

# A TWICE-MONTHLY ADMINISTRATION OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR MAINTAINS HEMOGLOBIN LEVELS AT LESSER DOSAGES THAN ONCE-MONTHLY ADMINISTRATION IN HEMODIALYSIS PATIENTS

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## INTRODUCTION

Continuous erythropoietin receptor activator (CERA) has a half-life of approximately 130 hours when administered intravenously or subcutaneously. CERA has been shown to maintain stable hemoglobin (Hb) levels in hemodialysis patients, at prolonged dosing intervals. However, the optimal dose dosing intervals remain unclear. We therefore compared the efficacy of maintaining normal hemoglobin levels with a twice-monthly CERA (TWICE) versus a once-monthly CERA (ONCE) administration.

## METHODS

Twenty hemodialysis patients receiving epoetin beta (EPO) were enrolled in this study. Patients were assigned to either the TWICE or the ONCE group so that Hb levels and EPO doses were matched. The starting dose of CERA was based on the weekly dose of EPO administered in the previous week. Patients receiving <2250 IU EPO were given 50µg CERA/month. Patients receiving 2250 to <4500 IU EPO were given 100µg CERA/month. Patients receiving 4500 IU EPO were given 150µg CERA/month. CERA doses were adjusted monthly to maintain Hb levels between 10 to 12g/dL. Patients with Hb levels below 10.5g/dL and ferritin levels less than 50ng/mL were given 40mg saccharated ferric oxide. Hb, reticulocyte count (Ret), ferritin, transferrin saturation (TSAT) and hepcidin-25 levels were monitored for 6 months, and then administration method of CERA was interchanged between the two groups.

## RESULTS

**Figure 1.** Hb levels increased at 1 month in the TWICE group and were then maintained following a reduction in CERA doses. Hb levels were well maintained for the first 6 months in the ONCE group. After the regimen interchange between the two groups at 6 months, Hb levels decreased in the TWICE→ONCE group, with significantly lower levels seen at 8 to 11 months compared to at 6 months. By contrast, Hb levels increased in the ONCE→TWICE group, with significantly higher levels noted at 9 and 11 months compared to levels in the TWICE→ONCE group at the same time points.

**Figure 2.** CERA doses in the TWICE group were reduced, leading to significant difference compared to the ONCE group at 3 months. After the regimen interchange between the two groups after 6 months, CERA doses increased in the TWICE→ONCE group, leading to a significant difference at 12 months compared to at 7 months. Monthly doses of 40 mg saccharated ferric oxide in each group are shown in the lower table. No remarkable differences in doses of saccharated ferric oxide between the two groups were noted during the first 6 months. After the regimen interchange, a decrease in Hb levels in the TWICE→ONCE group resulted in an increased need for rapid iron replenishment. More cases of iron replenishment were also seen in the ONCE→TWICE group after regimen switch compared to during the first 6 months.

**Figure 3.** Ret levels were significantly higher in the TWICE group than in the ONCE group at 1, 3, and 6 months. Ret levels in the ONCE group at 1, 3, and 6 months were significantly lower compared to basal levels.

