Middle-East Journal of Scientific Research 13 (1): 101-106, 2013
ISSN 1990-9233

DOI: 10.5829/idosi.mejsr.2013.13.1.7126

Liver Enzymes and Virologic Response to Combined Pegylated Interferon-Ribavirin Therapy in Saudi Chronic Hepatitis C Infected Patients

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Abstract: Chronic hepatitis C (HCV) affects more than 180 million people worldwide and it is the leading cause of liver disease in Middle East with the prevalence up to 20% in some populations. As one of the most important infectious diseases, it causes around 250,000 deaths per year. Liver cirrhosis eventuates in 20% to 30% patients with chronic HCV infection. HCV was estimated to be attributable to one third of hepatocellular carcinoma cases globally. The aim of this study was to detect liver enzymes and virologic response to combined Pegylatedinterferon-alfa (PEG-IFNα)-ribavirin therapy in Saudi chronic hepatitis C infected patients. One hundred patients with chronic HCV infection who have anti HCV antibodies detected by ELISA were selected to undergo Real-Time polymerase chain reaction (RT-PCR) and liver enzymes serum levels of aspirate aminotransferase (AST) and alanine aminotransferase (ALT) before starting treatment with combined pegylated interferon-ribavirin therapy, RT-PCR after 12 weeks of starting of treatment and RT-PCR and liver enzymes after 24 weeks of anti-viral treatment. Results revealed After 12 weeks of anti-viral treatment, RT-PCR was done on 5 resisted cases and as a result their treatment has been stopped, where 95 cases were sensitive, so they continued their combined pegylated interferon-ribavirin therapy. However, after 24 weeks of anti-viral treatment RT-PCR, AST and ALT were done again and 12 patients were resisted cases and 83 patients were sensitive to combined pegylated interferon-ribavirin therapy, also, there were statistical significant reduction in the mean values of AST and ALT after 24 weeks of anti-viral treatment. Conclusion: Combined Pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy is an effective treatment strategy for Saudi chronic hepatitis C infected patients.

Key words: Liver Enzymes · Virologic Response · Pegylated Interferon · Ribavirin · Chronic Hepatitis C.

INTRODUCTION

Chronic hepatitis C (CHC) is a worldwide problem leads to chronic liver disease (CLD) [1]. Liver cirrhosis eventuates in 20% to 30% patients with chronic HCV infection, generally after 2 to 3 decades [2]. Once cirrhosis occurs, hepatocellular carcinoma develops in 1% to 4% of these patients per year [3]. HCV was estimated to be attributable to one third of hepatocellular carcinoma cases globally [4-6]. HCV related health burdens are emerging quickly in Asian countries and represent a great public health burden [7].

Chronic hepatitis C (CHC) is is usually a blood-borne infection. Most patients will have subclinical infection at the onset, but patients who develop acute hepatitis can spontaneously clear the virus upon immune activation. Up to 80% of CHC patients will progress to chronic infection. CHC is unlikely to clear spontaneously [8].

The goal of treatment of chronic hepatitis C is to prevent complications of hepatitis C infection; this is principally sought by eradication of the infection [9]. Accordingly, treatment is aimed to achieve a virological response, defined as the absence of hepatitis C virus RNA in serum by a sensitive test at the end of treatment (end of treatment response (ETR)) and 6 months later (sustained virological response (SVR)). The most common treatments for hepatitis C are interferon-based therapies given with or without some co-intervention (e.g., ribavirin) [11, 12]. A combination of weekly subcutaneous injections of pegylated interferon and oral ribavirin represents the current standard of care according to The American Association for the Study of Liver Diseases practice guideline [10].

Hepatitis C virus (HCV) infection is a global blood-borne disease that affects almost 3% of the world's population [13]. The most characteristic feature of acute

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hepatitis C is the propensity to evolve into chronic infection [14]. Epidemiologic data from populations at risk of exposure suggest that 14-40% of people infected with HCV spontaneously clear the virus and have no detectable HCV-RNA in plasma [15]. More definite calculations revealed an overall chronic rate averaging 80% and implying a rate of self-limited infections of around 20% [14]. Other studies reported even higher rates of at least 50% spontaneous clearance of HCV in various populations [16]. Persistence of HCV infection is diagnosed by the detection of HCV-RNA in the blood for at least 6 months [17]. Recovery from HCV infection is defined by the presence of HCV-specific antibodies in the absence of detectable HCV-RNA [18].

Pegylated interferon in combination with ribavirin is currently the standard treatment for chronic hepatitis C virus (HCV) infected patients [19]. A sustained virological response (SVR), defined as an undetectable plasma HCV-RNA 24 weeks after cessation of therapy, is achieved in around 50% of patients infected [20].Furthermore, achievement of a rapid virological response (RVR, i.e. plasma HCV-RNA with undetectable, i.e. <50 IU/ml at week 4 of therapy) is regarded as a strong on-treatment predictor for SVR [21].

