Role of Iron and Erythropoietin in Management of Anemia in Chronic HCV Patients Treated by Interferon and Ribavirin

Sahar Zaghlol*, Mohamed H. Ibrahim*, Jehan Saeed*, Ahmad M. Hassaneen**
*Internal Medicine, Zagazig University, ** Clinical pathology department

Abstract

Background: Hepatitis C virus (HCV) infection is estimated to affect over 170 million people worldwide. The current therapy for HCV is pegylated interferon and ribavirin. Anemia is a common side effect of treatment for HCV infection. Recent evidence points to a beneficial role of erythropoietin (EPO) in alleviating INF-ribavirin induced anemia, thereby improving quality of life, enabling higher ribavirin dosage and consequently may improve sustained virological response (SVR). **Aim:** This study evaluated the incidence of anemia, its relation to serum iron and effect of EPO to maintain ribavirin (RBV) dose and hemoglobin (Hb) level in chronic HCV patients treated with antiviral combination therapy in Zagazig University Hospitals. **Patients and methods:** 130 patients are included in the study, 100 of them were early responder to treatment and 30 patients were excluded as they were either non responder to treatment or stopped treatment due to other cause including other hematological complications. When (Hb) dropped below 10 gm%, the dose of ribavirin will be reduced 400 mg from baseline dose with follow up weekly for Hb level, if Hb level increased the dose of ribavirin will be returned to full dose, if no improvement and Hb level decreased below 8.5 gm/dl, the patient stopped therapy of INF-ribavirin. Erythropoietin starting with 4000 lU/week subcutaneously if no response within 2 weeks, we increased EPO dose gradually up to12, 000 lU/week. ***Results:*** Incidence of anemia was 28%, 28 patients16 males and 12 females. Of our patients 99 patients completed 48 weeks of therapy in the form of either pegylated interferon α2a at a dose of 180 ug/week or α2b at a dose of 1.5 ug/kg body weight plus ribavirin at a dose of 1000-1200 mg/day according to body weight (15mg/kg) and only one patient stopped treatment due to anemia not responding to erythropoietin. Iron, folic acids and multivitamins alone without EPO resulted in significant improvement of anemia in only 13 patients (13/28, 46.4%). EPO was given to 15 patients and good response was obtained in 11 out of 15 patients (73.3 %); so of all 28 anemic patients, 27 completed the course of antiviral therapy. ***Conclusion:*** EPO therapy improve compliance to antiviral therapy in chronic HCV patients and may be considered one of standard treatment of anemia resulting from INF-ribavirin therapy as iron, folic acids and multivitamins alone not enough for treatment of anemia in those patients, but further larger studies with longer follow up are required to evaluate the impact on SVR and final outcome in those patients.

Key words: HCV, pegylated interferon, ribavirin, anemia, antiviral treatment.

Introduction

Hepatitis C Virus (HCV) is a small, enveloped, positive-sense single-stranded RNA virus of the family Flaviviridae. HCV infection is estimated to affect over 170 million people worldwide. The combination therapy of antiviral peg-interferon and ribavirin has evolved as one of the better treatments for hepatitis C. In spite of its success in controlling hepatitis C infection, it has also been associated with treatment-related adverse side effects. Anemia is a common complication of antiviral therapy for chronic hepatitis C virus (HCV) infection that necessitates dose reductions or therapy discontinuation.[1,2,3].

Combined peg- interferon and ribavirin represents the standard therapy for patients

with chronic hepatitis C, which allows for sustained viral response (SVR) in up to 90% of patients depending on certain viral and host factors. Clinical studies have demonstrated the importance of adherence to therapy, which is markedly impaired by treatment-related adverse effects [4,5].

Anemia is usually multifactorial, due to shortening of life span of erythrocytes, presence of inhibitors of erythropoiesis in plasma, inadequate production of endogenous erythropoietin (EPO) for the degree of anemia, blood loss, and iron and vitamins deficiency[5].

