IMMUNOSUPPRESSION AND LIVER TRANSPLANTATION

An Essay
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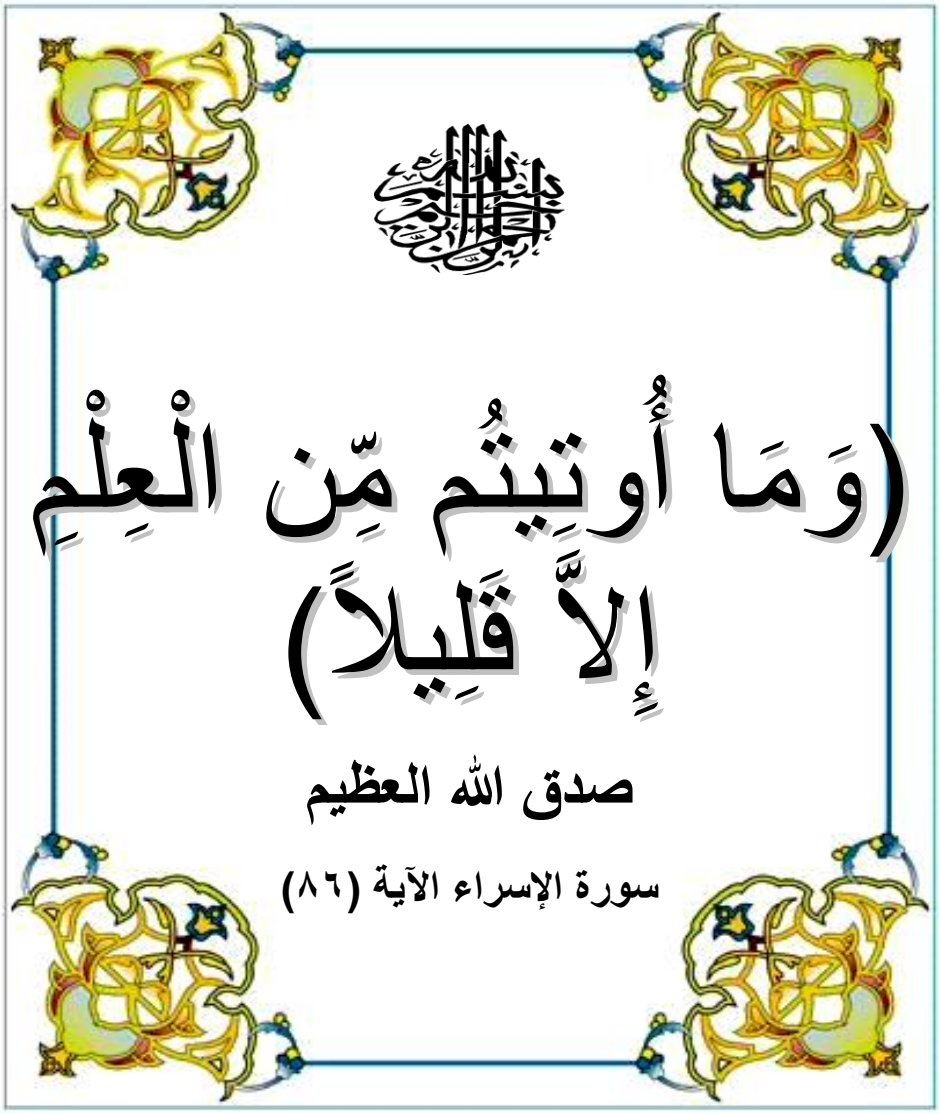

(وَمَا أُوتِيتُم مِّن الْعِلْمِ إِلاَّ قَلِيلاً)

