Comparative study between different immunosuppressive treatment regimens and acute rejection in renal transplant recipients in Nasr City Insurance Hospital

Thesis

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INTRODUCTION

Kidney transplantation is renal replacement modality of choice for ESRD and is associated with lower mortality and improved quality of life compared with chronic dialysis treatment however, this is therapy not without challenges and risks recipient need to continue to take immunosuppressive drugs for the rest of their life to prevent allograft rejection and this trades the morbidity and mortality of organ failure of infection and cancer ***(Tonelli et al., 2011).***

With the use of potent immunosuppressive agents immediately following and in the maintenance phase after renal transplantation, the incidence of acute rejection, generally defined as rejection within the first year following transplantation, has fallen dramatically over time, with current immunosuppressive protocols, acute rejection rates have fallen to approximately 10 percent at most transplant centers ***(Matas, et al., 2014).***

Acute renal allograft rejection is a major cause of allograft dysfunction, there has been a dramatic reduction in the incidence of acute rejection due to the introduction of potent immunosuppressive drugs in the past three decades, however optimizing immunosuppression to both prevent allograft rejection and minimize drug toxicity, infection, and malignancy remains challenging ***(Chon.et al., 2014).***

Acute renal allograft rejection is defined as an acute deterioration in allograft function that is associated with specific pathologic changes in the graft there are two principal histologic forms of acute rejection : acute cellular rejection, which is characterized by infiltration of the allograft by lymphocytes and other inflammatory cells and acute antibody-mediated rejection, the diagnosis of which requires morphologic evidence of acute tissue injury, circulating donor-specific alloantibodies, and immunologic evidence of an antibody-mediated process (such as C4d deposition in the allograft). Cellular infiltrates may not be present, it may be difficult to distinguish between acute antibody-mediated rejection and severe acute cellular rejection, and the two processes may also coexist ***(Chon.et al., 2014).***

The advent of calcineurin inhibitors and anti-proliferative agents has dramatically lowered the incidence of acute rejection, maintenance immunosuppressive therapy is administered to renal transplant recipients to prevent acute rejection and the loss of the renal allograft ,although an adequate level of immunosuppression is required to dampen the immune response to the allograft, the level of chronic immunosuppression is slowly decreased over time to help lower the overall risk of infection and malignancy; these risks directly correlate with the degree of overall immunosuppression. The major immunosuppressive agents that are currently being used in various combination regimens are corticosteroids (primarily oral prednisone), azathioprine, mycophenolate mofetil (MMF), mycophenolate sodium (Myfortic), cyclosporine , tacrolimus, everolimus, and rapamycin (sirolimus) ***(Hardinger.et al., 2014).***

AIM OF THE WORK

To study the prevalence of the acute rejection episodes and influence on renal graft and patient survival in relation to different immunosuppressive treatment regimens in renal transplant recipients in Nasr City Insurance Hospital.

LIST OF ABBREVIATIONS

Abbrev.	Full term
ACR	Acute cellular rejection
ARDS	Acute respiratory distress syndrome
ATN	Acute tubular necrosis
ATG	Antilymphocyte globulin
AMR	Antibody-mediated rejection
ANCA	Antineutrophil cytoplasmic antibody
AP-1	Activator protein 1
APCs	Antigen-presenting cells
AUC	Area under concentration-time curve
BENEFIT	Belatacept Evaluation of Nephro-protection and Efficacy as First-Line Immunosuppression Trial
BKV	BK polyoma virus
BMI	Body mass index
BPH	benign prostatic hyperplasia
CTLs	Cytotoxic T- lymphocytes
CTLA-4	cytotoxic T-lymphocyte antigen4
CNIs	Calcineurin inhibitors
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CRs	Corticosteroid receptors
CsA	Cyclosporine A
CsA-ME	Cyclosporine A microemulsion
CSF	Colony-stimulating factor
CVD	Cardiovascular disease

LIST OF ABBREVIATIONS (Cont....)

Abbrev.	Full term
CYP3A4	Cytochrome P450 3A4
C4d	Complement component 4 d
DCs	Dendritic cells
DGF	Delayed graft function
DM	Diabetes mellitus
DTH	Delayed-type hypersensitivity
DSA	Donor-specific antibody
EBV	Epstein-Barr virus
ECD	extended criteria donor
EC-MPS	enteric-coated mycophenolate sodium
ESRD	End stage renal disease
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FSGS	Focal segmental glomerulosclerosis
FKBP12	FK-binding protein 12
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GI	gastrointestinal intolerance
GMP	guanosine monophosphate
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HPLC	High-performance liquid chromatography

LIST OF ABBREVIATIONS (Cont....)

