Long-term effect of 1,25-dihydroxy-22-oxavitamin D₃ on secondary hyperparathyroidism in haemodialysis patients. One-year administration study

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Abstract

A trial on the long-term administration of 1,25-dihydroxy-22-oxavitamin D₃ (22-oxacalcitriol, OCT) was conducted among 124 patients with chronic renal failure on maintenance haemodialysis (HD) complicated with secondary hyperparathyroidism (2HPT). In the trial, OCT was administered three times weekly for 26 weeks subsequent to a 26-week pre-trial. As a result, intact-parathyroid hormone (PTH) levels fell significantly after the start of administration and, at the end of the trial, PTH was decreased by over 30% in 51.6% (64/124) of the patients, and the levels of bone metabolism markers such as alkaline phosphatase (ALP), bone ALP, and tartrate-resistant acid phosphatase (TRACP) were significantly decreased compared with those at the start of administration, suggesting a correction of high-turnover bone disease. Serum calcium (Ca) levels rose significantly following OCT administration, but were successfully maintained within a physiological level. Hypercalcaemia, which was diagnosed in 33.1% of patients, was found to resolve or ameliorate immediately after the withdrawal or dose reduction of OCT. OCT can be administered for as long as 1 year without any major problems other than hypercalcaemia. The final doses ranged from 2.5 to 20.0 µg/HD, and the optimal dose varied among patients depending on the intact-PTH and adjusted serum Ca levels. These results suggest that OCT is a highly effective drug for the suppression of PTH levels in 2HPT, and is an overall safe drug if the dosage is adjusted for serum Ca and intact-PTH levels. This study confirmed that the long-term (1-year) administration of OCT is very useful for the treatment of 2HPT.

Keywords: haemodialysis; long-term administration; OCT; 22-oxacalcitriol; parathyroid hormone; secondary hyperparathyroidism

Introduction

Typical complications of long-term haemodialysis (HD) include renal osteodystrophy, and a remarkable progress has been made in the therapy for this complication since the practical use of active vitamin D₃ derivatives was started in the 1980s. However, there are limitations to the medical treatment of advanced secondary hyperparathyroidism (2HPT) to adequately suppress parathyroid hormone (PTH) levels while avoiding hypercalcaemia. Although surgical therapies such as parathyroidectomy and percutaneous ethanol injection therapy (PEIT) have been performed [1], a more effective therapeutic tool is needed [2]. 1,25-Dihydroxy-22-oxavitamin D₃ (22-oxacalcitriol, OCT, generic name: maxacalcitol, INN) is a derivative of 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃, calcitriol), which was recently synthesized by Chugai Pharmaceutical Co., Ltd. This drug was made in order to separate the PTH-synthesizing and -secreting, cell growth-inhibiting, and cell differentiation-inducing
actions of calcitriol from the serum calcium (Ca)-elevating action [3–5].

A comparative, double-blind, placebo-controlled study of a four-dose regimen of OCT showed a dose-dependent suppressive effect on PTH in patients with 2HPT, and led to the conclusion that the initial optimal dose was 10 μg/HD [6]. However, as the severity of 2HPT varied greatly among patients, it appeared essential to adjust the dosage based on patient characteristics and concurrent therapies. In addition, as the administration period of OCT is assumed to be long, dosage adjustment based on the PTH, bone metabolic markers, serum Ca and phosphorus (P) levels seemed to be very important.

Thus, in order to examine the safety and efficacy of the long-term administration of OCT and to determine the effective dose in suppressing and maintaining PTH levels according to the severity of 2HPT, a year-long trial of OCT administration was conducted in which patients were administered OCT for as long as 26 weeks [7] and for an additional 26 weeks if they required a continuous treatment of OCT.

