Management of iron deficiency anemia in hemodialysis patients based on mean corpuscular volume

Kumiko Onda[1], Teruo Koyama[1], Sanae Kobayashi[1], Yoji Ishii[1] and Kazuo Ohashi[2*]

Abstract

Background: To manage the anemic status in hemodialysis (HD) patients, a well-balanced combination therapy based on the use of erythropoiesis-stimulating agents (ESAs) and iron supplementation is essential. Serum ferritin level and transferrin saturation rate (TSAT) are the current standard tests for screening iron deficiency status. However, these are not included in frequently checked regular blood measurements in many HD centers. Other parameters that could predict a hemoglobin (Hb) increase response from iron supplementation have yet to be established. To determine a frequently checked and regularly measured biomarker for predicting iron deficiency status, this study investigated the value of mean corpuscular volume (MCV) as a clinical parameter for HD patients receiving intravenous iron supplementation (Fe-IV) therapy.

Methods and results: One hundred thirty four HD patients, 88 non-HD patients with anemia, and 50 HD patients on Fe-IV therapy from the Nozatomon clinic were assessed. Comparison of MCV values of anemic HD patients and anemic non-chronic kidney disease (CKD) patients showed that anemic HD patients had significantly higher MCV values (93.9 ± 7.3 fL) compared with anemic non-CKD patients (82.8 ± 8.8fL). Fifty HD patients, who received Fe-IV therapy at ten consecutive HD sessions (inclusion criteria: Hb ≤ 12.0 g/dL, TSAT < 20%, and serum ferritin < 100 ng/mL) showed a rapid increase during the Fe-IV period in MCV, Hb, and TSAT levels. After the completion of the Fe-IV therapy, MCV persisted at the increased levels, whereas Hb levels further increased and peaked at 1 month with a gradual decline after, largely influenced by ESA dosage reductions. The 50 patients were divided into three groups according to the MCV levels obtained immediately prior to the Fe-IV therapy (MCV ≤ 85 fL, 85 fL < MCV ≤ 90 fL, MCV > 90 fL), and Hb changes at 50 days after the initiation of the Fe-IV therapy were compared. All the patients in the MCV ≤ 85 fL group and most of the patients in the 85 fL < MCV ≤ 90 fL group showed linear and consistent Hb increase during the 50-day period. In marked contrast, patients in the MCV > 90 fL group showed dispersed trends in their Hb increase. The present study also revealed that successful ESA dosage reduction could be achieved after the Fe-IV therapy in both the MCV ≤ 85 fL and 85 fL < MCV ≤ 90 fL groups.

Conclusions: The present study underscored the value of MCV in perceiving iron deficiency status as well as predicting iron-based therapeutic response in HD patients.

Keywords: Iron deficiency anemia, MCV, Intravenous iron administration

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* Correspondence: ohashikazuo@hotmail.com
[2]Graduate School and School of Pharmaceutical Sciences, Osaka University,
1-6 Yamada-oka, Suita, Osaka 565-0871, Japan
Full list of author information is available at the end of the article

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Background

Since erythropoiesis-stimulating agents (ESAs) were first authorized in 1990, maintaining targeted hemoglobin (Hb) levels in hemodialysis (HD) patients has been successfully achieved in many cases. Despite the application of ESAs however, patients on HD still occasionally face anemic status. One of the principal causes of this anemic status is iron deficiency. Blood loss during each HD session as well as an impaired nutritional status, could be major causes of iron deficiency [1]. To fulfill the ESA's potential, it would be crucially important for HD patients to be appropriately assessed for iron deficiency anemia and for those with the status to be corrected using systemic iron supplementation [2]. It should be noted that a recent report from a phase 2 clinical trial of a newly introduced oral hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor agent named Roxiadustat, an agent that upregulates intrinsic erythropoietin as well as activating its receptor, clearly showed higher Hb level increases in cohorts receiving iron supplementation than in cohorts without supplementation [3]. Since several HIF-PH inhibitors has recently been available for anemic HD patients, the importance of appropriately assessing for iron deficiency anemia status should further be highlighted.

In the Guidelines for Renal Anemia in Chronic Renal Disease set forth by the Japanese Society for Dialysis Therapy (JSDT) [4, 5], assessing serum ferritin levels and transferrin saturation (TSAT) rate has been recommended for evaluating iron deficiency status in HD patients and for consideration of intravenous iron supplementation. The guidelines propose that IV iron supplementation should be considered when the serum ferritin and TSAT rate levels are < 100 ng/mL and < 20%, respectively [4, 5]. They also recommend that measurement of the two parameters should be conducted at least every three months, but compliance in practice has occasionally been hindered because of the medical expenses from measuring the two parameters. The guidelines further recommend monthly measurement of ferritin, while HD patients are under iron supplementation [4, 5]. However, many HD centers are likely to hesitate providing monthly measurements of ferritin, possibly due to medical cost concerns. From the medical cost reduction standpoint, it would be valuable to establish alternative and promising indicators for an iron deficiency status, which could hopefully be included in frequently checked and regularly assessed blood parameters for HD patients. The importance of identifying alternative indicators could also be supported by the fact that both the TSAT and serum ferritin levels occasionally fluctuate if patients harbor systemic inflammation or heart failure status [1, 6–10].

