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Long-term treatment of evocalcet in hemodialysis patients with secondary hyperparathyroidism: a five-year prospective cohort study in 147 Japanese patients

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Abstract

Background Cinacalcet hydrochloride (cinacalcet), an oral calcimimetics for secondary hyperparathyroidism (SHPT), has been widely used worldwide. In contrast, evocalcet, an improved derivative of cinacalcet, was approved only in Japan in 2018 and has not received approval overseas. Consequently, the available information on the long-term use of evocalcet relies solely on data from a 1-year dosing phase III clinical trial.

Methods The cohort of 147 chronic hemodialysis patients on cinacalcet to manage SHPT was simultaneously switched to the lowest dose of evocalcet (1 mg/day) and prospectively followed for 5 years in real-world clinical settings.

Results The median evocalcet dose was 1 mg/day at 0.5 years, and it remained stable at 2 mg/day from 1 to 5 years after the prescription initiation. Additionally, serum parathyroid hormone, corrected calcium, phosphorus, and total alkaline phosphatase levels showed no significant changes compared with their levels at the time of the switch and remained stable over the 5-year period. Furthermore, no adverse events related to vital signs, serum biochemistries, or upper gastrointestinal symptoms were observed in patients during treatment with evocalcet.

Conclusions These results suggest that only a small number of patients require higher evocalcet doses, and that SHPT can be effectively managed with low-dose evocalcet for 5 years. Additionally, the drug's long-term safety has been confirmed.

Trial registration: name of the registry: Prescription change from cinacalcet hydrochloride to evocalcet in hemodialysis patients. Trial registration number R000041815. Trial registration UMIN000036702. Registered 10 May 2019—retrospectively registered. https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_his_list.cgi?recptno=R000041815.

Keywords Secondary hyperparathyroidism, Evocalcet, Cinacalcet hydrochloride, Evocalcet dosage, Serum parathyroid hormone levels

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Background

Secondary hyperparathyroidism (SHPT) is one of the major complications in chronic hemodialysis patients [1, 2]. Persistent high parathyroid hormone (PTH) secretion increases bone turnover, resulting in bone fractures and vascular calcification, which decrease the patient's quality



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of life and prognosis. Therefore, serum PTH levels should be appropriately controlled [3, 4].

Compounds that act on the calcium-sensing receptor (CaSR) on the parathyroid cell surface and inhibit PTH secretion are termed calcimimetics [5, 6]. The first-generation calcimimetic drug, cinacalcet hydrochloride (cinacalcet, Regpara Tablets®), caused a paradigm shift in the treatment of SHPT because, unlike vitamin D receptor activators (VDRAs), it can reduce both calcium (Ca) and phosphorus (P) levels in the blood [6–9]. However, cinacalcet has limiting side effects, particularly upper gastrointestinal (GI) symptoms such as nausea and vomiting, which lead to low adherence and insufficient dosage [10]. Additionally, it presents certain metabolic drawbacks, such as low bioavailability, primarily being metabolized by CYP3A4, and inhibiting CYP2D6 [11, 12]. In 2018, a new oral calcimimetic product, evocalcet (Orkedia Tablets®), was launched only in Japan to address these limitations and provide improved treatment options [12, 13]. Consequently, the available information on the long-term use of evocalcet relies solely on data from a 1-year dosing phase III clinical trial [14].

We have already reported in Japanese on the progress of 147 chronic hemodialysis patients who were initially treated with cinacalcet for their SHPT and subsequently switched to evocalcet, with follow-up assessments conducted up to 8 months [15] and 1 year later [16]. This study now presents prospective observations for the same cohort, spanning up to 5 years.

Subjects and methods

Subjects

Of the 539 chronic hemodialysis patients at our dialysis center (Heisei Hidaka Clinic, Takasaki, Gunma, Japan), 147 patients who had been on a stable prescription of cinacalcet for the past 3 months were included in this study.

