BRIEF REPORT

Effect of viral eradication with direct-acting antiviral agents on iron parameters in patients with chronic hepatitis c and hyperferritinemia

Agustin Castiella MD, PhD[1], María José Sánchez-Iturri RN[1], Iratxe Urreta[2], Silvia Torrente[1], Ana Alcorta[1], Eva Zapata[1]

ABSTRACT

BACKGROUND: Patients with chronic hepatitis C are at increased risk for hyperferritinemia (HF). Abnormalities of serum iron parameters are frequently observed in patients with chronic hepatitis C (CHC). About a third of patients have increased iron parameters. Recently, studies on the effect of direct-acting antiviral agents (DAAs) in HCV eradication in patients with increased serum iron has been published, demonstrating the restoration of normal iron status. The aim of this study was to evaluate the effect of viral eradication with DDAs in patients with CHC and HF. **METHODS:** Retrospective study conducted from January 2018 to December 2020 including patients treated with DAAs for HCV. Pre-treatment (PreT) and post-treatment (PostT) serum ferritin values were evaluated in all patients. Inclusion criteria: PreT HF (>400 µg/L); CHC patients treated with DAA achieving sustained viral response (SVR). Exclusion criteria: No PreT or PostT HF available; no SVR; lost patients. **RESULTS:** From 621 patients treated with DAAs for CHC, 77 presented HF (12.40%), and 74 were included in the study. Fifty nine were men (79.73%) with a mean age 58.33, SD 8.68; PreT mean ferritin: 893.20 (SD 1037.09); PostT: 264.17 (SD 161.33); PreT mean transferrin saturation: 40.96 (SD 15.71); PostT: 29.82 (SD 11.17); PreT mean serum iron 152.32 (SD 62.07), PostT: 109.32 (SD 39.49). When we compared PreT and PostT iron parameters, significant statistical differences were present considering ferritin (p = 0.0000), transferrin saturation (p = 0.0000), and iron (p = 0.0002) determinations. **CONCLUSIONS:** SVR after DAAs for CHC induces a statistically significant reduction on iron parameters.

KEYWORDS: direct-acting antivirals; hepatitis C virus; hyperferritinemia

Author Affiliation

[1]*Department of Gastroenterology, Donostia University Hospital, Donostia, Spain;* [2]*Epidemiology Unit, Donostia University Hospital, Donostia, Spain*

Correspondence: Agustin Castiella, Liver Unit, Gastroenterology Service, Donostia University Hospital, Paseo Dr. Beguristain 2014, Donostia, Spain. Telephone/fax: 0034660018823. E-mail: agustincastiella@yahoo.es

BACKGROUND

Alterations in iron parameters are frequently observed in patients infected with the hepatitis C virus (HCV), and can affect up to a third of people with chronic hepatitis C (CHC) (1). In these cases, elevations in serum iron levels, transferrin saturation, and / or ferritin are observed. Many studies have been published confirming the high prevalence of these abnormalities in HCV patients (2,3).

Recently, the appearance of direct-acting antivirals (DAA) has led to a real revolution in the treatment of this disease, with cure rates higher than 95%. Viral eradication restores normal iron metabolism in most patients with serum iron abnormalities before treatment, including those whose abnormalities raise suspicion of hemochromatosis (2,4–8).

The aim of the study was to determine the effect of viral eradication with DDAs in patients with chronic hepatitis C and hyperferritinemia (HF) in our hospital and to see if HF associated with HCV has clinical relevance.

PATIENTS AND METHODS

A retrospective study was conducted in a tertiary hospital of Spain (Donostia University Hospital) evaluating patients with CHC treated with DAA from January 2018 to December 2020. Pre-treatment (PreT) and post-treatment (PostT) serum ferritin values were determined in all included patients. Normal ranges were as follows: serum ferritin (N: 30–400 ng/mL), transferrin saturation index (TSI) (N: 15%–50%), and serum iron (N: 59–158 µg/dL in men; 30–160 µg/dL in women). Inclusion criteria were: PreT HF >400 ng/mL; CHC defined as HCV-RNA detectable for more than 24 weeks by polymerase chain reaction (PCR); sustained viral response (SVR) defined as HCV-RNA not detectable by PCR 12 weeks after the end of treatment. Exclusion criteria were no PreT HF or PostT ferritin available; no SVR; lost patients. Transient elastography for fibrosis assessment was performed in all patients using FibroScan (Echosens, Paris, France, www.echosens.com).

Statistics

All statistical analysis were performed with STATA 16.1, 1985–2019 StataCorp LLC software (StataCorp LLC, College Station, TX, USA).

