



ERYTHROPOIETIN ANALOGUES (EPOETIN®) IMPROVES SUSTAINED VIROLOGICAL RESPONSE OUTCOMES IN HCV PATIENTS WITH INTERFERON BASED TREATMENT INDUCED ANEMIA

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ABSTRACT

An interventional open-label randomized study to evaluate the hematological effect and its reflection on virological response of usage of erythropoietin analogues ‘Epoetin®’ in patients with HCV-treatment induced anemia with pegylated-interferon & Ribavirin, which are still used in triple therapy after the widespread of Direct Acting Anti-viral (DAAs). 83 patients with HCV-treatment induced anemia were enrolled into two groups; group A (48): received Erythropoietin analogues, and group B (35): received vitamin B & folic acid. Patients who achieved Hb $\geq$ 12 gm/dl were 29 in group A (60.42%) and 5 in group B (14.3%) with a very high statistical significance ($p<0.001$) for group A. The average Hb for group A increased from 9.1 gm/dl to 12.0 gm/dl (32%), and for group B increased from 9.1 gm/dl to 10.3 gm/dl (13%) ($p<0.001$). Moreover, week 72 PCR showed that 72.9% of patients were negative from group A, compared to 37.1% of in group B ($p<0.001$). The adverse event due to Epoetin was mostly bony pain (8.4%). None of the adverse events due to Epoetin were severe or serious. Epoetin® markedly improved anemia in patients receiving IFN.RBV with less treatment discontinuation and higher SVR and was proven to be safe.

KEY WORDS: Erythropoietin, chronic HCV, interferon, Ribavirin.

INTRODUCTION

The current standard of care for chronic HCV infection has changed starting from 2014, by the introduction of Sofosbuvir, either with Ribavirin (RBV) for 6 months, or with Interferon and Ribavirin (IFN-RBV) for 3 months for patients with genotype 4. In this study the standard care used was the combination of Pegylated-interferon Alpha and Ribavirin, which was used until mid-2014. The goals of treatment of chronic HCV infection are: To achieve sustained eradication of HCV (*i.e.*, sustained virological response [SVR]), defined as the persistent absence of HCV RNA in serum for 6 months or more after completing antiviral treatment, and preventing progression to cirrhosis, hepatocellular carcinoma, and decompensated liver disease requiring liver transplantation^[1-6]. Approximately 75% of HCV patients during treatment experience one or more of the adverse effects which are common with interferon and Ribavirin combined therapy. Anemia is considered one of the most clinically significant side effects of therapy, particularly in patients with conditions that can be exacerbated by anemia, such as coronary artery disease or chronic obstructive pulmonary disease. Ribavirin causes dosage-dependent hemolytic anemia, and interferon can suppress bone marrow production of red blood cells. This results in anemia, likely in >20% of patients treated with pegylated interferon and ribavirin at 1,000-1,200 mg/day^[7].

Management of treatment-induced anemia

Dosage reduction in Ribavirin is the first step in managing symptomatic drug induced anemia. Because the efficacy of Ribavirin is dosage related in part, doses should be maintained at 800 mg/day or more if possible.

Manufacturer guidelines recommend reducing ribavirin dosage by 25% with hemoglobin <10 g/dL, and discontinuing ribavirin with hemoglobin <8.5 g/dL.^[8] Since it is recommended to administer at least 80% of the RBV dose and in order to minimize the dose reduction we need to control the anemia, as patients can't receive or continue IFN. RBV treatment while they are anemic. Subcutaneous injections of recombinant erythropoietin (*e.g.*, Epoetin Alfa 20,000-40,000 units weekly or darbEpoetin 200-300 mcg every other week), can be used to treat anemia due to Ribavirin^[9]. Erythropoietin is a glycoprotein hormone which is mainly synthesized in the renal cortex, and to an extent in the liver. Erythropoietin controls erythropoiesis; since the production of erythropoietin occurs in response to blood oxygen reduced availability leading to the up regulation of red cell production. There are three erythropoietic agents that are currently available: Epoetin alpha, Epoetin beta and darbEpoetin alpha. Recombinant human erythropoietin (Epoetin alpha) is the genetically engineered form of the hormone erythropoietin (Epoetin®)^[10], which was used in this study. Erythropoietin will still have a role in drug induced anemic patients in IFN based regimens to achieve the sustained viral response.