صدق الله العظيم

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List of Abbreviations

ACR..... Acute cellular rejection

ALF..... Acute liver failure

APC ..... Antigen presenting cell

APC ..... Antigen-presenting cells

ATG..... Antithymocyte globulin

AZA ..... Azathioprine

CNI..... Calcineurin inhibitors

CS..... Corticosteroids

Csa ..... Cyclosporine

CYP ..... Cytochrome P

DDLT..... Deceased-donor liver transplantation

ECD ..... Extended criteria donor

Fc ..... Fragment crystalline

FKBP..... FK Binding protein

IMP..... Inosine monophosphate

IMPDH..... Inosine monophosphate dehydrogenase

IS..... Immunosuppression

JAK..... Janus activated kinases

LDLT..... Live-donor liver transplantation

LT ..... Liver transplantation

MELD..... Model for End-stage Liver Disease

MMF..... Mycophenolate mofetil

MPA..... Mycophenolic acid

MPAG ..... Mycophenolic acid glucuronide

mTOR..... mammalian target of rapamycin

OPTN..... Organ Procurement and Transplantation Network

PAP..... Pulmonary artery pressure

PTLD..... Post transplant lymphoproliferative disease

SIP Sphingosine-١-phosphate

STAT ..... Signal transcription and activation of transduction

TCR ..... T cell receptor

UNOS..... United Network for Organ Sharing

Introduction

Prior to the availability of liver transplantation, the management of end stage liver diseases was limited to correction and control of the complications associated with cirrhosis. However, liver transplantation has become now the treatment of choice for patients with end-stage acute or chronic hepatic diseases. The indications for liver transplantation are increasing and the number of absolute contraindications is decreasing. In the coming years, an increase in the number of transplant candidates can be expected ***(Groth, 2008)***.

Survival is excellent on both the short and long term, with patient survival rate of approximately ٨٥٪ one year after surgery. These remarkable results can be attributed to multiple factors including advances in intraoperative anaesthetic management, surgical techniques, better understanding of immunosuppressive therapy and the introduction of new agents to treat the post-transplant infectious complications ***(Geissler and Schlitt, 2009)***.

Effective immunosuppression in transplantation relies on preventing the immune system from rejecting the transplanted liver while preserving immunologic control of infection and neoplasia. Ideally, the long-term objective is to alter the recipient's immune system in order to promote long-term graft function without immunosuppressive therapy, while maintaining

immunity to infectious agents. Unfortunately, most recipients experience immunologic rejection with the discontinuation of these drugs and have to be maintained on at least low doses of these medications ***(Dharancy et al., 2009)***.

Immunosuppressive regimens include calcineurin inhibitors (CNIs), anti-metabolites, mammalian target of rapamycin (mTOR) inhibitors, steroids and antibody-based therapies. These agents target different sites in the T cell activation cascade, usually by inhibiting T-lymphocyte cell activation or proliferation or *via* T-lymphocyte cell depletion. The selection of agents is based on an individual's medical history as well as on institution experience and preference. Most immunosuppressive regimens combine drugs with different sites of action of T-lymphocyte cell response, allowing for dosage adjustments to minimize side effects and toxicities ***(Barrera et al., 2008)***.

Currently, the mainstay of maintenance immuno-suppressive regimens are calcineurin inhibitors, used in greater than ٩٥٪ of transplant centers upon discharge, although there is a known increased risk of renal impairment and neurotoxicity with the long-term use of these medications ***(Neff et al., 2008)***. They are used as induction therapy in the immediate peri- and post-operative period, as long-term maintenance medications to preserve graft function and as salvage therapy for acute rejection in liver transplant recipients ***(Maathuis et al., 2007)***.

Aim of the Work

The aim of this essay is to focus on the role of immunosuppressive drugs in liver transplantation and consider newer medications on the horizon.

Liver Transplantation

➢ *Introduction:*

Liver transplantation is a life saving procedure for patients who have chronic end-stage liver disease and acute liver failure (ALF) when there are no alternative treatment options. Dr. *Thomas Starzl* performed the first three human liver transplantations at the University of Colorado in ١٩٦٣, but did not achieve ١-year survival until ١٩٦٧. Over the next ١٥ years, relatively few liver transplantations were performed, and the ١-year survival rate was only ٣٠٪ until the late ١٩٧٠s and early ١٩٨٠s when the implementation of cyclosporine-based immunosuppression led to doubling of the ١-year survival rate ***(Murray and Carithers, 2005)***.

