



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكرو فيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



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شبكة المعلومات الجامعية التوثيق الإلكتروني والميكرو فيلم



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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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MONA MAGHRABY

Study of the Effect of CYP3A5 Single Nucleotide Polymorphism on Tacrolimus Metabolism in Liver Transplant Patients

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا انك لا تعلم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

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List of Abbreviations

Abb.	Full term
<i>ABCB1</i>	<i>ATP binding cassette subfamily B1</i>
<i>AP- 1</i>	<i>Activator protein 1</i>
<i>APC</i>	<i>Antigen-presenting cell</i>
<i>BCG</i>	<i>Bromocresol Green</i>
<i>CBC</i>	<i>Complete blood count</i>
<i>CCA</i>	<i>Cholangiocarcinoma</i>
<i>CMIA</i>	<i>Chemiluminescent Micro particle Immuno- Assay</i>
<i>CMIA</i>	<i>Chemiluminescent microparticle immunoassay</i>
<i>CMV</i>	<i>Cytomegalovirus</i>
<i>CNIs</i>	<i>Calcineurin inhibitors</i>
<i>CRF</i>	<i>Chronic renal failure</i>
<i>Cs</i>	<i>Cyclosporine</i>
<i>CYP</i>	<i>Cytochrome P450</i>
<i>DHPLC</i>	<i>Denaturing high-performance liquid chromatography</i>
<i>dNTP</i>	<i>Deoxyribonucleotide triphosphate</i>
<i>ELISA</i>	<i>Enzyme-linked immunosorbent assay</i>
<i>EMIT</i>	<i>Enzyme multiplied immunoassay technique</i>
<i>FAM</i>	<i>Fluorescein amidites</i>
<i>FKBP</i>	<i>FK binding protein</i>
<i>FRET</i>	<i>Fluorescence resonance energy transfer</i>
<i>HBV</i>	<i>Hepatitis B virus</i>
<i>HSV</i>	<i>Herpes simplex virus</i>
<i>ICU</i>	<i>Intensive Care Unit</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>IL-2</i>	<i>interleukin-2</i>
<i>IL-2Ra</i>	<i>Interleukin 2 receptor antagonists</i>
<i>INR</i>	<i>International normalized ratio</i>
<i>IQR</i>	<i>Inter-quartile range</i>
<i>JAK</i>	<i>Janus kinases</i>
<i>LC</i>	<i>Liquid chromatography- Mass spectrometry</i>
<i>LDH</i>	<i>Lactate dehydrogenase</i>
<i>LDLT</i>	<i>Living donor liver transplantation</i>
<i>LFA-1</i>	<i>Lymphocyte function-associated antigen 1</i>
<i>MBs</i>	<i>Molecular beacons</i>
<i>MDH</i>	<i>Malate dehydrogenase</i>
<i>MEIA</i>	<i>Microparticle enzyme-linked immuno-assay method</i>
<i>MELD</i>	<i>Model for End-stage Liver Disease score</i>
<i>MFOs</i>	<i>Mixed function oxidases</i>
<i>MHC</i>	<i>Major histocompatibility complex</i>
<i>MPAs</i>	<i>Mycophenolic acids</i>
<i>NAD</i>	<i>Nicotinamide adenine dinucleotide</i>
<i>NF-AT</i>	<i>Nuclear factor of activated T cells</i>
<i>NFQ</i>	<i>A non-fluorescent quencher</i>
<i>NF-κB</i>	<i>Nuclear factor</i>
<i>OLT</i>	<i>Orthotopic liver transplantation</i>
<i>PCR-RFLP</i>	<i>Polymerase chain reaction-restriction fragment length polymorphism</i>
<i>PML</i>	<i>Progressive multifocal leukoencephalopathy</i>
<i>PSMOs</i>	<i>Polysubstrate monooxygenases</i>
<i>PTLD</i>	<i>Post- transplant lymphoproliferative disorder</i>
<i>qPCR</i>	<i>Quantitative PCR</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>RIA</i>	<i>Radioimmunoassay</i>
<i>RT-PCR</i>	<i>Real Time- polymerase chain reaction technique</i>
<i>SNPs</i>	<i>single nucleotide polymorphisms</i>
<i>STAT</i>	<i>Signal transducers and activators of transcription</i>
<i>TDM</i>	<i>Therapeutic Drug Monitoring</i>
<i>TGF-β</i>	<i>Transforming growth factor-β</i>
<i>VLA-4</i>	<i>Very Late Antigen-4</i>
<i>WB I</i>	<i>Wash Buffer I</i>
<i>WB II</i>	<i>Wash Buffer II</i>

INTRODUCTION

In Egypt, there is no doubt that chronic liver diseases are a major health concern. The high prevalence of hepatitis C virus that is estimated to be 14.7% and the high prevalence of chronic liver diseases has led to increasing numbers of patients suffering from end stage liver disease, necessitating liver transplantation, so living donor liver transplantation are now routinely done in Egypt in an increasing numbers (*Khaled and Ibrahim, 2016*).

Recent studies showed that 32.8% of de novo adult recipients of living donor liver transplantation (LDLT) experienced acute cellular rejection within the first 4 weeks after transplantation, so immunosuppressive agents are used post-operative to prevent rejection. Calcineurin inhibitors as Tacrolimus are the principal choice, prescribed to nearly 97% of liver transplanted patients (*Eunhee et al., 2018*). Tacrolimus has a narrow therapeutic window and large variability in pharmacokinetics, particularly during the early posttransplant period, therefore to overcome this variability and to optimize the efficacy and minimize the toxicity, therapeutic drug monitoring of tacrolimus is widely performed (*Shuker et al., 2015*).

A number of factors influence the pharmacokinetics of tacrolimus, including time after transplant, patient demographics, comorbidities and the patient and donor genotypes associated