It is generally accepted that microcytic anemia, a decrease in mean corpuscular volume (MCV), is directly associated with iron deficiency anemia. MCV is one of the frequently screened and regularly assessed blood parameters. However, scientific data specific to HD patients, in studying MCV levels in association with iron supplementation, have been extremely limited [11]. Therefore, we initially determined MCV value distribution in 134 HD patients treated in our HD center. We also assessed differences in MCV values in those with anemia between HD patients and non-chronic kidney disease (CKD) patients. To identify the clinical applicability of using MCV values for predicting iron deficiency status and for measuring improvement after iron supplementation therapy, we further investigated MCV values and other clinical parameters in 50 iron deficiency-based anemic HD patients, who received intravenous iron (Fe-IV) supplementation. The primary objective of the study was to provide supporting information obtained from MCV values in HD patients in assessing an iron deficiency status and in predicting therapeutic response.

Patients and methods

Assessment of MCV values in HD patients

For this study, MCV and Hb values were determined using the XN-20 Hematology Analyzer (Sysmex, Kobe, Japan). All patients (134 patients; 90 men, 44 women) who had been undergoing HD at the Nozatomon Clinic for three consecutive months (April to June, 2015) were evaluated for mean MCV values at three months. Blood samples were drawn at the beginning of a dialysis session, conducted on the first Monday or Tuesday of each month.

Comparison of MCV values in anemic HD patients and anemic non-CKD patients

To evaluate MCV values in anemic HD patients, 88 HD patients treated in Nozatomon Clinic (63.5 ± 13.8 years old), who continuously had Hb levels ≤ 12.0 g/dL throughout 2013, were determined. In addition, 53 patients (42.3 ± 9.9 years old) diagnosed with anemia (Hb levels ≤ 12.0 g/dL) at the Nozatomon Clinic in 2013, who had no associated chronic kidney diseases (non-CKD), were enrolled for the assessment of their MCV values.

Intravenous Fe administration in anemic HD patients

Fifty HD patients (33 men, 17 women; mean age, 65.2 ± 10.2) treated at the Nozatomon Clinic between 2013 and 2015, who were diagnosed with iron deficiency anemia, were included in the study. Iron deficiency anemia was diagnosed when all the following parameters met the following criteria: Hb level ≤ 12.0 g/dL, TSAT ≤ 20%, and

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serum ferritin ≤ 100 ng/mL. All patients underwent regular dialysis therapy three times a week with a dialysis period of > 1 year. The primary diseases of the 50 HD patients were diabetic nephropathy (n = 11), glomerulonephritis (n = 10), chronic nephritis (n = 2), acute renal failure (n = 2), IgA nephropathy (n = 1), nephrotic syndrome (n = 1), rapidly progressive glomerulonephritis (n = 1), polycystic kidney (n = 1), pregnant toxicosis (n = 1), hypertensive nephrosclerosis (n = 1), and unknown etiology (n = 19). Fourteen patients had comorbidities (diabetes mellitus (n = 11) and post-gastrectomy (n = 3)) that may have had influence on their anemic status. There were no patients who suffered from alcoholism.

Intravenous administration of Saccharated ferric oxide (Fesin, NICHI-IKO, Toyama, Japan) at a dose of 40 mg was conducted alongside 10 consecutive dialysis sessions (Fe-IV), resulting in a 400-mg total administration. Since the Guidelines for Renal Anemia in Chronic Renal Disease released by the JSDT during the experimental period (2013–2015) provided recommendation that the frequency of intravenous Fe administration was up to a total of 13 times at every dialysis session [4]. To minimize the occurrence of iron overload, we have reduced to a total of 10 times infusion in this investigation. MCV, Hb, serum ferritin, TSAT, serum albumin, serum CRP levels, and the dosage of ESA were assessed at four months before and after the Fe-IV as well as during the Fe-IV period. In order to determine Hb and MCV values in relation to the Fe-IV treatment, the amount of change in the values relative to the value obtained immediately prior to the start of IV-Fe in each patient were calculated. Ferritin values were measured by latex agglutination method [12] using the FER-LATEX X2 "SEIKEN" CN Kit (Denka Seiken, Tokyo, Japan).

In addition, the 50 Fe-IV patients were divided into three groups categorized by the MCV values obtained immediately prior to the start of Fe-IV (MCV ≤ 85 fL (n = 8), 85fL < MCV ≤ 90 fL (n = 17), and MCV > 90 fL (n = 25)). Changes in Hb and MCV values were assessed for 50 days after the start of Fe-IV sessions.

Statistical analyses

All calculated values are presented as mean ± SD except for values in Fig. 2 (mean ± SE). The significance of differences between groups was tested using IBM SPSS Statistics 18.0 software (IBM Japan, Tokyo, Japan). Student's t test (normally distributed dataset) was used to compare two groups. In the analyses of parameters in 3 groups categorized by MCV values, one-way analysis of variance was conducted using Microsoft Excel 2010 for mean age, MCV value, hemodialysis vintage, serum ferritin level, medication of iron-based phosphate binders, ferric citrate hydrate, levocarnitine chloride, and vitamin B12. A P value of < 0.05 was considered to indicate significant difference.

