Safety of Methotrexate in Patients with Rheumatoid Arthritis and HCV

Thesis

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Abstract

This work aimed to study the safety and efficacy of methotrexate among Egyptian RA patients with concomitant HCV infection.

Twenty four patients fulfilling the 1988 ACR revised classification criteria for RA were included. Eight of the patients also had concomitant HCV. All the patients were subjected to full history taking, clinical examination, laboratory investigations as well as plain radiograph of hands. Baseline liver biopsy was taken from RA patients with HCV. All patients were then followed up for a 6 month period as regards clinical and laboratory manifestations.

No statistical difference was found regarding liver function tests of patients at baseline visit compared to last visit during the study. Also, none of the patients with HCV showed marked liver fibrosis on liver biopsy.

Key words: Rheumatoid Arthritis – Hepatitis C virus - Methotrexate

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List of Abbreviations

ACR	American College of Rheumatology
ADP	Adenosine diphosphate
AICAR	Aminoimidazole-carboxamide ribonucleotide
ALT	alanine transaminase
AMP	Adenosine monophosphate
AMPDA	Adenosine monophosphate deaminase
Anti-CCP	anti-cyclic citrullinated protien
AST	aspartate transaminase
ATP	Adenosine triphosphate
BRM	biologic response modifiers
CBC	Complete blood count
CsA	cyclosporin
DAMPA	di-amino-methylpteroic acid
DAS	Disease activity score
DHFR	dihydrofolate reductase
DMARD	disease modifying anti-rheumatic drug
EHM	extrahepatic manifestations
EIA	enzyme immunoassay
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GGT	gamma glutamyl transferase
GI	Gastero-intestinal
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus

HIV	Human immunedeficiency virus
IFN	Interferon
IL	interleukin
IM	Intramuscular
INR	International normalized ratio
IPF	Interstitial pulmonary fibrosis
IV	Intravenous
LFT	Liver function test
LPD	Lymphoproliferative disorder
MC	Mixed cryoglobulinemia
MCP	Metacarpophalangeal
MTP	Metatarsophalangeal
MTX	Methotrexate
MTXglu	Methotrexate polyglutamate
NHL	Non-Hodgkin’s lymphoma
NSAIDS	Non-steroidal anti-inflammatory drugs
PAT	Parenteral anti-schistosomal therapy
PC	Prothrombin concentration
PCR	Polymerase chain reaction
PEG-IFN	Pegylated interferon
PIP	Proximal interphalangeal
PT	Prothrombin time
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RFC	Reduced folate carrier
RNA	Ribonucleic acid

SC	Subdutaneous
TB	tuberculosis
THF	Tetrahydrofolate
TMA	Transcription mediated amplification
TNF	Tumor necrosis factor
TS	Thymidylate synthase

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Introduction

Rheumatoid arthritis (RA) is the second most common form of chronic arthritis and affects approximately 1% of the adult population worldwide ***(O'Dell, 2007)***.

Hepatitis C is a major global health problem. Egypt has the highest prevalence worldwide and hepatitis C is the most common etiology of chronic liver disease in Egypt ***(Strickland et al., 2002)***. The overall HCV antibody positivity in Egypt is 14.7% nationwide and 9.8% of Egyptians are chronically infected ***(El-Zanaty and Way, 2009)***.

Methotrexate (MTX), a folic acid antagonist, is the most widely used disease modifying anti-rheumatic drug (DMARD) in the treatment of RA, with the best efficacy/toxicity ratio. The major concern of its long term use is hepatotoxicity ***(Richard et al., 2000)***. Hepatic damage related to methotrexate includes elevation of aminotransferases, portal fibrosis and cirrhosis ***(Diouf et al., 2001)***.

The prevalence of concurrent rheumatoid arthritis and hepatitis C virus infection is probably underestimated because of the increasing spread of the virus worldwide ***(Parke and Reveille, 2004)***. Chronic HCV in the setting of RA is an obstacle to treatment due to the complications associated with immunosuppression as well as the potential hepatotoxicity documented with DMARDs conventionally used to treat RA ***(Ferri et al., 2007)***. For this reason, most rheumatologists refrain from the use of methotrexate in this setting.

Despite hepatotoxicity being an important, though uncommon, complication of long term MTX therapy, little is known about the safety of MTX in patients

with concomitant hepatitis C ***(Kujawska et al., 2003)***. Although studies have been performed on other therapeutic agents such as cyclosporine, anti-TNF, and rituximab for HCV affected patients, studies would be useful to prove that MTX can still be considered a treatment option in this setting. This is especially true in a country like Egypt, where the high prevalence of HCV among patients of lower economic standards makes these alternatives highly unattainable.

Aim of the Work

The aim of the study is to assess the short-term safety and efficacy of the use of methotrexate in patients with rheumatoid arthritis and concomitant HCV infection.

Methotrexate

Introduction:

Methotrexate (MTX) is a folate analogue originally synthesized in the 1940s ***(Cutolo et al., 2001)***. It was developed as a specific antagonist of folic acid and was shown to inhibit proliferation of malignant cells. Hence its original use was primarily as a chemotherapeutic agent ***(Elewaut, 2004)***. MTX has been used extensively for treatment of neoplastic diseases including leukemias and lymphomas.

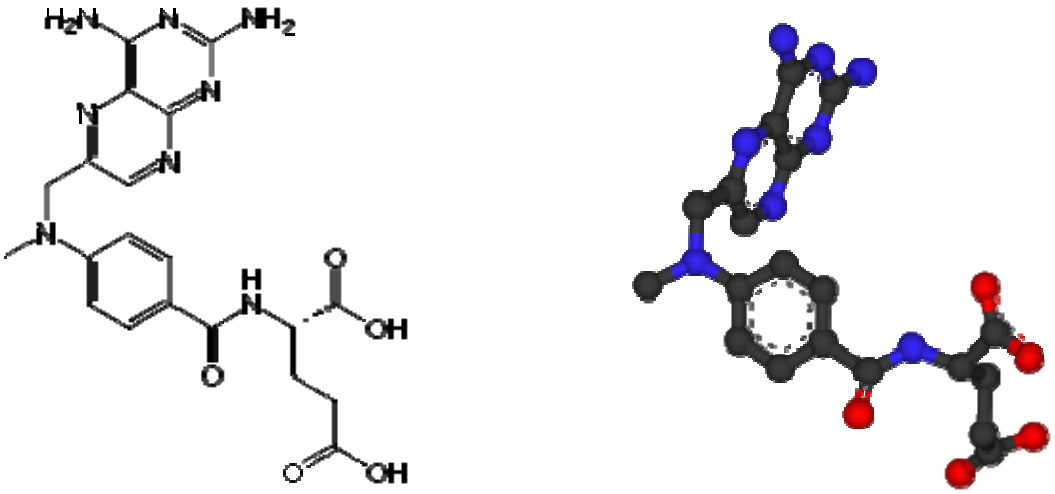

Figure (1): The chemical structure of methotrexate (wikepidia).

Figure (2): Different MTX vials.