Mammalian Target of Rapamycin (mTOR) Inhibitors in Pediatric Kidney Transplantation "A Systematic review"

Thesis

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﴿وَقُلْ رَبِّ زِدْنِي عِلْمًا﴾

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ABSTRACT

Key words: (mTOR – sirolimus – everolimus – kidney transplantation)

Kidney transplantation is the treatment of choice for most patients with end-stage renal disease (ESRD). Strategies to increase donor organ availability and to prolong the transplanted kidney's survival have become priorities in kidney transplantation. Current success in pediatric renal transplantation is mostly attributed to improvement in immunosuppressive therapy, and the provision of age – appropriate clinical care. This review aimed to evaluate the short and long-term benefits and harms of mammalian target of Rapamycin (mTOR) inhibitors; Sirolimus and Everolimus when used in primary immunosuppressive regimens for kidney transplant recipients.

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ABBREVIATIONS

ACE	Angiotensin converting enzyme
APC	Antigen presenting cell
ATG	Antithymocyte globulin
ATN	Acute tubular necrosis
AZA	Azathiprine
BAS	Basiliximab
BPAR	Biopsy-proven acute rejection
BUN	Blood urea nitrogen
CAN	Chronic allograft nephropathy
CBC	Complete blood count
CCTPT	Cooperative Clinical Trials In Pediatric Transplantation
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CSA	Cyclosporine
CVP	Central venous pressure
CXR	Chest X ray
CYP	Cytochrome p
DAC	Daclizumab
DGF	Delayed graft function
DIC	Disseminated intravascular coagulopathy
EBV	Ebstein-barr virus
ECG	Echo cardigram
EC-MPA	Enteric coated mycophynolic acid
ELISA	enzyme linked immunosorbent assay
ESRD	End-stage renal disease
GCSF	Granulocyte colony stimulating factor
GFR	Glomerular Filteration Rate
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus

HLA	Human leukocytic antigen
HPLC	High-performance liquid chromatography
HPV	Human papilloma virus
HSV	Herpes simplex virus
HTLV-1	Human T-lymphotropic virus type I
HTN	Hypertension
IFTA	Interstitial fibrosis and tubular atrophy
IGF	Insulin-like growth factor
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-2r	Interlukin 2 receptor
IQ	Intelligence quotient
IV	Intravenous
IVP	Intravenous pyelogram
IVIG	Intravenous immunoglobulin
LVH	Left ventricular hypertropy
MAP	Mitogen-activated protein
MCH	Major histocompitability complex
MMF	Mycophenolate mofetil
MMR	Mumps – Measels – Rubella
M-TOR	mammalian target of rapamycin
NAPRTCS	North North American Pediatric Transplant Cooperative Study
CS	Cooperative study
PCR	Polymerase chain reaction
PTDM	Post-transplant diabetes mellitus
PTH	Parathyroid hormone
PTLD	Post-transplant lymphoproliferative disease
PTT	Partial thromboplastin time
RCT	Randomized controlled trial
rhGH	Recombinant human growth hormone

RPR	Rapid plasma reagin
SDS	Standard deviation score
TAC	Tacrolimus
TB	Tuberculosis
TCR	T cell receptor
TT	Thrombin time
UTI	Urinary tract infection
VDRL	Verereal disease research laboratory
VZIG	Varicella-zoster immunoglobulin
VZV	Varicella-zoster virus
WOFIE	Window Of Opportunity For Immunologic Engagement

INTRODUCTION

End-stage renal disease (ESRD) is a rare but important health problem among children ***(Danovitch, 1996).*** Kidney transplantation is universally accepted as the therapy of choice for children with ESRD ***(USRDS, 2005)***. Successful transplantation not only ameliorates uremic symptoms, but also allows for significant improvement of delayed skeletal growth, sexual maturation, cognitive performance and psychological functioning ***(Fine et al., 2001).***

Current success in pediatric renal transplantation is mostly attributed to improvement in immunosuppressive therapy, and the provision of age – appropriate clinical care ***(Ghio et al., 2003).*** One-year renal graft survival is now in the order of 90% ***(UNOS, 2005)***, but ensuring very long-term graft survival (i.e up to 10 years) remains a challenge. Chronic allograft nephropathy is the main cause of graft loss ***(Racusen et al., 1999)*** and nephrotoxic effects associated with the calcineurin inhibitors have been proposed to be a major factor in chronic allograft nephropathy ***(Weir et al., 2001).***

Optimal immunosuppression requires a balance between the competing challenges of acute rejection associated with inadequate immunosupression and the risk of excessive immunosuppression with resulting infection, malignancy and drug associated side-effects ***(Gonin, 2000)***.