Results

Assessment of MCV values in HD patients

To understand the overall trend of the HD patient-specific MCV values, we first assessed all 134 HD patients treated in our clinic. The average MCV value was found to be 93.8 ± 6.5 fL (72.8–111.7 fL). Among the 134 HD patients, only four (3%) had MCV ≤ 80 fL, which met the general diagnostic criteria for microcystic anemia (iron deficiency anemia). In contrast, 101 HD patients (75%) showed relatively large MCV values (> 90 fL).

Comparison of MCV values in anemic HD patients and non-CKD patients

Since the above investigation revealed that our HD patients tended to have relatively large MCV values, we conducted this study to recognize MCV values of anemic HD patients. At the Nozatomon Clinic in 2013, 88 patients had consistently anemic status throughout the year (Hb levels ≤ 12.0 g/dL). We calculated the mean MCV values for 12 months in 2013 in all 88 anemic patients on HD, and the average annual MCV value was 93.9 ± 7.3 fL (77.8–120.4 fL). We also assessed the MCV values of anemic non-CKD patients (n = 53), and the value was 82.8 ± 8.8 fL (64.3–99.2 fL. On analysis, the anemic HD patients demonstrated significantly higher MCV values compared with those in anemic non-CKD patients (P < 0.01).

Intravenous Fe administration in anemic HD patients

Fifty anemic HD patients who received intravenous Fe supplementation therapy using Saccharated ferric oxide conducted at 10 consecutive dialysis sessions (Fe-IV) were enrolled in this investigation. MCV, Hb, serum ferritin, TSAT, CRP, and albumin, and the dosage of ESAs assessed for four months before and after Fe-IV administration, as well as during the Fe-IV period, are shown in Figs. 1, 2, and 3.

Significant increases in the MCV, Hb, serum ferritin, and TSAT values were demonstrated (Fig. 1a–d, g–j). The increase in these 4 values was noted during the Fe-IV period (indicated in the figures as mid and end during the Fe infusion). It is of note that the serum ferritin levels remained below 200 ng/mL both during and after Fe-IV administration. The TSAT values prior to Fe-IV therapy were 13.2 ± 5.6%, and these increased to 22.5 ± 9.5% at four week after the start of Fe-IV. The elevated TSAT value (> 20%) persisted during the four-month observation period after Fe-IV. In contrast, there were no observable changes in the serum CRP and albumin levels (Fig. 1e, f, k, l).