Methods

In September 2018 (baseline, BL), 147 patients who were initially treated with cinacalcet were simultaneously switched to the lowest dose of evocalcet (1 mg/day). The dose was subsequently adjusted at approximately monthly intervals to control serum intact PTH (i-PTH) levels according to the guidelines proposed by the Japanese Society for Dialysis Therapy (JSDT) [3].

For the patients prescribed evocalcet, dose, serum i-PTH, corrected Ca (cCa), P, and total alkaline phosphatase (ALP) levels were prospectively observed for 5 years until September 2023. Since the ALP measurement method was changed from the JSCC (Japan Society of Clinical Chemistry) method to the IFCC (International

Federation of Clinical Chemistry and Laboratory Medicine) method during the observation period, the value obtained by the IFCC method was multiplied by 2.84 to convert to the value determined by the JSCC method.

These evocalcet dosage and serum parameters were analyzed every 6 months over time for 5 years and statistically compared with the values at BL. Additionally, the prescription status of other intravenous VDRAs and calcimimetics (etelcalcetide hydrochloride; etelcalcetide) in patients who had withdrawn from evocalcet in this cohort was analyzed. Furthermore, regarding serum i-PTH levels, we calculated the percentage of patients within the management target range (60–240 pg/mL) recommended by the JSDT [3].

Statistical analyses

After normality was determined by the Shapiro–Wilk test, normally distributed data were expressed as mean ± standard deviation, while non-normally distributed data were expressed as median (first quartile –third quartile). Repeated tests of paired samples were performed using one-way analysis of variance (with Bonferroni adjustment) or Friedman test, as appropriate. Statistical analysis was conducted using SPSS software (version 21, IBM, NY). *P*-values less than 0.05, based on two-sided calculations, were considered statistically significant.

Research ethics

This study was conducted under the approval of the Hidaka Hospital Medical Ethics Committee (approved no. 244; UMIN000036702) and in the spirit of the “Declaration of Helsinki.” The analysis and reporting were conducted in compliance with the “Guidelines for Protecting Patient Privacy in the Society Meeting Presentations and Medical Papers, including Case Reports” by the JSDT.

Results

Patient characteristics

Table 1 presents the main characteristics, dialysis conditions, and prescription statuses of drugs related to chronic kidney disease–mineral and bone disorder (CKD–MBD) in the cohort of 147 patients at BL. The median dose of cinacalcet immediately before the switch was 25 (12.5–37.5) mg/day. Some of this data have been previously reported [15].

Evocalcet dosage

All patients were switched from cinacalcet to 1 mg/day of evocalcet at the BL. Subsequently, evocalcet doses were slightly increased, with the median reaching 2 mg/day after 1 year and remaining at a median of 2 mg/day

Table 1 Patient characteristics at BL

Characteristic	Unit	All patients n = 147
Patient background		
Gender (male)	n (%)	105 (71.4)
Age	Years	67.2 (61.4–71.8)
Dialysis history	Years	10.3 (5.6–17.1)
DW	kg	60.8 ± 13.5
Primary cause of ESRD		
CGN	n (%)	69 (46.9)
DM	n (%)	51 (34.7)
PKD	n (%)	11 (7.5)
NC	n (%)	5 (3.4)
RPGN	n (%)	2 (1.4)
Others - Unknown	n (%)	9 (6.1)
Dialysis condition		
3 times/week	n (%)	147 (100)
Time (4 h)	n (%)	130 (88.4)
Blood flow	mL/min	220 (200–250)
Modality (hemodialysis)	n (%)	81 (55.1)
(hemodiafiltration)	n (%)	66 (44.9)
Dialysate Ca (2.5 mEq/L)	n (%)	98 (66.7)
(3.0 mEq/L)	n (%)	49 (33.3)
Blood chemistries		
cCa	mg/dL	8.75 ± 0.57
P	mg/dL	5.10 ± 1.13
Mg	mg/dL	2.44 ± 0.39
i-PTH	pg/mL	142 (92–230)
ALP	U/L	263 (212–344)
Alb	g/dL	3.7 (3.4–3.9)
Prescription status		
Cinacalcet dose	mg/day	25 (12.5–37.5)
Phosphate binder user	n (%)	128 (87.1)
Ca carbonate user	n (%)	97 (66.0)
Dose	g/day	2.5 (1.5–3.0)
Oral VDRA user	n (%)	31 (21.1)
Alfacalcidol dose	µg/day	0.5 (0.25–0.5)
Calcitriol dose	µg/day	0.25 (0.25–0.25)
Intravenous VDRA user	n (%)	96 (65.3)
Dose	µg/month	4.5 (2.5–6.5)