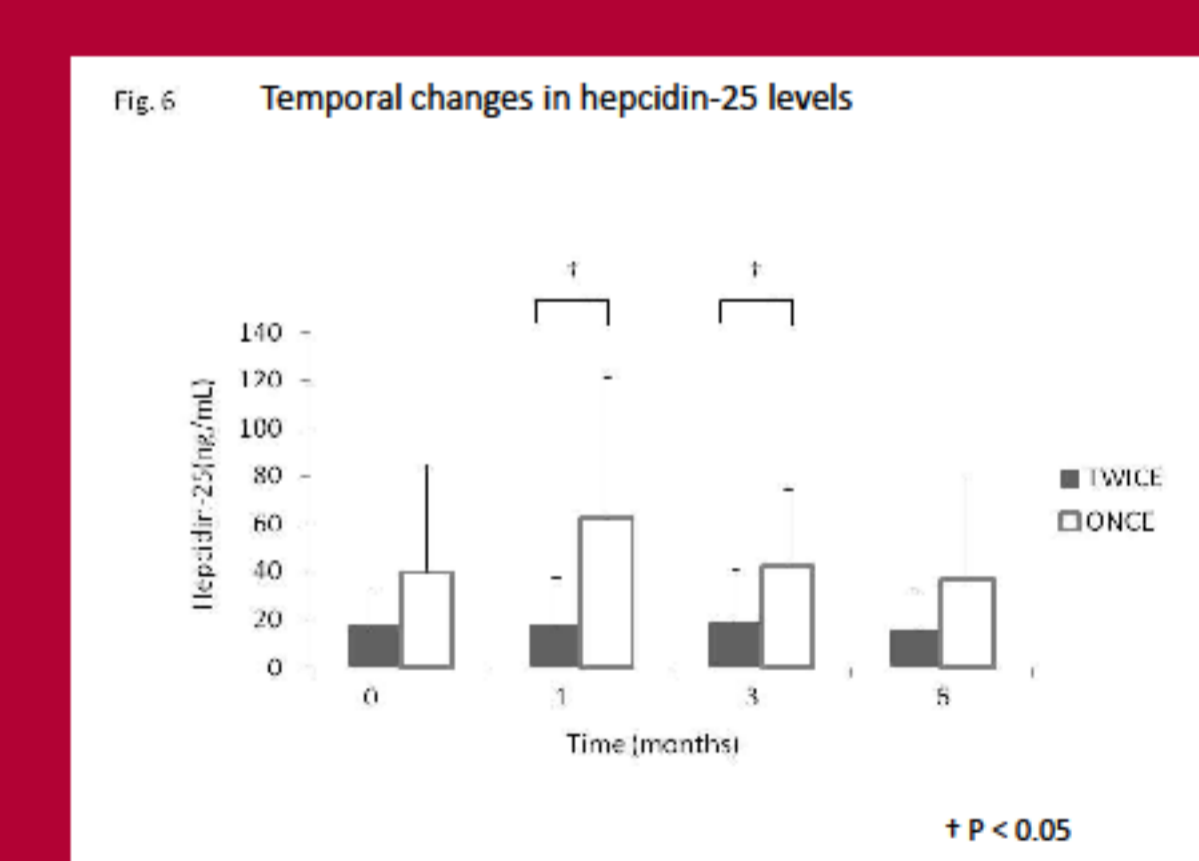
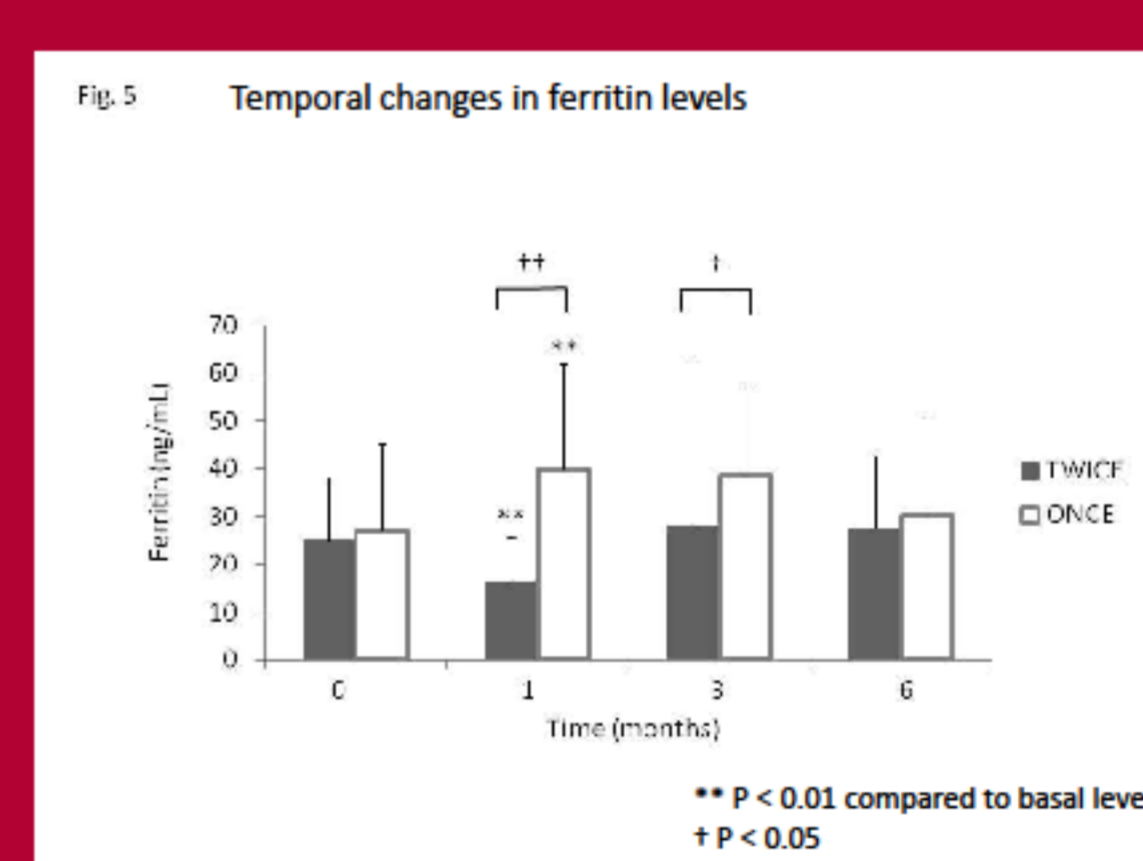