Ribavirin dose reduction is the initial anemia management strategy, but administration of erythropoietin (EPO) enable rapid return to full ribavirin dosage, good adherence to treatment and consequently may improve sustained virological response. [6,7,8].

Aim of this study is to evaluate the incidence of anemia, its relation to serum iron and effect of EPO to maintain ribavirin (RBV) dose and hemoglobin (Hb) level in chronic HCV patients treated with antiviral combination therapy in Zagazig University Hospitals.

Patients and methods

Patients: This study was carried out on 130 patients with chronic HCV infection (99 males and 31 females). Patients were studied from Zagazig University Hospitals. The study was performed from September 2012 to September 2013 and their ages ranged from 20 to 59 years. Written consent was taken from all patients before introduced in the study. Out of 130 patients are included in the study, 100 (79 males and 21 females) of them were early responder and 30 patients were excluded as they were either non responder to treatment for chronic hepatitis C or stopped treatment due to other cause including other hematological complications.

Inclusion criteria included all patients had serum antibodies to HCV and positive Polymerase Chain Reaction (PCR) tests to HCV-RNA.

Exclusion criteria included patients with decompensated cirrhosis, autoimmune hepatitis, hepatitis B co-infection, HIV infection, current intravenous drug abuse, age less than 18 years or more than 60 years, previous treatment with interferon and ribavirin, serum alpha-fetoprotein concentration above 25 ng/ml, history of alcohol intake or hemolytic disease, severe depressive illness, severe comorbid disease, organ transplant, pregnancy, hepatocellular cancer and Hb less than 12gm%.

The studied HCV patients were classified into two groups according to development of anemia during treatment, patients without anemia, they included 72 patients (63 males and 9 females) and patients with anemia, and they included 28 patients (16 males and 12 females). Patients were considered to have significant anemia requiring treatment and treatment modifications, when Hb level<10 gm/dl. The dose of ribavirin will be reduced 400 mg from baseline dose with follow up weekly for Hb level if Hb level increased the dose of ribavirin will be returned to full dose, if no improvement and Hb level decreased below 8.5 mg/dl, the patient stopped therapy of INF and ribavirin.

Methods: All patients were subjected to: thorough history taking, physical examination and laboratory examination including: Complete blood count (CBC) was done using Sysmex N 21 automated Cell counter, liver function tests (serum albumin, total bilirubin, AST, ALT and PT, and serum creatinine. In patients who developed anemia: Serum iron was measured by Cobas Integra 400 automated chemistry analyzer, the measurement range of this analyzer is from 5 to 1000 ug /dl, serum ferritin was measured by the VIDAS System using Enzyme Linked Fluorescent Assay (ELFA) technique, the measurement range is from 1.5 to 1200 ng/ml and

estimation of TIBC in serum: using TIBC kit (BioMeriux), transferrin was saturated by an iron solution and the excess iron was adsorbed on magnesium hydroxycarbonate. After finishing the procedure, the supernatant was used for determination of iron by Cobas Integra 400 autoanalyzer. TIBC is calculated as follow: TIBC= iron (in supernatant) x3. (Reference)

Therapy in the form of either peg-interferon α2a at a dose of 180 ug/week or α2b at a dose of 1.5 ug/kg body weight plus ribavirin at a dose of 1000-1200 mg/day according to body weight (15mg/kg). When Hb dropped below 10 gm%, the dose of ribavirin will be reduced 400 mg from baseline dose and follow up weekly for Hb level if Hb level increased the dose of ribavirin will be returned to full dose, if no improvement and Hb level decreased below 8.5 gm/dl, the patient stopped therapy of INF-ribavirin. The anemic patient (while decreasing dose of ribavirin) will take multivitamin preparation including folic acid without iron if serum iron, ferritin and TIBC level are normal. Those with low iron deficiency will take iron preparation in the form of ferrous sulphate (300 mg /day) and erythropoietin starting with 4000 lU/week subcutaneously /week if no response within 2 weeks, we increased EPO dose up to 12,000 lU/week.

