

Early, end of treatment and sustained virological response of interferon plus ribavirin, does it differ in patients with chronic hepatitis C with normal versus elevated transaminases?

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Abstract: Background: Up to 46% of patients with chronic hepatitis C have persistently normal ALT levels. The natural history of these patients is still uncertain but there are reports of marked fibrosis (5%-30%) and cirrhosis (1.3%), thus indicating that the presence of bridging fibrosis or even cirrhosis cannot be ruled out in patients with persistently normal ALT levels and detectable HCV RNA. Conflicting data regarding response to antiviral therapy, long term benefits, and safety concerns have led to controversy over the treatment of patient with chronic hepatitis C and persistently normal ALT levels. **The Aim of the work:** is to evaluate early, end of treatment and sustained virological response of treatment with pegylated interferon plus ribavirin in patients with chronic hepatitis C and normal ALT levels compared with those with elevated ALT levels, as well as comparing fibrosis score in both groups. **Methods:** The study included 206 patients from antiviral therapy outpatient clinic, of National Liver Institute, divided into 2 groups, group I included 104 patients with elevated ALT level and group II, 102 patients with persistently normal ALT levels. The Following investigations were utilized: liver function Profiles (Bilirubin, AST, ALT and albumin, prothrombin time and concentration), complete blood count,, viral markers (HCV Ab, HBs Ag),, HCV RNA level, Abdominal ultrasound and liver biopsy. Patients received either pegylated interferon α -2a (40 KD) (administered subcutaneously 180 μ g once weekly) together with ribavirin 13-15 mg /kg body weight/day orally in divided doses. The demographic features, difference in the stage of liver fibrosis and response to treatment (early, end of treatment and sustained virological response) were assessed in both groups. **Results:** As regard the Early Virological Response (EVR), out of the 104 patients in elevated ALT group, 10(9.6%) were non responders, 75 (72.1%) had complete EVR and 19 (18.3%) had partial EVR while out of 102 patients in normal ALT group, There was 21(20.6%), 77 (75.5%), 4 (3.9%) respectively with statistically significant difference between the two groups (p -value <0.05). In elevated ALT group, 41 (39.4%) had breakthrough and 53 (51.0%) had End of treatment response, while in normal ALT group, There was 23 (22.5%) and 58 (56.9%) respectively with no statistically significant difference (P >0.05). In elevated ALT group, a high statistically significant difference between the non responders and responders regarding stage of fibrosis (p -value <0.01) were found as 26 (42.6%) of non responders had mild fibrosis (F0-F2) vs. 35 (57.4%) had advanced fibrosis while in responders, 32 (74.4%) had mild fibrosis (F0-F2) vs. 11 (25.6%) had advanced fibrosis, While in normal ALT group, no statistically significant difference were found (p -value > 0.05) as 44 (69.8%) of non responders had mild fibrosis vs. 19 (30.2%) had advanced fibrosis, while in responders, 31 (79.5%) had mild fibrosis vs. 8 (20.5%) had advanced fibrosis. As regarding Body Mass Index and SVR, a high statistically significant difference was found between the non responders and responders In both elevated ALT and normal ALT groups. On other hand Age and level of HCV RNA viraemia had statistically significant difference. SVR was 41.3% in patients with elevated ALT group and 38.2% of normal ALT group without significant correlation. On other hand, SVR occurred in 65.5% of patients whose ALT above 3 times normal and only 32% of patients who had their ALT elevated less than 3times normal. **Conclusion:** SVR rates are comparable between patients with elevated and normal ALT, and the decision to treat HCV-infected patients with persistently normal ALT levels should be made on an individual basis and recommended factors that should be considered when deciding to proceed with HCV treatment in these patients should include the severity of liver disease, HCV genotype, age, presence of co-morbid disease, patient motivation and the presence or absence of symptoms. On other hand, ALT elevated more than 3 times normal was found to be significant dependent predictor of sustained virological response.

