

Original Article

Treatment failure in chronic hepatitis C: Predictors other than viral kinetics

Shahid Sarwar, Shandana Tarique

Department of Medicine, King Edward Medical University, Lahore

ABSTRACT

Objective

To determine variables, other than viral kinetics, associated with outcome in patients with chronic hepatitis C being treated with interferon and ribavirin therapy.

Patients and Methods

This retrospective analytical study was carried out at Hepatology clinic of Mayo Hospital Lahore and included 145 patients treated with interferon and ribavirin. Data regarding demographic characteristics, hematological and biochemical parameters and ultrasonographic findings before therapy were recorded. Type of therapy, duration, side effect profile and outcome of therapy were noted. Correlation of patient's variables with outcome of therapy were analyzed using analysis of variance (ANOVA) and receiver operating characteristic (ROC) curve.

Results

Out of 145 patients, 37 had sustained viral response (SVR), 48 relapse and 58 were non-responders to interferon therapy. Variables associated with SVR were younger age, less time interval between diagnosis and start of interferon therapy, high platelet count, high serum albumin value and absence of coarse texture on ultrasound abdomen. Area under curve (AUC) for SVR were 0.271 for age, 0.52 for interval between diagnosis and start of

therapy, 0.65 for serum albumin and 0.63 for platelet count. High negative predictive value for SVR was noted for time interval between diagnosis and interferon therapy more than 11 months (72.05%), serum albumin < 4 grams/dl (84.6%) and platelet count < $180 \times 10^9/L$ (85.7%) but these variables had poor positive predictive value and specificity, thus making them a good indicator of treatment failure.

Conclusion

Longer interval between diagnosis and treatment, low serum albumin and low platelet count at start of interferon therapy is associated with treatment failure in chronic hepatitis C patients. (Rawal Med J 2010;35:).

Key Words

Chronic hepatitis C, Interferon therapy, Non-responders, Relapse.

INTRODUCTION

Chronic hepatitis C can lead to decompensated liver disease and its catastrophic complications. Asymptomatic nature of disease at earlier stages results in delay in diagnosis and treatment. With introduction of interferon (IFN) therapy over last 2 decades, this infection is now amenable to treatment. Once ribavirin was added and later on with development of Pegylated interferon, sustained viral response (SVR) has increased up to 80% in patients with genotype 2 and 3.¹ Comparatively lesser benefit is seen in other genotypes i.e. 1, 4, 5 and 6 and treatment duration recommended is also 1 year as compared to 6 months in genotype 2 and 3.² Treatment options for non-responders or relapsers are either Pegylated interferon in those treated with standard IFN previously,³ consensus interferon or just follow up for those with failure with Pegylated IFN therapy.⁴

In order to reduce the possibility of treatment failure, new treatment guidelines have identified indicators of favorable response in the form of rapid viral response (RVR) i.e. negative polymerase chain reaction (PCR) after 1 month of treatment, and early viral response (EVR), i.e. negative PCR or 2 log reduction in viral load at week 12 of therapy.⁵ Now patient's treatment duration is being decided based on these results and is usually extended in those with slow response at start of therapy.⁶ Repeatedly checking for viral response with PCR adds to the cost of an already expensive therapy for hepatitis C. Objective of our study was to identify the indicators of treatment outcome in chronic hepatitis C apart from virological parameters.

PATIENTS AND METHODS

It was a retrospective study and patients having received combination therapy of interferon and ribavirin in past were included. Only those having completed 80% of duration with at least 80% dose of combination therapy were analyzed. Demographic characteristics, duration of diagnosis, symptoms at diagnosis and interval between diagnosis and treatment were noted. Hematological variables including complete blood count and clotting profile, biochemical variables i.e. serum bilirubin, serum aminotransferases, serum albumin, renal function tests and radiological features of liver disease including liver size, texture, portal vein diameter, size of spleen at start of treatment were recorded. Type of interferon, dose of ribavirin, duration of therapy, side effects experienced, dose modification during treatment if needed and treatment interruptions were also recorded. Liver function test, qualitative PCR at treatment completion and six months post treatment were noted to determine end of treatment and sustained viral response (SVR) respectively.

In case of re-treatment, type of interferon, dose and duration of therapy and outcome of treatment in terms of end of treatment response and sustained viral response for second therapy were recorded. Present status of patient in terms of well compensated asymptomatic status, symptomatic but compensated liver disease or de-compensated cirrhosis with complications was also noted.

