Safety and Efficacy of Combined Therapy with Pegylated Interferon Alpha-2b and Ribavirin for Egyptian Children with HCV Infection

Thesis

Submitted for Fulfillment of M.Sc. Degree in Pediatrics

By

Samah Abdel Hameed Mubarak

Resident of Pediatrics, Ministry of Health

Supervisors

PROFESSOR HANAA MOSTAFA EL-KARAKSY

PROFESSOR OF PEDIATICS

FACULTY OF MEDICINE-CAIRO UNIVERSITY

ASSISSTANT PROFESSOR DOA`A AHMED ESSAWI SALEH

Assistant Professor of Community Medicine

FACULTY OF MEDICINE-CAIRO UNIVERSITY

DR. ENGY ADEL MOHAMMAD MOGAHED

Lecturer OF PEDIATICS

FACULTY OF MEDICINE-CAIRO UNIVERSITY

٢٠١٥

Acknowledgment

Professor Dr. HanaaMostafa El-Karaksy, Professor of Pediatrics, Cairo University, for whom I owe her masterful teaching, continuous support and correction, and for whom I express my utmost gratitude.

Assistant Professor Doa`a Ahmed Essawi Saleh, Assistant Professor of Community Medicine, Cairo University, to whom I would like to express my optimum gratitude for her valuable guidance, help, advice, constructive criticism and supervision.

Dr. Engy Adel Mogahed, Lecturer of Pediatrics, Cairo University, to whom I will be extremely grateful forever for her constant valuable teaching and guidance on every level and for her kind supervision and continuous cooperation.

ABSTRACT

Introduction: Hepatitis C virus (HCV) infection is a serious health problem worldwide that leads to chronic infection in up to 85% of cases. Combined treatment with pegylated interferon (PEG IFN) α 2b and Ribavirin (RBV) is the only approved treatment for HCV infection in children until the present time. **Aim of work:** to assess the safety and efficacy of combined treatment with PEG IFN α2b and RBV in Egyptian children and adolescents with genotype 4 (GT 4) HCV infection. **Patients and methods:** The study was performed on 66 pediatric patients (3-18 years of age), of both sexes, infected with HCV GT4. Children were treated with PEG IFN α 2b in a dose of 60 μg/m^2, given as subcutaneous injection once weekly and RBV in a dose of 15 mg/kg in 2 divided doses orally, daily. Treatment outcome was assessed by the absence of detectable viral RNA in blood 24 weeks after end of treatment, i.e., sustained virological response (SVR). Safety was assessed by performing specific investigations, weight and height measurements and questionnaires directed to the patients at specific intervals**.** **Results:** Forty three out of the 66 included patients (65.2%) were males. Mean age of the patients at the time of enrollment in the study was 10.9 $\pm$ 3.5 years. SVR was achieved in 28 patients (42.4%). Comparing the group of responders to the non responders, history of treated malignancies was significantly commoner in non responders group (P= 0.03), responders had significantly higher levels of absolute neutrophilic count and lower levels of GGT (P= 0.009 and 0.003 respectively). HCV PCR level was significantly lower in responders (P=0.03). Fever was the most frequently reported side effect occurring in 98.5% of the patients followed by musculoskeletal symptoms. Neutropenia was observed in 36 patients (54.6%) which necessitated treatment discontinuation in only one patient. Seventy percent of children, who received the combined therapy for a total of 48 weeks, showed a drop in both weight and height percentiles at the end of the 48 weeks. **Conclusion:** The currently available treatment, PEG-IFNα 2b and RBV, for HCV GT 4 in pediatric patients has modest SVR of 42.4% with numerous adverse events necessitating meticulous monitoring to optimize care of the patients. Side effects could be managed with dose modifications and specific treatment when necessary.

Keywords: (HCV, INF, RBV, Chronic HCV infection).

