Nitazoxanide for Hepatitis C: A Systematic Review

Thesis Submitted for fulfillment of the Master Degree in Tropical Medicine

By

SHAHIRA AHMED MAHMOUD
(M.B.B.Ch., Cairo University)

Supervisors

AYMAN RASHAD AMER

A. Professor of Tropical Medicine
Faculty of Medicine, Cairo University

SHEREEN M. SHOUKRY HUNTER
Lecturer of Tropical Medicine
Faculty of Medicine, Cairo University

NAGLAA HASAN ZAYED
Lecturer of Tropical Medicine
Faculty of Medicine, Cairo University

Faculty of Medicine
Cairo University
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List of Abbreviations

AASD: American Association for the Study of Liver Diseases.

AIDS: Acquired Immunodeficiency Syndrome.

ALT: Alanine Transferase.

BMJ: British Medical Journal.

cEVR: complete End Virological Response.

CHBG: Cochrane Hepato-Biliary Group.

CI: Confidence Intervals.

CRG_S: Cochrane Review Groups.

ETR: End of Treatment Response.

EVR: Early Virological Response.

FL: Florida.

GRADE: Grading of Recommendations, Assessments, Development and Evaluation.

HBV: Hepatitis B Virus.

HCV: Hepatitis C Virus.

ICH: International Conference of Harmonisation.

IFN: Interferon.

ITT: Intention-to-treat.

NNT: Number Needed to Treat.

NTZ: Nitazoxanide.

OIS: Optimal Information Size.

OPTN: Organ Procurement and Transplantation Network.

PKR: Protein Kinase Phosphorylation.

RD: Risk Difference.

RNA: Ribonucleic acid.

RR: Relative Risk.

RVR: Rapid Virological Response.

SVR: Sustained Virological Response.

USA: United States of America.

WHO: World Health Organization.

Abstract

Background

Chronic HCV infection is the main cause of liver cirrhosis and liver cancer in Egypt and, indeed, one of the top five leading causes of death, and has long been refractory to conventional treatments.

Objectives

To evaluate the safety and efficacy of nitazoxanide as a monotherapy or given with peg-interferon alfa, with or without ribavirin.

Results

Many clinical trials were done in Egypt and suggest that the combination of nitazoxanide, peg-interferon alfa-2a and ribavirin increase the percentage of patients with Rapid Virological response (RVR) and Sustained Virological Response (SVR), compared with patients given peg-interferon plus ribavirin, without an increase in adverse events.

Conclusion

Nitazoxanide is a safe drug to be used in treatment of chronic hepatitis C, as an adjuvant to current treatments or as a monotherapy.

Key word:

Nitazoxanide is safe drug to be used in treatment of chronic hepatitis C, as an adjuant current treatments or as a monotherapy.

Review of literature

Description of the condition

Hepatitis C is a disease of the liver caused by the hepatitis C virus (HCV). HCV is an enveloped RNA virus that constitutes the genus *Hepacivirus* within the *Flaviviridae family* **(van Regenmortel et al, 2000; Penin et al, 2004).** HCV is divided into six genotypes, which differ from each other by up to 30% in the nucleotide sequence, and has a large and growing number of subtypes **(Rosenberg 2001).** Furthermore, HCV genotypes differ with geographic region **(Davis 1999).** Although a genotype does not predict the outcome of the infection, it does predict the likelihood of treatment response, and, in many cases, determines the duration of treatment **(Manns et al, 2001; Fried et al, 2002; Hadziyannis et al, 2004).** Globally, an estimated 170 million people are chronically infected with HCV and three to four million persons are infected each year **(WHO 2009),** and is particularly common in Egypt, with an estimated prevalence rate of 15% and approximately 90% of patients with hepatitis C in Egypt are infected with HCV genotype 4 **(Rossignol et al, 2009).** Chronic hepatitis C is likely to become an even greater burden during the next decades since most of the carriers are unaware of their infection. In the majority of patients, the initial presentation of hepatitis C infection is asymptomatic. Hepatitis C infection is generally recognised in the chronic phase **(Hodgson 2003).** Around 85% of patients who become infected with hepatitis C fail to clear the virus and become chronic carriers. Among these individuals, 5% to 20% are reported to develop cirrhosis over a period of approximately 20 to 25 years **(Strader&Seeff 1996; Seeff&Hoofnagle 2002).** Patients with advanced fibrosis or cirrhosis develop liver complications such as liver failure, portal hypertension, and hepatocellular carcinoma with the annual rate of approximately 2% to 4% **(Benvegnu&Alberti 2001; Fattovich et al, 2002).** Chronic hepatitis C is the single most common indication for liver transplantation **(OPTN 2005).** Patients with cirrhosis who have a life expectancy of 1-2 years without transplantation because of recurrent or refractory ascites, Child-Pugh C cirrhosis, uncontrolled gastrointestinal bleeding, severe encephalopathy, or bacterial peritonitis, should be considered for liver transplantation, where this is possible **(WHO 2009).**

A serendipitous observation (i.e. : mere accidental discovery) during drug development revealed that some patients with cryptosporidiosis and acquired immune deficiency syndrome (AIDS) who were co-infected with HCV or hepatitis B virus (HBV) had a reduction in serum alanine transferase (ALT) levels during therapy. Subsequent laboratory studies were conducted with nitazoxanide (NTZ) and its active metabolite, tizoxanide, using standard antiviral assays and demonstrated potent inhibition of both HCV and HBV

replication **(Rossignol et al, 2008).** This observation led to studies of the antiviral activity of nitazoxanide and its active metabolite, tizoxanide, in HCV genotype 1a and 1b replicons and a genotype 2 infectious clone, which showed potent inhibition of HCV replication by both compounds at submicromolar concentrations **(Rossignol et al, 2009).**