Materials and methods

Study protocol

Patients aged 20 years or older with stable chronic renal failure, who were on HD three times weekly and met the following criteria, were enrolled in this study. HD patients who: (i) had high-sensitivity mid-terminal PTH (HS-PTH) ≥20 000 pg/ml, a serum Ca adjusted for albumin [8] between 9.0 and 11.0 mg/dl, and serum P ≤7.0 mg/dl after the longest inter-dialytic interval 2 weeks before the start of a 26-week pre-trial; (ii) completed the 26-week pre-trial without experiencing severe adverse effects; and (iii) were judged to require further treatment with OCT. However, patients with severe cardiac and hepatic dysfunction, pregnant or lactating women, possibly pregnant women, patients with special conditions such as drug allergy, evident aluminum (Al) accumulation, with primary HPT, with serious complications such as malignant neoplasm and severe infections, and patients who were judged to be unsuitable for the trial by attending physicians were excluded from the study. An OCT injection containing 2.5, 5, or 10 μg/ampoule (1 ml) was used for this study.

Based on intact-PTH levels 2 weeks before the start of administration, the pre-trial was started with an initial dose of 10 μg/HD (for patients with basal intact PTH ≥500 pg/ml) or 5 μg/HD (for those with intact-PTH <500 pg/ml), followed by a dose between 15 and 2.5 μg three times weekly (if doses ≤2.5 μg/HD were judged to be necessary, adjustments were made by reducing the frequency of dosage) for 26 weeks according to the decreases in serum intact-PTH levels and the increases in adjusted serum Ca levels. Following observation for 2 weeks after completion of the pre-trial, this trial was started with the similar dose used at the end of the pre-trial. In prescribing dosage, doses were changed as necessary, monitoring decreases in serum intact-PTH levels and increases in adjusted serum Ca levels as in the pre-trial, except that, as the maximum dose of 5 μg/HD was not effective in several patients in the pre-trial, the maximum dose was increased to 20 μg/HD.

The total period of administration was 52 weeks (1 year), consisting of a 26-week pre-trial and an additional 26-week this trial. OCT was injected slowly into the venous blood of the HD circuit immediately prior to completion of each HD.

If the adjusted serum Ca levels just before HD exceeded 11.5 mg/dl in the pre-trial or this trial, OCT was interrupted briefly and was resumed after it was confirmed that the adjusted serum Ca levels had fallen below 11.0 mg/dl. If no elevation in adjusted Ca levels was observed, the dosage could be increased by one level or more, but was adjusted so that intact-PTH levels did not fall below 150 pg/ml.

During the trial, the administration of other drugs that were considered to clearly influence Ca and bone metabolism, such as vitamin D preparations, vitamin K, calcitonin, iripilavone, sex hormones, adrenocortical hormones, immunosuppressants, and protein anabolic hormones, was prohibited. In addition, serum P levels were controlled through the administration of Ca salts, and the dosages of Ca salts were changed as necessary. As a rule, the conditions of HD, such as the dialysate Ca concentration, were not changed during the trial.

The levels of the following laboratory items were measured immediately before HD periodically during the trial: intact-PTH, HS-PTH, Ca, P, albumin, tartrate-resistant acid phosphatase (TRACP) and type-I collagen C-terminal pyridinoline cross-linked telopeptide (ICTP) as markers of bone resorption; alkaline phosphatase (ALP) as a marker of bone formation; markers of bone metabolism such as bone ALP, osteocalcin (BGP), and type-I collagen C-terminal propeptide (PICP); and three fractions of vitamin D, 1, 25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, and 25-hydroxyvitamin D. Bone mineral density (BMD) was measured by dual X-ray absorptiometry (DXA) if applicable.

Symptoms and abnormal laboratory findings either developing or that became aggravated after the start of OCT were treated as adverse events. If patients showed adjusted serum Ca levels >11.5 mg/dl after the start of OCT, they were managed as hypercalcaemic patients. In patients in whom creatine kinase (CK) rose by >50% compared with that on the day on which the pre-trial was begun, and if a causal relationship with OCT could not be ruled out, an electrocardiogram was performed.

