Title

RISK FACTORS FOR ANAEMIA DEVELOPMENT DURING THERAPY WITH RIBAVIRIN PLUS DIRECT-ACTING ANTIVIRALS CP-019

Name *E. Molina[1], P. Nieto[1], S. Cañizares[1], B. Franco[1], B. Tauste[1], F. Sierra[1].*

Address [1]Hospital Torrecárdenas, Hospital Pharmacy, Hermandad de los Donantes de Sangre s/n Almeria, Spain. PC 04009

Background

Anemia is a common adverse event associated with ribavirin therapy of hepatitis C patients. Peginterperon/ribavirin was the cornerstone of the treatment of hepatitis C (HCV) patients until 2011

Purpose

To assess the incidence of anemia and the risk factors predictive of anemia in the new context of ribavirin plus new direct-acting antiviral (DAA) agents

Study Design

A one-year retrospective study was performed during a year. Anemia was defined as a single occurrence of hemoglobin <10g/dL at any point during treatment. Serum hemoglobin assessments were obtained at baseline and weeks 0, 4, 8, 12, 16, 20, and 24. Pre-treatment factor with potential to act as prognostic indicators of anemia including age, sex, type of treatment, genotype, FibroScan® score, cirrhotic yes/no, HCV RNA titer, dose 1000mg/1200mg, Glomerular filtration rate, alanine transaminase, albumin, treatment duration 12 vs >12 weeks and baseline hemoglobin and on-treatment factor as week 2 change from baseline were analysed by univariate and multivariate logistic regression analyses. For the resulting independent predictive factor, odds-ratio and 95% confidence intervals were calculated.

RESULTS

Table 1: Baseline characteristics of patients included in the study.

Mean age ± SD (years)		54.73 ± 8.6
Male patients n (%)		119 (78.30)
FibroScan® score ± SD (kPa)		17.60 ± 9.99
Grade of fibrosis n (%)	Non-cirrhoticpatients (total), of which:	57 (37.5)
	-F1 (minimal fibrosis)	5 (3.3)
	-F2(fibrosis within the liver and blood vessels)-	17 (11.2)
	-F3 (fibrosis spreading to other liver areas)	35 (23)
	Cirrhoticpatients: F4 (cirrhosis or advanced liver fibrosis)	95 (62.5%)
eGFR (CKD-EPI) ± SD (mL/min)		98 ± 16.81
Viral load ± SD x10⁶(RNA copies/mL)		2.79 ± 3.5
Platelet counts SD x10³(cels/µL)		157.99 ± 83.77
Albumin ± SD (g/dL)		4.11 ± 0.50
ALT ± SD (U/L)		83.11 ± 52.08
Patients with weight >75kg (%)		73 (48)
Naïve patientsn (%)		86 (56.6)
Treatment duration n (%)	12 weeks	128 (84.2)
	>12 weeks	24 (15.8)
Baseline Hb ± SD (g/dL)		14.93 ± 1.62
HCV genotype n (%)	1	102 (67.1)
	2	5 (3.3)
	3	24 (15.8)
	4	21 (13.8)
Drug combination (+RBV) n (%)	Sofosbuvir-Ledipasvir	59 (38.8)
	Ombistavir-Paritaprevir-Ritonavir-Dasabuvir	31 (20.4)
	Sofosbuvir-Simeprevir	17 (11.2)
	Sofosbuvir-Daclatasvir	18 (11.8)
	Sofosbuvir	5 (3.3)
	Sofosbuvir-PegInterferon	10 (6.6)
	Simeprevir-Peginterferon	3 (2)
	Ombistavir-Paritaprevir-Ritonavir	9 (5.9)

Abbreviations: ALT: Alanin Aminotransferase; eGFR CKD-EPI: Estimated Glomerular Filtration Rate (Chronic Kidney Disease Epidemiology Collaboration); Hb: Haemoglobin; HCV: hepatitis C virus; SD: standard deviation; RBV: Ribavirin.

Table 2: Compared baseline characteristics.

Parameter	Patients with Hb>10g/dL (n=129)	Patients with Hb<10g/dL (n=23)	p-value
Mean age ± SD (years)	53.75 ± 7.64	60.22 ± 11.44	p≤0.001[a]
Gender male n (%)	107 (82.90)	12 (52.2)	p≤0.01[b]
FibroScan® score ± SD (kPa)	17.20 ± 17.2	19.88 ± 19.89	ns[c]
Cirrhotic patients n (%)	78 (60.05)	17 (73.9)	ns[b]
eGFR ± SD (mL/min)	99.92 ± 11.03	73.05 ± 24.33	p≤0.001[a]
Viral load ± SD x10⁶ (copies/mL)	2.87 ± 3.7	2.32 ± 2.46	ns[c]
Platelet count ± SD x10³ (cels/µL)	164.64 ± 86.1	129 ± 57.57	p≤0.05[a]
Albumin ± SD (g/dL)	4.16 ± 0.47	3.85 ± 0.59	p≤0.01[a]
ALT ± SD (U/L)	83.48 ± 52.7	81.04 ± 49.52	ns[c]
Patients with weight >75kg (%)	66 (51.20)	7 (30.4)	ns[b]
Naïve patients n (%)	73 (56.6)	13 (56.5)	ns[b]
Treatment duration >12weeks n (%)	16 (20.40)	8 (34.8)	p≤0.05[a]
Baseline Hb ± SD (g/dL)	15.29 ±1.35	12.88 ± 1.45	p≤0.001[a]

[a] Student´s t-test; [b] χ2 test, [c] Mann-Whitney´s U test.