BL baseline, DW dry weight, ESRD end-stage renal disease, CGN chronic glomerulonephritis, DM diabetes mellitus, PKD polycystic kidney disease, NC nephrocalcinosis, RPGN rapidly progressive glomerulonephritis, cCa corrected calcium, P phosphorus, Mg magnesium, i-PTH intact parathyroid hormone, ALP alkaline phosphatase, Alb albumin, Ca calcium, VDRA vitamin D receptor activator

until 5 years (Fig. 1). The highest dose observed during the observation period was 10 mg/day in 1 patient at 1.5 years, followed by 9 mg/day in 1 patient, 8 mg/day in 8 patients, and 7 mg/day in 12 patients.

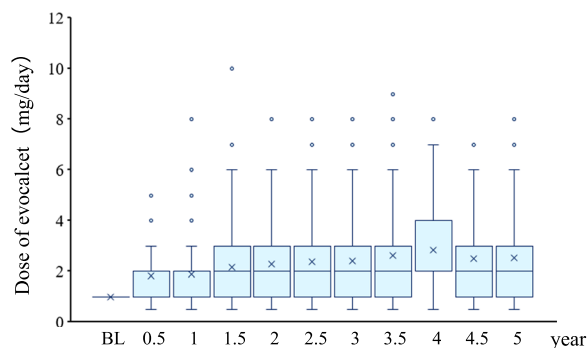


Fig. 1 Evocalcet dosage after switching from cinacalcet. The median evocalcet dose was 1 mg/day at 0.5 years and was maintained at 2 mg/day from 1 to 5 years after the switch. The number of patients receiving evocalcet at 1, 3, and 5 years is presented in Table 2. x mean values

Serum chemistries

Serum i-PTH levels during treatment with cinacalcet and at 6-month intervals for up to 5 years after switching to evocalcet are shown in Fig. 2, serum cCa and P levels in Fig. 3, and total ALP levels in Fig. 4. Comparing these four serum values with their respective BL levels, no statistically significant differences were observed at any time point. Additionally, the percentages of patients within the PTH control target range (60–240 pg/mL), below the lower target (< 60 pg/mL), and above the upper target (> 240 pg/mL) were also not substantially different over the 5-year period compared with when cinacalcet was prescribed (Fig. 5).

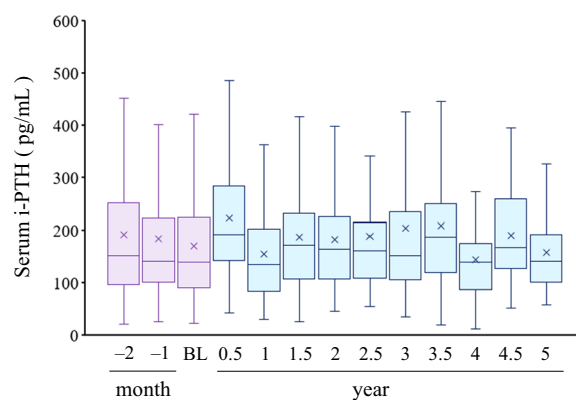


Fig. 2 Serum i-PTH levels before and after switching from cinacalcet to evocalcet. Purple columns represent values under cinacalcet treatment, while blue ones represent values under evocalcet treatment. No statistically significant differences were observed at any time point compared with the BL values. i-PTH intact parathyroid hormone, BL baseline, x mean values