Statistical Analysis: Numerical variables are described as mean \pm standard deviation (SD) while categorical variables as percentage. Variables were compared between those with SVR, non-responders and relapsers using Analysis of variance (ANOVA) for numerical variables and chi square for categorical variables. Receiver Operator Characteristic (ROC) curve was used to identify cut off values of variables with significant difference between those with and without response. P value of less than 0.05 was considered significant for all analysis. Data was analyzed using PASW 18 (IBM® SPSS ® Statistics).

RESULTS

Total of 143 patients were included in final analysis. Male to female ratio was 1.3/1 (81/62). We included 37 patients with sustained viral response, 48 with relapse and 58 with non-response. Majority (118, 82.5%) had standard interferon alpha 2a therapy while 25 (17.5%) were treated with pegylated interferon alpha 2a 40 KD along with ribavirin.

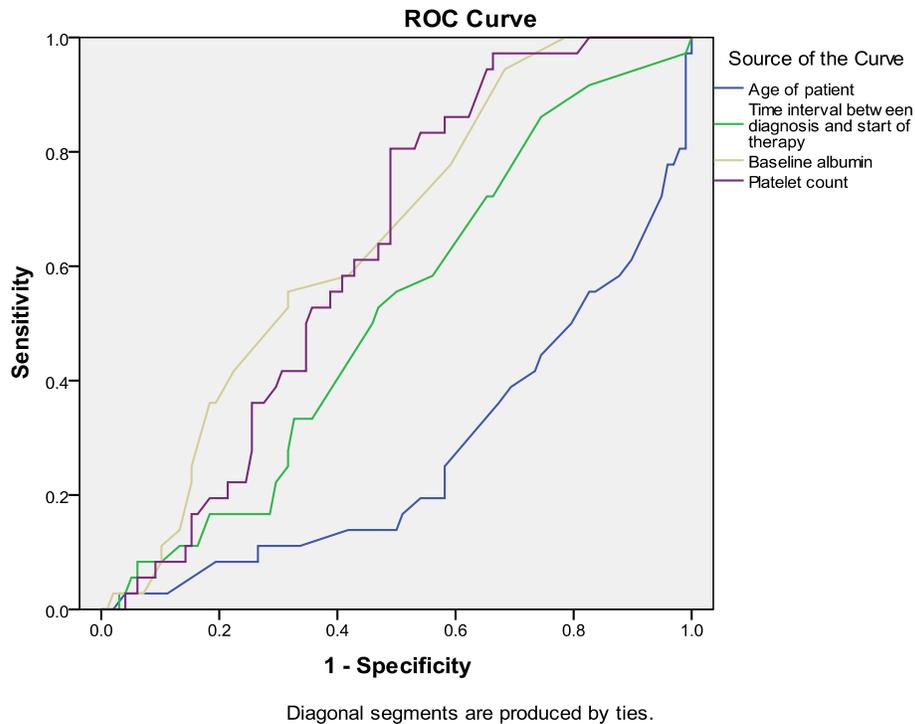
Table 1. Comparison of patients with SVR, Relapse and non-responders.

Variable	Mean \pm SD for patients with			P value SVR vs Relapse	P value SVR vs Non- responder
	SVR	Relapse	Non- responder		
Age (Years)	35.4(10.7)	45.4(10.2)	43(10.0)	0.00	0.001
Time since diagnosis (Days)	35.4(10.7)	45.4(10.2)	43(10.0)	0.002	0.142

ALT (IU/ml)	88.3(54.04)	90.9(112.15)	87.5	0.89	0.94
Albumin (g/dl)	4.2 (0.3)	3.94 (0.54)	4.02 (0.49)	0.006	0.048
Platelet	224(55)	182(82)	210(81)	0.01	0.39
Bilirubin (mg)	0.84(0.24)	0.82(0.25)	0.88(0.29)	0.60	0.21
PT (sec)	12.6(0.82)	13.1(1.5)	12.8(1.3)	0.06	0.39
Liver size (cm)	12.15(2.01)	11.8(1.57)	12.67(1.8)	0.48	0.83
Coarse texture liver (No of patients)	3	20	23	0.001	0.001
Spleen size (cm)	10.68(1.05)	11.5(1.9)	11.6(2.2)	0.013	0.017
Portal vein diameter (mm)	9.62(1.01)	10.2(1.2)	9.98(1.42)	0.018	0.182

Predominant genotype was 3 in 124 (86.7%) patients, 3 patients were of genotype 2 while 5 had genotype 1 and genotype was not checked in 8 of them. Duration of treatment was 6 months for genotype 3 and 2 while it was 12 months with pegylated interferon alpha 2a for genotype 1. Of patients with relapse, 36 (75%) had relapse of disease within 6 months of stopping treatment while 12 (25%) had late relapse. Decompensated liver disease developed in 5 patients, 3 of those had relapse while other 2 were non-responders. These 3 groups of patients were compared for demographic, biochemical and radiological variables using Analysis of variance (ANOVA) as shown in table I.