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1. Introduction

Hepatitis C virus (HCV) infection is a global public health problem. with an estimated 170 million people chronically infected with it, and 3–4 million people are newly infected each year, Approximately 80% of newly infected patients progress to chronic infection, Cirrhosis develops in about 10–20% of those with chronic infection and hepatocellular carcinoma develops in 1– 5% of them over a period of 20–30 years (WHO, 2005).

HCV genotype and baseline serum HCV ribonucleic (RNA) level are important predictors for sustained virological response (SVR) to interferon therapy and other factors such as age, gender, race, obesity, histological status and serum alanine aminotransferase (ALT) level can also influence SVR rates (Snoeck *et al.*, 2006).

Up to 46% of patients with chronic hepatitis C have persistently normal ALT levels (Alberti *et al.*, 2002), the prevalence of cirrhosis in this Subgroup of patients is 0.5–6% (Ahmed and Keeffe, 2004), and those patients with persistently normal ALT level have milder liver disease (stage 0–1 fibrosis) than those with elevated serum ALT levels (Pradat *et al.*, 2002).

Conflicting data regarding response to antiviral therapy, long term benefits, and safety concerns have led to controversy over the treatment of patient with chronic hepatitis C and persistently normal ALT levels (Bacon, 2002), however, a recent large international randomized trial in patients with chronic hepatitis C and persistently normal ALT level showed that interferon plus ribavirin has a similar efficacy, tolerability and safety profile as in patients with elevated ALT level (Zeuzem *et al.*, 2004).

Aim of the work

The aims of this study were to evaluate early, end of treatment and sustained virological response of treatment of pegylated interferon plus ribavirin in patients with chronic hepatitis C and normal ALT levels compared with those with elevated ALT levels as well as comparing fibrosis score in both groups.

2. Patients and Methods

This retrospective study was conducted on 206 patients who were selected from Interferon outpatient clinic of National Liver Institute hospital from January 2011 to October 2012. The number of the females in each group was equal to avoid the gender as a confounding factor.

The studied cases were classified into two groups:

- **Group (I):** Chronic hepatitis C patients with elevated serum alanine aminotransferase (ALT) level. This group comprised 104 patients, 85 males and 19 females. Their age ranged between

17 and 59 years with a mean \pm SD of 36.4 ± 9.5 years .

- **Group (II):** Chronic hepatitis C patients with persistent normal serum alanine aminotransferase (ALT) level (<30 IU/ml in males and <19 IU/ml in females). This group comprised 102 patients, 83 males and 19 females. Their age ranged between 18 and 59 with a mean \pm SD of 36.5 ± 9.5 years .

Inclusion Criteria:

- Age 18 years or older.
- Positive Anti-HCV antibody detected by means of a third generation enzyme immunoassay (Ortho HCV version 3.0 ELISA ; Ortho- Clinical Diagnostics INC., Raritan. NJ, USA).
- Serum HCV-RNA by means of Versant HCV RNA 3.0 Assay (bDNA), Siemens Medical Solution Diagnostic. Tarrytown, NJ, USA, with the following level of viraemia:

*600 - 2.5×10^5	IU/mL	→ Low viraemia
* 2.5×10^5 - 2.5×10^6	IU/mL	→ Moderate viraemia
* 2.5×10^6 - 5.0×10^6	IU/mL	→ High viraemia
* Above 5.0×10^6	IU/mL	→ very high viraemia.

- Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher).
- Compensated liver disease (total serum bilirubin <1.5 g/dL; INR ≤ 1.5 ; serum albumin >3.4 , platelet count $\geq 75,000$ mm and no evidence of hepatic decompensation (hepatic encephalopathy or ascites).
- Acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count $1500 /\text{mm}^3$ and serum creatinine <1.5 mg/dL).

❖ Exclusion criteria:

- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin.
- Untreated thyroid disease.
- Pregnant women or unwilling to comply with adequate contraception.
- Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease.
- Known hypersensitivity to the drugs used to treat HCV.