Results

A total of 100 subjects with chronic HCV infection under treatment with IFN and ribavirin,[79 (79%) males and 21(21%) females], their ages range from 20 to 59 years. Anemia developed and Hb dropped below 10gm/dl in 28 patients (28%), 57% in females (12/21) and 20.3% in males (16/79). The onset of anemia was mainly within the first 24 weeks. 99 patients complete 48 weeks of therapy and only one patient stopped treatment due to anemia not responding to erythropoietin. The 28 anemic patients submitted to decrease in ribavirin dose. All anemic patients were given folic acid 5mg/day and multivitamin. iron if serum iron and ferritin are low (5 patients 33.3% of anemic patients), 13 out of 28 anemic patients responded to this treatment (46.4%) with return to full dose of ribavirin. 15 patients showed no response to multivitamins and were treated with EPO, 4 of 15 patients responded on 4,000 u weekly (26.7%), 6 of 15 patients responded to 8,000 u weekly (40%), 5 of 15 patients were given 12,000 u weekly with good response in 11 of 15 patients (73.3%), while partial response was observed in 3 patients in whom Hb remained between 8.5-10gm% for 2 months, then increase above 10 gm%. 14 of 15 patients on EPO completed the course of INF-ribavirin (93.3%). One female patient stopped INF-ribavirin at 20 week as Hb continued below 8.5gm/dl even after EPO 12,000u weekly. There was a high significant relation between serum iron level, ferritin and total iron binding capacity; and response to erythropoietin. Ten of 15 cases had normal serum iron, ferritin and TIBC (107.8±21.5ug/dl, 130.2±56.7ug/l and 245.3±42.4ug/dl respectively) and 5 cases having low serum iron, ferritin and high TIBC (43.8±2.4ug/dl, 12.9±4.2ug/l and 330.5±10.8 ug/dl, respectively). In our study there was no adverse event of EPO administration was reported among included subjects. We found that the mean of hemoglobin of patients with HCV infection at base (14.01±1.41 gm/dl) was the highest on the onset than it at the different following weeks, and as expected lower level was observed in patients who developed anemia than those without anemia (table7).

Table (1): Patients' characteristics:

Sex Female Male	No 21 79	% 21 79
Age (years) Range Mean ± SD	 20-59 years 38.76 ± 9.44	
Serum creatinine (mg/dl) Mean ± SD	 0.827 ± 0.15	
Total bilirubin (mg/dl) Mean ± SD	 0.491 ± 0.2	
Indirect bilirubin (mg/dl) Mean ± SD	 0.345 ± 0.08	
albumin (gm/dl) Mean ± SD	 3.987 ± 0.3	
AST (U/L) Mean ± SD	 47.49 ± 25.2	
ALT (U/L) Mean ± SD	 48.71 ±27.8	
Prothrombin time (seconds) Mean ± SD	 11.2 ±0.7	

Table (2): Paired t for comparison of hemoglobin (gm/dl) during follow up with baseline Mean hemoglobin (gm/dl) at study follow-up period

Parameter	Mean ± SD	Paired t	p
Base	14.01 ± 1.41		
One week	13.4 ± 1.62	6.4	0
2 weeks	13.02 ± 2.03	6.47	0
4weeks	12.31 ±1.52	14.81	0
8 weeks	12±1.49	16.05	0
l2weeks	11.92± 1.76	13.25	0
l6weeks	11.69± 1.57	14.94	0
20 weeks	11.74 ± 1.63	15.1	0
24weeks	11.59± 1.63	15.14	0
28weeks	11.49±1.36	17.82	0
32weeks	11.44± 1.57	17.68	0
36weeks	11.35±1.42	18.95	0
40weeks	11.49± 1.25	19.47	0
44 weeks	11.49± 1.31	17.48	0
48weeks	11.62± 1.49	15.54	0

Table (3): Onset of anemia

Onset	No	%
1-12 weeks	11	39.3
12-24	14	50
24-48	3	10.7
Total	28	100

Table (4): Comparison between patients' sex and age in patients with and without anemia