This multi-institutional trial was conducted following examination and approval by the IRB at each institution.

Patients studied

The trial involved 124 patients (Table 1). Administration of OCT was discontinued in 10 patients during the trial: two patients by withdrawal of their consent; one patient due to the development of adverse events based on the judgment of the physician; four patients by developing an incidental disorder; one patient because of poor control of Ca and P levels; and two patients because of poor suppressive effect on PTH.

Statistical analysis

All patients who received even a single dose of OCT and presented any data were analysed. In consideration of the objective of the trial, a population of patients administered OCT for 1 year was also analysed. The rates of decrease in intact-PTH levels 12, 26, and 54 weeks after the initial drug administration or at discontinuation compared with intact-PTH levels on the day of the start of the pre-trial,
were assessed using a 5-rank scale: (1) markedly improved (a decrease of intact-PTH over 50% or maintenance below 200 pg/ml); (2) moderately improved (30%< PTH decrease <50%); (3) slightly improved (10%< PTH decrease <30%); (4) unchanged (PTH decrease <10%); and (5) aggravated (PTH increase of ≥10%). The individual degrees of PTH improvement were taken into account in the ranking, and the 95% confidence intervals of the improvement rates were calculated. For laboratory data, the mean ± standard error (SE) or the mean ± standard deviation (SD) was calculated; and changes from the start of pre-trial were compared using the Wilcoxon signed-rank test. P values of <5% (two-tailed) were considered significant. To accurately assess the direct effects of OCT on PTH secretion, intact-PTH levels were assessed if adjusted Ca levels were <11.5 mg/dl. If these levels were >11.5 mg/dl, they were traced back to the date of intact-PTH being <11.5 mg/dl to avoid the effect of hypercalcaemia on PTH suppression.

Results

The mean intact-PTH level was 821.0 ± 57.1 pg/ml (mean ± SE) at the start of the pre-trial, reached a plateau from 2 weeks after this trial, and then decreased to 504.3 ± 38.8 pg/ml at the end of this trial (Figure 1).

Table 2 shows the degree of PTH improvement in terms of the decrease rates of intact-PTH 12 and 26 weeks after the start and at the end or discontinuation of the trial. The rate of moderate or greater improvement 12 weeks after the start of the trial was as high as 62.1 (77/124), 52.5 (63/120) at 26 weeks, and 51.6% (64/124) at the end or discontinuation of the trial.

Patient characteristics and ranking of improvement rates of PTH showed that patients with an intact-PTH level of 500 pg/ml or higher (particularly those with a level of 1000 pg/ml or higher) and those with an adjusted serum Ca of <10.5 mg/dl at 2 weeks before the start of the pre-trial had a higher improvement rate. In contrast, patients with an intact-PTH level of <500 pg/ml or an adjusted serum Ca of 10.5 mg/dl or higher showed a lower improvement rate than the overall improvement rate (Table 3). Stratification for other factors, such as age, history of HD, and serum P level at entry, revealed no significant differences among factors (data not shown).

Figure 2 shows the mean weekly dosages and the distribution of dosage of OCT. At entry, based on intact-PTH levels, 77 patients were assigned to a 10 μg HD group, and 43 patients to a 5 μg HD group. At 4 weeks after the start and thereafter, the dosage was varied widely based on increases in adjusted serum Ca levels and decreases in intact-PTH levels: the final dose was increased or decreased compared with the initial dose in 22 patients (18.3%) and 67 patients (55.8%), respectively, and remained unchanged in 31 patients (25.8%).

The mean dose of 8.13 ± 0.23 μg (mean ± SE) per week at the start of the pre-trial was reduced gradually to 6.88 ± 0.41 μg at the start of this trial, and to 6.34 ± 0.42 μg at the end of the whole trial.

The levels of TRACP and ICTP were significantly lower at the end of this trial than at the start of the pre-trial. The level of bone ALP was lower at the start of this trial than at the start of the pre-trial, and remained unchanged at the end of the trial. PICP levels were lower at the start and end of this trial than at the start of the pre-trial, but tended to increase after the start of this trial (Figure 3).

