Multidrug Resistance 1 Gene Polymorphisms in Inflammatory Bowel Disease

Thesis

Submitted for Partial Fulfillment of M.D Degree in Clinical Pathology

by

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2017

Abstract

Introduction: Inflammatory bowel disease (IBD) comprises Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC). It is characterized by recurrent episodes of inflammation in the gastrointestinal tract. Among the genes regulating innate immunity is a member of adenosine triphosphate binding cassette superfamily which is also known as multidrug resistance1 (MDR1).

Aims: The aim of the present study is to investigate the MDR1 gene polymorphisms in patients with IBD and to study their association with the clinical course of the disease, its severity, prognosis and response to treatment.

Methodology: This study was conducted on 60 IBD patients recruited from the IBD Clinic of Tropical Medicine Department at Ain Shams University Hospital, in addition to 50 apparently healthy subjects serving as control group. Informed consents were obtained from all subjects before enrollment in the study according to the Ethical Committee of Faculty of Medicine, Ain Shams University.

Results: Subjects included in this study were classified into the following groups:

Group I: IBD Patients' Group (n=60): This group included sixty (60) adult patients with IBD. They included 50 UC patients and 10 CD patients. They were 16 males and 44 females. The mean age of the group was (31.7 ± 7.2) years.

Group II: Healthy Control Group (n=50): This group included fifty (50) age and sex-matched apparently healthy subjects with normal relevant laboratory tests serving as a healthy control group. They were 19 male and 31 female. The mean age of the group was (32± 6.7) years.

Conclusion: The study proved that MDR1 SNPs (C3435T, G2677T and C1236T) are involved in IBD predisposition as well as associated with disease severity and response to GCs therapy.

Keywords: MDR1, Resistance 1 Gene Polymorphisms, Inflammatory Bowel Disease.

سورة البقرة الآية: ٣٢

*First and Foremost I would like to thank **ALLAH THE MOST GRACEFUL** for giving me strength to accomplish this work.*

My deepest gratitude and profound appreciation to **PROFESSOR. MONA FATHY YOUSSEF,** *Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University for her sincere guidance, her support, her patience and endurance .*

My profound appreciation to **PROFESSOR MOHAMED AMIN SAKR,** *Professor of Tropical Medicine**,** Faculty of Medicine, Ain Shams University for his great help and guidance.*

I would like also to express my respect and gratitude to **PROFESSOR/ MANAL ABD EL BAKY MAHMOUD,** *Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University for her great help, support and valuable supervision, untiring help throughout this work.*

I owe a great debt of gratitude to **DOCTOR/ MANAL MOHSEN MOHAMED KAMAL EL-DIN,** *Assistant Professor of Clinical Pathology, Faculty of Medicine, Ain Shams University for her meticulous observation, her endless patience and fruitful advices.*

Also, I will never forget the one who helped me from the very beginning till the end of the practical part of this study, **DOCTOR/ RAMY MOHAMED MAHMOUD,** *Lecturer of Clinical Pathology, Faculty of Medicine, Ain Shams University.*

Finally, I would like to express my deepest and greatest thanks and gratitude to my family, my husband and my prince Youssef for their help, support, patience, endurance, understanding and encouragement to accomplish this work.

Shimaa Mostafa Ismail Mostafa

Contents

List of Abbreviations

Abbrev.	Meaning
ABCB1	ATP binding cassette subfamily B member 1
ALL	Acute lymphoblastic leukaemia
ASCA	Anti- saccharomyces cerevisiae antibody
CBC	Complete blood count
CD	Crohn's disease
CDAI	Crohn's disease activity index
CHO	Chinese Hamester ovary
CI	Confidence interval
CRP	C- Reactive protein
CT	Computed Tomography
CYP 450	Cytochrome p 450
DDI	Drug- drug interaction
dNTPs	Deoxynucleotide triphosphates
EDTA	Ehylenediaminetetraacetic acid
ELISA	Enzyme linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FC	Fecal calprotectin
GCs	Glucocorticoids
GIT	Gastrointestinal tract
HLA	Human leucocyte antigen
IBD	Inflammatory Bowel Disease
IBS	Irritable bowel syndrome
IC	Indeterminate colitis
Ig A	Immunoglobulin A
IL	Interleukin
INF-γ	Interferon gamma

MDR1	Multidrug resistance 1 gene
MHC	Major Histocompitability Complex
MRI	Magnetic resonance imaging
NF-KB	Nuclear factor kappa beta
NOD2	Nucleotide binding oligomerization domain 2
NPV	Negative predictive value
NSAID	Non steroidal anti inflammatory drugs
OR	ODDs ratio
P-ANCA	Anti-neutrophil cytoplasmic antibody, perinuclear pattern
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PCR-RFLP	PCR-Restriction Fragment Length Polymorphism
P-gp	Permeapility glycoprotein
POCT	Point of care test
PPV	Positive predictive value
RA	Rheumatoid arthritis
Rs	Reference sequence
SD	Standard deviation
SL	Stool lactoferrin
SNPs	Single nucleotide polymorphisms
TH1	T- helper 1 cell
TH2	T- helper 2 cell
TH17	T- helper 17 cell
TLC	Total leucocytic count
TNF-α	Tumor necrosis factor alpha
UC	Ulcerative Colitis
UGIT	Upper gastrointestinal tract

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Introduction

Inflammatory bowel disease (IBD) comprises Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC). It is characterized by recurrent episodes of inflammation in the gastrointestinal tract ***(Bodor et al., 2005 and Molodecky et al., 2012).***

The pathogenesis of IBD is thought to rely on defective mucosal barrier and dysregulated immune response to a host's microbiota in genetically susceptible individuals ***(Hisamatsu et al., 2013)***.

Among the genes regulating innate immunity is a member of adenosine triphosphate binding cassette superfamily which is also known as multidrug resistance1 (MDR1). The encoded product of the MDR1 gene is P-glycoprotein 170 (P-gp). The latter is expressed on epithelial cells of kidney, liver, pancreas, small intestine and colon. Due to its expression on epithelial surfaces of enterocytes and colon, it plays an important role in the secretion of toxic compounds from the intracellular area to extracellular area with its ATP-dependent efflux transporter pump function, in apoptosis and in the immune response. It is thought that the physiologic role of intestinal P-gp might prevent entry of bacterial toxins into the intestinal wall

mucosa and prevent intestinal inflammation. Moreover, alteration of P-gp expression and function due to MDR1 level may contribute to pathogenesis of IBD ***(Tahara et al., 2014)***.

Several drugs routinely used in IBD therapy including corticosteroids and immunosuppressants are substrates for P-gp. However, some patients are resistant to these drugs and require surgery. Many studies have suggested that Single nucleotide polymorphisms (SNPs) of MDR1 gene changes the level of expression of P-gp and might be associated with corticosteroid resistance in IBD and contribute to failure of medical treatment in IBD, increasing disease severity and therefore need for surgery ***(Brambila, 2013 and Yanju et al., 2015).***

Aim of the Work

The aim of the present study is to investigate the MDR1 gene polymorphisms in patients with IBD and to study their association with the clinical course of the disease, its severity, prognosis and response to treatment.