Although HCV treatment has shown advances, the Interferon Ribavirin combination (the main line treatment for HCV at time of study) has numerous side effects; depression, flu-like symptoms, fatigue, and hematological complications, such as thrombocytopenia, anemia, and neutropenia. The World Health Organization defines anemia as Hemoglobin levels <13g /dL in men and <12g/dL in women. Anemia occurs in up to 36% of

patients receiving Pegylated-interferon and Ribavirin combination therapy^[11, 12]. Furthermore; anemia has been identified in 30% -70% of patients with chronic liver disease^[13] which usually necessitates dose reduction in up to 32% of the patients. However, the European Association for the Study of the Liver (EASL) guidelines 2014 state that IFN will still be used with the DAAs. The objective of this study is to evaluate the hematological effect and its reflection on virological outcomes of usage of erythropoietin 'Epoetin®' analogues in patients who develop anemia during treatment of chronic HCV with pegylated-interferon & Ribavirin.

METHODOLOGY

The study was an interventional open-label randomized study performed at the Viral Hepatitis Center of Al Kasr Al-Ainy School of Medicine - Cairo University in Egypt. 83 patients with treatment induced anemia were enrolled in the study between November 2011 and February 2013 and their serum Hb level was evaluated weekly.

The 83 patients randomly chose folded paper with their group number, and were enrolled into two groups accordingly; the group was documented by the investigator.

Group A (48 patients; 8 males & 40 females): received erythropoietin analogues (Subcutaneous injections of Epoetin® 20,000-40,000 units weekly). The dose was given per body weight (300 IU/kg body weight) and adjusted as per hemoglobin level.

Group B (35 patients; 14 males & 21 females): received vitamin B & folic acid and were managed by up to 25% dose reduction of Ribavirin and/or Interferon or treatment discontinuation.

Vitamin B & folic acid; folic acid (5 mcg) tablets was administered once daily, and vitamin B complex injections every other day.

Investigational drug (Epoetin®)

Erythropoietin analogue; subcutaneous injections of Epoetin® 300 IU/kg body weight, twice weekly were administered to patients with a Hemoglobin level ≤ 10 gm/dl.

Hemoglobin was measured weekly; if hemoglobin level was 12 gm/dl or above; erythropoietin was stopped after a maintenance dose of 300 IU/Kg once weekly for two weeks, and if the hemoglobin level drops to less than 10 gm/dl; erythropoietin was re-administrated again as described above. The planned duration of treatment was variable according to hemoglobin level with a maximum of 48 weeks.

Patients were examined clinically with lab follow up (hematology and blood chemistry) and HCV RNA at week 12, week 24, week 48 and week 72 of treatment for viral response.

Inclusion criteria: Signed informed consent, all chronic HCV patients eligible for the national Interferon & Ribavirin therapy program who developed anemia (Hemoglobin level ≤ 10 gm/dl) during the course of treatment.

Exclusion criteria: Patients with chronic renal failure, patients with primary hematological diseases and patients with known hypersensitivity to mammalian cell derived products or known hypersensitivity to albumin.

The patients' outcomes were evaluated upon the following parameters:

Primary Efficacy Parameters: The percentage of patients who completed 48 weeks of HCV treatment and its reflection on SVR rate.

Secondary Efficacy Parameters: The percentage of patients who achieved Hb ≥ 12 gm/dl. Also, the achieved Hb level compared to the baseline and duration taken.

Primary Safety Parameters: The incidence of Adverse Events (AE) and Serious Adverse Events (SAE) in both groups.

Secondary Safety Parameters: The laboratory results for hematology and biochemistry.

In both groups either the Erythropoietin or vitamins, we started intervention by ribavirin dose reduction if after one week the HB continued to drop.