Parameter	With anemia		Without anemia		X^2	P
Sex	(n=28)		(n=72)			
	No	%	No	%		
Female Males	12 16	57.1 20.3	9 63	42.9 79.7	11.19	0.001
Age (years)	38.96 ± 10.49		38.68 ± 9.08		t 0.13	P 0.89

Table (5): Use of erythropoietin, doses and response

EPO dose	No of patients used	%
4,000u	4/15	26.7
8,000u	6/15	40
12,000u	5/15	33.3
Good response	11/15	73.3
Partial response	3/15	20.0
Stopped INF-ribavirin	1/15	6.7

Table (6): Relation between iron profile and response to erythropoietin

Serum iron (ug/dl)	Serum ferritin (ug/l)	TIBC (ug/dl)	Response to erythropoietin				Total		X2	P
			No response		Response					
Normal	Normal	Normal	No	%	No	%	No	%		
			0	0	10	100	10	100		
Low	Low	High	4	80	1	20	5	100	10.91	0.001
Total			4	26.7	11	73.3	15	100		

N.B. TIBC, total iron binding capacity

Table (7): comparison between pretreatment HB in anemic and patients without anemia

HB in anemic	**HB in patients without anemia**	t	P
12.96±0.95	14.41±1.35	t=5.153	0.00

Discussion

Anemia during combination therapy with pegylated interferon plus ribavirin (RBV) for chronic hepatitis C virus (HCV) patients usually leads to RBV dose reduction or discontinuation of treatment. Erythropoietin (EPO) is a hormone that controls red blood cell production. Binding of EPO to EPO-receptor results in increased numbers of red blood cells in circulation, which makes EPO a potent molecule to treat anemia in various groups of patients [(9).]

Recent evidence points to a beneficial role of EPO in alleviating ribavirin-induced anemia. thereby improving quality of life, enabling higher ribavirin dosage and consequently may improve sustained virological response (SVR) [(4).]

In the present study Hb levels continued to significantly decline from the first week after initiation of treatment and throughout the study and the onset of anemia was in the first 24 weeks. This in harmony with the findings of **Oze et al., 2006** [(10),] who examine the factors correlated with the progression of ribavirin-induced hemolytic anemia in patients with chronic hepatitis C treated by interferon and ribavirin combination therapy and found that early decline of hemoglobin correlates with progression of ribavirin-induced hemolytic anemia. In the current study, anemia was diagnosed in 28 % of the studied patients. This figure is similar to what found by **Sulkowski et al., 2011** [(11),] the authors reported anemia in 865 patients out of 3023 treated patients (28.6%).

However, our rate is markedly lower than that reported by **Giusto et al., 2011** [(12),] who studied the prevalence of anemia in HCV patients treated with peg-IFN-ribavirin treatment, they reported a rate of 61.0 % in the studied 160 patients on treatment. This discrepancy may be explained by the fact that this study included liver transplant HCV infected patients. Regarding the onset of anemia in the studied patients, the present study found that 11 patients (39.3 %) reported anemia in the first 1-12 weeks while 14 patients (50%) reported anemia in the subsequent 12- 24 weeks and 3 patients manifested anemia in the latter 24- 48 weeks. This is in agreement with **Afdhal et al., 2004** [(13),] who found a decrease in hemoglobin to less than 12 gm/dl most commonly during the first 24 weeks of HCV therapy. Comparison between patients with anemia and patients without regarding the demographic data has shown that anemic patients had significantly higher frequency in females when compared with patients without. This is in agreement with the results of **Sulkowski et al., 2004** [(14),] who found that the incidence of decreases in Hb to <10 gm/dl was higher in women. In our study, comparison between patients with anemia and patients without regarding the laboratory values had demonstrated that patients with anemia suffered lower Hb levels at baseline. This is in accordance with **Hiramatsu et al., 2011** [(15),] who aimed to develop a model to predict the development of anemia during pegylated interferon alpha-2b plus ribavirin combination therapy.