Calcineurin inhibitors (CNIs) exhibit significant toxicity, including nephrotoxicity, increased cardiovascular risk factors and neoplastic potentials. Cyclosporine (CsA) withdrawal has been used as a strategy to

improve renal allograft function and other CsA-related toxicities. The mTOR inhibitors are used either de novo or as a substitute for CNIs after renal transplantation. The mTOR inhibitors have a different mode of action and a different side effect profile than the CNIs ***(Eric Thervet, 2006)***, ***(Christian et al., 2007)***. It presents a good immunosuppressive efficacy associated with antiproliferative actions. Early withdrawal of CsA with mTOR introduction is associated with a significant improvement of renal function. Complete CsA avoidance has been already reported and is currently under clinical investigation ***(Eric Thervet, 2006)***.

Aim of the work:

The aim of this study is to determine the current best evidence regarding the use of mammalian target of Rapamycin (mTOR) inhibitors; Sirolimus and Everolimus, in pediatric kidney transplantation.

CHAPTER I

End Stage Renal Disease in Children

Epidemiology of end stage renal disease in children:-

Data from the United States Renal Data System (USRDS) revealed that in pediatric patients, the annual incidence of end stage renal disease (ESRD) increased marginally from 13 per million of the age-related population (MARP) in the 1988 cohort to 15 per MARP in the 2003 cohort, this is in contrast to the adult incidence rate of 119 per MARP for patients 20-44 years of age and 518 per MARP for those 45-64 years old in the 2003 cohort ***(United States Renal data system, 2005).***

The highest estimated incidences for ESRD in children were reported in the United States, New Zealand, and Austria with annual rates of 14.8, 13.6 and 12.4 per million children, respectively ***(Warady and Chadha, 2007)***. The lowest annual incidence of ESRD was reported in Japan with a rate of 4 per million children at or below 19 years of age.

Due to lack of national registries, the incidence and prevalence data from developing countries primarily originates as reports from major tertiary care referral centers ***(Hari et al., 2003).***

A number of factors influence incidence and prevalence rate variability of childhood ESRD. Factors such as racial and ethinic distribution, type of prevalent renal disease and quality of medical care available for preterminal chronic kidney disease (CKD) patients have a significant impact on patient outcome ***(Warady and Chadha, 2007).***

For race, the incidence rate for ESRD in black children in North America is two to three times higher than for white children, irrespective of gender ***(United States Renal Data System, 2001)***. Also, the incidence and prevalence rates are universally greater for boys than for girls ***(Ardissino et al., 2003)*.**

Etiology of CKD in children:-

Unlike adults in whom diabetes and hypertension are responsible for the majority of CKD, congenital causes are responsible for the greatest percentage of all cases of CKD seen in children. However, whereas this is the most common reported etiology from developed countries where CKD is diagnosed in its earlier stages, infectious or acquired causes predominate in developing countries, where patients are referred in the later stages of CKD ***(Warady and Chadha, 2007)*.**

In the chronic renal impairment (CRI) registry arm of North American pediatric renal transplant Cooperative study (NAPRTCS), almost one half of the cases are accounted for by patients with the diagnoses of obstructive uropathy (22%), Aplasia/hypoplasia/dysplasia (18%), and reflux nephropathy (8%). Whereas structural causes predominate in the younger patients, the incidence of glomerulonephritis (GN) increases in those older than 12 years. Among the individual glomerular causes, only focal segmental glomerulosclerosis (FSGS) accounts for a significant percentage of patients (8.7%), Whereas all other glomerulonephritides combined contribute less than 10% of the causes of childhood CKD. for reasons that are as yet not clear, FSGS is three times more common in blacks than in whites (18% vs.6%) and is particularly

common among black adolescents whit CKD ***(North American Pediatric Renal Transplant Cooperative Study, 2005).***

In the ESRD population reported by the European dialysis and transplant association (EDTA) registry, hypoplasia/dysplasia and hereditary diseases were the most common causes for ESRD in the 0- 4 year age group, whereas GN and pyelonephritis became progressively more common with increasing age in the majority of reporting countries ***(van der Heijden et al., 2004).***

Renal replacement therapy:-

Once the estimated GFR declines to less than 30 ml/min per 1.73 m2 (stage 4 CKD), it is time to start preparing the child and the family for renal replacement therapy ***(National Kidney Foundation, 2002).***

The choice of replacement therapy in children is variable. The registry of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reports that of patients initiating renal replacement therapy in pediatric centers: One quarter of children underwent preemptive renal transplantation, one half were started on peritoneal dialysis and one quarter were started on hemodialysis ***(Seikaly et al., 2001)***.

The high incidence of preemptive renal transplantation in children is in part due to having parents who are a half haplotype match, are relatively young and healthy, and are willing to donate a kidney. In addition, pediatric nephrologists frequently follow their patients from the early stages of CKD and can prepare the patient and their family for transplantation and avoid initiating dialysis ***(Seikaly et al., 2001).***