During this trial, adjusted serum Ca rose above the level at the start of the pre-trial and maintained at a constant level at 4 weeks and thereafter. Compared with the level at the start of the pre-trial, the serum P level rose to 6.41 ± 0.14 mg/dl at the end of this trial (Figure 4).

1,25-Dihydroxyvitamin D rose significantly at 12 weeks and 24,25-dihydroxyvitamin D levels decreased significantly during this trial. At the start of this trial, 25-hydroxyvitamin D rose significantly at 12 weeks and 24,25-dihydroxyvitamin D levels decreased significantly during this trial. At the start of this trial, 25-hydroxyvitamin D rose above the level at the start of the pre-trial, but at the end of the whole trial it was decreased to the level at the start of the pre-trial (Figure 5).

In 22 patients in whom measurements were performed before and after the trial, the BMD of the distal one-third of the radius by DXA decreased very slightly from 0.512 ± 0.030 to 0.501 ± 0.031 g/cm², and the BMD of the distal one-sixth of the radius also decreased very slightly from 0.411 ± 0.052 to 0.403 ± 0.054 g/cm² (n = 9) at the end of the trial.

There were 60 adverse events in 49 patients, for which a causal relationship to OCT could not be excluded. The most frequent adverse events were hypercalcaemia: 51 events occurred in 41 patients. These 41 patients, except for the one with severe hypercalcaemia...
(adjusted Ca > 12.5 mg/dl), had mild-to-moderate hypercalcaemia that resolved or improved after OCT was withdrawn or continued, except in a patient who required the discontinuation of calcium salts which were used as phosphorus binder.

Other adverse events included CK elevation in six patients, blood myoglobin elevation in five patients, pruritus in two patients, and loss of hair, insomnia, fatigue, chest X-ray abnormalities, serum P elevation, and serum total-protein decrease occurring each in one patient. These adverse events were mild to moderate, and no adverse events were judged to be severe. All of these adverse events, except for serum total-protein decrease and chest X-ray abnormalities in one patient each, resolved or improved.

A comparison between the adverse events in the 26-week pre-trial and the additional 26-week trial showed that loss of hair and fatigue occurred de novo in one patient each, respectively. However, these adverse events have been reported in other clinical trials for OCT [9], and no unknown adverse events were observed in this trial. The overall incidence of adverse events fell from 129 events in 92/166 (55.4%) patients in the pre-trial, to 60 events in 49/124 (39.5%) patients in this trial (Table 4). There was no particular deviation in the dates of onset of adverse events during the whole trial period (Table 5).

**Discussion**

OCT has been reported to strongly suppress PTH levels in patients with 2HPT for which conventional oral vitamin D preparations are not effective [10,11]. Considering that long-term administration is required for drug controlling 2HPT in dialysis patients, the long-term study to examine the safety and to determine the maintenance dose of OCT was planned and conducted in chronic HD patients.

This study was designed so that it allowed a wide selection of doses to enable the management of...
patients with severe 2HPT. For this reason, the maximum dose of OCT was increased to 20.0 μg HD because in the pre-trial, during which doses were varied according to the levels of intact-PTH and adjusted serum Ca, it appeared that a dose of 15.0 μg HD was not sufficiently effective in several patients.

As the long-term administration of OCT was expected for the treatment of 2HPT, a year-long trial (a 26-month pre-trial plus a 26-month trial) was designed for this study period. In this study, OCT was shown to exert a powerful effect for the treatment of 124 patients with severe 2HPT with high-turnover bone disease, as evidenced by the mean intact-PTH of 830.2±621.9 pg/ml, HS-PTH of 60 140 ± 35 440 pg/ml, and high bone metabolic marker such as ALP of 350.8±386.2 IU/l at entry into the pre-trial.