In their study, Hb values at baseline included in the model was useful for predicting the probability of anemia, and has the potential to support clinical decisions regarding early dose reduction of ribavirin[(15)].

In the present study, multivitamins were used for management of anemia in all anemic cases. However, the response was unsatisfactory (46.4 %). This is in line with the study of **Gonzalez et al., 2003**[(16)], who found that Folic acid supplementation does not prevent ribavirin-induced anemia and **Saeian et al., 2004**[(17)], who concluded that High-dose vitamin E supplementation does not diminish ribavirin-associated haemolysis in HCV treatment with combination standard alpha-interferon and

ribavirin. However, this is not in a line with **Lin and Yin 2009**[18], who found that anti-HCV therapy elevated oxidative stress and depleted B vitamins and iron, thus, the supplement of antioxidant agents, B vitamins and/or iron should be considered for patients with this therapy in order to avoid other healthy risk.

In the present study good response to erythropoietin was obtained in 11 out of 15 patients (73.3 %). This is in agreement with **Tseng et al., 2011**[19], who evaluated the effect of erythropoietin to maintain RBV dose and Hb level in chronic HCV patients treated with antiviral combination therapy. In this study, 88 chronic HCV patients who developed anemia during therapy were enrolled; 55 in the EPO-beta group and 33 in the untreated group. The mean Hb change from week 12 to week 20 was higher in the EPO-beta group when compared with the untreated group. The recent study performed by **Spaan et al., 2013** [9], tried to explain the mechanisms by which erythropoietin contribute to anemia correction in HCV patients treated with IFN-ribavirin. They observed at day 7 after EPO administration a significant decline of the frequency of monocytes producing various pro-inflammatory cytokines. These findings demonstrate an inhibitory effect of EPO on the secretion of effector molecules by monocytes.

Also, in agreement with our study, **Pockros et al., 2004**[20], have shown that epoetin alfa given for HCV treatment-associated anemia significantly improves patient quality of life. In our study, we measured serum iron level in cases not responding to multivitamin therapy. They were 15 cases, 10 cases of them having normal serum iron level (107.8±21.5ug/dl) and 5 cases having low serum iron level (43.8±2.4ug/d1) and given iron supplementation. This in the same line with **Stravitz, 2005** [21], who assessd that the most common cause for inadequate response to Epo is absolute or functional iron deficiency leading to a need for higher Epo dose levels.

In our study, we found that only one case stopped course of therapy at week 20 as Hb level decreased below 8.5 mg/dl. This is in agreement with **Hadziyannis et al., 2004** [22], who reported that less than 1 % of patients suffered from Hb less than 8.5 gm/dl leading to discontinuation of therapy of HCV.

However, this is not in a line with **Ferencei et al., 2008** [23], who found that one to each 5 patients (20%) stopped course of therapy of interferon and ribavirin due to anemia. However, this discrepancy may be due to HCV/HIV coinfection in these patients.

Where does this leave the clinician and the patient? The recommendations of **Sherman et al, 2006** [24], are reasonable and appropriate. Clearly, although patients would benefit from EPO both in terms of quality of life and maximizing the likelihood of a SVR, EPO has been reported to cause an increased incidence of nausea compared with placebo, it is generally well tolerated. There is risk of pure red cell aplasia, although real and something that should be discussed with patients a priori, is an infrequent occurrence of these side effect [21,25]. EPO, however, is costly. Many patients, with no private insurance coverage, cannot afford to use this adjuvant medication without suffering some economic hardship, and many provincial drug benefit programs will not cover it. We know that for many patients, a low hemoglobin level is just a number and aside from causing anxiety in both patient and health care provider alike, it is tolerable. Sometimes patients are able to tolerate significantly low hemoglobin levels without the need for dose modification.