We next closely observed the changes in MCV and Hb values (Fig. 2). For a four-month period prior to the start of Fe-IV, the MCV values tended to gradually decrease, indicating that the iron deficiency status had gradually
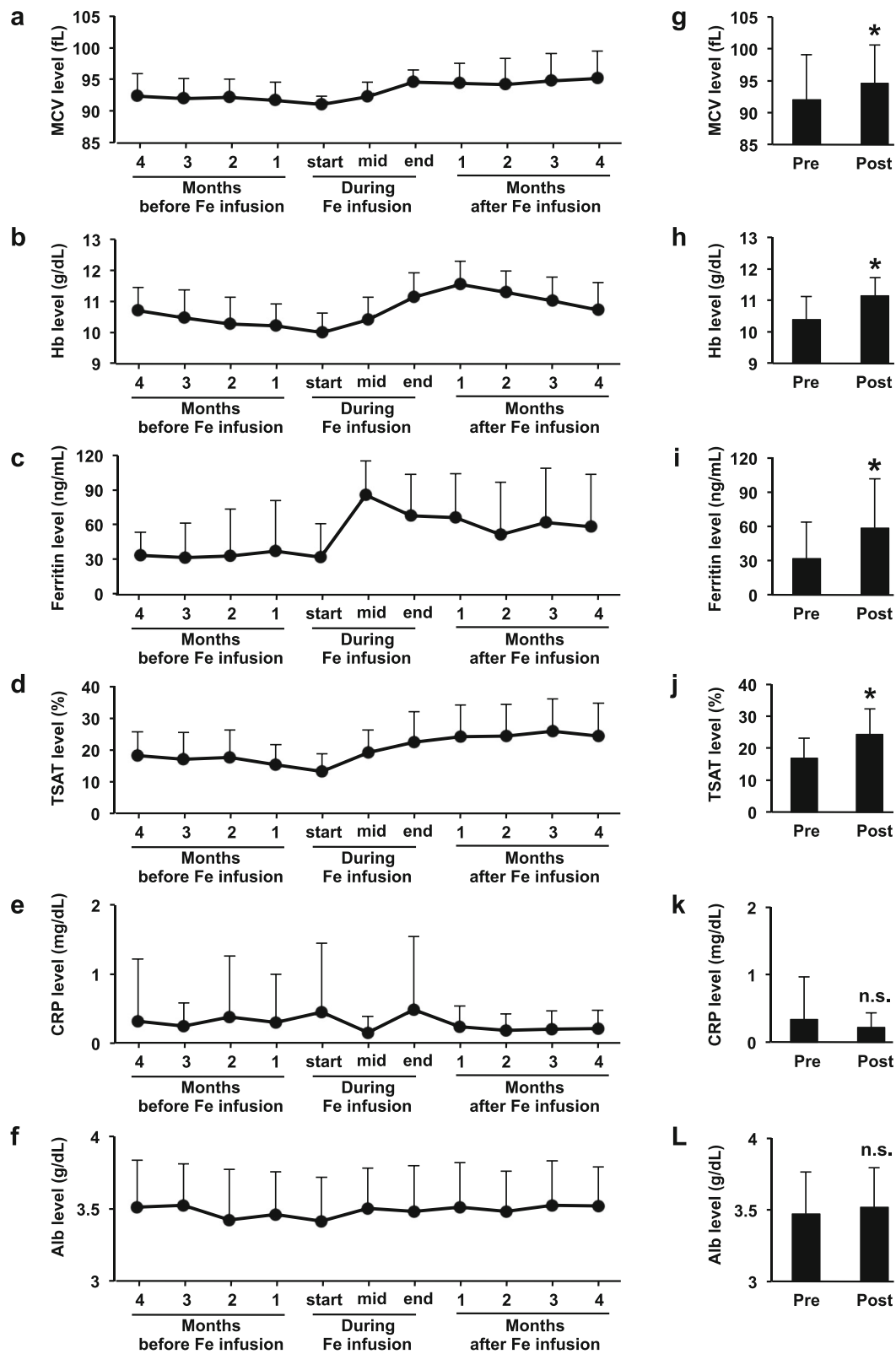
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Fig. 1 Blood test values of the 50 HD patients who received Fe-IV therapy alongside 10 consecutive HD sessions. **a**–**f** Average values of the 50 HD patients at indicated time point. **g**–**l**, Four months average blood test values from 1 to 4 months before (Pre) or after (Post) Fe infusion. Values for MCV (**a**, **g**), Hb (**b**, **h**), ferritin (**c**, **i**), TSAT (**d** ,**j**), CRP (**e**, **k**), and Alb (**f**, **l**) are shown. * $P < 0.05$ vs Pre. *n.s.*, not significant between groups
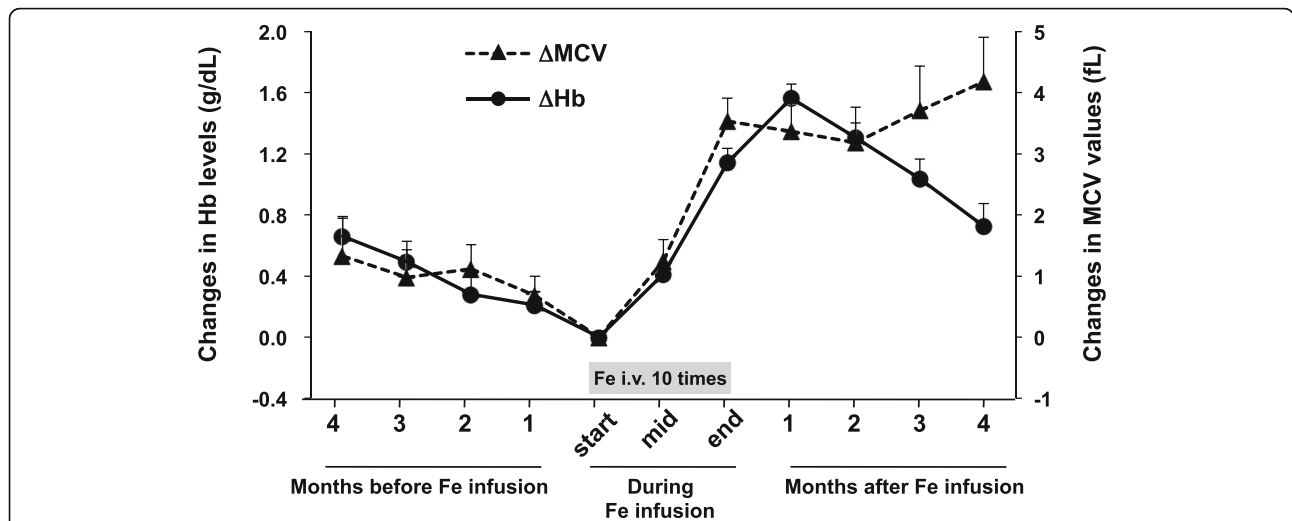
Fig. 2 Changes in Hb values (solid line) and MCV values (dotted line) of the 50 HD patients who received Fe-IV therapy alongside 10 consecutive HD sessions. Each data represents the average of differences in the values between at the time of start of Fe-IV and at indicated time point for the 50 HD patients

progressed. The MCV values obtained immediately prior to the Fe-IV (91.0 ± 1.33 fL), increased significantly to 92.3 ± 2.27 fL (1.3-fL increase) and 94.6 ± 1.98 fL (3.6-fL increase) at two and four weeks after the start of Fe-IV, respectively, indicating that MCV values showed a rapid increasing response to the Fe-IV therapy (Fig. 2). After completion of the Fe-IV therapy, there were no significant MCV changes during a four-month observation period with the values 95.3 ± 4.34 fL (4.3-fL increase) (Fig. 2). The Hb values also showed a rapid increase in response to Fe-IV, which was in parallel with the MCV response (Fig. 2). The Hb values were 10.0 ± 0.63 g/dL and 11.1 ± 0.78 g/dL (1.1-g/dL increase) immediately before and at four weeks after the Fe-IV therapy, respectively. The Hb values peaked at one month after the completion of Fe-IV therapy (11.6 ± 0.76 g/dL, 1.6-g/dL increase), then gradually declined, largely related to the ESA dosage reductions.