TABLE OF CONTENTS

Page

Chapter 4: Prevention and treatment of HCV infection

LIST OF ABBREVIATIONS

AHA	**:**	Autoimmune hemolytic anemia
ALT	**:**	Alanine aminotransferase
ANA	**:**	Antinuclear antibody
ANC	**:**	Absolute neutrophilic count
AP	**:**	Alkaline phosphatase
AST	**:**	Aspartate aminotransferase
BMI	**:**	Body mass index
BOC	**:**	Boceprevir
BT	**:**	Breakthrough
C	**:**	Core
CHC	**:**	Chronic hepatitis C
CNS	**:**	Central nervous system
DAAs	**:**	Direct acting antivirals
DCV	**:**	Daclatasvir
DNA	**:**	Deoxyribonucleic acid
DVR	**:**	Delayed virologic response
E	**:**	Envelope
EIA	**:**	Enzyme immunoassay
EPO	**:**	Erythropoietin
ETR	**:**	End of treatment response
EVR	**:**	Early virologic response
FDA	**:**	Food and Drug Administration
GCSF	**:**	Granulocyte colony stimulating factor
GGT	**:**	Gamma-glutamyle transpeptidase
GT	**:**	Genotype
HAI	**:**	Histological activity index
HBsAg	**:**	Hepatitis B surface antigen
HBV	**:**	Hepatitis B virus

HCC	**:**	Hepatocellular carcinoma
HCV	**:**	Hepatitis C virus
HAART	**:**	Highly active antiretroviral therapy
HIV	**:**	Human immunodeficiency virus
IL	**:**	Interleukin
IQR	**:**	Interquartile range
ISGs	**:**	Interferon stimulated genes
IU	**:**	International unit
MC	**:**	Mixed cryoglobulinemia
n	**:**	Number
NS	**:**	Non structural
NTR	**:**	Non translated region
ORF	**:**	Open reading frame
PCR	**:**	Polymerase chain reaction
PEG IFN	**:**	Pegylated interferon
PI	**:**	Protease inhibitor
PT	**:**	Prothrombin time
RBV	**:**	Ribavirin
RdRp	**:**	RNA-dependent RNA polymerase
RF	**:**	Rheumatoid factor
RIBA	**:**	Recombinant immunoblot assays
RNA	**:**	Ribonucleic acid
RT	**:**	Reverse transcription
RVR	**:**	Rapid virologic response
SD	**:**	Standard deviation
SIM	**:**	Simeprevir
SOF	**:**	Sofosbuvir
SPSS	**:**	Statistical Package for Social Science
SVR	**:**	Sustained virologic response
TLC	**:**	Total leucocytic count

TLV **:** Telaprevir

TSH **:** Thyroid stimulating hormone

WHO **:** World Health Organization

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION AND AIM OF WORK

Hepatitis C virus (HCV) infection is a serious health problem worldwide that establishes a chronic infection in up to 85% of cases **(Welbourn and Pause, 2007).** HCV genotype (GT) 4 is responsible for approximately 20% of the cases of chronic HCV infection worldwide **(Wantuck et al., 2014).** Egypt has the highest prevalence of HCV infection in the world. HCV is one of the 5 top leading causes of death in Egypt **(Miller and Abu-Raddad, 2010).** Studies of the magnitude of HCV infection in Egyptian children revealed a prevalence of 3% in upper Egypt and 9% in lower Egypt **(Kamal, 2011).** The main HCV GT in Egypt is type 4 **(Kamal and Nasser, 2008).**

Treatment of chronic HCV aims at slowing disease progression, preventing complications of cirrhosis, reducing the risk of hepatocellular carcinoma, and treating extrahepatic complications of the virus **(Reddy et al., 2009).** The percentages of patients achieving sustained virologic response (SVR), improved significantly with advances in the therapeutic regimens. However, SVR rates are still below target, especially for the difficult to treat HCV GT 1 and 4 **(Kamal, 2014).**

Combined treatment with pegylated interferon (PEG IFN) α 2b and Ribavirin (RBV) was approved by the United States FDA in December 2008 and by the European Medicines Agency in December 2009 for children aged 3 years and older **(Indolfi et al., 2012b)** and is still the only available treatment for HCV infection in children until the present time.

IFN-based regimens have moderate to severe side effects, including hematologic adverse events (neutropenia, thrombocytopenia), fatigue, irritability, fever, myalgia, arthralgia, inflammation at the injection site, and cardiac dysrhythmia, that negatively influence the tolerability and adherence of patients with therapy **(Kamal, 2014).**

The aim of the present work was to assess the efficacy and tolerability of combined treatment of PEG IFN α2b and RBV in Egyptian children and adolescents with GT 4 chronic HCV infection.

