بسم الله الرحمن الرحيم

قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

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Non haematologicalAdverse Drug Reactions Associated With Peginterferon alfa-Ribavirin Therapy in Management of Viral Hepatitis C : Retrospective Observational Study

THESIS SUBMITED FOR PARTIAL FULFILLMENT OF THE M.SC DEGREE IN INTERNAL MEDICINE

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ADRs ……. Adverse drug reactions

ALT……..…….. Alanine Aminotransferase

ANC …….....Absolute neutrophil count

ANA…….. Antinuclear antibodie

AST……..……..... Aspartate Aminotransferase

CDC ……..... Center for Diseases Control and Prevention

EHM ……. ..…..Extrahepatic manifestation

EIA …….……..…. Enzyme Immune Assay

ELISA …….……..… Enzyme Linked Immunosorbent Assay

ETR …….……..... End of treatment response

EVR …….……..... Early virological response

HBsAg ……..... Hepatitis B Virus surface Antigen

HBV ……. Hepatitis B Virus

HCC ……. Hepatocellular Carcinoma

HCV ……..…Hepatitis C Virus

HCV-Abs ……..… Hepatitis C Virus-Antibodies .

HCVcAg ……. Hepatitis C Virus Core Antigen

HCWs …….. Healthcare Workers

HD …….Hemodialysis

HIV ……Human Immunodeficiency Virus

IFN …….Interferon

IG ……...Immune globulin

IMPDH ……..…..Inosine monophosphate dehydrogenase

INR ……... International normalization ratio

LFTs ……..Liver Function test

ORF ……..…Open Reading Frame

List of Abbreviations

PCR …… Polymerase Chain Reaction

PWID …….. people who inject drugs

PEG-IFN ……. Pegylated Interferon

RIBA …….. Recombinant Immunoblot Assay

SSRIs…….. Selective serotonin reuptake inhibitors

TGF ……... Transforming growth factor

SVR …… Sustained Vibrologic Response

TMA …….. Transcription Mediated Amplification

URT ……... Untranslated region

WHO …… Word health Organization

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Mohamed Meshref Hamouda Meshref

Introduction

The high incidence of hepatitis C virus (HCV) makes it one of the greatest health threats facing the world ***(Rhoads،2003)***.The prevalence of HCV infection in Egypt is the highest reported world-wide ***(Frank et al.,2000)***. about %85 of those infected with HCV will develop chronic hepatitis of varying severity. Nearly 20 % of patients develop cirrhosis in 10 - 20 years and the incidence of hepato-cellular carcinoma (HCC) is 1 – 4% per year in patients with cirrhosis ***(Marcellin et al., 1997)*** . The majority of hepatitis C virus occurs among people who inject drugs (PWID) and the burden of HCV-related liver disease is still increasing HCV treatment is safe and effective among PWID and international guidelines encourage HCV treatment in this group ***(Dimova et al., 2013).***

Hepatitis C is a treatable disease, and over the last few years increasing numbers of patients have been offered antiviral treatment to eradicate the virus. However, treatment is cytotoxic and associated with a multitude of adverse side effects ***(Zucker and Miller,2001).*** The treatment for HCV involves a combination of two drugs: Pegylated Interferon (a subcutaneous injection that is given once weekly) and ribavirin tablets that are taken orally each day for one year ***(Fried, 2002).*** In some patients (depending on genotype),

this treatment has been shown to induce a sustained viral response (SVR), defined as undetectable hepatitis C (PCR) for six months after the end of treatment ***(Zic 2005).*** Studies have also found that patients who do not experience an SVR may benefit from the temporary decrease in liver inflammation and fibrosis while taking treatment ***(Shiffman et al.,1999).***

Adherence of patients to therapy is important because it can slow down the disease process. There are more than six genotypes of HCV identified and genotype determines the duration of treatment ***(Fried, 2002)***. The most common genotypes of HCV in Europe are genotypes 1, 2 and genotype 3. Other genotypes 4, 5 and 6, are uncommon, but with the increasing number of foreign national immigrants into Europe, these genotypes are becoming more prevalent. In relation to treatment, genotypes 2 and 3 have similar traits and have the highest response rates; usually about 80% of cases clear the virus. These genotypes of HCV require 24 weeks of antiviral treatment. Conversely, genotypes 1, 4, 5 and 6 require 48 weeks of treatment but have poorer response rates; usually about a 48% chance of clearing the virus ***(Levine and*** 2005Ghalib,). The most common genotype in Egypt is type 4 ***(Mezban and Wakil, 2006***).

Introduction

Side effects of antiviral therapy include nausea, pain and depression, which can also have a serious impact on the ability to work and on quality of life . Unfortunately HCV treatment can initially compound and worsen these effects. Side effects such as worsening fatigue, insomnia, alopecia and arthralgia are common. Side effects can appear in clusters at different times during patient's therapy, regardless of their genotype or length of treatment, Other side effects include anorexia, skin irritations, anaemia , neutropenia and flu like symptoms ***(Zucker and Miller, 2001)***. In some cases the side effects produced by therapy are so intense, patients feel forced to give up on treatment or doctors may even recommended this ***(Mulhall and Younossi, 2005)***. Furthermore, depression can also increase the risk for patient noncompliance with antiviral therapy, these side effects may lead the patients to stop the treatment ***(Maddrey, 1999)***.

Conclusion

- Flu-like symptoms usually occurred during the first weeks of treatment and severity declined over time.

-Eighteen patients had to reduce the dose of interferon and ribavirin due to respiratory complications and twenty six patients stopped therapy for1week.

-cutaneous ADRs were reported early and decreased with the end of treatment. They were mainly injection site reactions, skin rash and itching.

- neuropsychiatric ADRs were reported and they were mainly lack of concentration, insomnia, and depression , In week 24 Depression reached highest level 22%.

-weight loss, from week 2 to week 40 number of patients increased and reached highest level in week 16. Fifteen patients developed significant weight reduction i.e. lost 10% of their pretreatment weight

Aim of the study

To investigate the adverse drug reactions (ADRs) associated with peginterferon plus ribavirin therapy in the management of hepatitis C. in order to:

- Point out all possible ADRs attributed to the use of this therapy in selected patients.
- Classify these ADRs according to their effect on continuation of therapy

Design

Retrospective Observational Pharmacovigilance Study

Setting

Outpatient clinics, El-Kapary hospital, Alexandria, Egypt

HEPATITIS C VIRUS

The hepatitis C virus (HCV) is the major etiologic agent of non-A and non-B hepatitis (***Kim, 2002***). Chronic infection with HCV results in the development of liver cirrhosis and hepatocellular carcinomas (HCC) (***Tong et al., 1995***).

The World Health Organization (WHO) has declared hepatitis C a global health problem, with approximately 3% of the world's population (roughly 170-200 million people) infected with HCV (***Mezban and Wakil, 2006***). Of those infected, a reported 80% fail to clear the virus, a significant number of whom will go on to develop severe liver disease, including cirrhosis and HCC (***Tran, 2008***).

Hepatitis C is not known to cause disease in other animals. No vaccine against hepatitis C is currently available. The existence of hepatitis C (originally "non-A non-B hepatitis") was postulated in the 1970s and proven in 1989 (***Houghton, 2009***).

Infection with HCV results in a gamut of clinical outcomes ranging from viral elimination to the development of end-stage liver disease or HCC. Viral elimination, which occurs in a minority (~20%) of acutely HCV-infected individuals, is the result of effective immune control of HCV replication. The 80% of people who do not eliminate HCV progress to chronic HCV infection (***Thio, 2008***).