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Full Length Research Paper

Long-term outcomes of chronic hepatitis C patients treated with pegylated interferon 2a plus ribavirin in Iran

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Combination of interferon alfa and ribavirin is the first therapeutic choice in chronic hepatitis C. The aim of this study is to assess long-term outcome of chronic hepatitis C patients treated with pegasys plus ribavirin. We evaluated a cohort of 49 chronic hepatitis C patients who were treated for 48 weeks with pegylated interferon alpha 2a and ribavirin and followed up till week 72 in order to evaluate sustained virological response (SVR) and more than 70% of the patients were followed up over 5 years. In week 72 (the time of achieving SVR), 28 patients were found with SVR (57.14%), 10 were relapse and 11 no response. Long-term viral response (LTR) was defined as remained HCV RNA negativity during long time after SVR. LTR was found in 96.3% of those who had SVR. Late viral relapse occurred within first year after SVR in one patient. Three of 10 patients (30%) who were retreated, obtained SVR. Among the whole patients, 4 had cirrhosis in pre-treatment liver biopsy in which 2 of them got progress to clinical cirrhosis during follow up. No hepatocellular carcinoma occurred during the follow up. The patients who achieved SVR; remained in it chronically and had predictable outcome throughout long-term.

Key words: Chronic hepatitis C, long-term outcomes, pegylated interferon, ribavirin.

INTRODUCTION

Worldwide, infection with hepatitis C virus (HCV) has become a major cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma (Webster et al., 2009; Marcellin, 2009; Umar et al., 2010). The World Health Organization (WHO) has estimated that 170 million persons are chronically infected with HCV worldwide, and 3-4 million persons are newly infected each year (Alavian, 2010; Alavian et al., 2009; Mboto et al., 2010).

Antiviral therapy for the treatment of HCV infection has evolved in recent years from IFN monotherapy to combination therapy with IFN and Ribavirin, to the present standard of care, namely pegylated IFN (Peg-IFN) and ribavirin (Hoofnagle and Seeff, 2006; Pawlotsky, 2006). Two types of pegylated interferon, which differ in their pharmacokinetic and chemical properties have been developed, namely interferon alfa-2a (pegasys) and interferon alfa-2b (pegintron). In previous literatures, sustained viral response to pegylated IFN and ribavirin combination therapy were reported, more than 50% of individuals were treated with it (Fried et al., 2002; Alavian et al., 2004; Tacke, 2010; Alavian et al., 2010). Viral response to IFN-based therapy includes sustained viral response (SVR) and long-term viral response (LTR). SVR was defined as undetectable HCV RNA in 24 weeks after cessation of treatment and LTR as remained HCV RNA negativity during long time after SVR.Of patients who achieve SVR, beneficial clinical outcomes have been shown such as reduced progression of fibrosis,

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Abbreviations: HCV, Hepatitis C virus; **SVR,** sustained viral response; **LTR,** long-term viral response; **IFN,** interferon; **PEG-IFN,** pegylated interferon; **SD,** standard deviation; **RNA,** ribonucleic acid; **HCC,** hepatocellular carcinoma; **ALT,** alanine transaminase; **PT,** prothrombine time; **PLT,** platelet; **N,** number.