Reduction of ESA dosage after the Fe-IV

We determined the profile of ESA dosage before and after Fe-IV therapy (for 16 weeks each) in the 50 anemic HD patients. After Fe-IV, the weekly ESA dosage showed continuous reduction by week six. The reduced ESA dosage persisted throughout the observation period (Fig. 3a). The average weekly ESA dosage from 16 weeks before and after the Fe-IV was assessed, and it was found that there was a significant decrease in the ESA values after Fe-IV therapy (Fig. 3b). When the total ESA dosage required for the 16 weeks was determined, we found that a 42.5% reduction in the total ESA dosage was achieved by Fe-IV therapy (Fig. 3b).
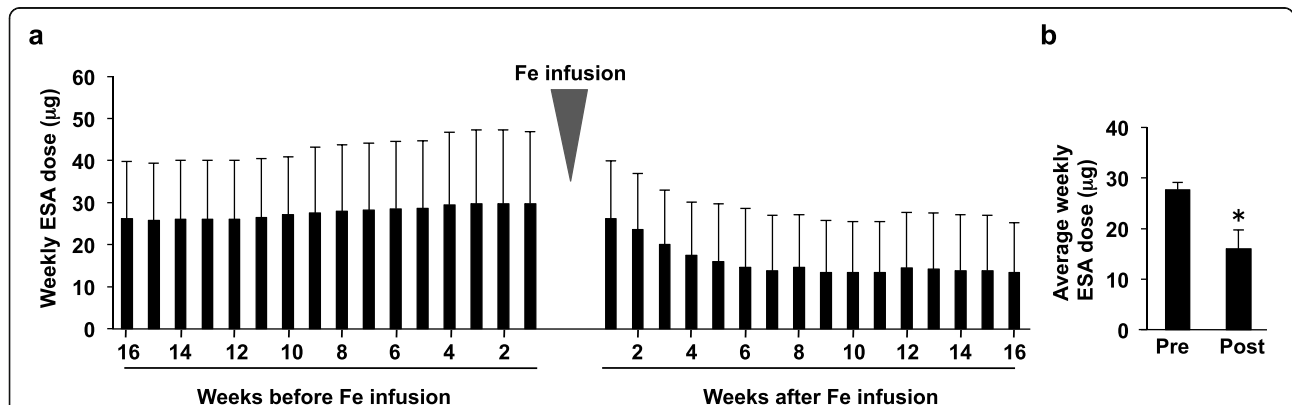

Fig. 3 Weekly ESA dosage and average ESA dosage in a 16-week period required for the 50 HD patients before and after the 10 consecutive Fe-IV infusions. **a** Changes in the weekly ESA dosage required in a 16-week period before and after the Fe-IV therapy. **b** Average of the ESA dosage in a 16-week period before (Pre) or after (Post) the Fe-IV therapy. * $P < 0.05$ vs Pre

MCV values as a valuable response indicator of the Fe-IV therapy

In order to evaluate MCV values as an Hb increase-response indicator to the Fe-IV therapy, we divided the 50 anemic HD patients into three groups according to the MCV value obtained immediately before the Fe-IV therapy (MCV ≤ 85 fL, 85 fL < MCV ≤ 90 fL, MCV > 90 fL), and assessed Hb changes for 50 days after the start of Fe-IV. The mean age and male ratio of the 3 groups were 65.4 ± 13.6, 64.8 ± 11.8, and 65.7 ± 8.9, and 62.5%, 58.8%, and 60% in MCV ≤ 85 fL, 85 fL < MCV ≤ 90 fL, and MCV > 90 fL groups, respectively, without showing significant intergroup differences. Hemodialysis vintage (years) was 17.3 ± 3.5, 27.8 ± 16.8, and 39.4 ± 41.0 in MCV ≤ 85 fL, 85 fL < MCV ≤ 90 fL, and MCV > 90 fL groups, respectively, without showing significant intergroup differences. In addition, there were no observable intergroup bias in parameters that might have affected the iron deficiency anemic status, including serum ferritin levels, medication of iron-based phosphate binders, ferric citrate hydrate, levocarnitine chloride, and vitamin B12.

In the MCV ≤ 85 fL group, all 8 patients showed Hb increase of more than 1 g/dL at day 28 (Fig. 5a). All patients showed further Hb increase beyond day 28. Patients in the 85 fL < MCV ≤ 90 fL group could be divided broadly into two categories: one showed sharp Hb increase of more than 1 g/dL at day 28 with further increases after (n = 9); and the other showed low Hb increase at day 28 at less than 1 g/dL with no remarkable increase afterward (n = 8) (Fig. 5b). All the patients in the MCV > 90 fL group showed an increased Hb response after the start of Fe-IV, but showed diversity in the Hb increase ratio (Fig. 5c). In any group, no strong correlation was observed between MCV values and serum ferritin levels (data not shown).