CHAPTER 1: HISTORICAL BACKGROUND, VIRAL CHARACTERISTICS AND EPIDEMIOLOGY OF HCV

HISTORICALBACKGROUND

With the development of assays specific for the hepatitis A and B viruses and their antibodies, it became clear that many cases of transmissible hepatitis were not related to either of these classic viruses. These cases were termed non-A, non-B hepatitis. It was shown, that most transfusion-associated cases of hepatitis were not due to the hepatitis B virus (HBV), but were caused by some other agents **(Feinstoneet al., 1975).** After a search of about 15 years, a new virus termed HCV was identified as the agent responsible for most transfusion-associated non-A, non-B hepatitis **(Chooet al., 1989).** Naturally, HCV infects only humans and chimpanzees **(Sandmann and Ploss, 2013).**

VIRAL CHARACTERISTICS

Description

HCV is a ribonucleic acid (RNA) virus that is estimated to chronically infect as many as 3% of the world's population. As a member of Flaviviridae **(Reed and Rice, 2000),** this viral family contains three genera – flavivirus, pestivirus, and hepacivirus. To date, only three members of the hepacivirus genus have been identified, HCV, GB virus B, and the recently detected canine hepacivirus **(Kapoor et al., 2011)**.

Structural analysis of HCV virions was very limited because the virus was difficult to cultivate in cell culture **(Thomssen et al., 1992).** HCV virions isolated from cell culturehave a spherical envelope (E) containing tetramers of the HCV E1 and E2 glycoproteins **(Wakita et al., 2005; Yu et al., 2007).** Inside the virions a spherical structure, representing the nucleocapsid (core; C) that harbours the viral genome **(Wakita et al., 2005**).The genome of the HCV consists of one singlestranded RNA molecule (9.6 kb) with positive polarity. Similar to other positive-strand RNA viruses, the genomic RNA of the HCV serves as messenger RNA (mRNA) for the translation of viral proteins **(Kupfer, 2013)**.

HCV genome **(Figure 1)** carries a long openreading frame (ORF) encoding a polyprotein precursor of 3010 amino acids. Translation of the HCV ORF is directed via a 340 nucleotide long 5' nontranslated region (NTR) functioning as an internal ribosome entry site; it permits the direct binding of ribosomes in close proximity to the start codon of the ORF. The HCV polyprotein is cleaved by cellular and viral proteases into ten different products, with the structural proteins (C, E1 and E2) located in the N-terminal third and the non-structural (NS2-5) replicative proteins in the remainder **(Beaulieu and Tsantrizos, 2004).** Among the NS proteins, the NS3 serine-like protease and the RNA-dependent RNA polymerase (RdRp) are essential for viral maturation and replication, and therefore represent ideal targets for the development of small molecule anti-HCV compounds **(De Francesco et al., 2003 ; Beaulieu and Tsantrizos, 2004).**

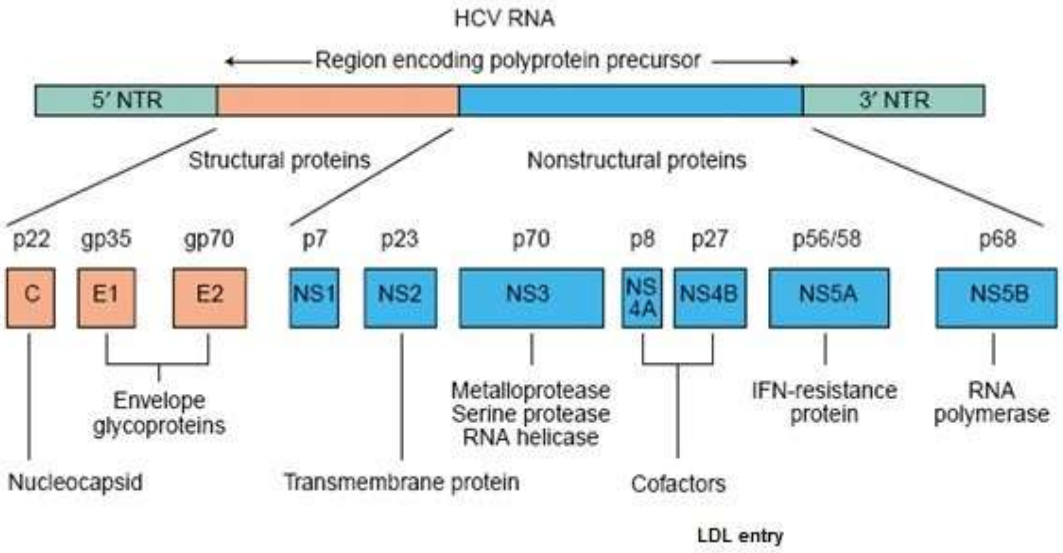

Figure 1: Proteins encoded by the HCV genome (Beaulieu and Tsantrizos, 2004).