Abbrev.	Full term
HSV	Herpes simplex virus
HSP	heat shock protein
HTN	Hypertension
IFTA	Interstitial fibrosis and tubular atrophy
IFN-γ	interferon-γ
IVIG	intravenous immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL1	Interleukin 1
IL2	Interleukin 2
IL2-RA	Interleukin-2 receptor antagonist
IκB	inhibitor of nuclear factor κB
IMPDH	inosine monophosphate dehydrogenase
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KTR	Kidney transplant recipient
MAC	membrane attack complex
mAbs	monoclonal antibodies
MHC	Major Histocompatibility Complex
MMF	Mycophenolate mofetil
MMDC	monocyte, macrophage, and dendritic cell
MPA	Mycophenolic acid
MPGN	Membranoproliferative glomerulonephritis

LIST OF ABBREVIATIONS (Cont....)

Abbrev.	Full term
MRPR2	multidrug resistance–related protein 2
mTOR	mammalian target of rapamycin
mTORi	Mammalian target of rapamycin inhibitor(s)
NAT	Nucleic acid testing
NF-κB	nuclear factor κB
NF-AT	nuclear factor of activated T cells
NK cells	natural killer cells
OKT3	Muromonab (anti–T-cell antibody)
PRA	panel reactive antibody
PTCs	peritubular capillaries
PTH	Parathyroid hormone
PTLD	Post-transplant lymphoproliferative Disease
PML	progressive multifocal leukoencephalopathy
PPIs	proton pump inhibitors
RAS	renin-angiotensin system
rATG	rabbit antithymocyte globulin
RIA	radioimmunoassay
SRTR	Scientific Registry of Transplant Recipients
SLE	systemic lupus erythematosus
TCMR	*T cell–mediated rejection*
TMA	thrombotic microangiopathy
Tregs	T regulatory cells
TNF-α	tumor necrosis factor α

Transplantation immunology

The mammalian immune system is an extraordinarily complex system that has developed in response to evolutionary stressors provided by co-existence with micro-organisms over millions of years, the system can be divided into two components: ***Natural immunity***, which refers to the nonspecific immune response, ***Adaptive immunity***, which refers to the response to a specific antigen In organ transplantation, the principal target of the immune response to the graft are the Major Histocompatibility Complex (MHC) molecules expressed on the surface of donor cells (allo-MHC); this feature is a form of adaptive immunity ***(Wyburn et al., 2005).***

Important to an effective immune response is the ability of T cells to recognize a wide variety of non-self antigens, which allows for restrained immune activation and subsequent antigen-specific killing, this is accomplished through the generation of a diverse repertoire of T cells in a single individual with specificity for an enormous number of potential foreign antigens presented as peptides on the surface of major histocompatibility complex (MHC) molecules. Variations in MHC structure from individual to individual increase the variety of peptides that can be presented to T cells, which protects the species as a whole by ensuring adequate T cell responses to a given foreign organism in at least one member of the population. Although slight, these MHC polymorphisms are recognized as foreign after kidney transplantation between non– genetically identical humans and induce allo-responses that in the absence of immunosuppression result in rejection of the allograft (see Box 1 for graft terminology) (***Heeger and Dinavahi, 2012).***

Graft Terminology

Autograft (autologous graft): A graft from one part of the body to another. Examples include skin and vascular grafts. No rejection occurs.

Isograft (isogenic or syngeneic graft): A graft from one member of a species to a genetically identical member of the same species. Examples include grafts between identical twins and between members of the same inbred rodent strain. No rejection typically occurs.

Allograft (allogeneic graft): A graft between nonidentical members of the same species. Examples include grafts between unrelated or related nonidentical humans and between members of different inbred rodent strains. Rejection occurs by lymphocytes reactive to alloantigens on the graft (i.e., alloresponse).

Xenografts (xenogeneic grafts): A graft between members of different species. Examples include pig or baboon to human, and rat to mouse. Rejection occurs by lymphocytes reactive to xenoantigen on the graft (i.e., xenoresponse).

Box -1: Graft terminology (Richard et al., 2010).

