DOES HEPATITIS C (HCV) TREATMENT – RELATED ANAEMIA PREDICT A GOOD RESPONSE?

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ABSTRACT

Objective: To determine if HCV treatment-related anaemia is associated with a better response to combination therapy with conventional interferon and ribavirin.

Study Design: A descriptive cross sectional study.

Place and Duration of Study: Pakistan Rangers Hospital, Lahore from December 2010 to November 2012.

Material and Methods: Two hundred thirty eight treatment naïve consecutive hepatitis C Virus (HCV) infected patients were enrolled by non-probability purposive sampling. Baseline labs included complete blood count and peripheral blood film, Alanine aminotransferase (ALT), hepatitis C Virus (HCV) ribonucleic acid (RNA) by qualitative polymerase chain reaction (PCR). All patients received combination treatment with standard interferon and ribavirin according to Pakistan Society of Gastroenterology (PSG) guidelines 2009 for 24 weeks. Complete blood counts and ALT were measured at weeks 2 and 4 and then every 4 weeks during treatment. Qualitative PCR for HCV RNA was repeated at the end of 24 weeks treatment. Chi square test was used to compare patients for anaemia and End of treatment response (ETR).

Results: Out of 238 patients enrolled initially, 213 patients completed treatment while 25 were lost to follow up (not because of treatment withdrawal). Mean age was 36 years. Of these 207 were male and 6 were female. Mean hemoglobin (Hb) at baseline was 14.72g/dl (SD +1.24) and after 12 weeks 12.3 g/dl (SD +1.53). Anaemia was noted in 127 (59%) patients. ETR was achieved by 155 (72.8%). Seventy eight percent patients with anaemia achieved end of treatment response (ETR) while only 64% of those without anaemia achieved this response (p=0.017). Development of early anaemia was associated with greater response rates as compared to late onset anaemia but this difference was not statistically significant (p=0.88).

Conclusion: Anaemia due to HCV treatment with conventional interferon and ribavirin is associated with a significantly better ETR.

Keywords: Anemia, Erythropoietin, Hepatitis C, Interferons, Ribavirin.

INTRODUCTION

Hepatitis C is one of the most prevalent problems faced by Pakistan[1] with an estimated prevalence of 4% which varies from place to place within the country and may be as high as 23% for general population in some parts of the country[2]. Current standard treatment for Hepatitis C as recommended in international guidelines is pegylated interferon and ribavirin but national guidelines[3] recommend conventional interferon and ribavirin as the standard treatment in Pakistan due to high cost of the former and fortunately good response to the latter[4]. Anaemia is a well documented and common side effect of both the regimens. Various recent studies have indicated that anaemia during treatment with pegylated interferon and ribavirin treatment predicts a better response to treatment[5]. However similar data for conventional interferon is not available as yet. Aim of present study was to see if anaemia which results as a side effect of the combination treatment with conventional interferon and ribavirin is associated with a better

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response at the end of treatment as assessed by the End of treatment response (ETR).

MATERIAL AND METHODS

It was a cross sectional descriptive study carried out at Pakistan Rangers Hospital Lahore from Dec 2010 to Nov 2012. All treatment naive patients with Chronic Hepatitis C who qualified for anti viral treatment presenting at Pakistan Rangers Hospital, Lahore during Dec 2010 and Nov 2012 were included in the study. Patients under 18 years of age, those with history of psychiatric disorders and those with a co-morbid condition likely to affect response to treatment e.g. hepatitis B virus infection, alcoholic or auto immune hepatitis, were not enrolled for the study. Total 238 consecutive patients fulfilling inclusion and exclusion criteria were enrolled (n=238). Baseline characteristics including HCV ribonucleic acid (RNA) by qualitative polymerase chain reaction (PCR), Hemoglobin (Hb), Alanine aminotransferase (ALT), ultrasound abdomen findings were recorded before starting treatment. All patients received treatment with conventional interferon alpha 3 million international units thrice a week in combination with oral ribavirin at a dose of 800mg/day according to Pakistan Society of Gastroenterology (PSG) guidelines 2009iii. Complete blood count and ALT were repeated at week 2, 4 and 8 (for early anaemia) and then again at weeks 12, 16 and 20 (for late anaemia) during treatment. Qualitative PCR was repeated at 24 weeks to assess ETR. Patients were considered to have achieved ETR if PCR for HCV RNA was negative at the end of treatment. Anaemia was defined as Hb <12.5 g/dl and patients who had anaemia at any stage during the treatment were identified. Early anaemia was defined as Hb <12.5 g/dl during first 8 weeks of treatment while anaemia developing at any stage after 8 weeks of treatment was defined as late anaemia. Magnitude of drop in Hb was also calculated and categorized as less than 3g/dl and 3g/dl or more. Ribavirin dose reduction was made if Hb dropped below a level of 10g/dl. ETR was assessed on the basis of PCR at 24 weeks. Analysis was done for patients who had at least one Hb measurement during 24 weeks treatment. Data were analysed through Statistical Package for Social Sciences (SPSS) version 17. Chi square test was used as test of significance to determine association of ETR with development of anaemia.