Statistical analysis

Analysis was performed using descriptive statistics for numeric continuous variables (mean, standard deviation, standard error of the mean, minimum, median, and maximum) and frequency distribution for categorical variables (count and percentage). T-test was used to obtain *p* value for numeric continuous variables, and Chi Square test was used to obtain *p* value for categorical variables.

RESULTS

The mean age of patients for groups "A" and "B" was 45.74 and 45.87 years respectively. Group "A" ranging from (23.79-61.28) years old, and mean age for group "B" ranging from (45.87-61.28) years old.

The mean study duration were 20.4 ± 15.0 and 12.4 ± 13.2 weeks for group A and group B, respectively, showing a high significant result (*p*-value 0.005) for group A.

Efficacy

The percentage of patients who completed week 48 were 81% from group A and 74% from group B, showing a non-significant statistical result, *p* value is 0.447 as seen in table 1. The difference in SVR between both groups can be explained through that the high relapse rate of patients of group B may be due to interferon and ribavirin dose reduction after the 24th week so HCV RNA positivity was at end of treatment or during follow up.

TABLE 1: % of Patients who completed week 48

Values	Group A (%)	Group B (%)	Chi-test
Pts. Completed 48 W	39 (81%)	26 (74%)	0.447
Pts. didn't Complete 48 W	9 (19%)	9 (26%)	

The number of patients achieving Hb $\geq$ 12 gm/dl were 29 from group A (60.42%) and the average duration to achieve the Hb level was 19.78 weeks, while only 5 from group B (14.3%) achieved Hb $\geq$ 12 gm/dl and the average duration was 28.23 weeks. These results show a very high statistical significance ($p < 0.001$) for group A, p -value < 0.001 (Fig.2).

Table 2 illustrates the difference in Hb between the first and last visit; the mean Hb in visit 1 for group A was 9.1 gm/dl which increased to 12.0 gm/dl during the last visit

(32% increase), and the average Hb in visit 1 for group B was 9.1 gm/dl increased to 10.3 gm/dl (13% increase), showing a very high statistical significant value ($p < 0.001$). The RBCs count also showed a very high significant result ($p < 0.001$) for group A.

Week 72 PCR was measured for both groups; it showed that 72.9% of patients were negative from group A, whereas only 37.1% of patients were negative from group B, showing a very high statistical significant value ($p < 0.001$) for group A.

TABLE 2: Hemoglobin level in last visit compared to first visit

Values		Group A (n=48)		Group B (n=31)		$P < 0.05$
		V1	VL	V1	VL	
HB at 1st and Last visit	Mean $\pm$ SD	9.1 $\pm$ 0.6	12.0 $\pm$ 1.5	9.1 $\pm$ 0.6	10.3 $\pm$ 1.2	< 0.001
	Range	7 - 10.2	8.6 - 15.7	7.9 - 10.7	8.7 - 13.1	
	VL-V1	2.88		1.22		
	% change	32%		13%		
	p - value	< 0.001		< 0.001		
RBCs*10 ⁶	Mean $\pm$ SD	3.4 $\pm$ 0.5	3.6 $\pm$ 0.7	3.2 $\pm$ 0.4	3.4 $\pm$ 0.4	< 0.001
	Range	2.7 - 4.9	3.0 - 5.4	2.9 - 3.8	3 - 4	
	% change	7%		5%		

Safety

Regarding the primary safety parameters of the study, table 3 shows the adverse events incidence rate in both groups; 11 (22.9%) from group A and 2 (5.7%) from group B, conveying a significant result (p -value 0.0332) in group A. The AEs due to Epoetin® were bony pains (8.4%), headache (1.2%), myalgia (1.2%), skin rash (1.2%), and increase in blood pressure (BP) (1.2%). Other AE's were abdominal pain, insomnia, pancytopenia, acute bronchitis, and diarrhea. None of the adverse events due to Epoetin® were severe. As for ribavirin dose reduction; in

the Epoetin® group this was needed for two patients (800 mg), while 8 patients in the vitamin group had Ribavirin dose lowered to 600 mg. The adverse events due to IFN.RBV occurred to 6 patients from group A and 2 patients from group B. Only one adverse event (pancytopenia) was severe (in group B patient), which led to discontinuation of the national program for HCV. Moreover, 64.7% of the adverse events from group A were drug (Epoetin®) related, whereas, in group B; 100% of the adverse events were IFN.RBV related. There were no serious adverse events reported during this study.