The ١٩٨٠`s was a decade in which new immune suppressive therapies after liver transplantation helped to increase graft and patient survival by acute and chronic rejection more effectively. One year survival for liver transplantation in Europe rose progressively from ٤٧٪ (١٩٦٨-١٩٨٨) to ٦٧٪ (١٩٨٨-١٩٩٦) ***(Emond et al., ١٩٩٦)***.

Liver transplantation then underwent a period of maturation fueled by significant advances in the surgical techniques of liver transplantation, improvements in

immunosuppressive drug regimens to manage rejection, and implementation of effective strategies to prevent post transplantation infections, all of which have led to further improvement in outcomes during the subsequent ٢٠ years ***(Yu and Keeffe, 2006)***.

Adherence to objective, evidence-based indications and contraindications for liver transplantation is crucial in maintaining these improved post transplantation outcomes and in appropriate selection of patients who can withstand prolonged waiting time on the liver transplant list. In the current environment of organ shortage, every effort should be made to avoid deviation from strict criteria for liver transplant evaluation and listing ***(Kotlyer et al., 2006)***.

The success of liver transplantation as treatment for most types of acute and chronic liver failure has led to increased referrals for transplantation in the setting of a relatively fixed supply of cadaver donor organs. These events have resulted in a marked lengthening of the waiting time for liver transplantation, resulting in increased deaths of those on the waiting list and sicker patients coming to transplantation ***(Kotlyar et al., 2006)***.

At the end of ٢٠٠٦, more than ١٧,٠٠٠ patients were listed for liver transplantation. The performance of more than ٦٠٠٠ liver transplantations annually in the United States during

the past several years attests to the growth of liver transplantation ***(Yu and Keeffe, 2006)***.

The two major goals of liver transplantation are to prolong survival and to improve quality of life. Data from the United Network for Organ Sharing (UNOS) on ٢٤,٩٠٠ adult patients undergoing liver transplantation from October ١٩٨٧ to September ١٩٩٨ showed that ١-year, ٤-year, and ١٠-year patient survival rates were ٨٥٪, ٧٦٪, and ٦١٪, respectively, confirming that liver transplantation results in prolongation of life. ***Roberts and colleagues*** showed that the ١-year survival improved over time in the ١٩٩٠s from ٧٤,٨٪ in ١٩٩٠ to ٨٦,٢٪ in ١٩٩٦. The best survival has been shown to occur among patients who undergo liver transplantation for chronic cholestatic liver diseases, including primary biliary cirrhosis and primary sclerosing cholangitis; the worst survival occurred in patients who underwent transplantation for hepatic malignancy ***(Roberts et al., 2004)***.

Multiple quality of life studies have consistently demonstrated significant improvement in the cognitive, physical, and psychological functioning of liver recipients after transplantation. Prolonged waiting times for a donor organ have hindered efforts to achieve ideal timing of liver transplantation during the natural history of advanced chronic liver disease ***(Maathuis et al., 2007)***.

➢ *Donor selection:*

Absolute contraindications to organ donation are infectious disease and active malignancy that can cause death of the recipient through transmission. Infectious diseases include HIV virus infection, disseminated and invasive infection by other viruses, mycobacterium, or fungi, and systemic infection by methicillin-resistant staphylococci. However, low grade skin cancer, as basal cell carcinoma, and many squamous cell carcinomas, carcinoma in situ (uterine and cervical), and primary brain tumors without extracranial metastases do not exclude donation ***(Nadalin et al., 2007)***.

1. Deceased liver donor

Selection of an appropriate donor is crucial to the successful outcome of deceased donor liver transplantation (DDLT). Among the most prominent donor characteristics that may influence the development of initial poor function or primary non function in the recipient include old donor age, prolonged ischemia, hypotension and excessive inotropic support, non-heart-beating donors and steatosis ***(Fondevila and Ghobrial, 2005)***.

Following characteristics described an ideal liver donor: ٥٠ years or younger; no hepatobiliary disease; hemodynamic and respiratory stability (systolic blood pressure >١٠٠ mmHg, and central venous pressure >٥ cm/$H_٢O$); an acceptable $PaO_٢$