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Original article

Monitoring of patients with sustained virological response treated with standard or pegylated interferon in combination with ribavirin for chronic hepatitis C

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Abstract

Monitoring of patients with sustained virological response treated with standard or pegylated interferon in combination with ribavirin for chronic hepatitis C.

Background-Aims: Sustained virological response (SVR) is defined as undetectable HCV-RNA at the end of 24 weeks of follow-up after treatment. This study aimed to determine the durability of this response beyond this time period and the long term management of patients with chronic hepatitis C.

Methods: We retrospectively analyzed viral response to treatment with either standard or pegylated interferon in combination with ribavirin in 63 patients followed-up for 3-65 months after the completion of 6 months follow-up. HCV-RNA was determined by polymerase chain reaction at baseline, week 12, end of treatment and every 3 months thereafter.

Results: End of treatment virologic response (ETVR) was achieved in 43/63 patients. Concerning sustained response 6 patients were lost during follow-up and 11/37 –10/11 with genotype 1- relapsed at week 12. No more patient relapsed until the end of the 24-week follow-up. All patients with SVR (n=26) (8 with genotype 1, 1 with genotype 2, 15 with genotype 3 and 1 with genotype 4) retained the SVR during the long term follow-up except for one with genotype 3 who relapsed two years after cessation of treatment.

Conclusions: Our findings suggest that patients with chronic hepatitis C receiving combination therapy usually relapse during the first 12 weeks of follow-up. Relapse is extremely rare there after. Thus, measurement of HCV-RNA at week 12 of follow-up can safely predict persistent virologic response to treatment. *Hippokratia 2006; 10(1):32-34*

Keywords: *chronic hepatitis C, sustained virologic response, SVR*

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Introduction

Hepatitis C virus (HCV) infection is currently the most common cause of chronic hepatitis, cirrhosis and hepatocellular carcinoma. Moreover it appears to be the leading cause for liver transplantation all over the world. Combination therapy with alpha-interferon and ribavirin is currently the approved therapy for this potentially serious viral disease. The primary therapeutic aim of this therapy is sustained virologic response (SVR), which is defined as undetectable HCV-RNA at the end of a 24-week follow-up period after treatment cessation. However, the durability of this response beyond this time period and the long term management of these patients has not as yet been determined.

Several studies have now confirmed that viral response to interferon (IFN) monotherapy usually persists if it is maintained for at least 6 months after treatment is stopped and that marked clinical and histologic improvement is seen in such patients in the long-term follow-up[1,2]. Furthermore, a recent study by St. Zeuzem et al has demonstrated that twelve weeks of follow-up is sufficient for the determination of sustained virologic response in patients treated with interferon α (standard or pegylated) for chronic hepatitis C revealing that virologic relapse mainly occurs within the first twelve weeks after cessation of treatment[3]. However few data have been published until now on the durability of viral response to combination therapy[4].

We performed this study to determine the durability of virologic response beyond standard 24-week follow-up after combination therapy for chronic hepatitis C and the earliest time point when this prolonged response can be safely previewed.

Material-Methods

In order to examine the durability of SVR, we retrospectively analyzed viral response to treatment with ei-

ther standard or pegylated interferon in combination with ribavirin in 63 patients followed-up for 3-65 months after the completion of a 6 months follow-up. Patients were treated either with standard interferon α-2b at a dose of 3MU subcutaneously three times per week in combination with ribavirin according to their body weight or with pegylated interferon α-2b plus ribavirin according to their body weight and genotype for the entire treatment period. HCV-RNA was determined by polymerase chain reaction (Amplicor HCV Monitor) at baseline, week 12, end of treatment and every 3 months thereafter. HCV genotyping was performed by reverse hybridization assay (InnoLiPA™).

Results

End of treatment response (ETVR) was achieved in 43/63 patients (68,2%). Among 49 patients who received standard interferon and ribavirin, 32 achieved end of treatment response (65,3%), whereas among 14 patients who received pegylated interferon and ribavirin 11 had ETVR (78,6%) (Table 1).

Table 1: *Virologic response according to therapy regimen*

	ETVR	*12W follow-up*	*SVR*
IFN-α+RBV	65,3%	46,9%	46,9%
PEG-IFN+RBV	78,6%	64,3%	64,3%

Six patients were lost during long-term follow-up due to personal reasons. The remaining 37 patients were followed-up for a period between 3 and 65 months after the end of 6-month follow-up period. Table 2 summarizes characteristics of this group of patients. As this table shows half of these patients had genotype 1 infection (48,6%), whereas few were cirrhotic (10,8%).

Eleven over thirty seven patients with ETVR – 10/11 with genotype 1- relapsed at week 12 (29,7%). Nine of the relapsing patients had received the standard interferon regimen and 2 the pegylated one. No more patients relapsed until the end of the 24-week follow-up period.