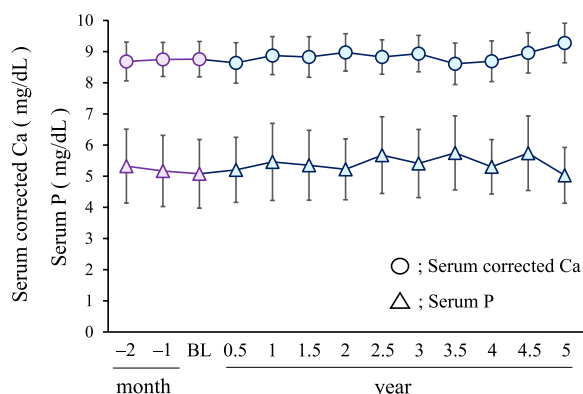


Fig. 3 Serum corrected Ca (○) and P (△) levels before and after switching from cinacalcet to evocalcet. Purple circles and triangles represent values under cinacalcet treatment, while blue ones represent values under evocalcet treatment. No statistically significant differences were found at any time point compared with the respective BL values. *Ca* calcium, *P* phosphorus, *BL* baseline, *x* mean values

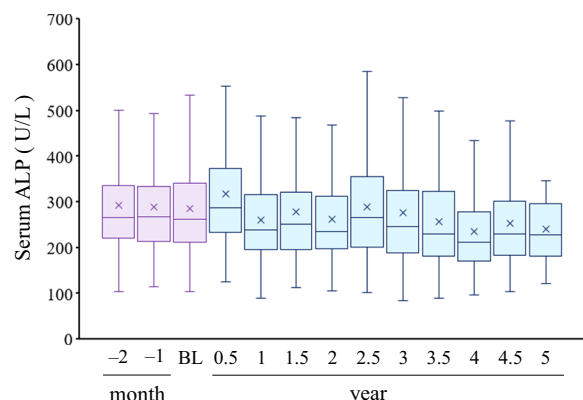


Fig. 4 Serum total ALP levels before and after switching from cinacalcet to evocalcet. Purple columns represent values under cinacalcet treatment, while blue ones represent values under evocalcet treatment. No statistically significant differences were observed at any time point compared with the BL values. *ALP* alkaline phosphatase, *BL* baseline, *x* mean values

Prescription persistence rate of evocalcet

In this cohort of 147 patients who switched from cinacalcet to evocalcet, the number of patients undergoing hemodialysis at our hospital gradually decreased due to hospital transfers or death: 133 (90.5%) at 1 year, 100 (68.0%) at 3 years, and 76 (51.7%) at 5 years (Table 2). Simultaneously, the number of patients prescribed evocalcet gradually decreased: 115 at 1 year, 68 at 3 years, and 42 at 5 years. Consequently, the prescription persistence rate of evocalcet was calculated as follows: 86.5% at 1 year, 68.0% at 3 years, and 55.3% at 5 years. However, no vital signs, serum biochemistries, or upper GI-related

adverse events were observed in patients during evocalcet treatment that would necessitate discontinuation of the evocalcet prescription or a switch to other drugs for SHPT.

Intravenous drugs for SHPT

Patients prescribed intravenous drugs for SHPT (VDRAs and etelcalcetide), from BL to 5 years later, in this cohort are presented in Table 2. The number of patients prescribed evocalcet gradually decreased, while the number of patients prescribed maxacalcitol or etelcalcetide gradually increased. Additionally, there were several patients who were not prescribed either evocalcet or intravenous drugs for SHPT.

Discussion

This is the first report on the long-term use of evocalcet in real-world clinical settings. With a median dose of 2 mg/day of evocalcet, serum i-PTH, cCa, P, and total ALP levels remained stable for 4 years without dose escalation or clinically problematic side effects.