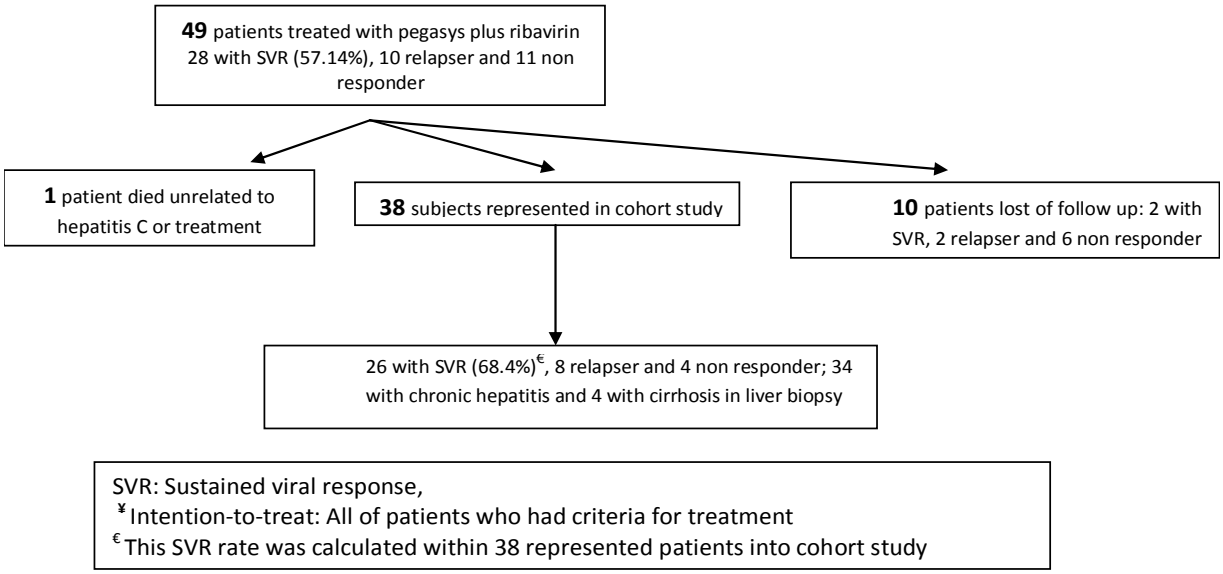

Figure 1. Diagram of intention-to-treat[¥] patients and study subjects with their proportion and SVR rate.

decreased risk of hepatocellular carcinoma, and improved post transplant survival (Aronsohn and Reau, 2009). In other words, patients who obtained SVR to PEG-IFN plus ribavirin, had well long-term outcomes versus non-SVR ones. There are several studies about follow up of chronic hepatitis C patients who were treated with interferon-based therapy (Aronsohn and Reau, 2009; Giannini et al., 2010; Annicchiarico et al., 2007; George et al., 2009; Desmond et al., 2006; Adamek et al., 2007; Dzekova et al., 2009; Arase et al., 2007; Braks et al., 2007; Imazeki et al., 2003; Ciancio et al., 2006; Pradat et al., 2007; Marcellin et al., 1997; Swain and Shiffman, 2004). Each study was conducted with individual forms of interferon-based treatment regimens. Thus, results are in controversy. In some study long-term biochemical, clinical and histological outcomes were assessed (George et al., 2009; Arase et al., 2007; Braks et al., 2007; Imazeki et al., 2003).

There are few studies about evaluation of outcomes of chronic hepatitis C who were treated with peg-interferon alfa-2a plus ribavirin (Giannini et al., 2010; Swain and Shiffman, 2004). These studies assess durability of SVR rate. Last ones by Giannini et al. (2010) conducted large cohort study that evaluated (Giannini et al., 2010; Desmond et al., 2006; Swain and Shiffman, 2004) SVR to pegylated IFN combination with ribavirin in chronic hepatitis C and demonstrated SVR prolonged in 99% of patients (Giannini et al., 2010). Majority of studies reported late viral relapse occurred in first year after SVR (Giannini et al., 2010; Desmond et al., 2006; Swain and Shiffman, 2004). Overall, all these studies emphasize that long-term outcomes (biochemical, histological, clinical and viral) of chronic hepatitis C patients who were treated with pegylated IFN plus ribavirin, is good particularity in those who attained SVR. Before this, there was no study like this in Iran. Thus, we would conduct a cohort study to elucidate outcomes of Iranian chronic hepatitis C patients who were treated with pegylated IFN alpha-2a (Pegasys) plus ribavirin.