Conclusion

Adjuvant treatment with EPO, must be an individualized decision and its use

should not be dogmatically applied to everyone with anemia. Even low doses of erythropoietin are effective in improving or maintaining the hemoglobin level in patients of hepatitis C who develop treatment induced anemia. EPO therapy improve compliance to antiviral therapy in chronic HCV patients and in future may be considered one of standard treatment of anemia resulting from INF-ribavirin therapy as iron, folic acids and multivitamins alone not enough for treatment of anemia in those patients, but further larger studies with longer follow up are required to evaluate the impact on SVR and final outcome in those patients. Fortunately, hepatitis research is a dynamic process and HCV antiviral therapies without significant anemia are in development. Hopefully, in a few years, both the recommendations of Sherman et al, 2006 and the present study, may become of historical interest only.

REFERENCES

1.Strader DB, Wright T, and Thomas DL (2004): AASLD practice guideline : Diagnosis, management, and treatment of HCV. Hepatology, 39:1147-71.

2. Krishnan SM, and Dixit NM (2011): Ribavirin-induced anemia in hepatitis C virus patients undergoing combination therapy. PLoS Comput Biol.:3;7(2): 1001-72.

3.DebRoy S, Kribs-Zaleta C, Mubayi A, Cardona-Meléndez GM, Medina-Rios L, Kang M, and Diaz E (2010): Evaluating treatment of hepatitis C for hemolytic anemia management. Math Biosci. 2010 Jun;225(2):141-55.

4.Stickel F, Helbling B, Heim M, Geier A, Hirschi C, Terziroli B, Wehr K, De Gottardi A, Negro F, and Gerlach T. (2012): Critical review of the use of erythropoietin in the treatment of anaemia during therapy for chronic hepatitis C. J Viral Hepat.;19(2):77-87.

5. Alavian SM, Tabatabaei SV, and Behnava B (2012): Impact of erythropoietin on sustained virological response to peginterferon and ribavirin therapy for HCV infection: a systematic review and meta-analysis. J Viral Hepat.;19(2):88-93.

6. Tabatabaei SV, Alavian SM, Keshvari M, Behnava B, Miri SM, Karimi Elizee P, Zamani F, Amini Kafiabad S, Gharehbaghian A, Hajibeigy B and Lankarani KB. (2012): Low dose ribavirin for treatment of hepatitis C virus infected thalassemia major patients; new indications for combination therapy. Hepat Mon. 2012 Jun;12(6):372-81.

7. Hynicka LM, and Heil EL (2013): Anemia management in patients with chronic viral hepatitis C. Ann Pharmacother.;47(2):228-36.

8. Alavian SM, Tabatabaei SV, Behnava B and Rizzetto M.(2012): Standard and pegylated interferon therapy of HDV infection: A systematic review and meta-analysis. J Res Med Sci.;17(10):967-74.

9. Spaan M, Groothuismink ZM, and Koning L (2013): erythropoietin administration suppress human monocyte function in vitro and during therapy-induced anemia in HCV patients. Antiviral Res, 98(3):469-75.

10. Oze T, Hiramatsu N, Kurashige N, Tsuda N, Yakushijin T, Kanto T, Takehara T, Kasahara A, Kato M, Yoshihara H, Katayama K, Kubota S, Hijioka T, Ishibashi K, Oshita M, Hagiwara H, Haruna Y, Mita E, Tamura S, and Hayashi N (2006): *Early decline of hemoglobin correlates with progression of ribavirin-induced hemolytic anemia during interferon plus ribavirin combination therapy in patients with chronic hepatitis C. J Gastroenterol.; 41(9):862-72.*

11. Sulkowski MS, Shiffman ML, and Afdhal NH (2010): Hepatitis C virus treatment-related anemia is associated with higher SVR rate. Gastroenterol.,: 139(5):1602-11.

12. Giusto M, Rodriguez M, Navarro L, Rubin A, Aguilera V, San-Juan F, Ortiz C, López-Andujar R, Prieto M, and Berenguer M (2011): Anemia is not predictive of sustained virological response in liver transplant recipients with hepatitis C virus who are treated with pegylated interferon and ribavirin. Liver Transpl.;17(11):1318-27.

13. Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, Bowers PJ; Proactive Study Group (2007): Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterol.; 126(5):1302-11.

14. Sulkowski MS, Felizarta F, Smith C, Slim J, Berggren R, Goodman R, Ball L, Khalili M, Dieterich DT; Hepatitis Resource Network Clinical Trials Group (2004): Daily versus thrice-weekly interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected persons: a multicenter randomized controlled trial. J Acquir Immune Defic Syndr. 15;35(5):464-72.

15. Hiramatsu N, Kurosaki M, Sakamoto N, Iwasaki M, Sakamoto M, Suzuki Y, Sugauchi F, Tamori A, Kakinnuma S, Matsuura K, and Izumi N.(2011): Pretreatment prediction of anemia progression by pegylated interferon alpha-2b plus ribavirin combination therapy in chronic hepatitis C infection: decision-tree analysis. J Gastroenterol.;46(9):1111-9.

16. González H, Ríos ME, Torres EA, Muñoz H, Arroyo J, and Castro FJ.(2003): Folic acid supplementation does not prevent ribavirin-induced anemia. P R Health Sci J.;22(4):359-62.

17. Saeian K, Bajaj JS, Franco J, Knox JF, Daniel J, Peine C, McKee D, Varma RR, Ho S; Midwest Hepatitis Study Group.(2004): High-dose vitamin E supplementation does not diminish ribavirin-associated haemolysis in hepatitis C treatment with combination standard alpha-interferon and ribavirin. Aliment Pharmacol Ther.;20(10):1189-93.

18. Lin CC, and Yin MC (2009): Vitamins B depletion, lower iron status and decreased antioxidative defense in patients with chronic hepatitis C treated by pegylated interferon alfa and ribavirin. Clin Nutr. Feb;28(1):34-8.

19. Tseng KC, Chen LH, Chen CY, Chang TT, Chou AL, Wu IC, and Cheng PN (2009): Low dose erythropoietin-beta improves anemia and maintains ribavirin dose in chronic hepatitis C patients receiving combination therapy with ribavirin plus pegylated interferon Alfa-2b. Hepatol Res.;39(6):539-45.

20. Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, Wright TL, Mody SH, Tang KL, Goon BL, Bowers PJ, Leitz G, Afdhal NH; PROACTIVE Study Group (2004): Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. Hepatology, Dec; 40(6):1450-8.

21. Stravitz RT, Chung H, Sterling RK, Luketic VA, Sanyal AJ, Price AS, Purrington A, and Shiffman ML (2005): Antibody-mediated pure red cell aplasia due to epoetin alfa during antiviral therapy of chronic hepatitis C. Am J Gastroenterol.;100(6):1415-9.

22. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A,Ackrill AM; PEGASYS International Study Group (2004): Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med.;140(5):346-55.

23. Ferenci P, Brunner H, Laferl H, Scherzer TM, Maieron A, Strasser M, Fischer G, Hofer H, Bischof M, Stauber R, Gschwantler M, Steindl-Munda P, Staufer K,Löschenberger K; Austrian Hepatitis Study Group (2008): A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3. Hepatology;47(6):1816-23.

24. Sherman M, Cohen L, and Cooper MA (2006): Clinical recommendations for the use of recombinant human erythropoietin in patients with hepatitis C virus being treated with ribavirin. Can J Gastroenterol;20:479-485.

25. Rossert J, Yue S, Smirnakis K, Mytych DT, Johnson L, Kouchakji E and Casadevall N (2014): *Risk of pure red cell aplasia in patients with hepatitis C receiving antiviral therapy and an erythropoiesis-stimulating agent. Clin Gastroenterol Hepatol.;12(2):341-5.*

Arabic summary

الملخص العربي

دور الحديد و الإريثروبيوتين في علاج الانيميا بمرضي الالتهاب الكبدي المزمن (سي) اللذين يعالجون بالانترفيرون و الريبافيرين

الخلفية العلمية:

تقدر الاصابة بالفيروس الكبدي سي بما يزيد عن 170 مليون شخص علي مستوي العالم. ويستخدم الانترفيرون و الريبافيرين في العلاج. وتعتبر الانيميا من اهم الاثار الجانبية لهذه الادوية. وهناك دليل يشير الى ثمة فائدة من علاج هؤلاء المرضى بالاريثروبيوتين الذى قد يؤدى الى عدم انقطاع العلاج وتحمل اثاره الجانبية مما قد يحسن الاستجابة المستديمة للعلاج.

