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Nermeen Ashoush

Contents

List of Abbreviations

AdoMet:	Adenosylmethionine
ALT:	Alanine aminotransferase
AST:	Aspartate aminotransferase
ATF:	Anti-thiamine factors
AThDP:	Adenosine thiamine diphosphate
AThTP:	Adenosine thiamine triphosphate
ATP:	Adenosine triphosphate
BH4:	Tetrahydrobiopterine
BP:	Bodily Pain
cEVR:	Complete early virologic response
CN:	Cyanide
CsA:	Cyclosporine
DAAs:	Direct-acting antiviral
DHF:	Dihydrofolic acid
EF:	Extrinsic factor
ETR:	End-of-treatment response
FA:	Folic acid
FIGLU:	Formiminoglutamic acid
GABA:	Gamma aminobutyric acid
GH:	General Health
GTP:	Guanosine-5'-triphosphate
H_2O_2:	Hydrogen peroxide
H_2SO_4:	Sulphuric acid
HCC:	Hepatocellular carcinoma
HCV-4:	Hepatitis C virus genotype 4
HCV:	Hepatitis C virus
Hcy:	Homocysteine
HIV:	Human immunodeficiency virus
HQLQ:	Health quality of life questionnaire
Hrp:	Horseradish peroxidase
HRQL:	Health related quality of life
HTAs:	Host-targeting antivirals
IF:	Intrinsic factor
IFNα:	Interferon alpha
MCS:	Mental Component Summary
MH:	Mental Health
MMA:	Methylmalonic acid
MTHFR:	Methylene THF reductase
MTR:	5-methyltetrahydrofolate-homocysteine methyltransferase
MUT:	Methylmalonyl Coenzyme A mutase

NADPH:	Nicotinamide adenine dinucleotide phosphate-oxidase
NIA:	Neuroleptic-induced akinesia
NIs:	Nucleos(t)ide inhibitors
NNIs:	Non-nucleoside inhibitors
NTD:	Neural tube defects
OD:	Optical densities
PCS:	Physical Component Summary
pEVR:	Partial early virologic response
PF:	Physical Functioning
PIFN/RBV:	Pegylated interferon in combination with ribavirin
PIFNα-2:	Pegylated IFNα-2
PIs:	Protease inhibitors
PL:	Pyridoxal
PLP:	Pyridoxal 5-phosphate
PM:	Pyridoxamine
PMS:	Premenstrual syndrome
PN:	Pyridoxine
Pte Glu:	Pteroglutamic acid
Pte:	Pteroic acid
QOL:	Quality of life
RBV:	Ribavirin
RE:	Role-Emotional
RNS:	Reactive nitrogen species
ROS:	Reactive oxygen species
RP:	Role-Physical
RVR:	Rapid virologic response
s/co:	Sample/Cut-off
SAM:	S-adenosylmethionine
SF:	Social Functioning
SF-36v2:	Short form-36 Health Survey version 2
SOF:	Sofosbuvir
SPSS:	Statistical package for social science
SVR:	Sustained virologic response
TBP:	Thiamine-binding protein
TCP:	Thrombocytopenia
ThDP:	Thiamine diphosphate
THF:	Tetrahydrofolic acid
ThMP:	Thiamine monophosphate
ThTP:	Thiamine triphosphate
TMB:	Tetramethylbenzidine
TMP:	Thiamine monophosphate
TPP:	Thiamine pyrophosphate
TTP:	Thiamine triphosphate

ULN:	Upper limit of normal
V:	Vitality
vWF:	von Willebrand factor

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Abstract

Background/Aims: Pegylated-interferon α-2a and ribavirin (PIFN/RBV), the current standard treatment for hepatitis C virus (HCV) infection in Egypt, is frequently associated with hematological adverse effects, leading to high treatment discontinuation rates. The objective of the present study is to explore the effectiveness of intervening with folic acid (F) and/or vitamin B complex (B) compared with placebo (C) in HCV-treatment Egyptian patients for the management of treatment-induced deterioration of health related quality of life (HRQOL) as well as hematological parameter.

Methods: In a randomized controlled trial, one hundred and sixty subjects were randomly assigned to receive PIFN/RBV in addition to BF, B, F, or C. Blood samples were collected at different time points during 48 weeks and at 12 and 24 weeks post treatment for complete blood count and for HCV RNA real time PCR. Short form SF 36V2 questionnaire were used to assess HRQOL at various time during and post treatment.

Results: Egyptian HCV patients treated with PIFN/RBV showed deterioration of HRQOL which were correlated with deterioration in the measured hematological parameter. Supplementation with vitamin B complex plus folic acid significantly ($P<0.001$) decreased the deterioration observed in physical and mental health as well as complete blood count. Supplementation with either vitamin B complex or folic acid were also effective but with lower potency than their combination.

Conclusion: BF supplementation can reduce adverse effects of PIFN/RBV therapy in chronic hepatitis C patients, which may improve patients' HRQOL and their adherence to combination antiviral therapy.