PATIENTS AND METHODS

Patients

Forty nine chronic hepatitis C patients, who fulfilled criteria for treatment with pegylated interferon alfa-2a (pegasys) plus ribavirin, were admitted in Tehran Hepatitis Center between February 2002 and April 2004. They were treated with mentioned regimen for 48 weeks and then followed up. In week 72 (the time of achieving SVR), it was found 28 patients with SVR (57.14%), 10 relapse and 11 no response. Alavian et al. (2004) conducted a study in same patients previously and we follow up these patients in a cohort study. One of them died unrelated 5 months after cessation of treatment. Ten patients lost the follow up and exclude from study. Finally, 38 underwent follow up more than 18 months after discontinuation of treatment and represented the cohort study. Figure 1 shows diagram of intention-to-treat patients and study subjects with their proportion and SVR rate. The criteria for treatment were abnormal ALT and positivity of HCV RNA and by exclusion of contraindication of therapy such as decompensated cirrhosis and psychological problems.

Cohort protocol

Patients were evaluated from 2003 to 2009 for at least every 6 months. In whom the serum HCV-RNA was positive during the follow up, we retested them in the following month and in cases of a negative HCV-RNA, the 6 months interval follow up was reserved.

For all patients biochemical, virological and physical exam was performed in any follow up period. HCV-RNA was defined as

Table 1. Baseline characteristic of patients.

	N	Minimum	Maximum	Mean	Std. Deviation
Age	38	26	74	46.00	10.403
Stage	38	0	6	2.62	1.639
ALT baseline	27	11	86	23.85	14.709
PT baseline	24	12.0	16.0	13.479	.9264
Follow up period(weeks)	38	52	313	255.13	85.875

ALT: Alanine transaminase; PT: Prothrombine time; N: Number; Std.: Standard.

undetectable by qualitative RT-PCR assay with a sensitivity of 50 IU/ml [Cobas Amplicor HCV Monitor (version 2), Roche Diagnostics, Branchburg, N.J]. For all patients, a pre-treatment liver biopsy was obtained. Because of non-compliance, a second biopsy was not done. For those who had histological cirrhosis in liver biopsy, routine para-clinical evaluation including upper GI endoscopy, abdominal ultrasonography, albumin, alfa fetoprotein and complete biochemical values were carried out every 6 months. In others with chronic hepatitis these evaluations was performed annually.

Because of the lake of facilities when trial started, we could not determine the HCV genotype in patients but throughout the follow up we found HCV genotype in some patients (25 of 38). In the end of the follow up, all patients carried out liver function tests such as alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphates (ALP), prothrombin time (PT), partial thrombin time (PTT), international normalized ratio (INR) and a serum HCV RNA RT-PCR. ALT and AST <40 U/L for men and <35 U/L for women was considered as normal values. Physical examination for all patients was performed by one individual Gastroenterologist and clinical finding was defined as normal and cirrhosis condition.

Statistics

Categorically, variables are reported as mean, standard deviation and minimum-maximum range. Qualitative variables are expressed as absolute and relative frequencies. Qualitative data are analyzed by Fisher exact test and in order to determine relationship. Quantitative variables are analyzed by student`s *t* test. To determine whether quantitative variables are normal or not, we used non-parametric tests (1-sample k-s).

All tests were 2-sided and *p* values less than 0.05 were considered to indicate statistical significance. Data analysis was done with the Statistical Package for Social Sciences (SPSS version 16.0; SPSS Inc., Chicago, IL).

RESULTS

Characteristics of patients

Thirty eight patients underwent follow up and were represented in our cohort study. Out of 38 patients 86.8% were male (male: female, 33:5). Mean age was 46 years (46+/-10.4 range 26 to 74). Table 1 shows the main baseline characteristic of patients. Of 25 patients with HCV genotyping, 84% had genotype 1(1a+1b). There were 34 chronic hepatitis and 4 cirrhosis in the pre-treatment liver biopsy (89.5% vs. 10.5%). Histological cirrhosis patients had not clinical evidence in the beginning of follow up. 26, 8 and 4 patients were SVR, relapsers and non responder, respectively.

