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Original

Effect of Improvement of Secondary Hyperparathyroidism Using Cinacalcet on Renal Anemia

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Objective: Secondary hyperparathyroidism (SHPT) is known to inhibit the erythropoiesis. To determine the effect of cinacalcet treatment on renal anemia, we investigated the response to erythropoiesis-stimulating agents (ESA) in hemodialysis patients started on cinacalcet. **Methods:** Eighteen patients on hemodialysis treated with cinacalcet were enrolled in this study. We divided the patients according to the response of the i-PTH level to treatment. The "effective" group was defined as the group in which the serum i-PTH level decreased to below 300 pg/ml, the "non-effective group" was above 300 pg/ml at 4 months after the initiation of cinacalcet. We compared serum levels of c-reactive protein (CRP), iron (Fe), the total iron binding capacity (TIBC), ferritin and hemoglobin before and at 4 months after the start of cinacalcet therapy. Darbepoetin Alfa was used as the ESA. We also compared the required dose of ESA. **Results:** Twelve patients (66.7%) were in the "effective" group. Four months after the start of cinacalcet therapy, the serum PTH level fell from 777 ± 292 to 200 ± 68 pg/dl (p=0.002), the mean dose of darbepoetin alfa (DPO) decreased from 28.3 ± 15.9 to 16.9 ± 15.8 μg/week (p=0.027), nonetheless, no significant difference was observed in relation to the hemoglobin level (10.2 ± 1.2 to 10.6 ± 0.9 g/dl) in the "effective" group. In the "non-effective" group, there were no statistically significant changes in the serum levels of i-PTH, or hemoglobin, or the dose of DPO. There were no changes in the serum level of CRP, ferritin or the Fe saturation in both groups. **Conclusions:** Improvement of SHPT using cinacalcet may effective in increasing the response to ESA in renal anemia.

Key words: anemia, calcimimetic, cinacalcet, hyperparathyroidism, parathyroid hormone

Introduction

Anemia is a common disorder in dialysis patients. Improvement of the quality of life of these patients can be achieved with the use of erythropoiesis-stimulating agents (ESA). However, factors exist in dialysis patients that contribute to the hyporesponsiveness to erythropoietin[1]. Secondary hyperparathyroidism (SHPT) is usually listed as one of the possible reasons for the impaired response to ESA in patients with chronic kidney disease[2]. SHPT is a common complication in patients with chronic kidney disease and is known to induce bone marrow fibrosis, impairment of erythropoiesis[3] and inhibition of endogenous production of erythropoietin[4]. On the other hand, the calcimimetic drug cinacalcet, which increases the sensitivity of the parathyroid calcium-sensing receptors to calcium, is a newly introduced drug for the treatment of SHPT in patients with chronic kidney disease[5]. Cinacalcet has been available since January 2008 in Japan.

To determine the effect of cinacalcet treatment on renal anemia, we investigated the response to ESA administered for the treatment of anemia in hemodialysis patients started on cinacalcet therapy

for the treatment of SHPT.

Subjects and Methods

Eighteen patients on hemodialysis therapy treated with cinacalcet at Sangenjaya Hospital from February 2008 to November 2008 were enrolled in this study.

Each hemodialysis therapy was performed for 4-5 hours and calcium (Ca) concentration of dialysis fluid was 2.5 mmol/*l*. Cinacalcets were started at the dose of 25 mg/dl for the patients whose intact parathyroid hormone (i-PTH) level remained above 300 pg/dl. The patients were advised to take the drug just before the start of the hemodialysis session on the hemodialysis days and at approximately the same time also on non-hemodialysis days.

The background data of the study participants (age, gender, duration of hemodialysis, primary cause of end-stage kidney disease (ESKD)) were recorded. All the blood samples were obtained before the first dialysis session of the week. Serum levels of i-PTH, albumin, Ca, phosphorus (P), alkaline phoshatase (ALP), c-reactive protein (CRP), iron (Fe), the total iron binding capacity (TIBC), ferritin and hemoglobin were measured before and at 4 months after the start of cinacalcet therapy. Routine chemistry profiles were determined by standard methods. Fe saturation was calculated as Fe divided by TIBC. Ca concentration was corrected for albumin concentration by using the following formula[6].

Corrected Ca (mg/dl)=measured serum Ca (mg/dl) + 0.8× [4−serum albumin (g/dl)]

We divided the patients according to the response of the i-PTH level to treatment and compared the required dose of ESA before and after the start of cinacalcet therapy. The recommended serum level of i-PTH in the K/DOQI guideline is 150-300 pg/ml[7], therefore, the "effective" group was defined as the group in which the serum i-PTH level decreased to below 300 pg/ml at 4 months of the initiation of cinacalcet therapy. The "non-effective" group was defined as the group in which the serum i-PTH level remained above 300 pg/ml at 4 months after the initiation of cinacalcet therapy.