At the start of this trial, during the 2-week observation period immediately after the pre-trial, intact-PTH levels rose to 637.2±457.1 pg/ml once, then rapidly fell 2 weeks after OCT re-administration, showing a gradual, sustained decrease thereafter until the end of this trial. In terms of the decrease rates of intact-PTH as an indicator of PTH improvement, the final rate of moderate or greater improvement (30% or greater decrease from the level at the start of pre-trial) was as high as 51.6%, which was similar to previously reported results obtained in 6-month trials [7,12]. A stratified analysis by intact-PTH levels showed that a rate of moderate or greater improvement of 66.7% was obtained even for patients with the most severe 2HPT with a basal intact-PTH level of 1000 pg/ml or higher, suggesting the strong therapeutic effect
of OCT on severe 2HPT. In several patients with an initial, relatively mildly increased intact-PTH level (below 500 pg/ml), OCT was to be discontinued rapidly after administration, necessitating withdrawal or the reduction of OCT. As a result, the rate of moderate or greater improvement remained 40.5%.

We speculate that a severe increase in PTH is accompanied by severe high-turnover bone disease...
as reflected by increased bone metabolic markers, and that Ca absorbed from the intestinal tract enters the bone rapidly, thus restricting the rise of serum Ca, whereas a mild increase in PTH is accompanied by relatively lower bone turnover, facilitating the rise of serum Ca.

Thus, patients with a high basal intact-PTH level tolerated the continuous administration of high doses of OCT without developing hypercalcaemia, and also showed a marked suppression of intact-PTH. Conversely, patients with a relatively low initial intact-PTH level tended to show an elevated serum Ca level associated with an OCT-induced decrease in PTH, which necessitated the withdrawal or dose reduction of OCT, presumably leading to a low degree of suppression of intact-PTH. However, in consideration of the fact that serum Ca levels were well controlled without the development of hypercalcaemia in some patients with a relatively high initial Ca level, we speculate that the resistance of uraemic bone to PTH varies widely among patients, making it unreasonable to apply the same OCT dosing regimen to all patients. It is thus necessary to adjust the OCT dosage according to the levels of intact-PTH, HS-PTH, bone metabolic markers such as ALP, and serum Ca.

From this perspective, OCT should be started with 5 μg/HD in patients with relatively low intact-PTH levels of below 500 pg/ml and with 10 μg/HD in patients with intact-PTH levels above 500 pg/ml, and the dosage should be tailored according to the subsequent response of the individual patient.

Sixty adverse events for which a causal relationship with OCT could not be excluded occurred in 49 patients after the start of this trial, with hypercalcaemia being the most frequent (33.1%, 41/124 patients, 51 events). As described above, this may partially have resulted from a reduction of the Ca buffering capacity of the bone due to the suppression of PTH or from a possible increase in Ca absorption from the small intestine.

The maximum range of variation in the mean level of adjusted Ca during the trial was 0.85 mg/dl (10.59 ± 0.61 mg/dl), which was considered to be within acceptable limits for HD patients. The hypercalcaemia
that developed in these patients, including one in whom calcium salts as a phosphorus binder were discontinued, resolved or improved after OCT was withdrawn or continued.

In particular, in 16 events in which OCT was withdrawn after the onset of hypercalcemia, the Ca level rapidly fell below 11.0 mg/dl in 10 of 11 events in which the adjusted Ca level was measured the next...
week, and in three of five events in which the adjusted Ca level was measured 2 weeks after the onset of hypercalcaemia, suggesting that it is possible to control serum Ca through OCT withdrawal. Other adverse events did not include severe or new events, a finding that was similar as obtained in our previously reported clinical trials [7,9,12]. A comparison of the adverse events occurring in the 26-week pre-trial and the 26-week trial showed a decreased incidence of adverse events in this trial. No new safety problems appeared during the year-long administration.

In conclusion, these results confirmed the efficacy and safety of the long-term administration of OCT in the treatment of 2HPT of HD patients.

References