The aim of this study was to detect liver enzymes and virologic response to combined pegylatedinterferon-alfa (PEG-IFNα)-ribavirin therapy in Saudi chronic hepatitis C infected patients.

MATERIALS AND METHODS

One hundred patients; 70 males and 30 females, their age ranged from 25 to 55 (32.6±6.53) years, were studied on referral to Gastroenterology and Hepatology Department, King Abdulaziz University Teaching Hospital, Saudi Arabia. All these patients were anti HCV positive by enzyme-linked immunosorbent assay (ELISA). None of the patients included in this study had other potential causes of liver disease, such as alcoholism, autoimmune phenomena, or metabolic disorders. All the patients were not treated previously with antiviral drugs. Only patients diagnosed with chronic HCV mono-infection and have anti HCV antibodies by ELISA were selected to undergo Real-Time polymerase chain reaction (RT-PCR) and liver enzymes serum levels of aspirate aminotransferase (AST) and alanine aminotransferase (ALT) before starting treatment with combined pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy, RT-PCR after 12 weeks of starting of treatment and RT-PCR and liver enzymes after 24 weeks of anti-viral treatment. This study was approved by the Scientific Research Ethical Committee, Faculty of Applied Medical Sciences at King Abdulaziz University. All participants were free to withdraw from the study at any time. If any adverse effects had occurred, the experiment will be terminated and the Human Subjects Review Board will be informed. However, no adverse effects occurred and so the data of all the participants were available for analysis.

Methods

Evaluated Parameters: Ten milliliter blood samples were collected from each participant at study entry. The blood samples were obtained using disposable needles and heparinized vacuum syringes and stored at -70°C until assayed. Serum samples of all participants were tested for Real-Time polymerase chain reaction (RT-PCR), serum levels of aspirate aminotransferase (AST) and alanine aminotransferase (ALT).

Real-Time Polymerase Chain Reaction (RT-PCR): Real-Time polymerase chain reaction (RT-PCR) test was done to detect serum HCV RNA levels by polymerase chain reaction using the COBAS TaqMan HCV test, v2.0 (Roche Diagnostics, Indianapolis, NJ, USA).

Liver Enzymes Measurements: Serum levels of aspirate aminotransferase (AST) and alanine aminotransferase (ALT) by serum chemistry autoanalyzer (Model 736, Hitachi, Tokyo, Japan) using commercial reagents (Biomerieux, Marcy L'Etoile, France).

RESULTS

One hundred Saudi patients with chronic HCV infection were studied on referral to Gastroenterology and Hepatology Department, King Abdulaziz University Teaching Hospital, all these patients were anti HCV positive by enzyme-linked immunosorbent assay (ELISA). Patient characteristics, shown in Table 1, were homogeneous when grouped into males and females. Real-Time polymerase chain reaction (RT-PCR) and liver enzymes serum levels of aspirate aminotransferase (AST) and alanine aminotransferase (ALT) before starting treatment with combined pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy. After 12 weeks of anti-viral treatment, RT-PCR was done on 5 resisted cases and as a result their treatment has been stopped, where 95 cases were sensitive, so they continued their combined pegylated interferon-ribavirin therapy. However, after 24 weeks of anti-viral treatment RT-PCR, AST and ALT

Table 1: Patient characteristics

	Mean ± SD		
	Males	Females	P value
Age (year)	46 (40–51)	43 (38–50)	0.758
BMI (kg/m^2)	22.63 (18.7–31.4)	23.78(19.3–32.6)	0.324
WBC, /mm^3	4900 (2150–11160)	4850 (2560–8230)	0.682
PLT, ×104/mm^3	15.8 (7.2–25.3)	15.4 (6.8–27.8)	0.241
Hb level, g/dL	14.1 (9.5–15.2)	13.7 (9.2–14.1)	0.098
FBS, mg/dL	96 (62–137)	94 (61–196)	0.054
HOMA-IR	2.4 (1.2–6.2)	2.2 (1.1–5.8)	0.018
HCV-RNA, KIU/mL	2350 (163–5010)	2290 (152–5000)	0.076
Viral load (copies/ml)	234 (156 –265)	215 (143–253)	0.448

Table 2: Mean value and significance of viral load after 12 weeks and 24 weeks of ant-viral treatment

	Viral load (copies/ml)	
	Mean ± SD	P. value
Sensitive cases after 12 weeks (No.= 95)	182.21± 72.14	0.732
Resistant cases after 12 weeks (No.= 5)	251.73± 65.28	
Sensitive cases after 24 weeks (No.= 83)	140.21± 67.15	0.461
Resistant cases after 24 weeks (No.= 12)	220.32± 61.93	

Table 3: Mean value and significance of liver enzymes before and after 24 weeks of ant-viral treatment

	Mean ± SD		
	Before	After	P-value
AST level, IU/L	44.42±8.56	25.51±6.38	0.004
ALT level, IU/L	58.17±7.13	27.25±5.92	0.008

were done again and 11 patients were resisted cases and 84 patients were sensitive to combined pegylated interferon-ribavirin therapy, also, there were statistical significant reduction in the mean values of AST and ALT after 24 weeks of anti-viral treatment.

