Original Article

The Sustained Virologic Response and Adverse Effects of Peg Interferon Alfa and Ribavirin in the Treatment of Patients with Chronic Hepatitis C: A Study from Iran

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Abstract

Background: Hepatitis C infection is a worldwide problem. In Iran, hepatitis C virus (HCV) infection prevalence is about 1-2%. A combination therapy of pegylated interferon alfa-2a and ribavirin (PEG-IFNa/RBV) is a standard treatment, but our aim was to determine the efficacy and safety of dual PEG-IFNa/RBV therapy in treating patients infected with HCV in Iranian context.

Materials and Methods: This study is a cross sectional conducted among 98 HCV infected patients who were admitted to Labbafinezhad Hospital (Tehran, Iran) for treatment from April 2014 to September 2016. Patients were medicated with Peg Interferon Alfa (INFα) and Ribavirin (RBV). Lab tests were monitored through the study and dose modification was done. We also assessed treatment responses at the defined time points. The incidences of adverse events were determined either. We investigated independent predictors of sustained virologic response (SVR) in the participants. Finally, data were gathered and statistical analysis was completed.

Results: Eighty-eight percent of patients were male and 11.2% were female. Mean age was 43.44 years. Patients were mostly male, single, with nongovernmental business and low level of education. Risk factors were known to be addiction with non-injectable substances and phlebotomy. Myalgia, fatigue and malaises were the most common complications and suicide intention was the least one. SVR was estimated 76.7%. AST and ALT were significantly reduced in treatment period.

Conclusion: Peg INFα and RBV are effective in treating HCV infection.

Keywords: Hepatitis C, Ribavirin, Peginterferon, Sustained virological response

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Introduction

Hepatitis C infection is a worldwide health problem with an incidence of 170 million universally[1]. Hepatitis C Virus (HCV) attacks principally the hepatocytes[2] where it replicates and kills liver cells[3], and thus HCV infected patients may possibly develop chronic liver disease and hepatocellular cell carcinoma

(HCC)[4]. A wide range of 60 to 80 percent of HCV infected patients shift from the acute state of hepatitis infection to chronic state, and then to hepatic steatosis[5,6]. The Center for Disease Control has found that HCV infection diagnosis remained underestimated and has recommended further screening especially in those people born during 1945-1965[5].

Hepatitis infection incidence rate in Iran is about1% annually and it is still increasing regarding the changes in people's lifestyle and addiction to injectable substances[7]. In 1960s, when only hepatitis A and hepatitis B were known, the treatment of these two types of hepatitis was limited to bed rest, nutrition, diet and symptomatic medications[8], but new medications have evolved therapy and have saved many lives. Though, there are still several disadvantages of new medications, including side effects that sometimes interruptthe treatment. In this study, we aimed to assess the response to dual therapy with pegylated INFα and RBV, as well as estimating side effects in Iranian population. Response to therapy is characterized with an indicator named Sustained Virological Response (SVR). SVR is defined as the absence of HCV RNA within 6 months following therapy and is related to the patient's outcome, mortality and disease symptoms[9].

Methods

The study had a cross sectional design with a prospective approach. Patients' data were analyzed before and after intervention within 24 months. Each patient's information was obtained before treatment, as well as 12, 24 and 48 weeks and 6 months later for follow up. SVR and medication side effects were estimated as each time ends. The study objectives were estimation of response to therapy during implementation of treatment protocol and 6 months later and identification of laboratory and clinical medication's side effects.