We regulated the dose of vitamin D and phosphate binder to achieve the level recommended by the Japanese Society of Dialysis Therapy guideline (corrected Ca 8.4-10.0 mg/dl and P 3.5-6.0 mg/dl)[8]. Darbepoetin alfa (DPO) was used as the ESA. We use DPO to keep hemoglobin level over 10-11 g/dl and Fe supplement was used intravenously to keep Fe saturation above 20%. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Mann−Whitney's U test was used to compare variables between "effective" group and "non-effective" group. Wilcoxon signed-ranks test was used to compare variables between before and 4 months after the therapy. The chi-square or Fisher's exact probability test was applied for categorical data. Data are presented as the means ± SD. A probability value of less than 0.05 was considered to denote significant difference. All the statistical calculations were performed using Stat View SE.

Results

Table 1 shows the background characteristics of the study participants, such as gender, the age, duration of hemodialysis and the primary cause of the ESKD.

The mean age was 64.3 ± 9.7 years, and the mean duration of hemodialysis, 21.9 ± 9.5 years. Out of the 18 patients, 11 were male (61.1%). The most prevalent cause of the ESKD was chronic glomerulonephritis (77.8%). There were 12 patients (66.7%) in the "effective" group. The age, duration of hemodialysis, gender and cause of ESKD did not differ significantly between the "effective" group and the "non-effective" group.

Table 2 shows the changes in the values of the various parameters examined and the ESA dose in the "effective" group. Four months after the start of cinacalcet therapy, the serum PTH level fell from 777 ± 292 to 200 ± 68 pg/ml (p=0.002). The serum level of ALP also decreased from 360 ± 138 to 282 ± 114 IU/*l* (p=0.009). No significant difference between the values measured before and after the start of treatment was observed in relation to the hemoglobin level (10.2 ± 1.2 to 10.6 ± 0.9 g dl). Nonetheless, the mean dose of DPO decreased from 28.3 ± 15.9 to 16.9 ± 15.8 μg/week (p=0.027) in the "effective" group. There were no changes in the se-

Table 1 Background characteristics of the study participants

Characteristic	Whole patients	Effective group	Non-effective group	p value
Number (Male/Female)	18 (11/7)	12 (7/5)	6 (4/2)	NS
Age (years)	64.3 ± 9.7	66.5 ± 7.4	59.9 ± 12.8	NS
Duration of hemodialysis (years)	21.9 ± 9.5	23.8 ± 9.0	18.4 ± 10.3	NS
Primary cause of ESKD, n (%)				
Chronic glomerulonephritis	14 (77.8)	10 (83.3)	4 (66.7)	NS
Diabetic nephropathy	2 (11.1)	0 (0)	2 (33.3)	NS
Nephrosclerosis	1 (5.6)	1 (8.3)	0 (0)	NS
Unknown	1 (5.6)	1 (8.3)	0 (0)	NS
Phosphate binder use, n (%)				
Calcium carbonate	7 (38.9)	5 (41.7)	2 (33.3)	NS
Sevelamer hydrochoride	6 (33.3)	4 (33.3)	2 (33.3)	NS
Both	5 (27.8)	3 (25.0)	2 (33.3)	NS
Vitamin D use, n (%)	18 (100)	12 (100)	6 (100)	NS

ESKD: end-stage kidney disease.

Table 2 Changes in the values of the various parameters examined and the erythropoietic-stimulating agents dose in the "effective" group

	Before	4 months after the therapy	p value
i-PTH (pg/ml)	777 ± 292	200 ± 68	0.002
Albumin (g/dl)	3.9 ± 0.2	3.8 ± 0.3	NS
Corrected calcium (mg/dl)	10.0 ± 0.5	9.9 ± 0.5	NS
Phosphorus (mg/dl)	5.9 ± 1.0	5.2 ± 0.9	NS
Alkaline phosphatase (IU/*l*)	360 ± 138	282 ± 114	0.009
C-reactive protein (mg/dl)	0.36 ± 0.43	0.27 ± 0.21	NS
Fe saturation (%)	25.3 ± 9.8	22.9 ± 7.8	NS
Ferritin (ng/ml)	212 ± 274	197 ± 181	NS
Hemoglobin (g/dl)	10.2 ± 1.2	10.6 ± 0.9	NS
Dose of phosphate binder			
Calcium carbonate (g/day)	1.7 ± 1.6	1.8 ± 1.5	NS
Sevelamer hydrochoride (g/day)	1.8 ± 2.0	1.4 ± 2.0	NS
Dose of vitamin D (i.v.)			
Maxacalcitol (μg/week, n=9)	18.3 ± 8.8	24.4 ± 16.1	NS
Calcitriol (μg/week, n=3)	1.5, 1.5, 4.5	1.5, 1.5, 3.0	
Dose of DPO (μg/week)	28.3 ± 15.9	16.9 ± 15.8	0.027

i-PTH: intact parathyroid hormone, DPO: Darbepoetin alfa.

rum level of albumin (3.9 ± 0.2 to 3.8 ± 0.3 g/dl) or CRP (0.36 ± 0.43 to 0.27 ± 0.21 mg/dl) or the Fe saturation (25.3 ± 9.8 to 22.9 ± 7.8%). The mean dose of cinacalcet was 25.5 ± 10.8 mg/day in the "effective" group 4 months after the start of cinacalcet therapy.