DISCUSSION

Hepatitis C virus (HCV) affects approximately 3% of the world population. The current standard of care for treatment of HCV is a combination of pegylated interferon and ribavirin [22]. It has been suggested that cellular immune responses, modulated by pegIFN-α and ribavirin, play a role in forced viral eradication, based on the immunological properties attributed to these anti-viral compounds [23]. Interferon (IFN) and ribavirin (RBV) combination therapy is a popular modality for treating patients with chronic hepatitis C (CH-C), but approximately 50% of patients usually relapse, particularly those with hepatitisC virus (HCV) genotype 1b and a high viralload [24].

Reichard *et al*. were the first to report the use of ribavirin in patients with chronic hepatitis C [25]. Several studies subsequently showed that ribavirin improved ALT levels but did not affect viral replication [26-28]. In the first trial of standard IFN–α and ribavirin combination therapy, HCV was eradicated in 40% of patients who received the combination, but in none of those on IFN–α monotherapy [29]. Further randomized controlled trials led to approval of the standard IFN–α–ribavirin combination as the standard treatment for chronic hepatitis C, before the development of pegylated IFNs [30, 31].

Chronic HCV infection is curable and cure is the goal of antiviral therapy. Successful treatment is characterized by a "sustained virological response" (SVR), defined by undetectable HCV RNA in a sensitive assay (detection limit ≤ 50 international units (IU)/ml) 6 months after the end of therapy. Recent large-scale follow-up studies have shown no relapse or recurrence after 4 to 6 years in more than 99% of patients who have an SVR [32, 33]. In the three main registration trials (randomized controlled studies involving patients without cirrhosis), pegylated IFN–α plus ribavirin gave global SVR rates of 54% to 56%, compared to 18% to 39% with pegylated IFN–α monotherapy [20, 34, 35].

This study aimed to detect liver enzymes and virologic response to combined Pegylatedinterferon-alfa (PEG-IFNα)-ribavirin therapy in Saudi chronic hepatitis C infected patients. One hundred HCV patients of both sexes (70 males and 30 females) were included in this study, their age ranged from 25 to 55 (32.6 ± 6.53) years. All the patients received no previous antiviral drugs before starting of this study. Only patients diagnosed with chronic HCV mono-infection and have anti HCV antibodies by ELISA were selected to undergo Real-Time polymerase chain reaction (RT-PCR) and liver enzymes serum levels of aspirate aminotransferase (AST) and alanine aminotransferase (ALT) before starting combined pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy, RT-PCR after 12 weeks of starting of treatment and RT-PCR and liver enzymes after 24 weeks of anti-viral treatment.

Concerning the results of virological response after 12 weeks in our study, RT-PCR was measured and 5 patients were found to be resistant and stopped their anti-viral treatment, while 95 cases were sensitive and continued their anti-viral treatment. These results agreed with previous studies that found early virological response after 12 weeks of combined pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy for

HCV patients (36,37). Early virological response was detected in 56% of HCV patients received combined pegylatedinterferon-alfa (PEG-IFNα)-ribavirin therapy for 12 weeks [36]. Where, Shiffman *et al*., (2007) reported early virological response in 79% of HCV patients received combined pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy for 16 weeks [37].

Concerning the results of sustained virological response after 24 weeks in our study with RT-PCR, the number of sensitive cases were 83 (83 %) and number of the resistant cases were 12 (12 %). These results agreed with many previous studies (37-39). Sustained virological response was found in 85% of HCV patients received combined pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy for 24 weeks [37]. Where, Nguyen *et al*., (2008) reported that the SVR in 12 patients treated with 48 weeks of PEG-IFNα therapy was significantly higher than that in those treated for only 24 weeks (75%vs 39%) [38]. Also, Thuy *et al*. (2012) recorded SVR in 60 % and 71% of HCV patients received combined pegylatedinterferon-alfa (PEG-IFNα)-ribavirin therapy for 24 and 48 weeks respectively [39].

Concerning the results of liver enzymes levels before and after 24 weeks of HCV patients received combined pegylatedinterferon--alfa (PEG-IFNα)-ribavirin therapy in our study, values of AST and ALT showed a statistically significant reduction after treatment. These results agreed with previous studies (40-41). As Flisiak *et al*., (2005) reported that HCV patients received combined PEG-IFNα-ribavirin therapy for 24 weeks experienced about 50% and 35% reduction in the mean values of ALT and AST respectively [40], another study found that Mean values of ALT were normalized after combined PEG-IFNα-ribavirin therapy for HCV patients [41].

CONCLUSION

Combined pegylated interferon-alfa -ribavirin therapy is an effective treatment strategy for Saudi chronic hepatitis C infected patients.

ACKNOWLEDGMENT

Author is grateful for the cooperation of all patients participated in this study.

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