الهدف من البحث :

تقييم معدل حدوث الانيميا وعلاقتها بالحديد و الاريثروبيوتين تأثير ذلك في الحفاظ علي جرعة الريبافيرين ومستوي الهيموجلوبين في مرضى التهاب الفيروس الكبدى المزمن (سى) الخاضعين للعلاج بالانترفيرون و الريبافيرين فى مستشفيات جامعة الزقازيق.

المرضى و طريقة البحث:

تمت الدراسة علي 130 مريض ,100 مريض منهم استجابوا استجابة مبدئيه, وتم استبعاد 30 مريض من الذين لم يحدث لهم استجابة مبدئية أو تركوا العلاج لأسباب أخرى. المرضى الذين وصل الهيموجلوبين لديهم الى أقل من 10 جرامات في الديسيليتر تم تقليل جرعة الريبافيرين بمقدار 400مجم مع استمرار الإنترفيرون فإن تحسنت نسبة الهيموجلوبين يتم الرجوع للجرعة السابقة من الريبافرين وإذا استمر انخفاض الهيموجلوبين ووصل الى أقل من 8.5 جرامات في الديسيليتر يتم ايقاف العلاج بالانترفيرون و الريبافيرين. ويبدأ العلاج بالإريثروبيوتين بجرعات متدرجة تبدأ من 4000وحدة تحت الجلد اسبوعيا و تزداد الجرعة حتى تصل الى 12000وحدة تحت الجلد اسبوعيا ويتم تغيير الجرعات كل اسبوعين حسب صورة الدم.

النتائج:

بعد اجراء الاختبارات الإحصائية اللازمة تبين أن نسبة حالات الأنيميا التي يقل فيها الهيموجلوبين عن 10 جرامات في الديسيليتر كانت 28% , 16مريضا منهم من الرجال و 12 مريضا من النساء. الذين أكملوا العلاج لمدة 48 اسبوعا كانوا 99 مريضا و مريض واحد تم ايقاف العلاج له بسبب الأنيميا ولم يستجيب للحديد أو الإريثروبيوتين. العلاج بالحديد وحمض الفوليك أدى الى تحسن الأنيميا في 13 مريضا (46.4%) دون الحاجة الى الإريثروبيوتين. 15 مريضا احتاجوا الى الإريثروبيوتين 11 منهم (73.3%) استجابوا استجابة جيدة حيث ارتفع الهيموجلوبين الى اكثر من 10 جرامات في الديسيليتر واستجابة جزئية في 3 مرضى كانت نسبة الهيموجلوبين بين 8.5 الى 10 جرامات في الديسيليتر ومريض واحد توقف عن العلاج حيث ظلت نسبة الهيموجلوبين أقل من 8.5 جرامات في الديسيليتر.

الاستنتاج:

العلاج بالإريثروبيوتين أدى الى تحسن في الاستمرار على العلاج بالانترفيرون و الريبافيرين ومن المحتمل أن يكون جزءا من علاج الأنيميا الناتجة عن هذا العلاج اذا ظل العلاج بالانترفيرون و الريبافيرين علاجا أساسيا لمرضي الالتهاب الكبدي المزمن من النوع سي حيث أن الاستجابة للعلاج بالحديد وحمض الفوليك و الفيتامينات الأخرى غير كاف واستمرار البحث و الدراسة على عدد أكبر من المرضى مع متابعة المرضى لفترات أطول بعد العلاج في مراكز بحثية مختلفة للوصول لنتائج أدق في هذا الموضوع حول الاستجابة المستديمة.