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Ferritin Elevation and Improved Responsiveness to Erythropoiesis-Stimulating Agents in Patients on Ferric Citrate Hydrate

Keitaro Yokoyama[1], Masafumi Fukagawa[2], Takashi Akiba[3], Masaaki Nakayama[4], Toshiya Otoguro[5], Kana Yamada[5], Yasuo Nagamine[6], Steven Fishbane[7] and Hideki Hirakata[8]

[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [2]Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Kanagawa, Japan; [3]Sekikawa Hospital, Tokyo, Japan; [4]Department of Nephrology, Hypertension, Fukushima Medical University School of Medicine, Fukushima, Japan; [5]Biostatistics Team, Clinical Development, Pharmaceutical Division, Japan Tobacco Inc., Tokyo, Japan; [6]Medical Affairs, R&D, Torii Pharmaceutical Co., Ltd., Tokyo, Japan; [7]Division of Kidney Diseases and Hypertension, Department of Medicine, Northwell Health System, Hofstra Northwell School of Medicine, Great Neck, New York, USA; and [8]Fukuoka Renal Clinic, Fukuoka, Japan

Introduction: In hemodialysis patients on ferric citrate hydrate, the increase in ferritin level is mainly due to the administration of the compound. We investigated possible other factors associated with ferritin level and how erythropoietin resistance index and erythropoiesis in those patients were affected. We looked at ferritin-elevating factors using data from a Japanese phase III long-term clinical trial of ferric citrate hydrate.

Methods: The factors with a strong association with ferritin levels at week 28 were selected by the process of variable selection. In addition, selected factors were analyzed by Mixed Model for Repeated Measurement. Subjects were divided into 3 groups by quantiles (<Q1, Q1–Q3, Q3<) of the most strongly correlated factors. Then the least-squares means of change of ferritin at each time point for each group were calculated. Finally, the differences of the least-squares means were examined. Changes of both erythropoiesis-stimulating agent dose and erythropoietin resistance index for each group were investigated. The differences in mean erythropoietin resistance index between groups at baseline, week 28, and week 52 were analyzed using *t* tests.

Results: Dose of ferric citrate hydrate showed the strongest correlation with change of ferritin and the second strongest was the reduction of erythropoiesis-stimulating agents. The mean erythropoietin resistance index was lowered in group <Q1. Group <Q1 showed significantly lower levels of ferritin at baseline.

Discussion: It is suggested that not only iron load but also the erythropoiesis-stimulating agent dose reduction may be involved in ferritin elevation during ferric citrate hydrate treatment, resulting in a decrease of erythropoietin resistance index.

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Hyperphosphatemia is associated with vascular calcification and mortality in patients on chronic hemodialysis.[1] In patients with chronic kidney disease (CKD), control of hyperphosphatemia with phosphate binders is expected to improve prognosis.[2,3] There are 2 types of phosphate binders currently available: those containing calcium and those that are calcium free. Calcium-free phosphate binders such as sevelamer hydrochloride (or carbonate) and lanthanum carbonate may be beneficial for avoiding calcium loading.

Ferric citrate hydrate was developed as a calcium-free phosphate binder.[4,5] It was launched in 2014 in Japan ahead of other countries, and later in the USA and Taiwan. Because patients with CKD have high levels of hepcidin that downregulates intestinal iron absorption, oral administration of iron is supposedly less likely to cause elevation of serum ferritin levels

Correspondence: Keitaro Yokoyama, Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, 3-25-8 Nishi-Shinbashi, Minao-ku, Tokyo 1058471, Japan. E-mail: Keitaro@jikei.ac.jp
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than i.v. administration.[6] Orally administered trivalent iron is reduced to bivalent iron in the digestive tract and is then absorbed via the divalent metal transporter 1 in the intestinal epithelium.[7] Thus, ferric citrate hydrate, a trivalent iron, might be considered not to have a significant effect on serum ferritin levels. In addition, it was reported that phosphorus in the intestine attenuates iron reduction and inhibits iron absorption in the intestine.[4,7]