RESULTS

Total 238 patients were enrolled in the study. Twenty five patients were lost to follow up. Data was analyzed for the remaining 213 patients. Table-1 shows the values for different variables measured during the study period. Mean age of the patients was 36 years with an age range of 21 to 58 years. Six (2.8%) patients were female while 207(97.2%) were males. Mean Hb at baseline was 14.72 g/dl (SD =1.24), mean Hb for first 8 weeks during treatment was 13.20 (SD=1.70) which dropped to a mean level of 12.3 g/dl (SD =1.53) after 8 weeks. Average drop in Hb from baseline to 8 weeks was 1.2g/dl and average drop over the remaining part of treatment (weeks 8-24) was again 1.2 g/dl. Anaemia (Hb<12.5g/dl) was noted in 127 (59%) patients at some stage during the treatment. Fifty four (25.4%) patients developed a drop in Hb of >3g/dl during first eight weeks of treatment while another 41 (19.2%) had a drop of same magnitude during later part of the treatment. ETR was achieved in 155 (72.8%) patients. All 213 patients completed 24 weeks treatment and in none treatment had to be stopped because of the side effects. Table-2 shows the cross tabulated numbers for occurrence of anaemia, magnitude of drop in HB and early vs. late anaemia and ETR. A total of 155 (72.8%) patients achieved ETR. Out of these 100 (64%) were patients who had experienced anaemia during treatment. Seventy eight percent (78%) patients with anaemia achieved ETR whereas only 63.9% of those who did not develop anaemia could achieve ETR (p=0.017). When analyzed for ALT, patients who had ALT more than 90U/L were not significantly more likely to achieve ETR (72%) than those with ALT less than 90U/L (75%) (p=0.677). Eighty one patients developed anaemia (Hb <12.5 g/dl) within first 8 weeks of treatment. Sixty five (80.2%) of these patients achieved ETR.

Forty six patients developed anaemia during week 8 to 24 of the treatment. Thirty four (73.9%) of these achieved ETR.

More patients who developed anaemia early on (before 8 weeks) during treatment achieved ETR than patients who developed anaemia later during the course of treatment. This difference however; was not statistically significant (p= 0.88).

Table-1: Description of age, ALT and Hb in all patients (n=213).

	Age (yrs)	ALT	Hb at baseline (g/dl)	Hb at 8 weeks (g/dl)	Hb after 8 weeks (g/dl)
Mean	36.3	69	14.7	13.2	12.3
Minimum	21	14	12.5	9.2	8.5
Maximum	58	258	17.0	17.1	16.6
Std Deviation	7.3	46.7	1.1	1.7	1.5

Table-2: Association of ETR with anaemia, magnitude of Hb drop and time of onset of anaemia.

		ETR		
		Achieved	Not Achieved	p-value
Anaemia	yes	100 (78.7%)	27 (21.2%)	0.017
	no	55 (63.9%)	31 (36.1%)	
Drop in Hb	≥3g/dl	95 (79.1%)	25 (20.9%)	0.017
	<3g/dl	60 (64.5%)	33 (35.5%)	
Time of Anaemia	Early	65 (80.2%)	16 (19.8/%)	0.88
	Late	34 (73.9%)	12 (26.1%)	

DISCUSSION

Management of HCV infection and its complications is a major burden on healthcare resources in Pakistan. Anaemia is a common complication[6] and often leads to interruption or discontinuation of treatment. Treatment costs rise even further when anaemia is treated by expensive erythropoietin injections. Up to 56% patients receiving interferon may experience a decrease of more than 3 g/dl[7] and one study reported a decrease of at least 1g/dl in 95% of patients[8]. Most studies have reported a frequency of anaemia from 15% to 20%[9-11] which is in sharp contrast to present study. Reason for this contrast is that most other studies defined anaemia as Hb less than 10g/dl instead of 12.5g/dl as was done in this study.

ETR in present study was achieved by 72.8% patients which is in keeping with some studies[12] but slightly lower than other local studies[13,14]. Many of the participants were serving in remote areas of Punjab province where weather gets very hot during summers and electricity is only available for a few hours each day precluding proper storage of interferon injections. This could possibly have resulted in reduced efficacy of the medicine.

Remarkable correlation was seen between development of anaemia and response rate. Patients who developed anaemia were more likely to achieve ETR (78%) than those who did not develop anaemia (63.9%). Such correlation has already been found for pegylated interferon by Sulkowski et al[5]. The correlation found in this study is not much different than what was reported by Sulkowski et al as in their study 65% of anaemic patients achieved ETR while 52% of those without anaemia could achieve a response. It is important to remember that the study by Sulkowski et al differed from present study as it was carried out on patients with genotype 1 only and used pegylated interferon. Genotype was not tested for patients in present study as per PSG guidelines but most patients are expected to have genotype 3[15]. Ribavirin dose was reduced when Hb dropped below 10 g/dl and was stopped at a level of 8.5 g/dl or lower.

Patients who developed anaemia before 8 weeks were more likely to achieve ETR (80%) than those who developed anaemia after 8 weeks

of treatment (73%). Patients who did not develop anaemia during treatment were even less likely to achieve ETR (65%). The difference between these groups however; was not statistically significant. Similar findings were reported by Sulkowski et al although they reported a significantly better ETR when erythropoiesis stimulating agents were used to correct anaemia during early phase of treatment. It remains to be seen through well controlled trials whether use of erythropoietin for treatment of anaemia further improves the response rates to the combination treatment with conventional interferon and ribavirin. If future studies reveal an insignificant effect of use of erythropoietin on response to HCV treatment, it might be appropriate to delay its use in asymptomatic anaemic patients till Hb drops to further low levels (<8.5g/dl). This can save a significant amount of money being currently spent on treating anaemia with erythropoietin during HCV treatment in Pakistan, making a positive impact; however small it may be, on the national exchequer.

CONCLUSION

This study is consistent with the finding that HCV treatment with conventional interferon and ribavirin is commonly associated with anaemia. It has further shown that as with pegylated interferon and ribavirin treatment, combination of conventional interferon and ribavirin also has a better response in patients who develop anaemia during such treatment. This is in absence of use of eythropoiesis stimulating agents. Further well controlled trials are required to determine effect of erythropoietin for treatment of anaemia on the response rates to combination treatment with conventional interferon and ribavirin.

CONFLICT OF INTEREST

The authors of this study reported no conflict of interest.

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