The following data were collected from the file of each patient:

- A- **Liver function tests:-** Serum bilirubin, total protein, albumin, AST, ALT, ALP, GGT and prothrombin time, concentration and INR. Liver tests were done using Cobas Integra 400, Hoffman La Roche Company, Switzerland. The only exception was prothrombin time,

concentration and INR which were assessed using Thromboreal S, Behring fibrin timer II, Behring Inc., 1999, Germany.

- B- Kidney tests:** Blood urea, serum creatinine, sodium and potassium.
- C- Complete blood count including** haemoglobin, WBCs, neutrophil count and platelet count.
- D- Liver biopsy:** Fibrosis and necro-inflammatory activity were staged according to Ishak *et al.* (modified HAI and staging) which was used to assess fibrosis stage on a scale range from 0 to 6 corresponding to absent fibrosis up to liver cirrhosis.

Fibrosis	Ishak <i>et al.</i> , 1995
Non	0
Portal fibrosis (some)	1
Portal fibrosis (few)	2
Bridging fibrosis (few)	3
Bridging fibrosis (many)	4
Incomplete cirrhosis	5
Cirrhosis	6

No fibrosis (0), (1) minimal, (2) mild, (3-4) moderate and (5-6) severe fibrosis.

E- Other laboratory investigations included serology for HBV, thyroid functions, random blood glucose.

- Electrocardiogram in patients with preexisting cardiac disease.
- Fundus examination for retinopathy in patients with diabetes or hypertension.

F-Abdominal ultrasound (U/S): for size, echopattern, surface of the liver and hepatic veins, portal vein diameter, spleen, portosystemic collaterals, gall bladder

❖ **The treatment used:**

A- **Interferon:** Pegylated interferon α -2a (40 KD) (administered subcutaneously 180 μ g once weekly) (Fried *et al.*, 2002).

B- **Ribavirin:** 13-15 mg /kg body weight/day orally in divided doses (Fried *et al.*, 2002).

❖ **Dose modification:**

Ribavirin: The dose of ribavirin was reduced when the hemoglobin decreased to less than 10 g/mL and or by more than 4g/dL from the pretreatment baseline by a one-step (200 mg at a time).and was discontinued if the hemoglobin decreased to less than 8.5 g/dL (Fried *et al.*, 2002).

Interferon: the dose of pegylated interferon was reduced when the absolute neutrophil count decreases to ≤ 750 cells/ml (Fried *et al.*, 2002). And some patients was instructed to receive granulocyte colony stimulating factor.

❖ **Monitoring During and After Therapy**

Patients were monitored during therapy to assess the response to treatment and for the occurrence of side effects by monthly visits during

the first 12 weeks of treatment followed by visits at 8 to 12 week intervals thereafter until the end of therapy.

- **At each visit patients were questioned about:** The presence of side effects and adherence to treatment.
- **Laboratory monitoring included:** CBC, ALT, creatinine, HCV RNA by a by means of branched DNA (bDNA) at weeks 12, 24, the end of treatment, and 24 weeks after discontinuation of treatment.

The demographic features, difference in stage of liver fibrosis and response to treatment (early, end of treatment and sustained virologic response) were assessed in both groups.

The term early virologic response (EVR) referred to either patients who became HCV RNA undetectable by branched DNA (bDNA) within 12 weeks after the initiation of treatment (complete EVR) or had a 2-log decline in HCV RNA from the pretreatment baseline (partial EVR) and those patients were allowed to complete the treatment for 24 weeks and another HCV RNA were performed. Those who were still HCV RNA negative complete the treatment for 48 weeks and those who became positive stopped the treatment.

Breakthrough referred to patients who initially became HCV RNA negative during treatment but then became positive despite ongoing treatment.

End of treatment response (ETR) were confirmed by HCV RNA negative at the end of 48 weeks of treatment.

Sustained virologic response (SVR) were confirmed by HCV RNA negative by branched DNA (bDNA) 24 weeks after discontinuation of treatment.

Relapse referred to patients who became and remained HCV RNA undetectable in serum throughout treatment but then had reappearance of HCV RNA after treatment was discontinued.