The noninferiority of evocalcet to cinacalcet in suppressing serum i-PTH levels, along with fewer GI-related adverse events, has been robustly demonstrated in a phase 3, randomized, double-blind, double-dummy clinical trial [17]. In our present cohort study, we also reported using a questionnaire that switching from cinacalcet to evocalcet significantly reduced the number of patients complaining of GI-related symptoms [15]. Additionally, we successfully discontinued the prescription of GI-promoting medications in some patients after switching [15]. However, it is important to note a significant limitation in our study; specifically, the absence of a control group continuing to receive the cinacalcet prescription. Therefore, it is not possible to make a rigorous comparison of the efficacy and safety of cinacalcet and evocalcet.

Several factors may explain why evocalcet was able to control PTH levels for a long time without requiring dose escalation. First, some patients whose PTH was not adequately suppressed with low-dose evocalcet had been switched to etelcalcetide prescriptions rather than increasing their doses to medium or high levels. The maximum dose of evocalcet is 12 mg/day. However, due to the availability of only two formulations (1 mg and 2 mg tablets), a pill burden occurs when prescribing higher doses. In fact, during the 5-year study period, only a few patients were prescribed more than 8 mg (i.e., 4 pills of 2 mg tablet), and at the end of the 5-year period, 22 patients had switched to intravenous etelcalcetide to avoid this pill burden. We have previously reported, based on medical information data, that the prescription persistence rate for cinacalcet treatment at 3 years was

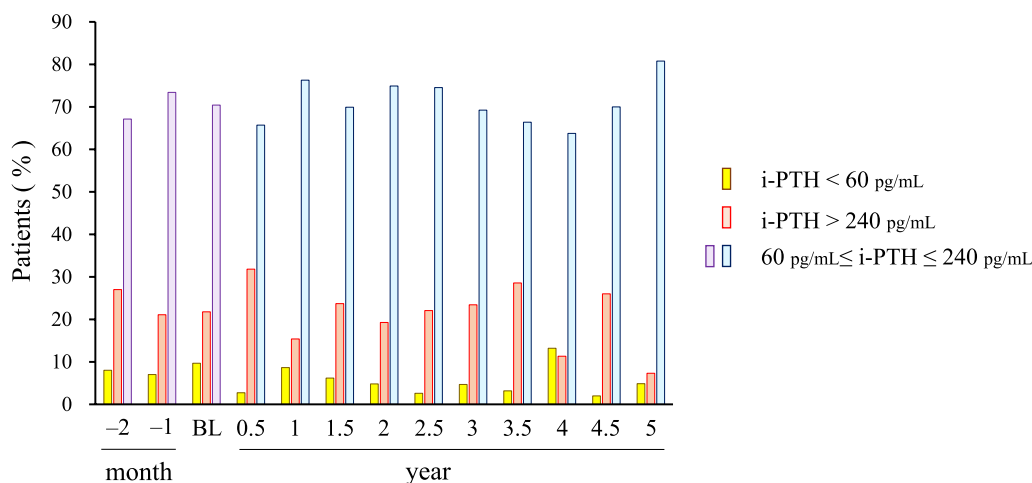


Fig. 5 Percentage of patients within PTH control targets before and after switching from cinacalcet to evocalcet. Purple columns represent patients with i-PTH within target values under cinacalcet treatment, while blue ones represent those with i-PTH within target values under evocalcet treatment. Yellow columns represent patients with i-PTH < 60 pg/mL, while orange ones represent those with i-PTH > 240 pg/mL. *i-PTH* intact parathyroid hormone, *BL* baseline

Table 2 Prescription persistence rate of evocalcet and prescription status of intravenous drugs for SHPT

Evocalcet and intravenous drugs for SHPT	BL n = 147	1 year n = 133	3 year n = 100	5 year n = 76
Evocalcet	n (%) 147 (100)	115 (86.5)	68 (68.0)	42 (55.3)
Intravenous calcitriol	n (%) 54 (36.7)	51 (38.3)	35 (35.0)	25 (32.9)
Maxacalcitol	n (%) 42 (28.6)	47 (35.3)	41 (41.0)	32 (42.1)
Etelcalcetide hydrochloride	n (%) 0 (0)	7 (5.3)	15 (15.0)	22 (28.9)
None	n (%) 0 (0)	4 (3.0)	7 (7.0)	3 (3.9)