Each variable was described using the most appropriate statistic for the nature and the measure: mean and standard deviation (or median and p25, p75) for quantitative variables, and absolute and relative frequencies in percentage for quantitative variables.

We performed a χ^2 test or Fisher exact test, to compare the distribution of quantitative variables. To compare the pre and post treatment levels of iron parameters (serum iron, IST, ferritin) we used paired *t*-test or the non-parametric Wilcoxon signed-rank test.

In all analyzes, a $p < 0.05$ was considered statistically significant (p level of significance was two-tailed).

Ethics

The study was approved (23-06-2020) by the Comité Ético de Investigación Clínica del Área Sanitaria de Gipuzkoa (Acta 04/2020). The need for informed consent was waived by the Comité Ético de Investigación Clínica del Área Sanitaria de Gipuzkoa.

RESULTS

Out of 621 patients treated with DAAs for HCV (January 2018–december 2020), 77 presented HF (12.40%), and 74 met the inclusion criteria. Three patients were excluded: one refused treatment and two did not have PostT ferritin. Fifteen patients were women, 59 men (79.73%), and mean age at initiation of treatment of the included patients was 58.33 (SD 8.68) years, range: 44–85. Clinical characteristics of the included patients are described in Table 1.

Table 1: Principal clinical and laboratory data

	Mean (SD)	Range
AST (U/L)	126.67 (244.71)	24–1578
ALT (U/L)	173.83 (349.99)	6–2274
GGTP (U/L)	202.16 (217.55)	17–1082
AP (U/L)	96.27 (43.37)	48–250
Bilirrubin (mg/dL)	0.92 (1.28)	0.24–10.6
Cholesterol (mg/dL)	171.94 (45.28)	77–298
Triglycerids (mg/dL)	140.07 (76.72)	46–382
Glucose (mg/dL)	114.39 (37.98)	71–309
Albumin (g/dL)	4.24 (0.44)	2.9–5.07

AST = Asparte aminotransferase; ALT = Alanine aminotransferase; GGTP = Gamma glutamyl transpeptidase; AP = Alkaline phosphatase

We studied iron parameters in our patients. The patients of the study presented a PreT mean ferritin of 893.20 (SD 1037.09) and PostT mean ferritin of 264.17 (SD 161.33); PreT mean TSI was 40.96 (SD 15.71) and PostT mean TSI was 29.82 (SD 11.17); PreT mean serum iron was 152.32 (SD 62.07) and PostT serum iron was 109.32 (SD 39.49).

When we compared pre and post treatment iron parameters, significant statistical differences were present with ferritin ($p < 0.00001$), transferrin saturation ($p < 0.00001$), and iron (p: 0.0002) determinations. As these three variables did not have a normal distribution, we used non-parametric test (Wilcoxon signed-rank test) and median, p25 and p75 were obtained (Table 2). The results were statistically significant for the three variants (ferritin PreT-PostT $p < 0.00001$; TSI PreT-PostT $p < 0.00001$; Fe PreT-PostT $p < 00001$) (Figure 1).

Only in two patients ferritin did not normalize after treatment. One patient was bone marrow transplant recipient after lymphoma, and HF was very probably due to Graft-Versus-Host-Disease. The other one, was a heavy drunker patient with high alcohol consumption after SVR.

Different treatment regimens were used in our patients. Sofosbuvir-velpatasvir (Epclusa®) for 12 weeks was used in 10 patients (13.51%), glecaprevir-pibrentasvir (Maviret®) for 8–12 weeks in 61 patients (82.43%), sofosbuvir (Sovaldi®)-Maviret®-ribavirin for 24 weeks in only one patient

Table 2: Seric iron parameters

	Mean (SD)	Range	p50	p25	p75
Ferritin (PreT)	893.20 (1037.09)	403–8344	623	471	872
Ferritin (PostT)	264.17 (161.33)	36–1261	246.5	207	310
TSI (PreT)	40.96 (15.71)	5.9–85.3	39.75	30.5	49.5
TSI (PostT)	29.82 (11.17)	9.3–60.3	29.7	21.6	37.5
Serum iron (PreT)	152.32 (62.07)	25–372	144	115	181
Serum iron (PostT)	109.32 (39.49)	20–229	107	83	130