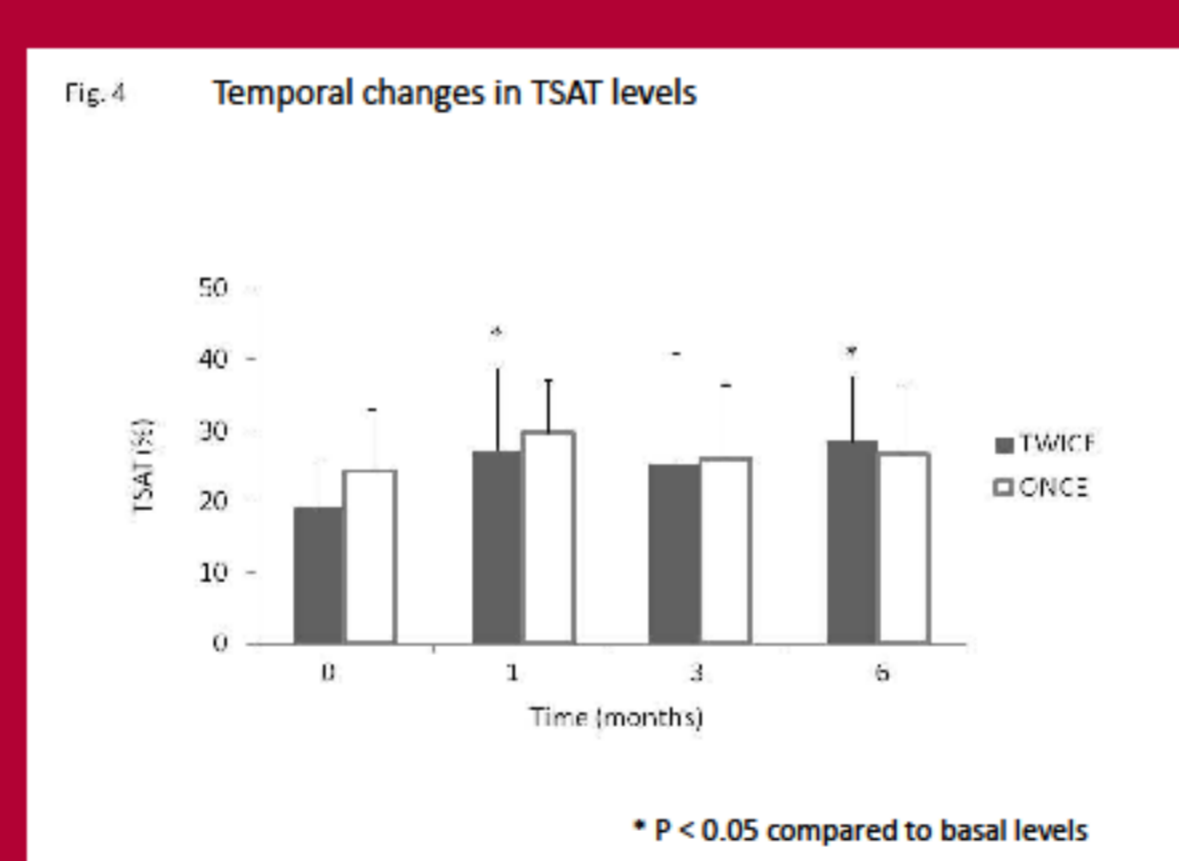
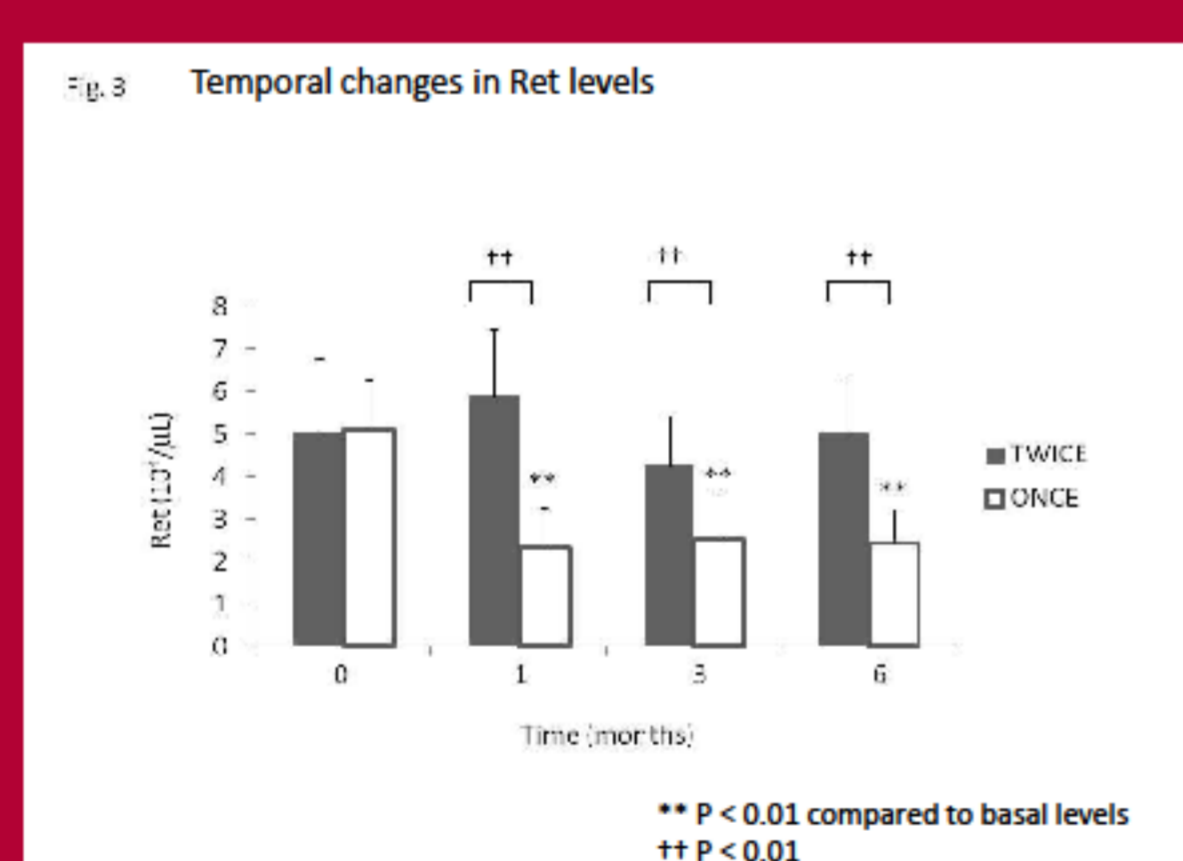
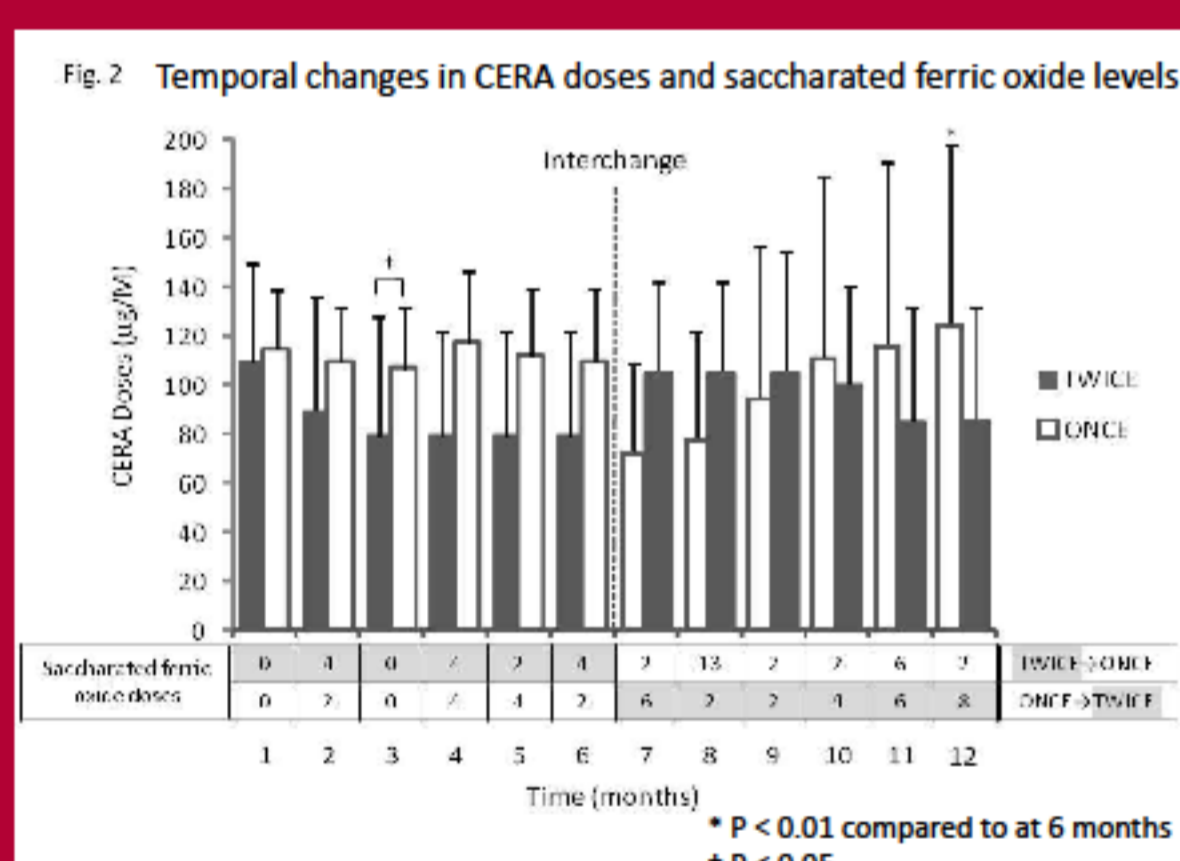