TABLE 3: Overall Adverse Events in the studied groups

Values	Epoetin	IFN.RBV	
	Group A (%)	Group A (%)	Group B (%)
Bony Pains	7 (8.4%)	1 (1.2%)	0 (0%)
Increased Blood pressure	1 (1.2%)	0 (0%)	0 (0%)
Skin Rash	1 (1.2%)	0 (0%)	1 (1.2%)
Myalgia	1 (1.2%)	0 (0%)	0 (0%)
Headache	1 (1.2%)	0 (0%)	0 (0%)
Abdominal pain	0 (0%)	1 (1.2%)	0 (0%)
Insomnia	0 (0%)	2 (2.4%)	0 (0%)
Pancytopenia	0 (0%)	0 (0%)	1 (1.2%)
Acute Bronchitis	0 (0%)	1 (1.2%)	0 (0%)
Diarrhea	0 (0%)	1 (1.2%)	0 (0%)
Grand Total	11 (13.2%)	6 (7.2%)	2 (2.4%)

TABLE 4: Sample Disposition

Number of Patients	
Enrolled	83
Completed	79
Discontinued	4
Main Reasons for Discontinuation	
Lost to Follow Up	1
Adverse Event(s)	2
Unsatisfactory Therapeutic Effect to INF/RBV	1

As for study completion; 45 patients (93.8%) completed the study from group A and 34

patients (97.1%) from group B. Four patients didn't complete the study due to various reasons; one patient (group A) lost to follow up, 2 patients stopped IFN due to adverse events (one from group A due to bony pains & one from group B due to pancytopenia), and one (group A) due to unsatisfactory therapeutic effect to IFN at week 12, as seen in *table 4*.

DISCUSSION

Although the standard care for HCV treatment is changing, due to the widespread use of Direct Acting Anti-viral (DAAs), however IFN & RBV still has a role in the triple therapy, (IFN- α and RBV) contribute to the etiology of the induced anemia, it is called 'mixed anemia'. Dose dependent hemolytic anemia results from use of RBV and IFN induces anemia by suppression of erythropoiesis, possibly as a result of down-regulation of erythropoietin receptors^[13-15]. Previous studies have shown that IFN-related leukopenia and thrombocytopenia, and Ribavirin-related hemolytic anemia and decreased Health Related Quality of Life (HRQL) are reasons often cited by patients for the discontinuation of combination therapy or dose reduction^[11,12,16,17].

Patients randomized for vitamins and dose reduction of RBV did not complete the study after enrollment and randomization, as they did not have satisfactory increase in their daily activity or HB level, so 35 patients only in group B while 48 patients from group A continued the study. It was seen in a multicenter retrospective study including 441 patients, aimed at assessing the real world discontinuation rates of IFN- α /RBV combination therapy it was discovered that 108 (24.5%) of the patients discontinued due to adverse events, and anemia represented about one-third of these patients. This was less than the 27% discontinuation rate seen in other randomized studies^[18], bearing in mind those studies were on different HCV genotypes. Erythropoietin (Alfa Epoetin) was shown to increase hemoglobin levels during Ribavirin administration, allowing maintenance of the Ribavirin dose, and to improve HRQL during therapy, principally by reducing fatigue due to anemia^[19-23]. Dieterich *et al.*^[24] demonstrated that Epoetin alpha is well tolerated and maintained Ribavirin dose at 800 mg/day for 83% of patients. It was seen that erythropoietic agents are effective in the management of anemia, minimizing ribavirin dose reduction, and can improve the quality of life of HCV patients; however studies haven't examined their impact on SVR.¹⁶

The average hemoglobin level was increased by 32% in group A patients (receiving Epoetin®), while was increased by 13% in group B patients (who received vitamins with reduction and/or discontinuation of interferon/Ribavirin therapy). The difference between the 2 groups was very high statistically significant, p -value < 0.001 and 0.003, respectively.