Statistical analysis:

Data was statistically analyzed using SPSS (statistical package for social science) program version 13.0, SPSS Inc., Chicago, Illinois, USA for windows and Epi info program version for all the analysis a p value < 0.05 was considered statistically significant. Data are shown as mean, range or value and 95% confidence interval (95% CI) and frequency and percent.

Chi square test, Fischer exact test, student t-test, Mann-Whitney test paired t-test, and Wilcoxon rank test were used in data analysis.

3. Results

As regard the Early Virological Response (EVR), out of the 104 patients in elevated ALT group, 10 (9.6%) were non responders, 75 (72.1%)

had complete EVR and 19 (18.3%) had partial EVR while out of 102 patients in normal ALT group, There was 21(20.6%), 77 (75.5%), 4 (3.9%) respectively with statistically significant difference between the two groups (p -value <0.05).

Out of the 104 patients in elevated ALT group, 41 (39.4%) had breakthrough and 53 (51.0%) had End of treatment response, while out of the 102 patients in normal ALT group, There was 23 (22.5%) and 58 (56.9%) respectively with high statistically significant difference between the two groups (P >0.05).

As regarding complete EVR achieving SVR, 40 patients out of 75 (53.3%) in elevated ALT group and 39 out of 77 (49.4%) in normal ALT group who had complete EVR achieved SVR, with no statistically significant difference between the two groups (P -value >0.05).

As regarding partial EVR achieving SVR, 3 out of 16 (18.8%) in elevated ALT group and no one out of 4 in normal ALT group who had partial EVR achieved SVR, with no statistically significant difference between the two groups (P value >0.05).

No significant difference was found between the Age and SVR in elevated ALT group and in normal ALT group

As regarding Body Mass Index and SVR, a high statistically significant difference was found between the non responders and responders In both elevated ALT and normal ALT groups .

In elevated ALT group, a high statistically significant difference between the non responders and responders regarding stage of fibrosis (p -value <0.01) were found as 26 (44.8%) of non responders had mild fibrosis (F0-F2) vs. 35 (76.1%) had advanced fibrosis while in responders, 32 (55.2%) had mild fibrosis (F0-F2) vs. 11 (23.9%) had advanced fibrosis . While in normal ALT group, no statistically significant difference were found (p -value > 0.05) as 44 (58.7%) of non responders had mild fibrosis vs. 19 (70.4%) had advanced fibrosis, while in responders, 31 (41.3%) had mild fibrosis vs. 8 (29.6%) had advanced fibrosis.

On the other hand, no significant difference between the HCV RNA viraemia and SVR was found as in elevated ALT group, 35 (66.0%) of non responders had high and moderate viraemia vs. 26 (51.0%) had low viraemia, while in responders, There was 18 (34.0%) vs. 25 (49.0%) respectively. While in normal ALT group, 38 (59.4%) of non responders had high and moderate viraemia vs. 25 (65.8%) had low viraemia, while in responders, it was 26 (40.6%) vs. 13 (34.2%) respectively.

A high statistically significant difference between the non responders and responders was found regarding the pre-treatment ALT elevation and SVR in the elevated ALT patients where SVR occurred in 65.5 % of patients whose their ALT was above 3 times normal and only in 32.0% of those who their ALT was Less than 3 times normal.

Table (1): Early, end of treatment and sustained virological response of interferon plus ribavirin in Both elevated ALT and normal ALT groups

virological response	ALT		X ² test:	P-Value
	Elevated	Normal		
Early virological response :	(n=104)	(n=104)		
Non responders	No 10 %	No 21 %		
Complete responders	75 9.6	77 20.6		
Partial responders	19 72.1	4 75.5	8.29	< 0.05*
End of treatment response:	(n=104)	(n=102)		
Non responders	No 10 %	No 21 %	1.72	> 0.05
Breakthrough	41 9.6	23 20.6		
Responders	53 39.4	58 22.5		
Complete EVR and achieving SVR	(n=75)	(n=77)	0.44	> 0.05
	No 40 %	No 38 %		
partial EVR and achieving SVR	(n=16)	(n=4)	0.44	> 0.05
	No 3 %	No 0 %		
Sustained virological response (SVR)	(n=104)	(n=102)	0.21	> 0.05
	No 43 %	No 39 %		
	43 41.3	39 38.2		

Table (2) : Demographic Data of patients with sustained virological response

Studied variables	Non responders Elevated ALT-n=61- Normal ALT-n=63		Responders Elevated ALT-n=43- Normal ALT-n=39		t- test	P- Value
Age	<i>Mean ±SD</i>		<i>Mean ±SD</i>			
Elevated ALT	37.2 ± 9.7		35.5 ± 9.3		0.88	> 0.05
Normal ALT	35.9 ± 9.7		35.3 ± 9.4		0.33	
BMI	<i>Mean ±SD</i>		<i>Mean ±SD</i>			
Elevated ALT	24.46 ± 2.79		23.09 ± 3.23		2.29	< 0.05*
Normal ALT	23.82 ± 2.44		22.41 ± 2.55		2.79	< 0.01**
fibrosis	No	%	No	%		
Elevated ALT						
F0 – F2	26	42.6	32	74.4	10.34	<0.01**
F3 – F6	35	57.4	11	25.6		
Normal ALT					1.15	> 0.05
F0 – F2	44	69.8	31	79.5		
F3 – F6	19	30.2	8	20.5		
Viremia	No	%	No	%		
Elevated ALT					2.43	> 0.05
High and moderate	35	66.0	18	34.0		
Low	26	51.0	25	49.0		
Normal ALT					0.41	> 0.05
High and moderate	38	59.4	26	66.6		
Low	25	65.8	13	33.3		
ALT	No	%	No	%		
> 3 folds	10	34.5	19	65.5	9.69	< 0.01**
< 3 folds	51	68.0	24	32.0		

4. Discussion

In the current study, significant difference was found between the elevated ALT group and normal ALT group regarding the stage of fibrosis where 55.8% in elevated ALT group, had mild fibrosis and 44.2% had advanced fibrosis, while in normal ALT group most patients had mild fibrosis (73.5% mild fibrosis and 26.5% advanced fibrosis).

These results were in agreement with *Martinot-Peignoux et al., (2001)* and *Pouti et al., (2005)* who found that HCV positive patients with persistently normal ALT values have significantly less liver fibrosis than those whose ALT levels are abnormal but some had marked fibrosis (5%-30%) and even cirrhosis (1.3%). Also, *Keating and Plosker., (2005)* reported that patients with persistently normal ALT levels exhibit a range of disease severities, with an important minority of patients demonstrating moderate (F 2) or advanced (F 3–4) liver fibrosis, and *Alberti et al., (2002)* found that 17% of HCV carriers with normal or nearly normal ALT had advanced fibrotic changes (F3 or F4). (*EASL Clinical Practice Guide Line 2011*) recommended that disease severity evaluation should be performed regardless of ALT levels and assessment of the severity of liver fibrosis is important in decision making in patients with chronic hepatitis C ..

In our study, a negative correlation was found between increased BMI and SVR, where the mean BMI in elevated ALT group was 24.46 in non responders and 23.09 in responders, and in normal

ALT group it was 23.82 in the non responders and 22.41 in the responders.

This finding is similar to findings by *Berg et al., (2006)* who found that a high BMI was inversely correlated with SVR in both IFN and PEG IFN treated individuals and that a lower baseline body weight (≤ 75 –80 kg) was significantly associated with achieving an SVR across all genotype. Also *Crawford et al., (2008)* found that a low BMI was associated with higher probability of SVR.

In the present work, a negative correlation was found between stage of fibrosis and SVR in patients with elevated ALT level, while it had no significant effect on response in the normal ALT group (in the elevated ALT group, 74.4% of the responders and 42.6% of non responders had mild fibrosis and in normal ALT group 70% of non responders and 80% of the responders had mild fibrosis). This lack of demonstrable difference in the normal ALT group may be attributable to small number of patients and that most of them had mild fibrosis.