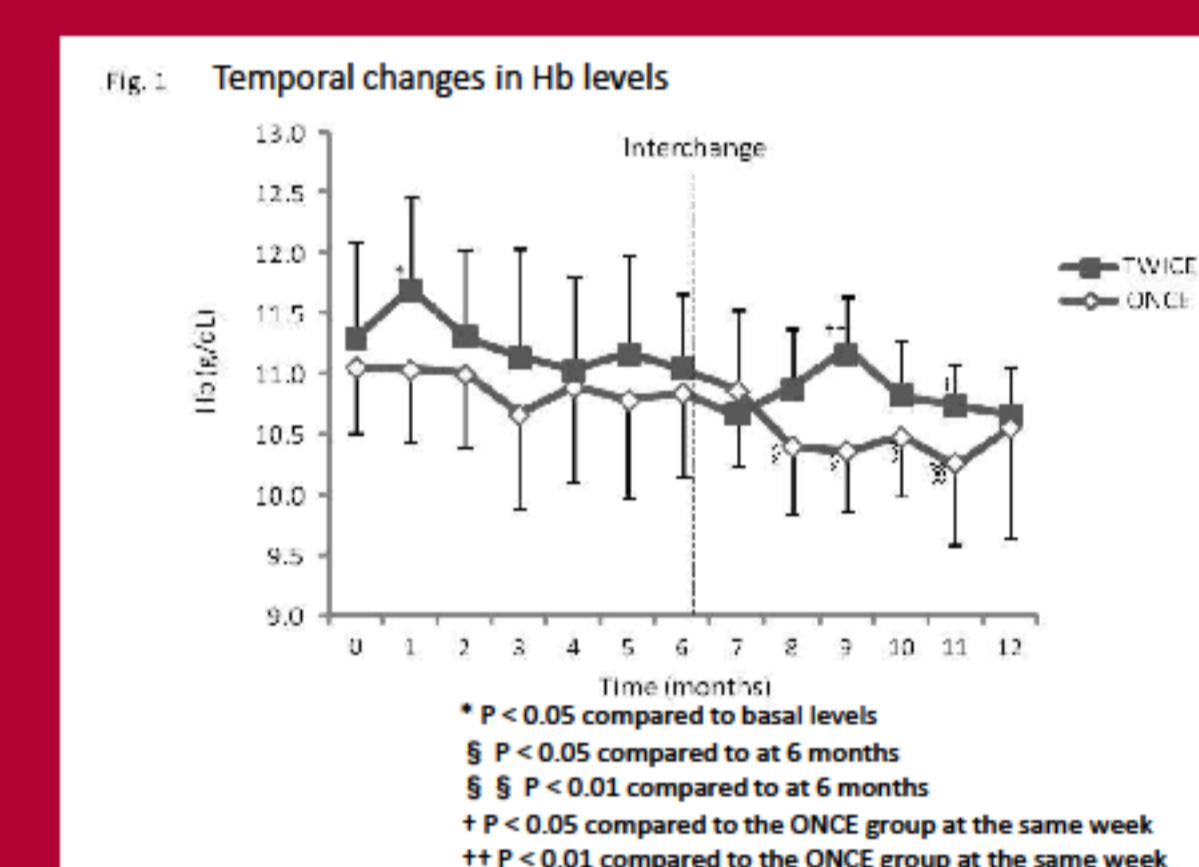
**Figure 4.** TSAT levels are expressed in percentages. TSAT levels in the TWICE group measured at 1 and 6 months were significantly higher than the basal levels.