Patients follow up

Mean, +/-SD of follow up period was 255, +/-85.8 weeks (range 52 to 313) and more than 70% were followed over 5 years. Ten non responder or relapsed patient, were retreated. Just, 3 (30%) had response to retreatment (2 relapsers, 1 non responder). In other words, 3 patients had SVR to retreatment.

Overall, we found 29 SVR patients; 26 to first treatment and 3 to second therapy. Of 26 SVR to first treatment, 2 with IDU addiction become serum HCV-RNA positive because of re-infection. These re-infected patients were excluded from SVR group and in result, we had 27 SVR patients. Out of 27 SVR above, 26 remained their serum HCV-RNA negativity finally. In other hand, LTR was found in 96.3% (26 of 27). One patient had late viral relapse in one year after SVR. This patient was a 44 years old man, unknown way of infection with HCV genotype 1b, baseline ALT 20 mg/dl, grade and stage 5;1 in liver biopsy. He had normal biochemical and clinical values in the end of follow up. Table 2 shows association between LTR/non-LTR by Total SVR and clinical outcomes.

One patient of non-SVR group (relapse in month 3 after discontinuation of treatment) had negative HCV-RNA at the end of follow up. This case had not any response even to retreatment but during the long-term follow up, achieved negativity dramatically. He was a 44 years old man with unknown way of infection, genotype 1a, chronic hepatitis in liver biopsy (grade 3, stage 0) who had normal clinical condition at the end of follow up.

In clinical point of view, about 90% of all of patients (34 of 38) had normal clinical condition in the end of follow up. Four of them had elevated liver enzymes. Just 4 patients had clinical cirrhosis (3 with compensated and 1 with uncompensated cirrhosis). Two of them had previous histological cirrhosis in their liver biopsy and another two patients had chronic hepatitis. One of cirrhotic patients was SVR to treatment. Overall, we had 12 non-SVR patients which 9 of them had normal clinical outcome and the reminders had clinical cirrhosis.

Hepatocellular carcinoma was not detected in any of

Table 2. LTR/non-LTR by total SVR and clinical outcomes.

Variable		LTR	non-LTR	P
		No. (% within)	No. (% within)	
Total SVR	Yes	26(96.3)	1(3.7)	0.000
	No	0(0)	11(100)	
Clinical outcomes	Normal clinical condition€	25 (73.5)	9 (26.5)	0.084
	Cirrhosis condition¥	1 (25)	3 (75)	

LTR: long-term viral response, SVR: Sustained viral response, total SVR: summation of SVR to first and second treatment, p: *p* value, % within: proportion of cases in each row, No: number of cases, €Normal clinical condition include normal and elevated liver enzyme ones, ¥ Cirrhosis condition includes compensated and uncompensated cirrhosis.

Table 3. Baseline and endpoint biochemical parameters.

Variable	N	Minimum	Maximum	Mean	Std. Deviation
Baseline ALT	38	11	86	23.85	14.709
Baseline PT	38	12.0	16.0	13.479	0.9264
Baseline PLT	38	100000	285000	186250	50371.878
Endpoint ALT	38	8	94	33.05	21.664
Endpoint PT	38	11.5	19.0	13.082	1.2278
Endpoint PLT	38	63000	317000	188696.9	53677.559

ALT: Alanine transaminase, PT: Prothrombine time, PLT: Platelet, N: Number, Std.: Standard Baseline: values in the beginning of study, Endpoint: values at the end of follow up.

patients. HCV related death was not seen too. Table 2 shows association between LTR/non-LTR by clinical outcomes.

Mean, +/-SD value of endpoint Alt was 21.664, +/-33.05 (range 8-94). Table 3 shows baseline and end point biochemical parameters in patients. There was significant difference between mean ALT in LTR and non-LTR groups at the end of follow up (*26.31 vs. 47.67; p=0.030).* Other biochemical values had not significant difference between two mentioned groups.

