular filtration rate at 12 months (62-66ml/1.73m^2/min) and decreased incidence of chronic allograft nephropathy. There were 3 episodes of post-transplant lymphoproliferative disease, two of which were related to primary Epstein-Barr virus infection. Thus the concern regarding its use in children is the potentially higher risk of post-transplant lymphoproliferative disease. However, this has to be balanced agents its potential benefit of improving compliance since it is administered monthly, particularly in adolescents.

Table 2 Biologic agents in the transplant pipeline

Antibody	Pharma/Biotech	Status
LEA29Y	Bristol Myers	Phase III trial
Efalizumab*	Xoma-Genetech	Phase II
Alemtuzumab*	Genzyme	IS
Rituximab	Genentech	IS
mIL-5/Fc	Roche	Preclinical
Anti-IL-15	Amgen	Preclinical
Anti-CD40	Bristol Myers Chiron Novartis	Preclinical Preclinical Preclinical

IS - investigator initiated trials.
** US Food and Drug Administration (FDA) approved for other indications*
Adapted from: Vincenti F, Hirose R. Novel Immunosuppressants. In: Fine RN, Weber SA, Olthoff KM, Kelly DA, Harmon WE, eds. Pediatric Solid Organ Transplantation, 2nd Edition. Massachusetts USA: Blackwell Publishing Ltd. 2007: 89-94.

Conclusion

To date the majority of paediatric renal transplant recipients are treated with triple immunosuppression [95]. The increasing number of agents available has increased the number of combinations and to date there are over 60 possible reported protocols [96]. These large number of protocols bear testimony to the fact that there is no single defined approach to immunosuppression for children. The final common goal is to achieve long-term graft acceptance with the fewest possible chronic medication.

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From: Department Of Maternal & Child Health, Nelson R Mandela School Of Medicine, University Of Kwazulu-Natal, Durban, South Africa.

Address for Correspondence: Rajendra Bhimma, Department Of Maternal & Child Health, Nelson R Mandela School Of Medicine, University Of Kwazulu-Natal, Private Bag 7, Congella, 4013, Durban, South Africa. E-mail : bhimma@ukzn.ac.za