We also determined the profile of ESA dosage in the 3 groups by comparing the total ESA dose for 16 weeks prior to and after the Fe-IV therapy. After the Fe-IV therapy, a gradual and obvious reduction in the weekly ESA dosage was observed in both the MCV ≤ 85 fL and 85 fL < MCV ≤ 90 fL groups (Fig. 4a–c). The 16-week average ESA dosage reduction rate achieved by Fe-IV was 64.5, 40.2, and 33.9% in the MCV ≤ 85 fL, 85 fL < MCV ≤ 90 fL, and MCV > 90 fL groups, respectively. We confirmed that the Fe-IV therapy significantly lowered ESA dosage in both MCV ≤ 85 fL and 85 fL < MCV ≤ 90 fL groups (Fig. 4d and e).
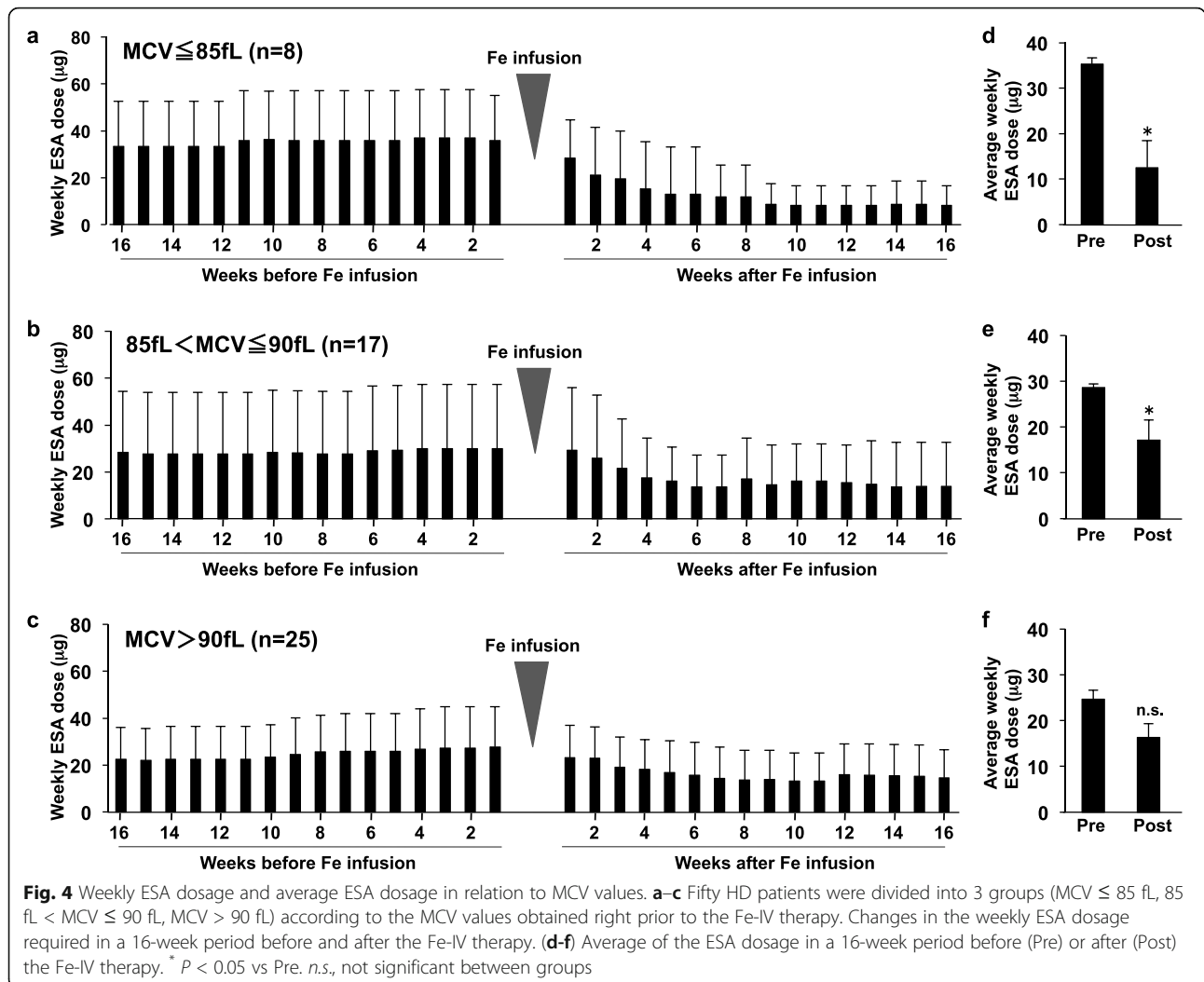
Discussion

This study assessed MCV values in anemic HD versus anemic non-HD patients and found that MCV values were significantly higher in the anemic HD patient cohort. This study also investigated Hb and ESA dosage changes in anemic HD patients in relation to Fe-IV therapy and established that MCV values are valuable parameters for predicting the therapeutic response of the Fe-IV. Since rapid Hb increase and significant ESA dosage reduction were observed in the MCV ≤ 85 fL and 85 fL < MCV ≤ 90 fL groups, it would be reasonable to conclude that MCV ≤ 90 fL would be a valuable parameter for considering Fe-IV supplementation in anemic HD patients.