DISCUSSION

The SVR in treated HCV infected patients showed a good outcome in long-term follow up. LTR rate in our study is near to other studies (Giannini et al., 2010; Desmond et al., 2006; Swain and Shiffman, 2004). These studies were demonstrated SVR remained in a proportion over 99%. In other words, more than 99% of SVR patients had LTR. Giannini et al. (2010) conducted largest cohort study among 231 chronic HCV patients who obtained SVR to peg-interferon plus ribavirin with a mean 3.5 years follow up in 2009. Desmond et al. (2006) evaluated durability of SVR in mentioned patients treated by interferon-based among 147 SVR with mean 2.3 years follow up in 2006. Another by Swain and Shiffman (2004) was preliminary study which was assessed durability of SVR to Pegasys monotherapy or combination with ribavirin in 2004. Our follow up period is the longest in contrast with other studies but our sample size is lesser than others. Probably this little difference between ours and others has been because of our small sample size. If our sample size had been large enough, LTR rate would have been similar to mentioned studies. Less important reasons for this difference are more sensitive RT-PCR method, high prevalence of HCV genotype 1 in Iran, low treatment compliance in ours or etc. Our LTR rate is more than the rate of Dzekova et al. (2009) (80%). However, this study was conducted among 18 haemodialysis infected chronically with HCV. For more precise on our result, it should perform large prospective cohort study among Iranian patients.

We obtained a late relapse rate of 2.6% (1 of 38) which is near with Marcellin et al.'s (1997) result (3.7%; 3 of 80). In other studies late relapse occurred in none of patients (George et al., 2009; Adamek et al., 2007) or less than 1% of SVR patients (Giannini et al., 2010; Desmond et al., 2006; Swain and Shiffman, 2004). Time of viral relapse in our study was first year after achieving SVR which is keeping with other literatures. However, Ciancio et al. (2006) reported the late relapse may happen 2 years after SVR. According to the above, it's necessary to carry out bi-annual HCV-RNA PCR at least in first year after SVR time.One patient with genotype 1a, who was non-SVR, obtained negative HCV-RNA RT-PCR finally.

Annicchiarico et al. (2007) by 5 years evaluation of 68 patients who were non responder, breakthroughs or relapsers to treatment understood that few of patients (5 of 68; 1 non responder, 3 breakthroughs, and 1 relapsed) were resolved of virus RNA during long-term follow up. In addition, this resolution is possible in genotype 2 or 3 with low viral load (viral load< 10 IU/ml).

We found that retreatment has low percentage of viral response (30%). This finding was anticipated regarding to previous studies. Therefore, retreatment should be considered individually for each patient according to his predisposing and risk factors. Most of our patients (~79%) had normal biochemical and clinical manifestations in the long-term. This proportion is more than of virological response (68%). Thus, it emphasize that treatment of chronic hepatitis C by pegasys plus ribavirin should been performed regardless of viral response. Therefore, in chronic hepatitis C patients treated by pegasys plus ribavirin, clinical response was more than biochemical and viral response. One of cirrhotic patients was SVR to treatment. Similar to Pradat et al. (2007), we found that cirrhosis can develop among patients who had SVR. Although, number of cirrhosis group is too little to attain meaningful relationship. Braks et al. (2007) in elucidating of 113 HCV-related cirrhosis patients, reported that in the SVR and non-SVR patients, rate of HCC and death were 1/37 vs. 24/76 and 0/37 vs. 20/76 respectively (p=0.01). According to the above, we don't have these endpoint outcomes. In addition, ALT level had significant reduction in patients who had LTR. In summary, patients treated with pegasys and ribavirin, will have considerable outcomes as Giannini et al. (2010) and George et al. (2009) reported.

Conclusion

Regarding to our study results and comparing with other studies, it seems combination of pegasys and ribavirin in treatment of chronic hepatitis C has beneficial viral, biochemical and clinical outcomes. Thus, it's considered patients who achieved SVR, were cured from hepatitis C virus. Despite little differences between ours and previous study, it could emphasize Iranian chronic hepatitis C with SVR treated by pegasys and ribavirin, will have predictable outcomes as in other countries. However, the response to treatment is durable, optimal follow up for chronic hepatitis C is unclear and it's important that long-term follow-up of patients are of low yield and largely unnecessary.

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