**Figure 5.** Ferritin levels were significantly higher in the ONCE group than in the TWICE group at 1 and 3 months. A significant increase in ferritin levels was noted in the ONCE group at 1 month compared to basal levels. Similarly, a significant decrease was seen in the TWICE group at 1 month compared to basal levels.

**Figure 6.** Hepcidin-25 levels were significantly higher in the ONCE group than in the TWICE group at 1 and 3 months.

Table 1. Baseline characteristics of the patients. No significant differences were found in male percentage, age, HD vintage, Hb level, ferritin level, hepcidin 25 level, EPO dose, albumin level, CRP level, or whole PTH level.

	TWICE (N=10)	ONCE (N=10)
Male (%)	50	40
Age (yr)	72.5±7.5	67.7±8.4
Dialysis Vintage (yr)	9.2±9.0	7.6±9.0
Hb (g/dL)	11.3±0.8	11.1±0.6
Ferritin (ng/mL)	25.0±13.0	27.1±18.2
Hepcidin 25 (ng/mL)	17.6±13.9	39.6±45.6
EPO (IU/wk)	3675±1983	3750±1118
Albumin (g/dL)	3.4±0.4	3.4±0.3
CRP (mg/dL)	0.5±0.7	0.2±0.3
Whole PTH (pg/mL)	114.0±103.8	73.6±60.0



## DISCUSSION

- The present study showed that Hb levels were maintained equally constant with twice-monthly or once-monthly administration of CERA in patients undergoing HD after switching from EPO. However, twice-monthly administration was advantageous, as it required a lower dose of CERA. In the TWICE group, an increase in Hb levels allowed a reduction in CERA doses as shown in the first half of the study. The advantage of the twice-monthly administration was then confirmed in the second half of this crossover study.
- Low Ret levels in the ONCE group were observed at 1, 3, and 6 months. A rapid decrease in circulating levels of erythropoietin causes neocytolysis through stimulation of reticuloendothelial phagocytosis (1,2). This could account for the larger doses of CERA required in the ONCE group.
- CERA may affect hepcidin levels through a mechanism other than via erythropoietic effects. The gradual decrease in ferritin levels seen in the ONCE group may be a result of the decrease in hepcidin-25 levels. However, the precise mechanisms underlying the discrepancies between the short-term and long-term effects of once-monthly CERA administration are unclear. Further studies are required to elucidate the long-term effects of CERA on iron metabolism.

## CONCLUSION

- Although stable Hb levels were maintained in both the ONCE and TWICE groups, a twice-monthly administration is more advantageous. A twice-monthly administration required a lesser dosage and continuous erythropoiesis is better achieved.

## REFERENCES

- Alfrey CP, Fishbane S. *Nephron Clin Pract* 2007;106:c149-56.
- Trial J, Rice L, Alfrey CP. *J Investig Med* 2001;49:335-345.