Keywords: Hepatitis C virus, Quality of life, Folic acid, Vitamin B complex, Peginterferon, Ribavirin

Introduction

Introduction

Hepatitis C is a worldwide health problem as approximately 180 million people are chronically infected. Chronic hepatitis C is considered a major cause of end-stage liver disease and hepatocellular carcinoma **(Hoofnagle, 2002)**. Hepatitis C virus genotype 4 (HCV-4), which is prevalent in Egypt, Middle East and Africa, comprises approximately 20% of the world's HCV-infected population **(Kamal and Nasser, 2008)**. Recently, HCV-4 started to cross borders and spread to several regions in Europe **(Fernandez-Arcas et al., 2006)**, particularly among injecting drug users and patients co-infected with human immunodeficiency virus (HIV) (**Roulot et al., 2007**).

The disappointing sustained virological response (SVR) rates with conventional interferon alpha (IFNα) monotherapy or IFNα and ribavirin combination therapy **(Koshy et al., 2000)** led to the concept that HCV-4 was a 'difficult-to-treat' genotype. A steady improvement in the overall response rates of chronic HCV-4 to anti-hepatitis C therapy was achieved with the introduction of pegylated IFNα-2 (PIFNα-2) **(Kamal, 2009)**.

In order to eradicate HCV from infected patients, the treatment with pegylated interferon alfa-2a or alfa-2b in combination with ribavirin (PIFN/RBV) has been widely used because its sustained virological responses rate is beyond 50% compared with interferon alone or interferon in combination with ribavirin **(Omata et al., 2005)**. The clinical significance of this therapy is due to its effect in lowering serum HCV-RNA level and reducing the activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) **(McHutchison and Fried, 2003)**.

Although this PIFN/RIB therapy seems effective and safe for hepatitis C, several side effects such as anemia, depression, severe weight loss and flu-like syndrome from this anti-HCV therapy have been reported **(Hung et al., 2006; Younossi et al., 2007)**.

Anemia, neutropenia, leukopenia, and thrombocytopenia are among the numerous side effects of currently available HCV treatments (**Dusheiko et al., 1996)**. Preliminary data suggest that the infection itself can also induce autoimmune hemolytic anemia, leukopenia, and thrombocytopenia **(Spivak, 2000)**. These complications can influence HCV treatment and adherence, which could compromise outcomes **(Moccia et al., 2001)**.

The most important factors in successful eradication of HCV are adherence to therapy and dose maintenance. However, combination therapy significantly increased the risk of dose modifications and discontinuations due to treatment-related adverse effects **(Cummings et al., 2001)**, and, as has been observed clinically, dose modifications appeared to be less than optimal for HCV eradication. Thus, treatment success may be compromised by the adverse effects of HCV therapy **(McHutchison, 2002)**.

Hepatitis C virus patients commonly experience fatigue, anxiety, and depression. These symptoms negatively affect patients' functional health, ability to work, self-perceived health, health related quality of life (HRQL) and well-being. Psychosocial issues and reduced HRQL are frequently experienced by HCV patients (**Kraus et al., 2003**). HCV patients have more HRQL impairment than the general population (**Spiegel et al., 2005**). There is some evidence that HCV patients who experience greater fatigue, greater psychiatric symptoms, and poorer HRQL are more likely to discontinue treatment prematurely with

its negative impact on virologic response **(Bernstein et al., 2002)**. In addition to well-known side effects of interferon, one important determinant of HRQL during anti-viral therapy for HCV is development of ribavirin-induced anemia **(Tod et al., 2005)**. Treatment of anemia improves HRQL, potentially impacting adherence to antiviral regimen and improving virologic response. These issues emphasize the importance of investigating the physical and psychosocial experiences and HRQL of HCV patients **(Afdhal, 2004).**

B vitamins including vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin B_6 (pyridoxine), vitamin B_{12} and folate are involved in many important physiological functions such as energy metabolism, protein biosynthesis and cell reproduction. If this therapy interferes with the metabolism of B vitamins, this therapy for HCV patients might lead to other healthy risk **(Lin and Yin, 2009)**.

HCV infection led to the decline of vitamin B_6, vitamin B_{12} and folate in HCV patients. Furthermore, this PIFN/RBV therapy not only decreased vitamins B_1 and B_2 in plasma and/or RBC but also exacerbated the depletion of vitamin B_6. Apparently, HCV infection and this therapy worsened B vitamins status. It is known that vitamin B_2 affects epithelial integrity, rate of prostaglandin biosynthesis, and vitamin B_6 is a cofactor for many enzymes involved in metabolism **(Talwar et al., 2003)**. Thus, the depletion of these vitamins in HCV patients with this therapy might impair many physiological functions and induce other complications. On the other hand, it has been documented that vitamins B_2 and B_6 could exhibit antioxidant activity *via* scavenging oxygen radicals and organic radicals. Thus, the decrease in vitamins B_2 and B_6 in these HCV patients also suggested that HCV infection and this PIFN/RBV therapy diminished their antioxidant defense **(Ksendzova et al., 2004)**.