The mechanism of action of NTZ in protozoa and anaerobic bacteria has been shown to result from direct inhibition of pyruvate ferredoxin oxidoreductase enzyme-dependent electron transfer reduction, which is essential to anaerobic energy metabolis **(Rossignol et al, 2009) .**However, the antiviral mechanism of action of NTZ appears to be different. Recent studies suggest that NTZ and other thiazolides, selectively induce double-stranded RNA-activated protein kinase phosphorylation(PKR), which leads to increased cell concentration of phosphorylated eukaryotic initiation factor 2 alpha, a naturally occurring antiviral intracellular protein**(Rossignol et al, 2009).**

This mechanism of action is triggered only when a cell is infected with HCV whereas NTZ has no effect in uninfected cells, which provides a potential explanation for its very low rate of toxicity **(Rossignol et al, 2009).**

Description of the intervention

The goal of the treatment of chronic hepatitis C is to prevent complications of hepatitis C infection; this is principally sought by the eradication of the infection **(Strader et al, 2004).** Accordingly, treatment is aimed to achieve a virologic response, defined as the absence of HCV RNA in serum by a sensitive test at the end of treatment (end of treatment response (ETR)) and six months later (SVR). Monotherapy with interferon produces SVR in less than 20% of patients **(Myers et al, 2002).** The introduction of combination therapy with interferon and ribavirin was considered a major advance. Combination therapy produces SVR in approximately 40% of previously untreated patients **(Brok et al, 2005).** A combination of weekly subcutaneous injections of long-acting peginterferon alpha and oral ribavirin achieves the highest overall SVR rates of 56% **(Strader et al, 2004).** This represents the current standard of care according to The American Association for the Study of Liver Diseases practice guidelines **(Strader et al, 2004).** However, this standard treatment is still suboptimal, with a high rate of failure of SVR and adverse events rate 75% (e.g., influenza-like symptoms, depression, neutropenia, thrombocytopenia, etc.) **(Strader et al, 2004).**

How the intervention might work

A number of emerging treatments have shown promising results in early phase clinical trials as an adjuvant to current treatments **(**De Francesco&Migliaccio 2005**).** It has been speculated that such multi-combination treatments may especially find use for non-responding and relapsing patients. As more treatments become available, it might become possible to conceive combination schemes based entirely on novel drugs, and thus, shift away from the limitations of current standard treatment **(**De Francesco &Migliaccio 2005**).** Nitazoxanide is a thiazolide with activity against anaerobic bacteria and protozoa. Nitazoxanide was originally developed for the treatment of infectious diarrhoea caused by *cryptosporidium parvum* and *Giardia lamblia*. Currently, the licensed product of nitazoxanide is Alinia (Romark Laboratories, USA), in the form of tablets and oral suspension. Following oral administration in humans, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide) **(**FDA 2005**).** The antiviral activity of nitazoxanide was discovered by serendipity in patients with AIDS who were treated for cryptosporidial diarrhoea and had HBV or HCV co-infection **(**Rossignol et al, 2001**).** Nitazoxanide and tizoxanide are believed to exhibit a potent inhibition of both HBV and HCV replication **(**Korba et al, 2008**).**

With the absence of previous meta-analysis or systematic reviews, this review aims to assess the benefits and harms of nitazoxanide in the treatment of patients with hepatitis C.

Objectives

To systematically evaluate the benefits and harms of nitazoxanide for chronic hepatitis C patients.

Methods

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials irrespective of language or publication status.

Types of participants

Patients with chronic hepatitis C were included. Patients were treatment-naive (not previously treated), relapsers (patients with a transient response to

previous treatment), or non-responders (patients without response to previous treatment).

Types of interventions

This review included randomised clinical trials comparing nitazoxanide with control given with or without co-intervention(s). Trials were included regardless of the dose or the duration of the interventions. Co-interventions were permitted if received by all trial groups and applied equally.

Types of outcome measures

- Sustained virological response (SVR): number of patients with undetectable HCV RNA in serum by sensitive test six months after the end of treatment.
- Liver-related morbidity plus all-cause mortality: number of patients who developed cirrhosis, ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, or died.
- Adverse events: number and type of adverse events defined as patients with any untoward medical occurrence not necessarily having a causal relationship with the treatment. We will report on adverse events that lead to treatment discontinuation and those that have not lead to treatment discontinuation separately. Serious adverse events are defined according to the International Conference on Harmonisation (ICH) Guidelines **(ICH1997)** as any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, and any important medical event, which may have jeopardised the patient or requires intervention to prevent it. All other adverse events will be considered non-serious.

Search methods for identification of studies

Electronic searches

We searched *The Cochrane Hepato-Biliary Group Controlled Trials Register (*Gluud 2008*), The Cochrane Central Register of Controlled Trials* in *The Cochrane Library* (the latest issue)*, MEDLINE, EMBASE, LILACS,* and *Science Citation Index EXPANDED* using the search strategies and periods given in Appendix 1 **(Royle&Milne 2003).**

Searching other resources

We identified further trials by searching national(Ministry of scientific Research along with Pan African medical journals, journal watch, Encyclopedia and South Africa medical journal) and topic-specific databases,