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Original Research Article

Hepcidin serum levels and resistance to recombinant human erythropoietin therapy in hemodialysis patients

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ABSTRACT

Objective: The aim of this study was to analyze the factors that are associated with the response to erythropoiesis-stimulating agents (ESAs) and its association with hospitalization and mortality rates; to evaluate the serum hepcidin level and its associations with iron profile, inflammatory markers, ESA responsiveness, and mortality; and to determine independent factors affecting ERI and hepcidin.

Materials and methods: To evaluate a dose-response effect of ESAs we used the erythropoietin resistance index (ERI). Patients were stratified in two groups: nonresponders and responders (ERI $>$ 15, n = 20, and ERI ≤15 U/kg/week/g per 100 mL, n = 153, respectively). Hematological data, hepcidin levels, iron parameters, inflammatory markers, hospitalization and mortality rates were compared between the groups. Multiple regression analysis was used to determine independent factors affecting ERI and hepcidin.

Results: C-reactive protein (CRP) (β = 0.078, P = 0.007), albumin (β = −0.436, P = 0.004), body mass index (β = −0.374, $P < 0.001$), and hospitalization rate per year (β = 3.017, $P < 0.001$) were found to be significant determinants of ERI in maintenance hemodialysis (MHD) patients. Inadequate dialysis was associated with higher ERI. Patients with concomitant oncological diseases had higher ERI (31.2 ± 12.4 vs 9.7 ± 8.1 U/kg/week/g per 100 mL, P = 0.002). The hepcidin level was 158.51 ± 162.57 and 120.65 ± 67.28 ng/mL in nonresponders and responders, respectively (P = 0.33). Hepcidin correlated directly with ERI, dose of ESAs, ferritin and inversely with Hb, transferrin saturation, and albumin. ERI (β = 4.869, P = 0.002) and ferritin (β = 0.242, P = 0.003) were found to be significant determinants of hepcidin in MHD patients. The hospitalization rate per year was 2.35 ± 1.8 and 1.04 ± 1.04 in nonresponders and responders, respectively (P = 0.011). The mean length of one hospitalization was 25.12 ± 21.26 and 10.82 ± 17.25 days, respectively (P = 0.012). Death occurred in 30% of the patients from the responders' group and in 50% from the nonresponders' group (P = 0.289). The mean hepcidin concentration of patients who died was 141.9 ± 129.62 ng/mL and who survived, 132.98 ± 109.27 ng/mL (P = 0.797).

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Conclusions: CRP, albumin, BMI, and hospitalization rate per year were found to be significant determinants of ERI in MHD patients. Inadequate dialysis was associated with higher epoetin requirements. There were no difference in patient mortality by ERI, but a significant difference in hospitalization rates and mean length of one hospitalization was revealed. A significant positive relation between hepcidin and ERI was revealed. ERI and ferritin were found to be significant determinants of hepcidin in MHD patients. Hepcidin was not related to mortality.

1. Introduction

Resistance to erythropoiesis-stimulating agents (ESAs) has been observed in a considerable proportion of patients with chronic kidney disease (CKD) and it is associated with increased cardiovascular (CV) morbidity and all-cause mortality. ESAs improve the quality of life and reduce transfusion requirements; however, they have not been demonstrated to improve other adverse outcomes associated with anemia of CKD, such as CV disease and mortality. Conversely, recent clinical trials have raised important safety concerns about using ESAs, including an increased risk of death, CV events and stroke, particularly when ESAs are used in higher doses to target higher hemoglobin (Hb) and in hyporesponsive patients [1,2]. Besides, ESA therapy is expensive and leads to enormous costs for the health care system. Approximately 50% of total ESA costs are spent on 15% of patients requiring the highest dosage [3]. Therefore, strategies to reduce ESA resistance and to avoid unnecessary ESA usage are required.

Iron deficiency is an important cause of anemia and resistance to ESAs in CKD patients. The causes of iron deficiency are multifactorial. Some patients with CKD have true iron deficiency, other patients have ''functional'' iron deficiency, which results in ESA resistance in 10%–20% of cases and can occur even in the context of normal or increased body iron stores [4,5]. Hepcidin, a small antimicrobial peptide discovered in 2001, has turned out to be a key regulator of iron homeostasis [5–7]. Excess levels of hepcidin in patients with CKD especially in those receiving maintenance hemodialysis (MHD) are thought to contribute to anemia by decreasing iron availability from the diet and body stores. Hepcidin induces internalization and degradation of ferroportin-1 (Fp-1), which is a cellular iron exporter on enterocytes, macrophages, and hepatocytes. Many studies have reported a strong relationship between hepcidin and iron profile in MHD patients [8–10], whereas data on the relationship with the maintenance dose of ESAs and ESA resistance is controversial [11,12].

Recently, the role of hepcidin as a cardiovascular marker has gained considerable attention in the CKD population [5,13,14]. New data support the hypothesis that hepcidin may be involved in the progression of atherosclerosis, and its measurement may help to stratify individual risk of patients. It may be associated with the high rate of mortality and CV disease in MHD patients [15,16]. An increasing understanding about the molecular mechanisms governing iron homeostasis regulation and its disturbance in CKD may lead to improved diagnosis and therapeutic strategies for management of this patient population [17].

The aims of this study were to analyze the factors that are associated with the response to ESAs in MHD patients and its association with hospitalization rates and mortality; to evaluate serum hepcidin levels in MHD patients and to observe the correlation of serum hepcidin with conventional iron, inflammatory markers and ESA responsiveness; to determine independent factors affecting ERI and hepcidin; and to study whether hepcidin is related to all-cause mortality in MHD patients.

2. Materials and methods

The study was initiated on January 1, 2010, and included 173 adult patients who received MHD at least for 6 months from 5 MHD units. All patients used bicarbonate dialysate and had been subjected to regular MHD procedures for 3–4 h 3 times per week. Routine patient care and prescription of medications were practiced according to the local MHD patients care guidelines. Patients received ESAs at a dose aimed to maintain Hb between 100 and 105 g/L, according to our local renal anemia management algorithm at that time, which defined a target range of Hb 100–105 g/L. Iron was administered IV according to the local algorithm (Table 1) and suspended when the ferritin level was above 500 μg/L. However, transferrin

Table 1 – A local algorithm for IV iron administration in MHD patients.

Ferritin (μg/L or ng/mL)	IV iron therapy
<100	100–500 mg per day, not exceed 1000 mg. Repeat ferritin test one week after the last dose of IV iron, if it is still less 100 mg/L, repeat the same treatment course
100–300	100 mg of iron per week. Measure ferritin concentration every 3 months
>300–500	100 mg of iron every second week. Measure ferritin concentration every 3 months
>500	Suspend IV iron therapy. Measure ferritin concentration after 1–3 months

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