Abbreviations: ALT: Alanin Aminotransferasa; eGFR: Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration); HCV: hepatitis C virus; ns, non-significant; SD: standard deviation.

Fig. 1 Time to development of anemia (Hb<10g/dL)

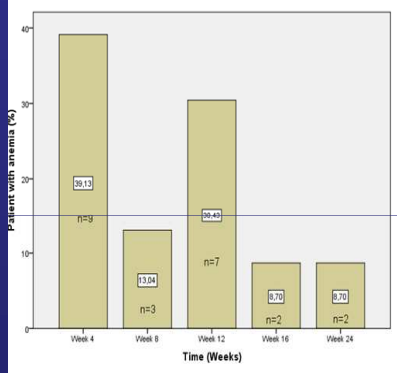


Fig. 2 Change in hemoglobin concentration during the treatment.

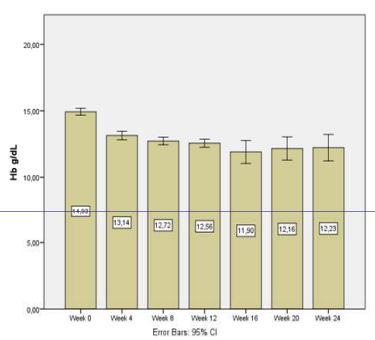


Fig. 3 Comparable change in hemoglobin concentrations (g/dL) from start of treatment to week 12.

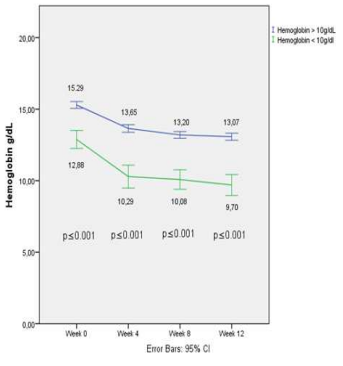
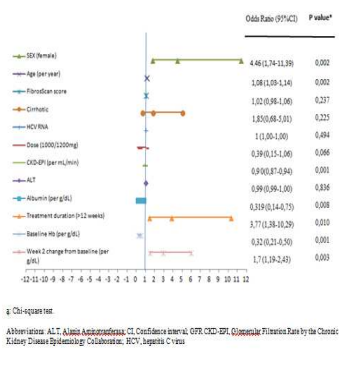


Fig. 4 Outcome of the univariate logistic regression analysis.



a: Chi-square test

Abbreviations: ALT, Alanin Aminotransferasa; CI, Confidence interval; GFR CKD-EPI, Glomerular Filtration Rate by the Chronic Kidney Disease Epidemiology Collaboration; HCV, hepatitis C virus

Table 3. Results of Multiple Logistic Regression Analysis (Ribavirin-Induced Anemia).

Parameter	Initial multivariate model			Final pre-treatment multivariate model			Final on-treatment multivariate model		
	B.C	P value[a]	OR (CI 95%)	B.C.	P value[a]	O (CI 95%)	B.C.	P value[a]	OR (CI 95%)
Age (per year)	-0.11	**0,168**	0,89 (0,76-1,05)						
Sex (female)	-0.52	**0,629**	0,59 (0,07-4,88)						
CKD-EPI (per mL/min)	-0,14	0,005	0,86 (0,78-0,96)	-0,10	0,001	0,91 (0,86-0,96)	-0,11	0,003	0,89 (0,83-0,96)
Albumin (per g/dL)	0,02	**0,982**	1,02 (0,15-6,87)						
Treatment duration (12weeks>12weeks)	2,78	0,022	16,10 (1,49-173,39)	2,01	0,023	7,43 (1,31-41,97)	2,97	0,013	19,45 (1,86-202,65)
Baseline Hb (per g/dL)	-2,58	0,002	0,07 (0,01-0,38)	-0,91	0,001	0,40 (0,24-0,65)	-1,99	0,001	0,14 (0,04-0,41)
Week 2 change from baseline (per g/dL)	4,90	0,001	139,95 (6,94-2825,70)				4,50	0,001	89,91 (5,70-1418,50)
Dose (1000mg/1200mg)	0,47	**0,711**	1,61 (0,13-19,80)						

a: Wald Chi-squared test
Abbreviations: CI Confidence interval; OR, Odds ratio; RC, Regression coefficient

Table 4A Pre-treatment mathematical formula as a prognostic indicator of anemia

			Observed ANEMIA YES	Observed ANEMIA NO	Total	PPV	NPV
Predicted ANEMIA		YES	13	2	15	**86.60**	-
		NO	10	127	137	-	**92,70**
Total			23	129	152		

4B On-treatment mathematical formula as a prognostic indicator of anemia

			Observed ANEMIA YES	Observed ANEMIA NO	Total	PPV	NPV
Predicted ANEMIA		YES	19	1	20	**95,00**	-
		NO	4	128	132	-	**96,96**
Total			23	129	152		

Abbreviations: PPV, Positive predictive value; NPV, Negative predictive value.

CONCLUSION

The incidence of anemia with DAA has been less than with peginterferon combinations. Glomerular filtration rate, baseline hemoglobin, treatment duration > 12 weeks and estimated week 2 change from baseline have demonstrated predicting the risk of anemia.

There is not any conflict of interest at all.

✓**Acknowledgements**

We thank Torrecardenas´ s hospital pharmacists for their support

JUNTA DE ANDALUCIA Servicio Andaluz de Salud CONSEJERÍA DE SALUD

eahp european association of hospital pharmacists