Ninety-eight patients admitted in Labbafinezhad Hospital for HCV infection treatment. First of all, approval from the institutional ethics committee was obtained. The study was conducted from April 2013 to September 2014 among HCV positive patients attending the hospital. HCV positive patients above 15 years of age whose HCV PCR turned positive within the recent year and whose lab tests consist of Hemoglobin (Hg) more than 12.5, Absolute Neutrophil Count (NAC) more than 1500 mm^3 and Platelet (PLT) Count more than 80000 were included in the study after taking informed consent. Patients with comorbidities such as human immunodeficiency virus infection, other active liver disease, Hepatocellular Cell Carcinoma, untreated Diabetes, Malignant Neoplastic disease, severe cardiopulmonary disease, Retinopathy, immunodeficiency disorders, untreated psychological disorder and major depression were excluded. A detailed clinical evaluation (history and clinical examination) of all the recruited subjects was done and relevant laboratory investigations were accomplished in specific time intervals as mentioned. Patients' side effects were retrieved and documented after telephone call. Side effects were categorized into three types: life-threatening, severe, modified and mild. Patients must be excluded if life-threatening side effects were detected, and further therapy must be implemented to cure the possible complications. Modified and mild side effects were treated by dose reduction and administrating appropriate medications like antidepressant agents for treating depression.

Our paraclinical indicator for dose modification is illustrated in table 1. Those patients who had experienced side effects were followed every two weeks and treatments were restarted if lab tests turned normal.

All collected data were entered manually into Excel sheets. Statistical analysis was performed using SPSS software. P value was determined and p value <0.05 was considered to be statistically significant. Mean, median, mode and standard deviation were also estimated. To investigate the independent factor related to SVR, a multivariate analysis was performed through a stepwise logistic regression analysis.

Results

Eighty-eight percent of patients were male and 11.2% were female. Mean age was 43.44 years. Patients were mostly male, single, with nongovernmental business and low level of education. Risk factors were addiction with non-injectable substances and phlebotomy. Myalgia, fatigue and malaises were the most common complications and suicide intention was

Table 1: Guidelines for Dose Modification of Pegylated INFα-a2b and Ribavirin During Treatment of Chronically HCV-Infected.

Laboratory values	PEG-INF-a2b	Ribavirin
Hemoglobin 8.5-10.5 g/dL		Reduction to half the treatment dose
Neutrophils 500-750/mm3 Platelets 50,000-75,000/mm3	Reduction to half the treatment dose	
Hemoglobin <8.5 g/dL		Permanently discontinue
Neutrophils <500/mm3 Platelets <50,000/mm3	Permanently discontinue	

Table 2: Socio-demographic characteristics of subjects.

Demographic variable		percent
sex	female	11.2
	male	88.8
Business	House hold	9.2
	unemployed	5.1
	Small business	69.4
	Governmental business	16.3
Marital status	unmarried	12.2
	married	87.8
Education	Diploma	65.3
	Bachelor	32.7
	upper	2
genotype	1a	45.9
	1b	5.1
	2	4.1
	3	44.9

the last one. Eighty-three point seven percent of patients completed their therapy. The most genotype known was 1a. Monthly monitoring of ALT, AST, WBC, PMN, PLT and Hg showed no statically significant differences within the different periods of treatment. TSH was the only variable which was not significantly different in treatment timeline. Most occurrences in lab complication were neutrophilia and anemia. SVR was seen in 76.7%. AST and ALT were significantly reduced in treatment period.

Discussion

In medicine benefits of every treatment regimen must be weigh subsequently in order to determine its use in clinical practice. Among different medications, recombinant interferon α in combination with RBV seems to be effective for the treatment of viral hepatitis in recent researches[10]. Although at first there were several disadvantages of the medications – as INFα was available only in injectable form and the minimum treatment duration was 1 year of weekly injection with many side effects such as myalgia, asthenia, cytopenia, influenza-like symptoms and depression[11] and RBV was accompanied by anemia[12]. As compared with other antiviral drugs, the encouraging results of the dual therapy with INFα and RBV persuaded the researchers to use interferon for several dose administration, treatment length and drugs combination trials to treat NANB hepatitis[13]. For the first time when RBV and *INFα* were used in combination for 24 weeks, the rate of SVR raised up

Table 3: Selected Adverse Events Among Patients Treated With the Combination Therapy.

