بسم الله الرحمن الرحيم

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Nitazoxanide Based New Regimens versus Metronidazole Standard Quadrable Regimen As Rescue Therapy in Treatment of Resistant H.Pylori Gastritis

A thesis

For fulfillment of Master Degree in Internal Medicine: Hepatology and gastroenterology

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قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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LIST OF ABBREVIATIONS

Abb	Full Term
AD	Alzheimer's disease
AGS	gastric cancer cells
ALT	
AQP3	aquaporin 3
ARMS	amplification refractory mutation system
ASEAN	Association of Southeast Asian Nations
BabA	blood group antigen-binding adhesin
BLI	blue laser imaging
BUN	
CAD	Coronary artery disease
CME	Continuing Medical Education
DCs	dendritic cells
ddPCR	droplets by the droplet digital PCR
DLBCL	B cell lymphomas
DM	diabetes mellitus
EGC	
ELISA	
EMT	epithelial mesenchymal transition
FD	functional dyspepsia
FFPE	formalin-fixed, paraffin-embedded
FIB	fecal indicator bacteria
FLOT	flolitin-like protein
GGT	glutamyl transpeptidase
GIT	Gasto-intestinal tract
GTP	
HBg	
HBsAG	
HCV	
HIF	hypoxia-induced factor
HOMA-IR	Homeostatic model assessment of insulin resistance
HP	Helicobacter pylori
HpD	H. pylori-associated dyspepsia
ICT	immunochromatography
IDA	Iron deficiency anemia
IFNc	interferon-gamma
IL	
INR	

ITP	immune thrombocytopenic purpura
ITT	intention to treat
LCI	linked color imaging
lPS	inhibiting lipo-polysaccharide
MALT	mucosa-associated lymphoid tissue
MCV	
MHC	major histocompatibility complex
MTZ	Metronidazole
NAFLD	Nonalcoholic fatty liver disease
NBI	narrow band imaging
NfU	
NTZ	nitazoxanide
NUD	nonulcer dyspepsia
OLGA	
OMPLA	outer-membrane phospholipase A
P-CAB	potassium competitive acid blocker
PCR	polymerase chain reaction
PP	per protocol
PPI	proton-pump inhibitor
RA	retinoic acid
RNS	nitrogen species
ROS	radical oxygen species
RUT	Rapid urease test
SAT	Stool antigen tests
SpeE	spermidine synthase homologue
StoP	Stomach Cancer Pooling
TBil	
TfR1	transferrin receptor 1
TFSS	the cag type four secretion system
Tip-α	TNF-α inducing protein
TLR	toll-like receptor
TNFa	tumor necrosis factor alpha
UBT	Urea Breath Test
WBC	
WGO	World Gastroenterology Organization

ABSTRACT

Background: H. pylori infection has become highly resistant to traditional first-line treatment regimens because of antibiotic resistance coupled with poor patient compliance with completing the treatment course. Many clinical studies proved that nitazoxanide (NTZ) was found to be well tolerated by humans, with an encouraging rate of eradication when it was administered with omeprazole, **Aim and objectives;** to evaluate the efficacy of nitazoxanide and doxycycline as a rescue therapy in treatment of H.pylori, **Subjects and methods;** This study is an prospective observational cohort study, was carried out on 70 patients at outpatient clinic: Hepatology and gastroenterology clinic of Internal Medicine Department– Ain Shams University hospital, from January 2021till June 2021, **Result;** There is significant difference between both studied groups as regards H.pylori Ag in stool 3 weeks after finishing course, **Conclusion**; LOAD therapy is preferable to clarithromycin-contained triple therapy in H. pylori infection eradication particularly in countries like Egypt with great clarithromycin resistance. This is at least until we can get the bismuth in our country. Recently, the increasing concepts about levofloxacin resistance and decreasing efficacy as a second line treatment directed us towards thinking in levofloxacin contained quadruple therapy including doxycycline and NTZ as alternative line of regimen therapy for better H. pylori eradication in our country, **Keywords; Helicobacter-Pylori, Nitazoxanide, rescue therapy.**

INTRODUCTION

Helicobacter pylori (HP) is a small, Gram-negative spirochete inhabiting the mucous layer overlying the gastric epithelial cells in humans.It is the most common prevalent chronic human bacterial infection estimated in 50% of the global population (Alsahafi et al., 2020).

HP infection is one of the most common chronic bacterial infections in humans, affecting approximately 4.4 billion individuals worldwide. Reports of infection prevalence rates range widely among geographic regions, reaching the highest levels in developing countries and showing a well-established relationship with socio-economic status and hygiene conditions (Hooi et al., 2017).