Not only was the hemoglobin level increased in the current study, but also the RBCs count showed a very high significant result ($p < 0.001$) between the two groups; group A showed an increase by 7% and group B a 5% increase.

Out of the patients who completed HCV treatment, the week 72 PCR results were negative in 72.9% of group A

and in only 37.1% of group B. This favors the effect of treating drug-induced anemia in the sustained virological response of treatment. In another prospective, double-blind, placebo controlled trial conducted in the USA, a significantly greater percentage of patients treated with erythropoietin were able to receive 80% or more of their target Ribavirin dose, had a significantly greater cumulative Ribavirin exposure, and reported a significantly better quality of life^[25-26]. A significant reduction in relapse and increase in SVR were also observed in those patients who received a higher starting dose of Ribavirin along with erythropoietin in the current study.²³

Regarding the safety, the most common adverse event due to the study drug (Epoetin®) was bony pains with incidence of 8.4% of the sample size, which was managed by either administering a concomitant medication or no action was taken because of their mild nature. No serious adverse events were reported during the study due to Epoetin®.

CONCLUSION

Epoetin® is proved to be significantly effective to achieve Hemoglobin level of 12gm/dl and to reduce treatment discontinuation rate in treatment induced anemia in HCV patients who received National Program's Interferon/Ribavirin's treatment in Egypt and to increase SVR for patients with drug induced anemia.

Epoetin® is proved to be safe.

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REFERENCES

- [1]. World Health Organization. Global surveillance and control of hepatitis C. J Viral Hepat 1999; 6: 35-47
- [2]. Dixit NM, Layden-Almer JE, Layden TJ, Perelson AS. Modelling how ribavirin improves interferon response rates in hepatitis C virus infection. Nature. 2004 Dec 16;432(7019):922-4.
- [3]. Mazzella G, Accogli E, Sottili S, Festi D, Orsini M, Salzetta A, Novelli V, Cipolla A, Fabbri C, Pezzoli A, Roda E. Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. J Hepatol. 1996 Feb;24(2):141-7.
- [4]. S M Kamal, A A El Tawil, T Nakano, He Q, Rasenack J, Hakam SA, Saleh WA, Ismail A, Aziz AA, Madwar MA. PegInterferon α -2b and Ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. Gut 2005; 54: 858-866
- [5]. Jean-Michel P. Therapy of hepatitis C: From empiricism to eradication: Hepatology 2006; 43: 207-220