Description	percent
Itching	23.5
Cutaneous lesions	21.4
Respiratory distress	5.1
Nausea and vomiting	7.1
distraction	6.2
Pulmonary infection	6.1
headache	43.9
myalgia	53.1
fatigue	69.4
Suicide thoughts	4.1
depression	13.3
Irritability	9.2
Palpitation	9.2

Table 4: Virologic response to the therapy.

Time intervals	12 weeks after treatment	24 weeks after treatment	48 weeks after treatment	6 months after treatment
SVR (%)	69.4	79.6	81.6	76.5

Table 5: Change of lab parameters along the treatment.

Variable	Plat	WBC	Hg	TSH	PT	PMN	ALT	AST
P value	0.006	0.007	0.084	0.13	0.006	0.008	0.001	0.001

to 34% and when the length of treatment exceeded to 48 weeks, the rate of SVR increased even higher up to 42%[14,15]. Using today's protocol in HCV combination therapy; patients revealed long-term prognosis, and it turned to be the earliest milestone in HCV treatment[4]. Nowadays, many new drugs have shown more advantages in HCV treatment such as Simeprevir, sofovir[16], Telaprevir[17], and Daclatasvir[18] but as World Gastroenterology Organization mentioned in 2014, the dual therapy of PEG-IFNa2b and RBV for patients with HCV in resource-limited regions like our country is still recommending due to the high cost of new medications[19]. On the other hand, at that time we had faced restrictions to access these medications for treating our HCV infected patients due to goods and medication sanctions as well as poor patients' economic status.

Numerous studies have worked on the efficacy of dual therapy with pegylated INFα and RBV in the last decades and have confirmed sensible results for its use[20,21]. We had done a research to assess the real response to treatment in Iranian population. We found little drug related complications and an acceptable response of about 76.5%. In addition, We noted that, compared with the reports of the initial INFα -2b/RBV trials, our study had a greater number of dose modifications and fewer patients who discontinued therapy. This reality could explain the higher response rates compared with initial response to the standard treatment previously observed in large clinical trials (38–41%)[14,22]. Comparable rates of SVR were found in 75% of patients in Pakistan [23]. This was higher than the response rate in a Canadian study (54%)[24]. Our results were also correlated with Naing and colleagues and Namazi et al. in terms of response to therapy[25,26]. Testing for HCV genotype is recommended to guide the selection of the most appropriate antiviral regimen[27]. Genotyping is useful in epidemiological studies and in clinical management for predicting the likelihood of response and determining the optimal duration of therapy as well[28]. The current study reported that genotype 1a and 3 were the most prevalent. In a serological study on HCV-infected patients in Myanmar, 75% (18/24) were with genotype 3[29]. A faster progression of liver fibrosis in these patients was reported in empirical studies[30]; the high rate of SVR to the dual treatment in the present study has therefore resulted to more clinical benefits from reduction of liver-related morbidity and mortality.

Identification of factors associated with positive HCV RNA level is critical to minimize prevalence and prevent adverse events and expense. Opiate use is still a very significant public health problem in Iran especially in its traditional form[31]. However, the most known risk factors for hepatitis C infection are addiction with injectable substances and blood transfusion from unknown donors[32]. Besides, our findings proved that the most common side effects in our patients were Myalgia, fatigue and malaises. It was similar to Hajaghmoradi in Iranian contexts[33], but Yang reported Neutropinia and Juvendice as the most common prevalence of complications[34]. Our non-responder patients were 7% and it was lower than Namazi findings[26].

Conclusion

Our results show that treatment with peg-IFN plus ribavirin is relatively well-responding in Iranian context. The rate of treatment discontinuation found in this study is low and side effects are tolerable. However, novel drug regimen is coming but dual therapy with the mentioned medication is reasonable to be the standard of therapy in our country according

to the economic aspects. The short duration of therapy (6 months instead of 12) in patients with HCV can be the other contributed reason explaining this drugs as choice medication.

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