بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

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Clinical, Laboratory, Endoscopic and Histological Correlation to Assess Actual Remission in Patients with Ulcerative Colitis

Thesis

Submitted for Partial Fulfillment of Master Degree in Gastroenterology

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Mohammed Sobhy Ibrahim Elmokemy

Contents

List of Abbreviations

Abb.	Full Term
ACG	American College of Gastroenterology
ADCY7	Adenylate cyclase 7 gene
ALT	Serum alanine aminotransferase
AST	Serum aspartate aminotransferase
ATP	Adenosine triphosphate
BMI	Body mass index
BWT	Bowel wall thickness
cAMP	cyclic adenosine mono phosphate
CBC	Complete blood count
CD	Crohn's disease
CRC	Colorectal cancer
CRP	C-reactive protein
DC	Dendritic cells
ECCO	European Crohn's and Colitis Organisation
ELISA	Enzyme-linked-immunosorbent assay
ESR	Erythrocyte sedimentation rate
FC	Fecal calprotectin
FMT	Fecal microbiota transplantation
GS	Geboes score
GWA	Genome-wide association
GWAS	Genome-wide association studies
HLA	Human leukocyte antigen
IBD	Inflammatory bowel disease
IFN	Interferon
IL	Interleukin
INR	International normalised ratio
IPAA	Ileal pouch-anal anastomosis
IUS	Intestinal ultrasound
JAK	Janus kinase
MES	Mayo Endoscopic Subscore
MH	Mucosal healing
MMX	Multimatrix
MRI	Magnetic resonance imaging

Abb.	Full Term
NHI	Nancy histological index
NI	Nancy index
NSAIDs	Non-steroidal anti-inflammatory drugs
PSC	Primary sclerosing cholangitis
PT	Prothrombin time
PTT	Partial thrombopalastin time
RHI	Robart' histopathology index
SCFAs	Short chain fatty acids
STAT	Signal transducer and activator of transcription
STRIDE	Selecting Therapeutic Targets in Inflammatory Bowel Disease
T2T	Treat to target
TB	Tuberculosis
TNF	Tumor necrosis factor
UC	Ulcerative colitis
UCEIS	Ulcerative colitis endoscopic index of severity
WGS	Whole genome sequencing

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the most common types of inflammatory bowel disease (IBD) with up to 12.7 and 24.3 of incidents per year for 100,000 individuals in Europe, respectively ***(Molodecky et al., 2012).***

The severity of Ulcerative colitis and therefore, the adverse impact to the individual and the society can be reduced by appropriate medical treatment. In this regard, monitoring the response to therapy is a precondition for choosing the right therapeutics and the optimal dosage for individual patients. Traditional therapies of ulcerative colitis result in an unspecific inhibition of inflammation with reduced clinical symptoms. Therefore, treatment end-points focused for many decades on the measurement of symptom severity, which shows only weak correlation with mucosal inflammation or disease related morbidity and mortality ***(Levesque et al., 2015).***

With the advent of biological therapies such as anti-tumor necrosis factor α (TNF) antibodies, which modulate specific pro-inflammatory pathways of Ulcerative colitis pathogenesis, the requirement for more reliable, well-defined end-points of therapeutic success became evident. Although these therapeutics show superior response even in patients with highly active disease, about 30% of

patients initially do not response to anti-TNF treatment and further 10–50% of patients lose response after initial successful treatment in each subsequent year ***(Allez et al., 2010)***.

The idea of using mucosal healing (MH) as an endpoint for the assessment of disease activity in patients with Ulcerative colitis started gaining popularity with the demonstration that medical therapy with azathioprine and then novel biologics could induce symptomatic improvement as well as endoscopic healing. A recent meta-analysis shows that MH achieved during medical therapy was associated with long-term clinical remission, colectomy avoidance, and corticosteroid-free clinical remission in patients with UC. MH was defined as Mayo Endoscopic Subscore (MES) of 0 or 1 in most relevant clinical trials ***(Shah et al., 2016).***

Although the concept of "deep remission" has developed in CD, it has not been replicated in those with UC. Most studies on mucosal healing focus on endoscopic scores, and the data from various trials suggests that patients with Mayo score 0 (complete mucosal healing) have longer-lasting remissions. However, patients with UC who are in clinical and endoscopic remission may still have histologically active disease and are at a high risk of having a relapse ***(Bryant et al., 2016).***

Histological abnormalities are prevalent in patients with clinically quiescent colitis. Appreciable microscopic inflammation, especially acute inflammatory cells, were associated with increase in relapse rate. ***Geboes et al. (2000),*** found a good correlation between the location of neutrophil and occurrence of crypt destruction. Thus, reduction or disappearance of neutrophils in the epithelium in consecutive biopsies is most likely a sign of reduction of disease activity and could indicate the efficacy of a given treatment.

Since prolonged remission reduces the cost of health care and improves the patient's quality of life, increasing attention has been paid to assessing the best condition that would guarantee a lower risk of recurrence. To date, the best prognostic factor of long-term remission is so-called mucosal healing (MH), which is evaluated by endoscopy. MH is associated with less need for steroids, avoidance of colectomy and long-term patient wellness ***(Iacucci et al., 2015).***

This finding is easily understandable since endoscopy directly describes lesions while clinical evaluation refers only to signs and symptoms of intestinal inflammation. On the basis of the observation that microscopic inflammation can underlie even macroscopically normal mucosa, histological healing has become the focus of growing attention as a more powerful