In the "non-effective" group, there were no statistically significant changes in the serum levels of i-PTH (1,039 ± 289 to 947 ± 215 pg/ml), ALP (415 ± 149 to 461 ± 198 IU/*l*), CRP (0.20 ± 0.08 to 0.30 ± 0.27 mg/dl), the Fe saturation (19.4 ± 12.0 to 20.4 ± 7.9%), hemoglobin (10.1 ± 1.4 to 10.1 ± 1.4 g/dl) or the dose of DPO (26.7 ± 20.7 to 28.3 ± 22.3 μg/week). The mean dose of cinacalcet was 45.8 ± 18.8 mg/day in the "non-effective" group 4 months after the start of cinacalcet therapy.

Discussion

SHPT is known to induce bone marrow fibrosis and impairment of erythropoiesis[3] and excess parathyroid hormone has been reported to exert direct inhibitory effects on bone marrow erythropoiesis[4,9,10]. Some studies have suggested that parathyroid hormone shortens the erythrocyte survival[11,12]. Several studies have reported improvement of ane-

mia after surgical treatment for SHPT[13)~16)]. Ureña et al. observed a significant increase of the mean serum erthyropoietin levels in dialysis patients by 2 weeks after surgical parathroidectomy[13)]. A single-center, uncontrolled study reported higher serum erythropoietin levels at 3-12 months after parathyroidectomy in some out of a total of 29 maintenance hemodialysis patients, although the required doses of erythropoietic agents did not decline[14)]. In a multicenter trial, Coen et al. described the long-term benefit of enhanced erythropoiesis after parathyroidectomy in patients undergoing long-term dialysis[15)]. Chow et al. reported significant elevation of the hemoglobin level at 6 months after parathyroidectomy in patients with severe SHPT[16)]. Al-Hilali et al. reported that HPT is a predictor of rHuEPO hyporesponsiveness in dialysis patients[17)].

Calcimimetic agents, such as cinacalcet, have been developed for controlling PTH secretion; these agents act by enhancing the sensitivity of the parathyroid calcium receptors to extracellular calcium ions[18)]. Because of its unique mechanism of action cinacalcet may represent a promising new medical therapeutic alternative for SHPT in Japanese patients undergoing hemodialysis therapy, just as in Western populations[19)].

In our study also, cinacalcet was found to be highly effective in controlling SHPT. There have been no reports of the effect of cinacalcet on renal anemia. In this study, 4 months after the start of cinacalcet therapy, while no significant change of the hemoglobin was observed, significant decrease of the required ESA dose was observed in the "effective" group. Other reported predictors of a poor response to ESA besides SHPT include functional iron deficiency, blood loss, aluminum toxicity, concomitant administration of other drugs, infections and inflammatory conditions[17)]. No significant changes in parameters related to anemia, such as the Fe saturation, ferritin, or serum CRP, were observed in the "effective" group. Neither significant decrease in the hemoglobin level nor significant change in the required dose of ESA was observed in the "non-effective" group.

Even though the small number of subjects, this is the first article which suggest the effect of cinacalcet on renal anemia. It is not clear whether cinacalcet acts directly on bone marrow and improve the sensibility of ESA or cinacalcet suppress the production of PTH and acts on bone marrow indirectly. But reduction in the required dose of ESA was noted only in the "effective" group, which suggested that treatment with cinacalcet might improve the response to ESA by controlling the SHPT.

The limitation of study is small number of subject and more trials with large scale are needed to corroborate the effects of cinacalcet on renal anemia.

Conclusions

Improvement of SHPT using cinacalcet may effective for the response to ESA on renal anemia.

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シナカルセトの二次性副甲状腺機能亢進症改善が腎性貧血に及ぼす効果

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〔目的〕エリスロポエチン抵抗性貧血の原因の一つとして，二次性副甲状腺機能亢進症が知られている．シナカルセトは2008年に日本で使用可能となった二次性副甲状腺機能亢進症に対する新しい薬剤である．今回，シナカルセトの貧血に対する効果を検討した．〔方法〕シナカルセトを使用した18名を対象とし，開始4ヵ月後の血清i-PTH 300 pg/ml以下をeffective群，それ以上をnon-effective群と分け，ヘモグロビン，鉄飽和率，フェリチン，c-reactive protein(CRP)を使用前と4ヵ月後で比較した．赤血球生成刺激剤はダルベポエチン（DPO）を使用し，その投与量も比較した．〔結果〕12名（66.7%）がeffective群で，シナカルセト開始4ヵ月後に血清i-PTH値は777±292から200±68 pg/dl（p=0.002）に，DPOの使用量は28.3±15.9から16.9±15.8 μg/week（p=0.027）に低下したが，ヘモグロビン値は10.2±1.2から10.6±0.9 g/dlと変化なかった．non-effective群ではヘモグロビン値10.1±1.4から10.1±1.4 g/dlと変化なく，DPOの使用量は26.7±20.7から28.3±22.3 μg/weekと低下を認めなかった．両群とも鉄飽和率，フェリチン，CRPに変化を認めなかった．〔結論〕シナカルセトは二次性副甲状腺機能亢進症を改善することにより貧血を改善する可能性がある．