SHPT secondary hyperparathyroidism, BL baseline

approximately 75% in Japan [18]. This result was obtained before the introduction of etelcalcetide to the market in Japan. Therefore, the current 3-year prescription persistence rate (68.0%) is considered to be somewhat lower than this. As supplementary information, Orkedia Tablets® 4 mg were launched in November 2023, with an expected improvement in prescription persistence due to reduced pill burden.

Second, the bioavailability of evocalcet is significantly higher than that of cinacalcet [12, 13], which means there were no patients with difficulty achieving adequate blood concentrations [19]. As a result, all patients were able to maintain effective blood concentrations even at low doses.

Third, because evocalcet has a potent inhibitory effect on parathyroid cell proliferation [20], it may have prevented the development of parathyroid hyperplasia during the treatment period. It is worth noting that the

administration of cinacalcet to hemodialysis patients has been reported to lead to a reduction in parathyroid gland volumes [21, 22]. Due to the positive correlation between blood PTH levels and total parathyroid gland volumes [23], it is likely that evocalcet not only suppressed PTH secretion acutely but also maintained low PTH levels by inhibiting parathyroid cell proliferation and preserving a small gland size. Additionally, in our present cohort, seven patients were not prescribed evocalcet, intravenous VDRA, or etelcalcetide even after 3 years. It is interesting to consider the possibility that these patients may have experienced complete regression of hyperplastic parathyroid glands.

Finally, cinacalcet can increase the number of CaSRs on the surface of parathyroid cell membranes through a pharmacological chaperone action [24–26]. Since evocalcet and cinacalcet bind to the same site on the CaSRs [27], it is assumed that the CaSRs on the surface of parathyroid cell membranes would be either maintained or increased under evocalcet treatment, which may explain why the low dose remains effective.

Switching from cinacalcet to evocalcet did not further decrease i-PTH, nor did it markedly increase the percentage of patients within PTH control targets. Consequently, there was no marked change in serum cCa, P, or total ALP levels, which fluctuate with blood PTH levels, compared with the BL. The reason for the lack of further improvement in PTH may be that this cohort was already on cinacalcet for PTH control. Future studies should be conducted in patients who have not previously been prescribed any calcimimetics.

Conclusion

The present results indicate that SHPT can be managed for a long period of time under low-dose evocalcet use.

Abbreviations

ALP	Alkaline phosphatase
BL	Baseline
Ca	Calcium
CaSR	Calcium-sensing receptor
cCa	Corrected calcium
CKD-MBD	Chronic kidney disease–mineral and bone disorder
GI	Gastrointestinal
i-PTH	Intact parathyroid hormone
JSDT	Japanese Society for Dialysis Therapy
P	Phosphorus
PTH	Parathyroid hormone
SHPT	Secondary hyperparathyroidism
VDRAs	Vitamin D receptor activators

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Author contributions

N.N. designed and performed the study, analyzed the data, and wrote the manuscript. T.T. and K.I. reviewed and revised the manuscript, and T.O. is responsible for the final version of the manuscript. T.I., M.Y., Y.K., M.M., N.T., S.M., T.O., and K.I. were responsible for drug prescription for patients. K.I. and T.O. supervised the study. All the authors read and approved the final version of this manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Hidaka Hospital Medical Ethics Committee (approval number: 244). This study took place in a real clinical setting, and patient consent was obtained verbally when changing the prescription from cinacalcet to evocalcet.

Consent for publication

Consent for publication was obtained from all co-authors. Patient consent was not obtained due to the unfortunate circumstances where many patients had either passed away or been transferred to other hospitals.

Competing interests

N.N. has received consulting fees and lecture fees from Kyowa Kirin Co., Ltd. The other authors declare no conflict of interest.

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