According to the data report provided by the Committee of Renal Data Registry of the Japanese Society for Dialysis Therapy (JSDT) in 2006, approximately 87% of HD patients were on ESA treatment [13]. This JSDT report also provided evidence that 36.1 and 27.3% of HD patients who were on the ESA treatment were TSAT ≤ 20% and serum ferritin ≤ 100 ng/mL, respectively [13], indicating that a considerable percentage of anemic patients on HD required treatment for their iron deficiency status. In managing anemic HD patients, it would be ideal to appropriately assess and treat iron deficiency status.

Although serum ferritin levels and TSAT rates are known to be suitable parameters for iron deficiency status, they are not normally included in a regularly checked blood assessment in many HD centers worldwide. Considerable cost for measuring serum ferritin levels and TSAT rates could be a preventive factor for the frequent assessment of iron deficiency status. In addition, both parameters are subject to profound fluctuations when a patient harbors systemic inflammation, infection, or heart failure [1, 6–10, 14]. It should be noted that serum ferritin levels largely depend on the assay kit adopted by each examination facility because of large inter-method differences in ferritin measurement [15]. These current circumstances prompted us to explore alternative biomarkers for predicting iron deficiency status chosen from regularly assessed blood parameters in HD patients, focusing on MCV values for this study.
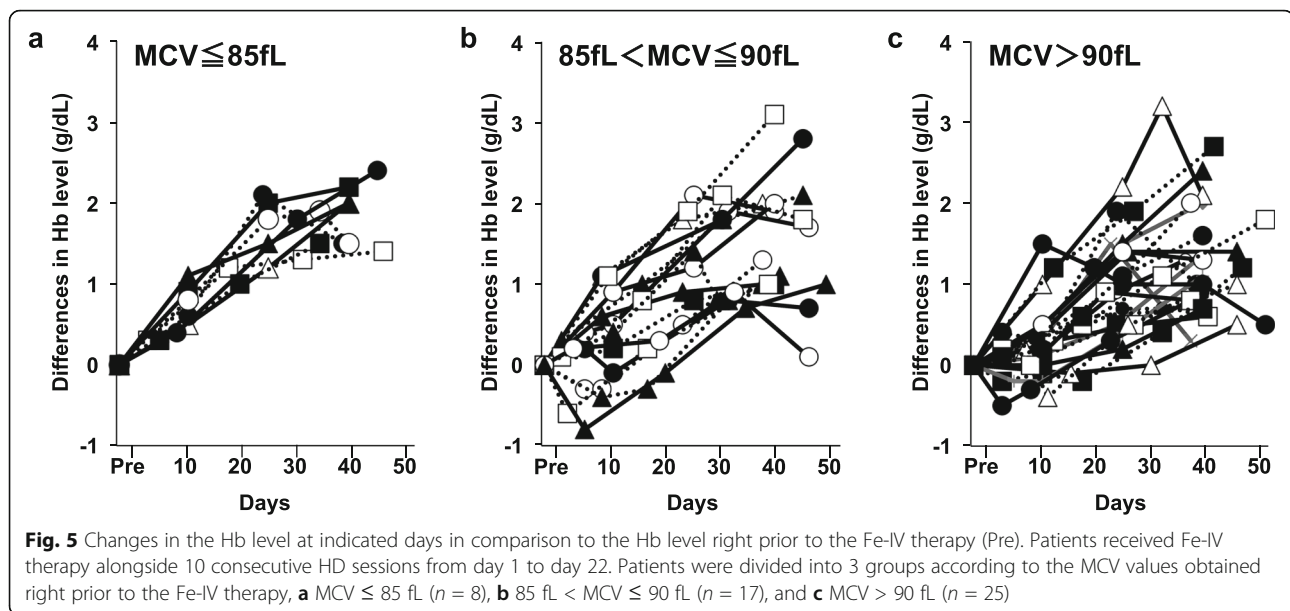
MCV has been considered a valuable and quick diagnostic parameter for microcystic anemia related to iron deficiency status. Although MCV ≤ 80 fL has generally been used as a criterion [16], MCV-based criteria specific to HD patients have not been fully addressed. The present finding that the average MCV values of all the HD patients treated in our clinic were 93.9 ± 7.3 fL, which were approximately 10 fL higher than those in anemic non-CKD patients (82.8 ± 8.8 fL), is extremely informative. On the basis of these findings, adding 10 fL to the conventional cutoff value of MCV ≤ 80 fL, MCV ≤ 90 fL could be proposed as a potential criterion for diagnosing iron deficiency anemia in HD patients. Conversely, the present result that a certain population in the MCV > 90 fL group showed therapeutic response of the Fe-IV suggests MCV > 90 fL could not always be an indicator for denying the consideration of Fe-IV supplementation.