PreT = Pre-treatment; PostT = Post-treatment; TSI = Transferrin saturation index

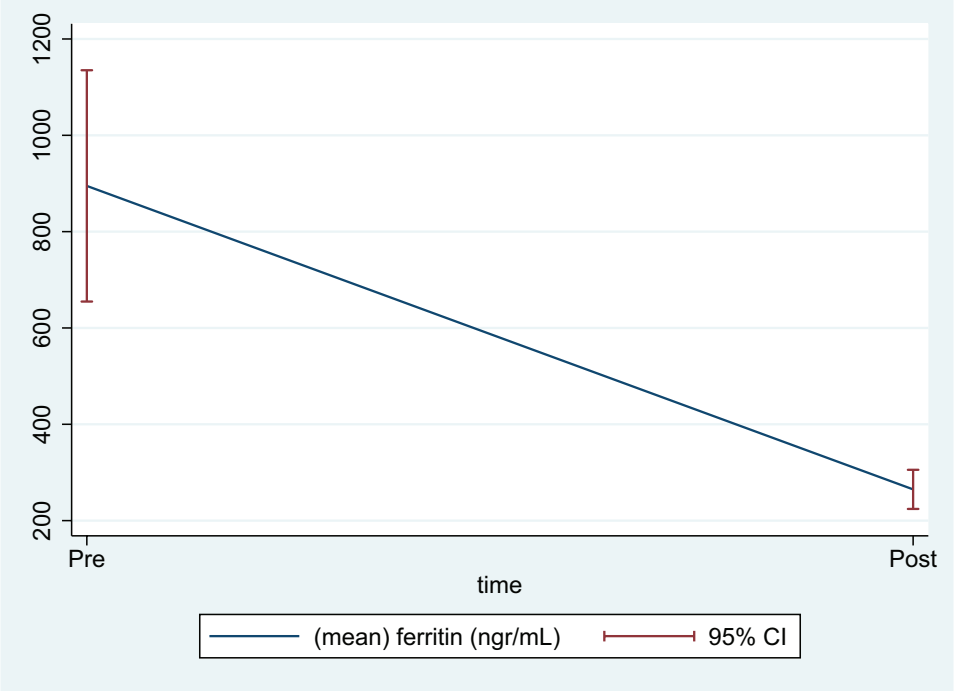

Figure 1: Pre- and post-treatment serum ferritin: significant statistical differences were ($p < 0.00001$)

(1.35%), and voxilaprevir-velpatasvir (Vosevi®) for 12 weeks in two patients (2.70%).

Liver fibrosis was determined by liver transient elastography with FibroScan. Pretreatment determinations revealed F1 liver fibrosis in 29 patients (39.19%), F2 in 13 (17.56%), F3 in 10 (13.51%), and F4 in 22 (29.72%). No liver biopsies were done in our series.

The study of viral genotypes (G) revealed that G1A was present in 25 patients (33.78%), G1B in 24 (32.43%), G2 in 2 (2.70%), G3 in 15 (20.27%), and G4 in 8 (10.81%).

DISCUSSION

HF is a common laboratory finding in many liver diseases, particularly in chronic HCV infection, alcoholic liver disease, and metabolic associated fatty liver disease (3). Ferritin synthesis and release are increased in chronic immune stimulation and inflammation situations (3,9,10). Increased levels of serum ferritin in non-treated HCV patients may be a consequence of actions of the HCV itself or of chronic inflammation, which stimulates immune response (3).

Numerous studies were carried out in the interferon era to determine whether the decrease in iron, through bleeding, was associated with better therapeutic results, less fibrosis progression, and a decrease in the risk of hepatocarcinoma (2,3,11), with disparate results.

Recently, three small studies, with 12 patients (4), 27 patients (2) and 55 patients (5), as well as one prospective and larger study (6) with 350 patients, seem to indicate that viral eradication restores normal iron metabolism. Other studies have demonstrated that ferritin serum levels significantly decreased after SVR (7) and that hepcidin-to-ferritin ratios were increased (8).

HF may be present in patients with chronic hepatitis C in up to a 33%. In our series HF was only present in 12.40% of the HCV chronic hepatitis patients.

All 74 patients were treated with DDAs (different regimens) and SVR was 100%. HF disappeared in 72 patients, and persisted in two. These patients had pathologies that justified chronic HF. DAAs induced a statistically significant reduction in serum ferritin. TSI and Iron levels decreased significantly with SVR, and the difference was statistically significant.

Our study has certain limitations. First, the sample size is relatively small and it is a retrospective study. However, the fact that we are comparing pre- and post-treatment iron parameters in the same patient makes our study less vulnerable to individual biases and confounding variables.

In conclusion, SVR after DAAs for CHC induces a statistically significant reduction in serum ferritin, TSI, and iron levels. HF associated with HCV has not clinical relevance in our study. HF in patients with HCV chronic hepatitis rarely persists after treatment and SVR and only in these cases further study would be justified.

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INFORMED CONSENT: N/A.

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