HP infection causes chronic progressive gastric inflammation and a variety of diseases, including gastric and duodenal ulcers and gastric cancer (Malfertheiner et al., 2017). In 1994 and 2009, the International Agency for Research on Cancer classified HP as a Group 1 carcinogen on the basis of a thorough review of relevant laboratory and epidemiologic studies. Eradication of HP infection has been proven to reduce the incidence of gastric cancer (Rokkas et al., 2017)

In the face of rising prevalence of antibiotic resistance, the demand for rescue therapies is increasing. Refractory HP infection usually refers to patients who fail after 2 or more eradication therapies. Many of them are left untreated because susceptibility testing is not widely available. Whereas the earlier Maastricht Consensus and the ASEAN (Association of Southeast Asian Nations) Consensus recommended the use of susceptibility testing–guided therapy after 2 or more eradication failures,

more recent consensus reports recommended the use of empirical therapy according to medication history (Mahachai et al., 2018).

Triple therapy has been modified in that it is now recommended to use double-dose (80 mg) proton-pump inhibitor (PPI), quadruple dose (2 g) amoxicillin, and clarithromycin (1 g) for at least 10 days, and preferably 14 days (Gisbert et al., 2017).

Levofloxacin remains one of the most favored second-line therapies; however, bismuth, when available, is an increasingly successful option. Sequential therapy remains in use in areas of high resistance, but may prove challenging in terms of compliance, and is no longer recommended (Gatta et al., 2018).

Nitazoxanide (NTZ) is an antibiotic with microbiological characteristics similar to those ofmetronidazole with nearby cost. It was settled as atherapy having a broad spectrum of activity against micro-aerobic and anaerobic bacteria, anaerobic protozoa, and helminthes (Wang et al., 2018).

Nitazoxanide and levofloxacin considered as apart from LOAD regemin recommended in American Colleage of Gastroenterology.

AIM OF THE WORK

The aim of this study was to evaluate the efficacy of nitazoxanide and doxycycline as a new regimen in treatment of H.pylori

Helicobacter Pylori

Helicobacter pylori (H. pylori) is a motile, curved, Gram negative bacillus and spiral microorganism. The occurrence of infection is very much geographical, age, and ethnicity related. The occurrence of this disease was documented to be in greater numbers, in developing countries when compared to under developing countries, the region for this could be due to their finical situations (Rehman, 2020).

Recent studies have shown a critical role of H. pylori in the development of peptic ulcers, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer (Abadi, 2018).

The features displayed by H. pylori allow it's survived in very adversative conditions, such as high acidic environment in the stomach. Spreading of the infection occurs mainly through contaminated water and food. Spreading of this bacterium has been shown in the saliva and dental plaque (Mladenova and Durazzo, 2018).

Epidemiology

H. pylori, as the most commonly prevalent and recognized bacterium, is carried by more than half of the world population (Elhariri et al., 2017; Hu et al., 2017; Mladenova-Hristova et al., 2017)

H. pylori infection is the most common chronic bacterial infection worldwide. Genetic sequencing studies estimated the presence of H. pylori infection since first migration from Africa around 58,000 years ago. It is not exaggerative to say that about 50 percent of planet population of all ages has H. pylori infection. Infection is more common

in younger age in developing compared with industrialized countries (Alsahafi et al., 2020).

Pathogenesis of H. pylori infection

H. pylori infection is the main cause of continuing inflammation of the protective lining of the stomach. About 80% of the infected subjects develop a small cavity and the inflammation associated with changing of the gastric homeostasis with normal levels of gastric acid secretion. These patients may not develop intense problems. A low percentage of these patients may suffer from this gastric disease, where the gastrin level may be equal or greater than 99 - 125 pg/ml. With these high levels, often duodenal ulceration is associated. Some patients may also develop body inflammation and other gastric disease (Rehman, 2020).

Virulence Factors Associated with Escape to High Acidic Environment

After transit to the gastric lumen, the H. pylori encounters extremely harsh conditions of pH around 2. However, H. pylori possesses several factors like urease, bacterial shape and flagella mediating motility to interact with the harsh gastric environment. The acidic conditions help the bacteria to express some genetic determinants that neutralize the acidic environment (Ansari and Yamaoka, 2017).

1. Urease

A large amount of intracellular urease is produced by H. pylori, constituting around 10% of the total bacterial protein production. In addition to intracellular urease, H. pylori also contains extracellular urease on the bacterial surface due to the lysis of some bacteria in the stomach (Schoep et al., 2010).