Fig. 4 Weekly ESA dosage and average ESA dosage in relation to MCV values. **a–c** Fifty HD patients were divided into 3 groups (MCV ≤ 85 fL, 85 fL < MCV ≤ 90 fL, MCV > 90 fL) according to the MCV values obtained right prior to the Fe-IV therapy. Changes in the weekly ESA dosage required in a 16-week period before and after the Fe-IV therapy. (**d-f**) Average of the ESA dosage in a 16-week period before (Pre) or after (Post) the Fe-IV therapy. * *P* < 0.05 vs Pre. *n.s.*, not significant between groups

Potential factors that have been associated with higher MCV values in patients with anemia should be discussed. It has been reported that the MCV values tend to increase as patient age increases [17, 18]. Therefore, the older population in our anemic HD patient group could be one of the factors (mean age of the anemic HD and anemic non-CKD patients were 63.5 and 42.3 years, respectively) that could have confounded our results. Alternatively, frequent exposure of the blood cells to osmotic pressure changes from each HD session could result in erythrocyte swelling and an increase in MCV [19]. In addition, it has been reported that HD status-based malnutrition may lead to the erythrocyte membrane being further vulnerable to osmotic pressure changes related to erythrocyte damage [20]. Low albumin status, frequently associated with HD patients, is one of the key factors that may lead to osmotic pressure changes and has been reported to be associated with larger MCV values as well [21]. Researchers have also reported that higher MCV has occasionally been observed in heart failure [7], which might have a relative association

with HD patients. Another potential factor for increased MCV values in HD patients could be ESA therapy itself. ESA therapy increases the reticulocyte population, which can lead to an increase in MCV values [22].

The present study established that the MCV value could be a valuable parameter for predicting the treatment response of Fe-based anemic HD patients. As shown in Fig. 5, in the MCV ≤ 85 fL group, all the patients who received Fe-IV showed rapid and remarkable Hb increase. Most of the patients in the 85 fL < MCV ≤ 90 fL group also showed remarkable Hb increase. In the group with MCV > 90 fL, patients showed scattered tendency in the Hb increase, although all the patients showed Hb increase with Fe-IV therapy. In all the groups, if Hb values increased by 0.5 g/dL at week two after the start of Fe-IV, continuous and gradual Hb increase thereafter could be anticipated, resulting in an approximately 2 g/dL Hb increase. If Hb increase was lower than 0.5 g/dL at week two after the start of Fe-IV, the Hb increase was limited to approximately 1 g/dL. In

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Fig. 5 Changes in the Hb level at indicated days in comparison to the Hb level right prior to the Fe-IV therapy (Pre). Patients received Fe-IV therapy alongside 10 consecutive HD sessions from day 1 to day 22. Patients were divided into 3 groups according to the MCV values obtained right prior to the Fe-IV therapy, **a** MCV ≤ 85 fL (*n* = 8), **b** 85 fL < MCV ≤ 90 fL (*n* = 17), and **c** MCV > 90 fL (*n* = 25)

any case, predicting the Hb increase response from the Fe-IV administration should be important for adjusting the ESA dosage with appropriate timing.

In managing patients with anemia, assessing for iron deficiency status and the need for possible iron supplementation should always be considered. Several concerns have been documented regarding long-term treatment with ESAs, including hypertension, occurrence of seizures, cancer progression, and thromboembolic events [23, 24]. Therefore, a restricted use of ESAs would be considered safe, and balance needs to be maintained between iron supplementation and the use of ESAs for maintaining Hb levels [25]. In addition, reducing ESA dosage is valuable from a medical economic standpoint. In this regard, the successful reduction of ESA dosage after Fe-IV in MCV ≤ 85 fL and 85 fL < MCV ≤ 90 fL achieved in the present study is noteworthy. After the completion of 10 consecutive Fe-IV therapies, the ESA dosage was stably maintained for 16 weeks at reduced levels.

Kuragano et al. [26] reported that an upward trend from low to high ferritin levels is associated with higher mortality in HD patients treated with ESA and iron supplementation. Overdose iron administration has been linked to increased inflammation and infection risks [27]. The ferritin levels observed in the present study did not exceed 300 ng/mL, which is the upper limit recommended by JSDT [5], as shown in Fig. 1c. We also confirmed that there was no CRP elevation during and after Fe-IV (Fig. 1e, k). These data suggest that Fe-IV conducted at 10 consecutive dialysis sessions may be a safe and effective therapy.

Conclusions

The present study underscored the importance of MCV values in assessing iron deficiency status and predicting therapeutic response by specifically investigating MCV values in HD patients. It is proposed that a certain level of iron deficiency status could be involved in HD patients with MCV ≤ 90 fL, and therefore iron supplementation may be considered in these patients. Among the various Fe administration therapies currently available, Fe-IV therapy at ten consecutive HD sessions is an effective and safe therapy for correcting the iron deficiency status.

Author details
[1]Nozatomon Clinic, 1 Bouzumachi, Himeji, Hyogo 670-0011, Japan. [2]Graduate School and School of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, Osaka 565-0871, Japan.

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