The immunologic responses after kidney transplantation occur in well-defined stages, ***(Heeger and Dinavahi, 2012)*** as depicted in ***Figure -1***. ***(Richard et al., 2010)***

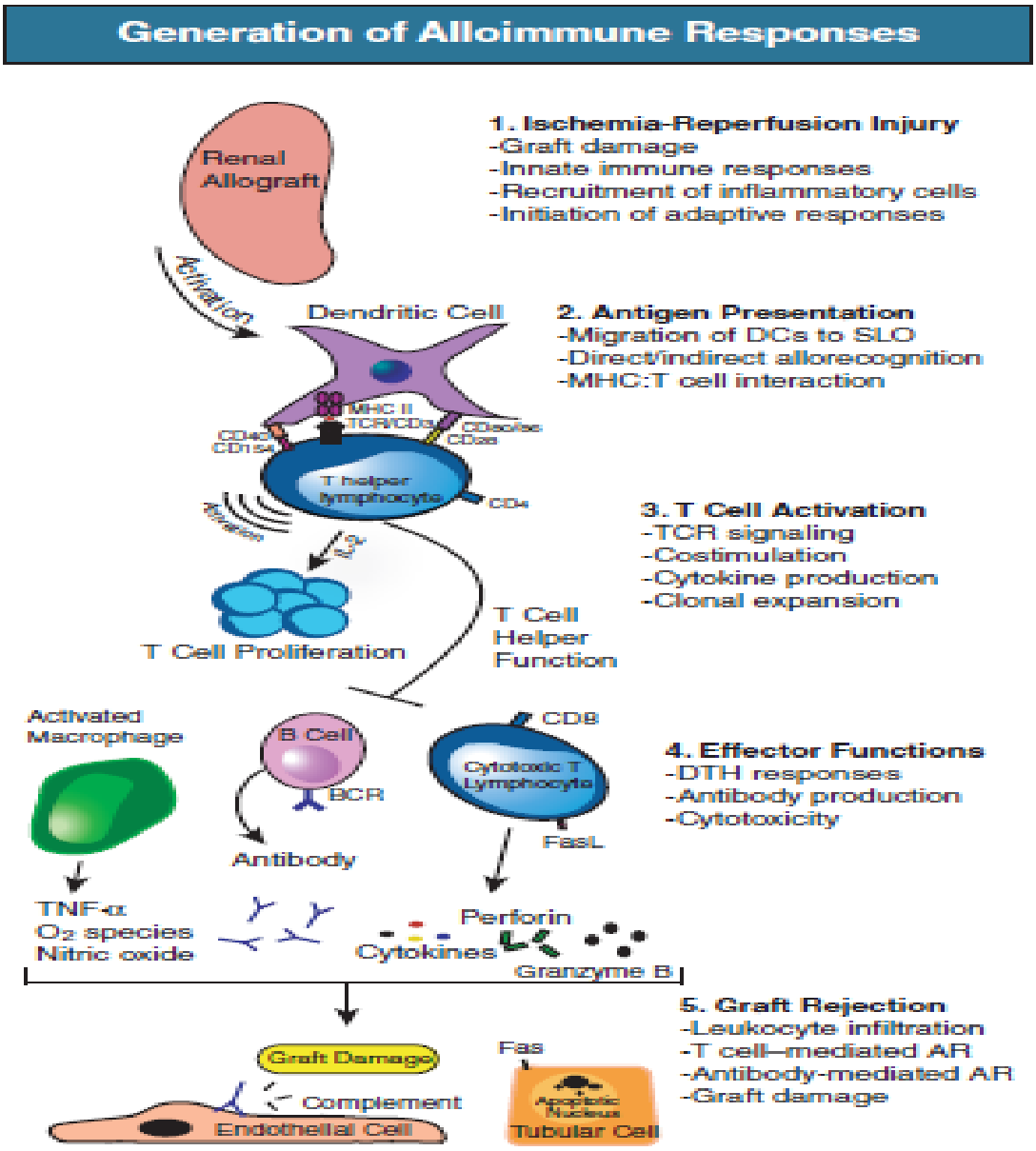

***Figure-1*:** Generation of alloimmune responses. Immunologic responses after renal transplantation represent a series of well-defined stages that result in rejection of the allograft in the absence of exogenous immunosuppression. Graft damage after ischemia-reperfusion injury during procurement and transplantation activates innate (antigen-nonspecific) immune responses, which recruit inflammatory cells and initiate adaptive (antigen-specific) immune responses. After activation, dendritic cells (DCs) of donor (direct pathway) or recipient (indirect pathway) origin migrate to secondary lymphoid organs (SLO), where they present alloantigen to T cells through major histocompatibility (MHC) structures on their cell surface. Following T cell receptor (TCR) signaling and appropriate costimulation, T cells become activated to produce large amounts of cytokine and undergo clonal expansion. CD4 T cells provide help to B cells, CD8 T cells, and macrophages for the production of alloantibody, cellular cytotoxicity, and delayed-type hypersensitivity (DTH) responses, respectively. These effector functions result in destruction of the graft by acute rejection, which may be T cell and/or antibody mediated. AR, Acute rejection; IL-2, interleukin-2; TNF-α, tumor necrosis factor α.