The finding in the elevated ALT group are in agreement with *Poynard et al., (2003)* who found that the presence of advanced liver fibrosis and cirrhosis were associated with lower response rates to IFN-based treatment where 43% of patients with no or portal fibrosis achieved SVR and only 36% with septal fibrosis or more had SVR. Also *Hadziyannis et al., (2004)*, showed in a study of PEG IFN/RBV combination therapy that SVR rates ranged from 41% to 44% in patients with bridging fibrosis or cirrhosis,

compared with an SVR of up to 65% in those with less advanced hepatic fibrosis.

Berg et al., (2006) found that a low baseline viral load (<600,000–800,000 IU/ml or less) was shown to be an independent predictor of SVR regardless of genotype. Similarly, **Jacobson et al., 2007**, found that, of patients in the flat dose ribavirin group, 7% of those with high baseline viral loads (>600,000 IU/mL) and 18% of those with low baseline viral loads (<600,000 IU/mL) achieved SVR and, in weight based recipients, the corresponding figures were 16% and 33%, respectively.

In this work, no significant difference was found between viral load and the response in both groups as in elevated ALT group SVR was achieved in 34% of patients with high and moderate viremia and 49% of those with low viremia, while in normal ALT group it was 40.6% and 34.2% respectively. This may be attributed to that most of our patients had low and moderate viraemia and only a small number had high viraemia.

Regarding the relationship between the level of pre-treatment ALT elevation and SVR in the elevated ALT patients, SVR occurred in 65.5% of patients whose ALT was above 3 times normal and only in 32.0% of patients who had their ALT elevated less than 3 times normal. This result is in agreement with **Foster et al., (2007)** who found that the likelihood of achieving SVR was higher in patients with an ALT elevation ≥ 3 times the upper limit of normal, and also with **Rodriguez-Torres et al., (2007)** who found positive correlation between SVR and an ALT level above 3 times normal.

Arora et al., (2006) and Yu et al., (2006) Found that SVR rate were comparable between patients with elevated and normal ALT. In the present study, the pretreatment ALT level was found to be not significantly correlated with the sustained virological response (SVR) as 41.3% of patients in elevated ALT group and 38.2% in normal ALT group achieved SVR. This low response may be due to that large number of our studied patients who had advanced fibrosis (44.2% in elevated ALT group and 26.5% in normal ALT group).

These results are also in agreement with **Ghany et al., (2009)** who reported that SVR rates with standard-of-care treatment in persons with normal ALT levels did not differ from those achieved in persons with abnormal ALT level. Similarly, in a study by **Zeuzem et al., (2004)**, an SVR was achieved by 13% and 40% of the patients with HCV genotype 1 with normal ALT treated for 24 and 48 weeks, respectively with PEG IFN/RBV combination therapy. Also **Berg et al., (2006)** found that baseline ALT levels were not associated with treatment response. On the other hand, others (**Shiffman et al.,**

2007) found that such a correlation was observed in HCV genotypes 2 and 3 infected patients.

Our results also agree with the prospective controlled study done by **Bini and Mehandru., (2005)** who demonstrated that the SVR rates in HCV infected patients with persistently normal ALT levels who were treated with interferon- α 2a and ribavirin was not different from the response rates seen in subjects with elevated ALT levels (**Lee and Sherman., 2001**).

In our study, 49.1% of patients with elevated ALT who received pegylated-IFN-alpha-2a (40 KD) and 31.9% of those who received pegylated-IFN-alpha-2a (20 KD) achieved SVR, and in the normal ALT group, SVR was 44.1% and 30.2% respectively. The increased response in the 40 KD treated arms did not reach statistical significance (p -value >0.05), but this is probably a type 2 error (due to the small number of patients). This finding could not be compared to the literature, as no previous published studies compared the 2 types of pegylated interferon.

In conclusion, our data suggest that SVR rates are comparable between patients with elevated and normal ALT, and the decision to treat HCV-infected patients with persistently normal ALT levels should be made on an individual basis and recommended factors that should be considered when deciding to proceed with HCV treatment in these patients should include the severity of liver disease, HCV genotype, age, presence of co-morbid disease, patient motivation and the presence or absence of symptoms.

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