- [6]. Adeel AB, Xiaoqiang W, Charity GM. Effect of hepatitis C virus and its treatment on survival. *Hepatology* 2009; 50: 387–392.
- [7]. R. Mac Nicholas, S. Norris. Optimizing SVR and management of the haematological side effects of pegInterferon/Ribavirin antiviral therapy for HCV – the role of Epoetin, G-CSF and novel agents. *Alimentary Pharmacology & Therapeutics* 2010; 31: 929-937.
- [8]. Sulkowski MS, Wasserman R, Brooks L, Ball L, Gish R. Changes in haemoglobin during interferon alpha-2b plus ribavirin combination therapy for chronic hepatitis C virus infection. *J Viral Hepat.* 2004 May; 11(3):243-50.
- [9]. Stefan S., Marjolein B., Arthur R. Side Effects of Interferon- α Therapy. *Pharmacy World and Science* 2005; 27: 423-431
- [10]. John G McHutchison, Michael P Manns, Robert S Brown Jr, K Rajender Reddy, Mitchell L Shiffman and John B Wong. Strategies for Managing Anemia in Hepatitis C Patients Undergoing Antiviral Therapy. *The American Journal of Gastroenterology* (2007) 102, 880–889.
- [11]. Costiniuk CT, Camacho F, Cooper CL. Erythropoiesis-stimulating agent use for anemia induced by Interferon-Ribavirin treatment in patients with hepatitis C virus infection is not associated with increased rates of cardiovascular disease, thrombosis, malignancy, or death. *Clin Infect Dis* 2008; 47: 198–202.
- [12]. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçalves FL Jr, Häussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med.* 2002 Sep 26;347(13):975-82.
- [13]. Canonico PG, Castello MD, Cosgriff TM, Donovan JC, Ross PE, Spears CT, Stephen EL. Hematological and bone marrow effects of ribavirin in rhesus monkeys. *Toxicol Appl Pharmacol.* 1984 Jun 30; 74(2):163-72.
- [14]. de Franceschi L, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F, Noventa F, Stanzial AM, Solero P, Corrocher R. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology.* 2000 Apr;31(4):997-1004.
- [15]. Van Vlierbergh H, Delanghe JR, De Vos M, Leroux-Roel G. Factors influencing Ribavirin-induced hemolysis. *BASL Steering Committee. J Hepatol* 2001; 34:911–6.
- [16]. Nicholas RM, Norris S. Review article: optimizing SVR and management of the hematological side effects of pegInterferon/Ribavirin antiviral therapy for HCV – the role of Epoetin, G-CSF and novel agents. *Aliment Pharmacol Ther* 2010; 31: 929–937
- [17]. David Bernstein, Leah Kleinman, Chris M. Barker, Dennis A. Revicki, and Jesse Green. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. *Hepatology* 2002; 35:704 –708.
- [18]. Gaeta GB, Precone DF, Felaco FM, Bruno R, Spadaro A, Stornaiuolo G, Stanzione M, Ascione T, De Sena R, Campanone A, Filice G, Piccinino F. Premature discontinuation of interferon plus Ribavirin for adverse effects: A multicentre survey in ‘real world’ patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2002;16:1633-9.
- [19]. Pawlowsky, J. Therapy of Hepatitis C: From Empiricism to Eradication. *Hepatology* 2006; 43: 207-220.
- [20]. Talal AH, Weisz K, Hau T, S Kreiswirth and D T Dieterich. A preliminary study of erythropoietin for anemia associated with Ribavirin and Interferon-alpha. *Am J Gastroenterol* 2001; 96:2802-2804.
- [21]. Gergely AE, Lafarge P, Fouchard-Hubert I, Lunel-Fabiani F. Treatment of Ribavirin/Interferon-induced anemia with erythropoietin in patients with hepatitis C. *Hepatology* 2002;35:1281-1282.
- [22]. Dieterich DT, Wasserman R, Brau N, Hassanein TI, Bini EJ, Bowers PJ, Sulkowski MS. Once-weekly Epoetin alfa improves anemia and facilitates maintenance of Ribavirin dosing in hepatitis C virus-infected patients receiving Ribavirin plus Interferon alfa. *Am J Gastroenterol* 2003; 98:2491-2499.
- [23]. Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, Wright TL, Mody SH, Tang LK, Goon BL, Bowers PJ, Leitz G, Afdhal NH. Epoetin alfa improves quality of life in anemic HCVinfected patients receiving combination therapy. *Hepatology* 2004;40: 1450-1458.
- [24]. Sulkowski MS. Anemia in the treatment of hepatitis C virus infection. *Clin Infect Dis* 2003; 37 (Suppl 4):315-22..
- [25]. Shiffman ML, Salvatore J, Hubbard S, Price A, Sterling RK, Stravitz RT, Luketic VA, and Sanyal AJ. Treatment of hepatitis C virus genotype 1 with pegInterferon alfa-2b, high weight-based dose Ribavirin and Epoetin alfa enhances sustained virologic response. *Hepatology* 2005;42 (Suppl 1):217A.
- [26]. Afdhal NH1, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, Bowers PJ; Proactive Study Group. Epoetin alfa maintains Ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology* 2004; 126:1302-1311.