All patients with sustained virologic response (n=26) (8 with genotype 1, 1 with genotype 2, 16 with genotype 3 and 1 with genotype 4, Table 3) retained the SVR during the long term follow-up except for one patient with genotype 3 who relapsed two years after cessation of treatment. This patient never reported risk-behavior associated with reinfection, although he was using intravenous drugs before starting therapy. Moreover, the genotype prior to treatment was identical to that found at recurrence of his viraemia. Thus, this patient was considered to have true late virological relapse.

Discussion

According to several studies, it has been shown that sustained responders to interferon therapy usually have a durable long-term response[1,2]. The institution of combination therapy with standard or pegylated interferon and ribavirin seems to increase end of treatment response and decrease relapse rates[5-7]. A recent study investigated the durability of viral response to antiviral combination therapy beyond a 24-week follow-up period in 393 patients with sustained virologic response[4]. Only nine of 393 patients (2,8%) relapsed more than 6 months after treatment was discontinued.

In the present study, which examined retrospectively

Table 2: *Patient characteristics of the long-term followed-up group*

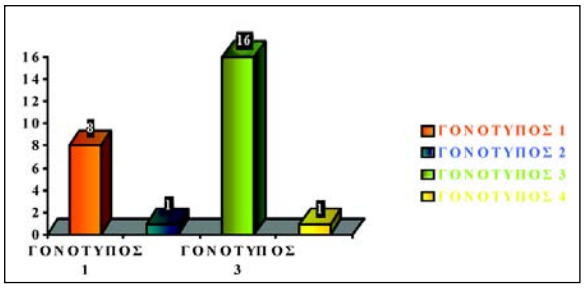
GENDER			
	Male	24/37	(64,8%)
	Female	13/37	(35,2%)
AGE			
	<40	22/37	(59,5%)
	>40	15/37	(40,5%)
ALT LEVELS (*before treatment*)			
	>3xUNL	16/37	(43,2%)
	<3xUNL	21/37	(56,8%)
HISTOLOGY			
	Cirrhosis	4/37	(10,8%)
	Non-cirrhosis	29/37	(78,4%)
	No biopsy	4/37	(10,8%)
GENOTYPE			
	1	18/37	(48,6%)
	Non-1	19/37	(51,4%)

the response rate in 63 patients with chronic hepatitis C receiving combination therapy this small percentage of relapse was confirmed and even more was found to be the same (2,8%). This number virtually reflects only one patient who relapsed two years after treatment cessation. We also found that virologic relapse usually occurred within the first twelve weeks of follow-up in all our patients. Testing for HCV-RNA 12 weeks after the end of therapy by a sensitive molecular test must therefore be considered as the most appropriate time point for assessment of virologic response and identification of probable relapse adding up to the results of previous study[3].

In conclusion, our findings suggest that in chronic hepatitis C patients receiving combination therapy relapse can occur mainly during the first 12 weeks of follow-up. Relapse after the completion of 24 weeks of follow-up is extremely rare. Thus, measurement of HCV-RNA at week 12 of follow-up can safely predict virologic response.

Early knowledge of the response status for treated patients is helpful for making decisions related to further management and may enable relapsed patients to pursue alternative therapies at an earlier time period. Reducing the follow-up period to 12 weeks from the current standard of 24 weeks could also result in reduced costs associated with monitoring response.

Table 3: *Genotype of patients with sustained virologic response (SVR)*



References

1. Reichard O, Glaumann H, Fryden A, Norkrans G, Wejstal R, Weiland O. Long-term follow-up of chronic hepatitis C patients with sustained virologic response to alpha-interferon. J Hepatol 1999; 30:783-787
2. Marcellin P, Boyer N, Gervais A, et al. Long-term histologic impovement and loss of detectable intahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Intern Med 1997; 127:875-881
3. Zeuzem St, Heathcote E.J, Shiffman, et al. Twelve weeks of follow-up is sufficient for the determination of sustained virologic response in patients treated with interferon α for chronic hepatitis C. J Hepatol 2003; 39:106-111
4. Davis G, M$_c$Hutchison J, Poynard T, et al. Durability of viral response to interferon alone or in combination with oral ribavirin in patients with chronic hepatitis C. Hepatology 1999; 30(Suppl):303A
5. M$_c$Hutchison JG, Poynard T. Combination therapy with interferon plus ribavirin for the initial treatment of chronic hepatitis C. Semin Liver Dis1999; 19(Suppl 1):57-65
6. Reichard O, Schvarcz R, Weiland O. Therapy of hepatitis C: alpha interferon and ribavirin. Hepatology 1997; 26(Suppl 1):108S-1011S
7. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alpha-2$^{\alpha}$ plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2000; 347:975-982