Fig 1. ROC curve for predicting SVR.



Variables noted to be significantly associated with likelihood of achieving SVR were younger age, less time interval between diagnosis and start of interferon therapy, high platelet count, high serum albumin value and absence of coarse texture on ultrasound abdomen.

Table 2. Predictive value of variables for sustained viral response.

Variable	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Albumin \geq 4 gms/dl	78	42	32.2	84.6	52.11
Platelet count \geq 180 x 10 ⁹ / L	77.8	48.48	35.4	85.7	56.29
Interval between diagnosis and treatment \leq 11 months	48.6	53.7	24	72.05	46.85

Area under curve (AUC) on ROC curve for achieving SVR were 0.271 for age, 0.52 for interval between diagnosis and start of therapy, 0.65 for serum albumin and 0.63 for platelet count at start of treatment (Fig 1). Time interval between diagnosis and interferon therapy less than or equal to 11 months, serum albumin ≥ 4 grams/dl, platelet count $\geq 180 \times 10^9/L$ were identified to be cut off values for these variables and their predictive value for achieving SVR (Table 2).

Eighteen patients had retreatment, 16 with Pegylated interferon/ribavirin while 2 with standard interferon. One year of therapy was completed in 15 patients while treatment was abandoned prematurely in 3 patients due to non-compliance. Only 4 (25%) patients achieved SVR, 3 of those with relapse with first treatment while one non-responder had SVR with retreatment. Relapse with second treatment was seen in 8 patients, 4 each from groups of non-responders and relapsers of first therapy. No response at end of retreatment was seen in 6 patients.

DISCUSSION

Individualization of interferon therapy is standard of care these days instead of uniform duration of treatment.⁶ This decision purely lies with physician and he needs to have parameters to ascertain which patient is going to need extended duration of therapy as studies have shown better outcome with longer duration of interferon therapy in selective group of patients.⁷ Mangia A et al in a study identified platelet count less than 140000/mm³ and body mass index more than 30 to be associated with relapse in patients of genotype 2 and 3.⁸ Labarga P et al found plasma ribavirin trough concentration at week 4 to be predictive of sustained viral response.⁹ In another study, good indicators for response were young age, non-diabetic status, high serum albumin, low aspartate

aminotransferase (AST), low alpha fetoprotein and being treatment naïve. However, in multivariate analysis only young age, low AST and treatment naïve status were associated with SVR.¹⁰ Elefsiniotis IS et al noted that association of early histological stage and non-1 genotype with SVR is influenced by the age of patient.¹¹

Different formulae, based on age, RBC count, WBC count, serum ALT, serum AST and platelet count of patient at start of therapy, were suggested in a study for prediction of response at week 4, 12 and 24 weeks of treatment.¹² Kurosaki M et al proposed a predictive model for response assessment to interferon therapy using Classification and Regression tree (CART) analysis that included hepatic steatosis <30%, low density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dl, age < 50 years, blood glucose <120 mg/dl and serum GGT <40 IU/L.¹³ Lukasiewicz E et al has suggested checking for likelihood of non-response by a model based on HCV RNA value at week 8 of treatment along with age, gender and body mass index of patient.¹⁴ Model should be based on simple parameters so as not to increase the cost of therapy which is already expensive for third world countries.

We identified three variables i.e. platelet count $< 180 \times 10^9/L$, serum albumin less than 4 grams/dl and duration between diagnosis and treatment of hepatitis C more than 11 months to be associated with non-response to interferon therapy in chronic hepatitis C. These parameters are easy to determine as are routinely checked before starting therapy in every patient and treatment duration may be extended based on presence of these bad indicators for achieving SVR. Our results are compromised by retrospective and non-randomized nature of study as consecutive patients with past interferon therapy were included. Further large size studies with randomization and modification of treatment

plan based on presence or absence of variables identified in our study will optimize management plan for chronic hepatitis C patients to achieve best possible outcome of therapy.

CONCLUSION

Platelet count $<180 \times 10^9/L$, serum albumin less than 4 grams/dl and duration between diagnosis and treatment of chronic hepatitis C more than 11 months at start of interferon therapy were associated with treatment failure in chronic hepatitis C patients.

Correspondence: Shahid Sarwar
153-D Muslim Road, Jinnah Colony, Samanabad, Lahore
Tel: 042-7583489, 0300-4174650
drnawalshahid@yahoo.com
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