Efficacy and safety of long-term oral falecalcitriol treatment in patients with renal osteodystrophy

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Abstract: We investigated, in a multicenter study, the efficacy and safety of long-term administration of falecalcitriol, a new active vitamin D₃, in patients with renal osteodystrophy of the osteitis fibrosa type associated with secondary hyperparathyroidism caused by chronic renal failure. Falecalcitriol was orally administered every day for 48 weeks. Administration was started at a dosage of 0.3µg/day, and the dosage was changed whenever necessary according to serum calcium (Ca) level. As a result, significant inhibition of the bone resorption markers, i.e., intact parathyroid hormone (i-PTH), pyridinoline (Pyr), and deoxypyridinoline (D-Pyr), was observed from the 8th week, and the bone formation markers, i.e., total activity and bone fraction of alkaline phosphatase, were also significantly inhibited from the 12th week. The bone mineral density (BMD) change rate in the bones of the whole body determined by dual-energy X-ray absorptiometry remained almost constant. When subjects were stratified according to the inhibition rate of bone metabolic parameters, BMD tended to increase in the group with strong inhibition and to decrease in the group with weak inhibition. Mean serum Ca level significantly increased from 9.5mg/dl, but mean level was subsequently maintained at about 10mg/dl until the end of administration by adjustment of the doses. These findings suggested that falecalcitriol may inhibit and normalize accelerated bone metabolic turnover without inducing excessive increases in serum Ca level in secondary hyperparathyroidism. With respect to safety, no specific adverse reactions associated with the prolonged administration period were observed.

Key words: falecalcitriol, ST-630, renal osteodystrophy (ROD), secondary hyperparathyroidism, hemodialysis

Introduction

Progress in dialysis therapy has made it possible to prolong the life of patients with chronic renal failure. However, the treatment of several complications takes on more importance as the number of long-term survivors increases. Secondary hyperparathyroidism, in which the parathyroid hormone (PTH) level is abnormally high, is common even in early renal failure [1,2]. Its severity increases in association with advancement of chronic renal failure, inducing bone lesions such as osteitis fibrosa and osteomalacia.

Active vitamin D₃ has been reported to have the action of directly lowering PTH level, in addition to indirectly suppressing PTH secretion by increasing serum calcium (Ca) concentration [3]. Because active vitamin D₃ inhibits PTH production at the genetic level [4], administration of pharmacological doses of 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃) has been attempted by various methods in the treatment of secondary hyperparathyroidism. Existing active vitamin D₃ preparations, however, may cause hypercalcemia and
hyperphosphatemia, and therefore it is impossible to maintain the therapeutic effects over a prolonged period. Thus, development of drugs with high selectivity for PTH inhibition is awaited.

Falecalcitriol, a newly synthesized active vitamin D₃ derivative, features a chemical structure in which all hydrogens at positions 26 and 27 of 1,25(OH)₂D₃ have been replaced by fluorine [5]. In rats subjected to either five-sixth nephrectomy (Nx), falecalcitriol suppressed the elevated blood N-terminal PTH concentration, and the inhibition of PTH was partially mediated by decreases in expression of prepro-PTH mRNA. Moreover, falecalcitriol inhibited osteoid volume (OV/TV) and fibrous tissue volume (Fb.V/TV) [6].

Intravenous or oral pulse therapy is conducted when daily repeated administration of 1α-hydroxyvitamin D₃ (1α(OH)D₃) or 1,25(OH)₂D₃ fails to provide sufficient therapeutic effects in patients with secondary hyperparathyroidism associated with chronic renal failure [7,8]. Our previous clinical studies of daily oral falecalcitriol administration have shown that desirable therapeutic effects may be obtained even in patients for whom pulse therapy is indicated. These studies, however, had limited relatively short administration periods of 8 or 12 weeks. Accordingly, we set a relatively long administration period (48 weeks) in the present study. We determined a variety of bone metabolic markers including PTH, analyzed bone mineral density (BMD) using dual-energy X-ray absorptiometry (DXA), used bone scintigraphy for efficacy evaluation, and also evaluated safety. The study was conducted from November 1993 to December 1995.

Method

Subjects

This study was conducted in patients with renal osteodystrophy (ROD) who appeared to have osteitis fibrosa associated with secondary hyperparathyroidism on continuous hemodialysis. Inclusion criteria were as follows: hemodialysis treatment for at least 3 months; stable clinical symptoms; age between 20 and 65 years; and 1–84 intact PTH (i-PTH; normal range, 10–65 pg/ml, Nichols Institute, San Juan Capistrano, CA, USA) of 150 pg/ml or more (initially, 65 pg/ml or higher was employed as the standard, but this was changed during the study). Exclusion criteria were as follows: hypercalcemia or a serum Ca × P level of 60 (mg²/dl²) or greater, suspected aluminum osteopathy (serum aluminum level of 100µg/l or more), and a serum alkaline phosphatase (ALP) level below the lower limit of the normal range.

A 4-week washout period was set for patients who had been receiving active vitamin D₃, and administration was started after a certain observation period. Approval of implementation of the study was obtained from the institutional review board of each center before the study was started. Details of the study were explained to all patients, and their informed consent was obtained before the start of the washout period.

Study design

We investigated the efficacy and safety of falecalcitriol during 48-week administration in this study. We determined changes in bone metabolic parameters as primary parameters for efficacy evaluation and effects on bone lesions and subjective symptoms as secondary parameters. An observation period was set before falecalcitriol administration. After confirming compliance with inclusion criteria, we started administration at a dosage of 0.3µg/day, which is believed to be the optimal dosage from the results of our previous studies. The dosage was adjusted whenever necessary according to such parameters as serum Ca or PTH. The serum Ca concentration of 11.0mg/dl was regarded as a target, and the dose was reduced when serum Ca concentration exceeded this level. The drug was orally administered once daily for 48 weeks at the same hour of the day as nearly as possible, using tablets containing 0.15µg of falecalcitriol.

Evaluation parameters

The following parameters for efficacy evaluation were determined in the 0th, 4th, 8th, 12th, 24th, 36th, and 48th weeks of administration: i-PTH; 65–84 carboxy-terminal PTH (c-PTH; normal range, <1.3 ng/ml; INCSTAR, Stillwater, MN, USA); 44–68 midregion PTH (m-PTH; normal range, 186–560 pg/ml; Yamasa, Chiba, Japan); serum pyridinoline (Pyr; normal range not defined); serum deoxypyridinoline (D-Pyr; normal range not defined); tartrate-resistant acid phosphatase (TRACP; normal range not defined); total alkaline phosphatase (t-ALP; normal range, 98–279 IU/l); bone-specific alkaline phosphatase (b-ALP; normal range, <150 IU/l for males and <120 IU/l for females); intact osteocalcin (i-BGP; normal range, <6.8 ng/ml); procollagen-I C-terminal propeptide (PICP; normal range not defined); and calcitonin (normal range, 15.1–86.1 pg/ml). All these bone metabolic markers were measured by Teijin Bio-Laboratories (Tokyo, Japan).

For investigation of the effects on bone lesions, BMD (bone of the whole body, as well as one-third and one-sixth of the radius from the distal end) was measured by the DXA method using QDR-2000 or 1000/W (Hologic, Waltham, MA, USA), or DPX-L (Lunar, Madison, WI, USA) densitometers, and bone X-ray photography of lesion sites, bone scintigraphy, and bone biopsy were