However, both phase III long-term clinical trials of ferric citrate hydrate in hemodialysis patients that were conducted in Japan and the USA showed increases in serum ferritin, as well as dose reduction of erythropoiesis-stimulating agent (ESA) and i.v. iron preparations by administration of ferric citrate hydrate.[5,8] It has been confirmed in the clinical trials that iron from administered ferric citrate hydrate is partially absorbed and increases serum ferritin and hemoglobin levels.[5,8]

There are factors other than simply iron absorption that can cause serum ferritin concentrations to rise during iron therapy. Because ferric citrate hydrate's primary role is as a phosphate binder, it would be important to better understand factors that lead to the increase in serum ferritin found with its use. This would also aid further understanding of the pathology of iron-deficiency anemia in CKD. In this study, we investigated serum ferritin-elevating factors using data from the Japanese phase III long-term trial conducted in hemodialysis patients with hyperphosphatemia.[5] Because ferric citrate hydrate administration enables the dose reduction of ESA and elevates serum hemoglobin levels, we also examined the erythropoietin resistance index (ERI) and investigated erythropoiesis.

METHODS

Data from the Japanese long-term trial were used to identify the factors causing the elevation of serum ferritin and to investigate changes in ERI and the association between administration of ferric citrate hydrate and erythrocyte indices (mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]). The trial recruits were Japanese patients with hyperphosphatemia, and who were undergoing hemodialysis. The methods used in this study were as follows.

Identification of Serum Ferritin-Elevating Factors in Patients on Ferric Citrate Hydrate

In the Japanese long-term trial, serum ferritin levels had risen for 28 weeks after the start of ferric citrate hydrate administration (baseline; 0 wk). After week 28, the levels stabilized until week 52. Therefore, the factors with a strong association with serum ferritin levels (change of ferritin level from baseline) at week 28 were selected from the obtained data by the process of variable selection (stepwise method). The selected candidate variables were factors for which it is considered clinically plausible for there to be an association with a change of ferritin: age, gender, body weight, and serum phosphorus level (P[0 wk]), serum ferritin level (Ferritin [0 wk]), serum hemoglobin level (Hb [0 wk]), MCV [0 wk], MCH [0 wk], and transferrin saturation (TSAT [0 wk]), plus change in ESA dose at week 28 from baseline (change of ESA), average dose of ferric citrate hydrate over 28 weeks (dose of ferric citrate hydrate), and change of ERI at week 28 from baseline (change of ERI).

To avoid multicollinearity problems at variable selection by inclusion of factors that are strongly related to each other in the model, one factor was excluded using correlation analysis and single regression analysis. In addition, to investigate the correlation between the most strongly related factors and change of ferritin at each time point, selected factors were analyzed by Mixed Model for Repeated Measurement using the model described here. The exception to this was the dose of ferric citrate hydrate. We divided subjects based on their ESA dose administered by using quantiles. The calculated quantiles were that Q1 (lower 25% points) was −2500 IU/wk, median was 0 IU/wk, and Q3 (upper 25% points) was also 0 IU/wk. It was shown that the median equaled Q3 by chance. Therefore we combined a group (Q1 through to less than median) and another group (median through to less than Q3), and accordingly subjects (N = 146) were divided into 3 groups (group <Q1: n = 36, group Q1–Q3: n = 74, group Q3<: n = 36) by quantiles (<Q1, Q1–Q3, Q3<) of the most strongly correlated factors based on the change of ESA dose administered. Then the least-squares means of change of ferritin at each time point for each group were calculated, and the differences of the least-squares means were examined.

Model

The response variable was the change of ferritin level. The fixed effect was the factor with the lowest *P* value among selected factors by variable selection (except dose of ferric citrate hydrate). The covariates were selected factors as chosen by variable selection, time point, and time point × fixed effect except fixed effect.

Investigation of the Correlation Between Administration of Ferric Citrate Hydrate and Erythrocyte Indices

Subjects were divided into 3 groups by using quantiles of fixed effect. The dose of ESA and change of ERI for each group were investigated. The dose of ESA was calculated using the following equation: