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The calcimimetic AMG 073 reduces parathyroid hormone and calcium x phosphorus in secondary hyperparathyroidism

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The calcimimetic AMG 073 reduces parathyroid hormone and calcium x phosphorus in secondary hyperparathyroidism.

Background. A need exists for a therapy that lowers parathyroid hormone (PTH) without increasing calcium x phosphorus in patients with secondary hyperparathyroidism. The calcimimetic AMG 073 increases the sensitivity of the parathyroid calcium-sensing receptor to extracellular calcium, thereby reducing PTH secretion. Consequently, AMG 073 may provide a novel therapy for secondary hyperparathyroidism.

Methods. Seventy-eight hemodialysis patients with secondary hyperparathyroidism were enrolled into this 18-week, double-blind, randomized, placebo-controlled, dose titration study. Daily oral AMG 073 doses were administered to determine the effect on PTH, serum calcium, phosphorus, and calcium x phosphorus.

Results. The mean baseline PTH was similar in patients administered AMG 073 or placebo (632 ± 280.1 pg/mL vs. 637 ± 455.9 pg/mL, respectively). PTH decreased by 26.0% in the AMG 073-treated group, compared with an increase of 22.0% in the placebo group ($P < 0.001$). A greater proportion in the AMG 073 group (38%) had a decrease in PTH ≥30%, compared with the placebo group (8%) ($P = 0.001$). Decreases in PTH were independent of baseline vitamin D usage. Patients receiving AMG 073 had an 11.9% decrease in calcium x phosphorus compared with a 10.9% increase in the placebo group ($P < 0.001$). Use of vitamin D sterols, as well as both calcium and noncalcium-containing phosphate binders. were similar between treatment groups. Administration of AMG 073 was safe and well tolerated in this 18-week study.

Conclusions. The calcimimetic AMG 073 decreases both PTH and calcium x phosphorus levels in hemodialysis patients with secondary hyperparathyroidism.

Key words: calcimimetic, calcium-sensing receptor, parathyroid hormone, calcium x phosphorus, secondary hyperparathyroidism, end-stage renal disease.

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Secondary hyperparathyroidism is characterized by parathyroid gland hyperplasia and increased concentrations of parathyroid hormone (PTH) [1, 2]. Elevated PTH levels may adversely affect a variety of organs, including the central nervous system, cardiac and pulmonary function [3–5]. Furthermore, Block et al found that elevated PTH levels are associated with an increase in the relative risk of mortality [6]. Abnormalities of bone and mineral metabolism are another important complication in these patients. Bone histology in these patients often reveals the pathology of osteitis fibrosa cystica [7, 8].

Current strategies for managing secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) utilize large oral doses of calcium or noncalcium-containing phosphate-binding agents to control hyperphosphatemia while the vitamin D sterols, calcitriol, paricalcitol or doxercalciferol, are administered to lower PTH levels [9–12]. Unfortunately, episodes of hypercalcemia are common in patients treated with calcium-containing phosphate-binding agents and serum calcium and phosphorus levels often rise after the administration of supraphysiological doses of vitamin D [13–15]. Both therapeutic interventions may contribute to vascular and soft-tissue calcification [16]. Moreover, neither treatment immediately decreases PTH synthesis and secretion. Consequently, an unmet medical need exists for a therapy that can control PTH levels without raising serum calcium or phosphorus levels in patients with secondary hyperparathyroidism.

AMG 073 represents a new class of compounds known as calcimimetics. These small molecules act on the parathyroid gland calcium-sensing receptor, increasing its sensitivity to extracellular calcium, thereby reducing PTH secretion [17, 18]. Calcimimetics have been shown to inhibit PTH release from parathyroid cells both in vitro and in vivo and have been proposed as a therapy for

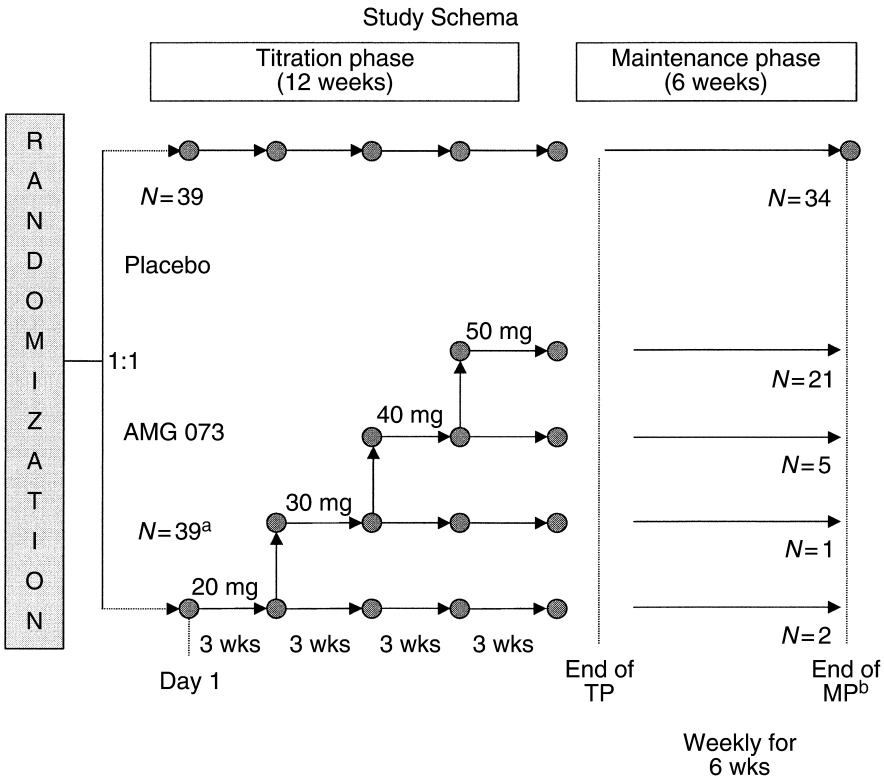

Fig. 1. Study schema. [a], one patient withdrew consent before receiving study drug; [b], three patients were on a dose of 10 mg at the end of the maintenance phase.

hyperparathyroidism [19]. These agents reduce plasma PTH levels within 1 to 2 hours of oral administration in humans [20]. The rapid onset of the effects of calcimimetic agents suggests that these compounds may permit precise pharmacological control of PTH secretion in patients with secondary hyperparathyroidism.

Single oral doses of AMG 073 have resulted in dose-dependent decreases in PTH when administered to hemodialysis patients with secondary hyperparathyroidism, while daily doses of 50 mg over 8 days reduced PTH by 39% [20]. Importantly, decreases in serum calcium, phosphorus, and the calcium x phosphorus product were also observed in this study. In the present 18-week study, the efficacy and safety of AMG 073 were assessed in reducing PTH without concomitant increases in calcium x phosphorus in hemodialysis patients with secondary hyperparathyroidism.

METHODS

Patients

This study was approved by each study center's Institutional Review Board or ethics committee and all patients gave written informed consent before participation. The study was conducted at 23 centers in the United States and two in Canada. These centers enrolled 78 patients treated for at least 3 months with hemodialysis who had PTH levels ≥300 pg/mL despite receiving standard of care (phosphate binders and/or vitamin D sterols). Patients were eligible for this study if they met criteria, including age ≥18 years; serum calcium corrected for serum albumin ≥8.8 mg/dL and <11.0 mg/dL; serum phosphorus ≥2.5 mg/dL; and calcium x phosphorus <70 $(mg/dL)^2$. Patients receiving vitamin D sterols were required to be on a stable dose for at least 21 days before enrollment. Dialysate calcium concentration and calcium supplements/oral phosphate binders dose could not be changed during the 7 days before enrollment. Patients were required to be medically stable with no evidence of an active infection, malignant process, or disease known to cause hypercalcemia. Patients were also required to have a hemoglobin >9.0 g/dL or a hematocrit >27%, as well as liver transaminases and bilirubin levels no more than twice the upper limit of normal.

Study design

This was a placebo-controlled, double-blind, randomized, multicenter study consisting of two phases: a 12-week dose-titration phase, followed by a maintenance phase in which the final dose from the end of the dose-titration phase was maintained for 6 weeks (Fig. 1).

Patients were randomized 1:1 to receive AMG 073 or placebo. Patients began on a once daily dose of 20 mg which could then be titrated up to 30, 40, or 50 mg, or down to 10 mg, every 3 weeks until they had achieved a reduction in PTH values of ≥30% from baseline and

to ≤250 pg/mL, unless the patient had symptoms of hypocalcemia or the serum calcium was <7.8 mg/dL. The dose of study drug was reduced if patients experienced PTH values <100 pg/mL on two consecutive weekly visits.

Laboratory assessments were made at weekly visits throughout the study to determine the effect of AMG 073 on PTH, serum calcium, serum phosphorus, and calcium x phosphorus. These assessments were made immediately before administering the daily oral dose of study medication (24 hours after the dose on the preceding day).

Efficacy was assessed by determining the proportion of patients with reductions in PTH ≥30% between treatment groups during the maintenance phase. The mean percent change from baseline for PTH, serum calcium, phosphorus, and calcium x phosphorus were also compared between treatment groups during the maintenance phase. Safety was assessed by monitoring adverse events, laboratory variables (hematology and biochemistry), and vital signs.

Concomitant medication

In addition to AMG 073 or placebo, patients continued to receive their prescribed therapy for secondary hyperparathyroidism (phosphate binders and vitamin D sterols) during the study. The study protocol provided guidance on the use of vitamin D sterols. Reductions in vitamin D dose were allowed if serum calcium was ≥11.0 mg/dL, phosphorus was ≥6.5 mg/dL, calcium x phosphorus product was ≥70 $(mg/dL)^2$, or if PTH was <100 pg/mL on the lowest dose of study drug. Increases in vitamin D dose were allowed if PTH was ≥50% of baseline and the PTH was ≥600 pg/mL. Phosphate binders could be adjusted as needed throughout the study.

Biochemical determinations

All laboratory determinations were conducted at a central laboratory (Covance Laboratory Services, Inc., Indianapolis, IN, USA). Chemistries included alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bone alkaline phosphatase, blood urea nitrogen, bilirubin, uric acid, calcium, creatinine, glucose, cholesterol, triglycerides, sodium, phosphorus, potassium, choloride, bicarbonate, total protein and lactate dehydrogenase. These assessments were performed using standard methodology. PTH levels were determined using a double-antibody immunoradiometric assay for the intact hormone (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Serum calcium values were adjusted for the albumin concentration as follows. For each 1.0 g/dL decrease in albumin below 4.0 g/dL, the serum calcium was increased by 0.8 mg/dL.

Table 1. Baseline characteristics of study patients

	Placebo $N = 39$	AMG 073 $N = 39$	Total $N = 78$
Gender *number* (%)			
Women	17 (44)	15 (38)	32 (41)
Men	22 (56)	24 (62)	46 (59)
Race *number* (%)			
Black	29 (74)	26 (67)	55 (71)
White	6 (15)	10 (26)	16 (21)
Asian	2 (5)	2 (5)	4 (5)
Hispanic	2 (5)	1 (3)	3 (4)
Age *years*			
Mean (SD)	48.8 (15.6)	52.7 (16.4)	50.8 (16.0)
Duration of dialysis *months*			
Number	39	38	77
Mean (SD)	69.7 (53.9)	60.3 (58.3)	65.1 (55.9)
Range	5–277	3–241	3–277
Vitamin D use *number* (%)	24 (62)	26 (67)	50 (64)
Phosphate binder use *number* (%)	34 (87)	34 (87)	68 (87)

Statistical analysis

All patients randomized into the study were included in determining the proportion of patients with reductions in PTH ≥30% (drop outs before the maintenance phase were considered not to have achieved this reduction). The mean percent change from baseline through the maintenance phase was determined for PTH, serum calcium, phosphorus, and calcium x phosphorus. All patients who received at least one dose of AMG 073 or placebo were included in the analysis of safety.

The proportion of patients with reductions in PTH ≥30% between treatment groups was compared using the two-group χ^2 test. The mean percent change from baseline for PTH, serum calcium, phosphorus, and calcium x phosphorus were compared between treatment groups using an analysis of variance (ANOVA) model.

Stepwise logistic regression analysis was used to assess the effect of the baseline demographic factors, gender, age, race, duration of dialysis, and vitamin D use on PTH reductions. This method was also used to assess the effect of baseline PTH, serum calcium, phosphorus, and calcium x phosphorus levels on PTH reductions. Baseline demographic and biochemical data is presented as the mean ± the standard deviation. Other data are presented as the mean ± the standard error.

RESULTS

Patient demographics and disposition

The baseline patient demographic characteristics were similar between treatment groups (Table 1). The range in duration of dialysis among all patients varied from 3 to 277 months.

Subject disposition at baseline and at the end of the maintenance phase are shown on the study schema (Fig. 1). Six subjects receiving AMG 073 and five receiving pla-

Table 2. Baseline biochemistry of study patients

	Placebo $N = 39$	AMG 073 $N = 38$
iPTH *pg/mL*		
Mean (SD)	637 (455.9)	632 (280.1)
Range	67, 2254	165, 1377
Serum calcium *mg/dL*		
Mean (SD)	9.7 (0.64)	9.7 (0.67)
Range	8.5, 10.8	8.4, 11.1
Serum phosphorus *mg/dL*		
Mean (SD)	5.6 (1.38)	6.3 (1.42)
Range	2.5, 8.7	3.5, 10.7
Ca x P mg/dL^2		
Mean (SD)	53.8 (13.63)	60.7 (13.21)
Range	21.8, 92.5	30.5, 92.7

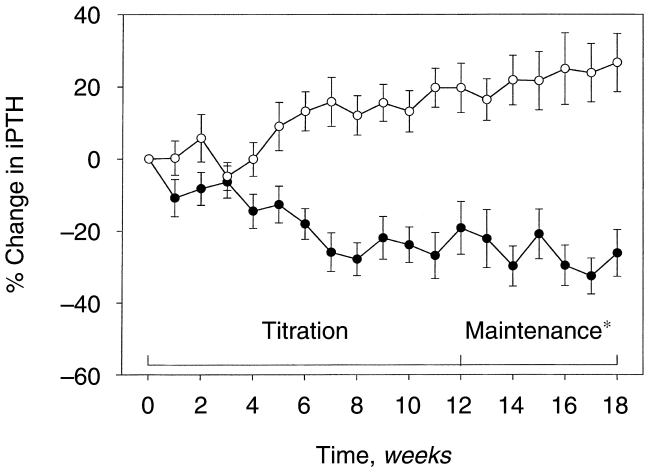

Fig. 2. Mean percent change in PTH from baseline levels. Patients received AMG 073 (●) or placebo (○). Values are means ± SE. *$P <$ 0.001.

cebo were discontinued before week 18. Doses of AMG 073 or placebo at the end of the maintenance phase are also shown in Figure 1.

PTH results

The baseline PTH levels were similar between treatment groups (Table 2). Figure 2 illustrates the percentage change from baseline in PTH at each time point for both treatment groups. The mean PTH level over the maintenance phase decreased by an average of 26% below baseline levels in patients receiving AMG 073 while it increased by an average of 22% in patients receiving placebo ($P < 0.001$). The mean PTH over the maintenance phase was 460 ± 47.4 pg/mL in patients administered AMG 073 and 701 ± 70.3 pg/mL in placebo treated patients.

AMG 073 reduced PTH regardless of baseline vitamin D use. Sixty-seven percent of the AMG 073-treated subjects received vitamin D sterols at baseline, compared with 62% of the placebo patients. In AMG 073 patients,

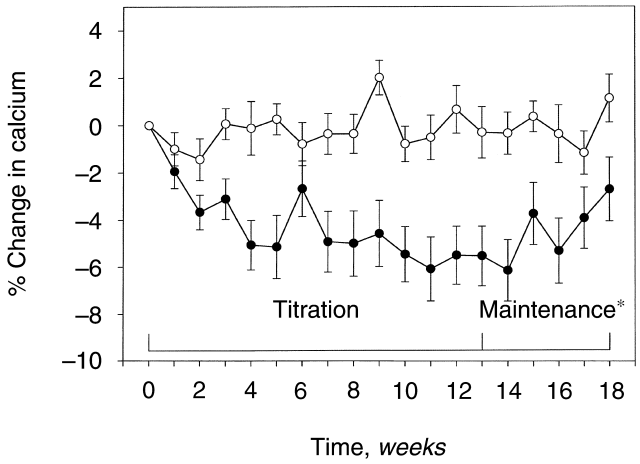

Fig. 3. Mean percent change in serum calcium from baseline levels. Patients received AMG 073 (●) or placebo (○). Values are means ± SE. *$P < 0.001$.

PTH decreased by 24.0% and 29.9% in patients on vitamin D or not on vitamin D, respectively. In placebo patients, PTH increased by 19.1% and 27.4% in patients on or not on vitamin D, respectively.

Stepwise logistic regression analysis indicated that the baseline demographic factors, gender, age, race, duration of dialysis, and vitamin D use were not significantly correlated with reduction in PTH in patients receiving AMG 073. Baseline PTH, serum calcium, phosphorus, and calcium x phosphorus levels were also not significantly correlated with reductions in PTH. Mean percent change in serum calcium was not significantly correlated with mean percent change in PTH. However, a positive correlation between the mean percent change in phosphorus and calcium x phosphorus with the mean percent change in PTH levels was observed ($r = 0.341$, $P = 0.057$; $r = 0.304$, $P = 0.091$, respectively).

A significantly greater proportion of patients (38%) in the AMG 073-treated group had a ≥30% decrease in mean PTH from baseline over the maintenance phase compared with the placebo group (8%) ($P = 0.001$). Also, a decrease in mean PTH ≥30% from baseline for at least one time point during the study occurred in 90% of patients administered AMG 073.

Calcium, phosphorus, and calcium x phosphorus results

The mean baseline serum calcium level was 9.7 mg/dL in patients administered both AMG 073 and placebo (SD of ± 0.67 and ± 0.64, respectively). Figure 3 illustrates the percentage change from baseline in serum calcium at each time point for both treatment groups. The mean serum calcium level over the maintenance phase decreased by 4.7% in the patients receiving AMG 073 compared with no change in the placebo group ($P <$ 0.001).

The mean baseline serum phosphorus was 6.3 ± 1.42

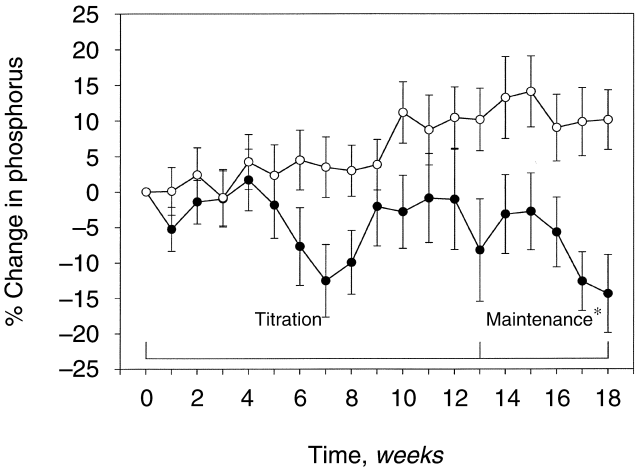

Fig. 4. Mean percent change in phosphorus from baseline levels. Patients received AMG 073 (●) or placebo (○). Values are means ± SE. *$P < 0.001$.

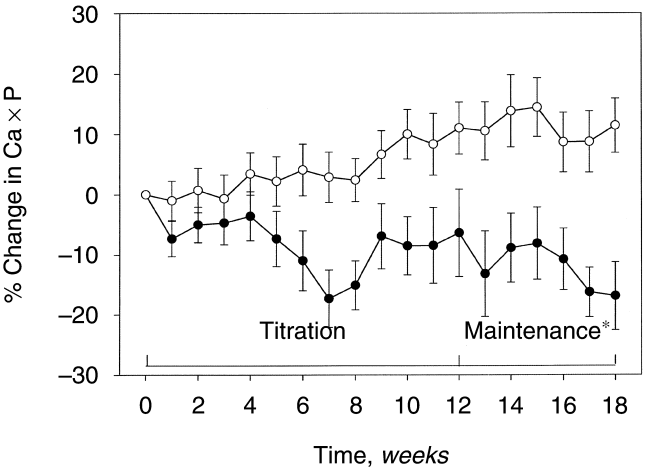

Fig. 5. Mean percent change in calcium x phosphorus (Ca x P) from baseline levels. Patients received AMG 073 (●) or placebo (○). Values are means ± SE. *$P < 0.001$.

mg/dL and 5.6 ± 1.38 mg/dL in patients administered AMG 073 and placebo, respectively. As shown in Figure 4, patients receiving AMG 073 experienced a 7.5% reduction in mean serum phosphorus over the maintenance phase, compared with a 10.9% increase in the placebo patients ($P = 0.003$).

The mean baseline calcium x phosphorus was 60.7 ± 13.21 $(mg/dL)^2$ and 53.8 ± 13.63 $(mg/dL)^2$ in patients administered AMG 073 and placebo, respectively. Figure 5 presents calcium x phosphorus product levels that decreased by 11.9% over the maintenance phase in patients administered AMG 073 compared with an increase of 10.9% in patients receiving placebo ($P < 0.001$).

The effect of AMG 073, compared with placebo, in reducing both PTH and calcium x phosphorus is presented in Figure 6.

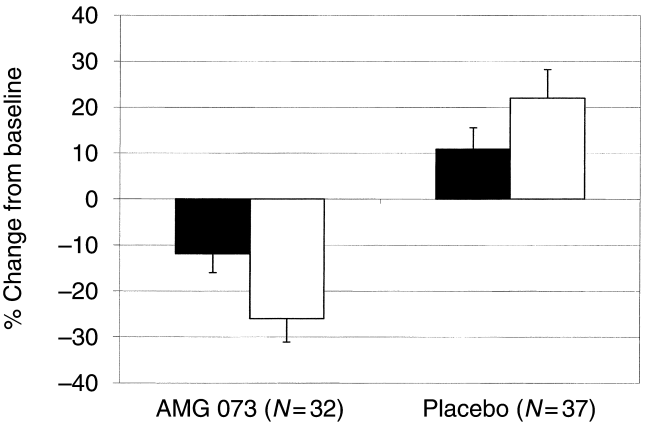

Fig. 6. Concurrent mean percent change from baseline in PTH (□) and calcium x phosphorus product (■) during the maintenance phase. Values are means ± SE.

Concomitant therapy

Calcitriol and paricalcitol were the predominant vitamin D sterols that patients received during this study. The mean weekly dose of calcitriol, the most frequently administered vitamin D therapy, was similar for both treatment groups (Fig. 7). The mean weekly dose of paricalcitol was also similar for both treatment groups.

Usage of either calcium-containing or noncalcium-containing phosphate binders was similar between treatment groups.

Safety results

AMG 073 was safe and well-tolerated when titrated up to a maximum dose of 50 mg/day in this study. The safety profile of AMG 073 was similar to that of placebo with respect to the incidence and severity of adverse events. Most adverse events were mild to moderate in severity. The most frequent of these events were nausea (21% AMG 073, 31% placebo) and dyspnea (18% AMG 073, 13% placebo). Transient, asymptomatic hypocalcemia occurred in 3/38 subjects treated with AMG 073 (serum calcium <7.5 mg/dL). No clinically meaningful changes in laboratory values, vital signs or electrocardiograms were evident.

DISCUSSION

This 18-week dose-titration study demonstrated that AMG 073 doses up to 50 mg/day are effective in reducing PTH and calcium x phosphorus levels in hemodialysis patients with secondary hyperparathyroidism. PTH decreased by 26% below baseline levels in patients receiving AMG 073 compared with an increase of 22% in patients receiving placebo.

The ability of AMG 073 to reduce PTH was indepen-

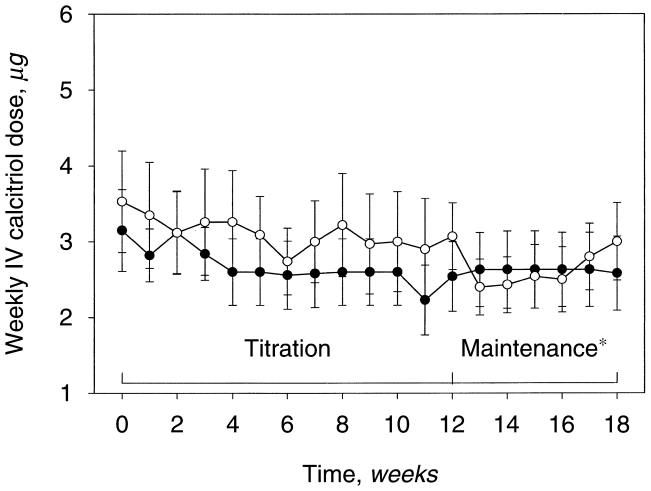

Fig. 7. Mean weekly intervenous (IV) calcitriol dose. Patients received AMG 073 (●) or placebo (○). At baseline, 16 patients received AMG 073 and 15 received placebo. Values are means ± SE

dent of baseline demographic characteristics, including dialysis vintage. Dialysis vintage has been noted to be a key determinant in the severity of secondary hyperparathyroidism [21], indicating that the calcimimetic may benefit patients regardless of disease severity. Consistent with this, patients administered AMG 073 experienced reductions in PTH independent of baseline PTH levels.

Previous research in hemodialysis patients administered AMG 073 has shown that, while PTH levels remain below baseline levels for more than 24 hours after administration of single doses of AMG 073, the greatest decrease in PTH occurs 2 to 4 hours after AMG 073 administration [20]. As the effect of AMG 073 on PTH levels in the current study was assessed 24 hours after the previous dose, the reductions observed here may underestimate the full benefit of this therapy on 24-hour PTH control.

Patients enrolled in this study received standard therapy, including phosphate binders and vitamin D sterols, yet had inadequate control of their secondary hyperparathyroidism at the start of the study. Mean baseline PTH levels were approximately 635 pg/mL in both treatment groups, indicating the severity of the disease in these patients and the difficulty in controlling it before study enrollment. Nonetheless, AMG 073 was effective in significantly reducing PTH levels in these subjects. Previous studies of second-generation vitamin D sterols have also demonstrated reductions in PTH levels [11]. However, these reductions were achieved in patients where baseline PTH levels were elevated after withdrawal of calcitriol therapy at least 4 weeks before the start of the study.

In the current study, PTH was significantly reduced in the AMG 073 group relative to the placebo group regardless of baseline vitamin D usage. The magnitude of the PTH reduction was similar for subjects on or not on vitamin D at baseline (24.0% vs. 29.9%, respectively) and the effect of AMG 073 on PTH reductions was not significantly correlated with baseline vitamin D use. In addition, vitamin D usage was similar between treatment groups throughout the study, indicating that the PTH changes were not the result of modulating this concomitant therapy.

In AMG 073-treated patients, reductions in PTH occurred in conjunction with reductions in serum calcium, phosphorus, and calcium x phosphorus. Serum calcium and phosphorus decreased significantly in the AMG 073-treated group relative to patients administered placebo while calcium x phosphorus levels decreased by 11.9% in patients administered AMG 073. A therapy that reduces PTH while also reducing serum calcium, phosphorus, and calcium x phosphorus represents a significant advance for ESRD patients. Hyperphosphatemia and elevated calcium x phosphorus are prevalent in this population [6, 16, 22, 23]; 50% of ESRD patients have serum phosphorus levels greater than 6.0 mg/dL and 40% have calcium x phosphorus levels greater than 60 $(mg/dL)^2$. Baseline serum phosphorus and calcium x phosphorus for patients in this study were consistent with these reports. Elevated serum phosphorus and calcium x phosphorus are related to the risk of coronary artery disease and sudden death in ESRD patients, particularly in the setting of elevated PTH levels [22, 23]. In addition, recent work using electron-beam computed tomography has shown an association between elevated calcium x phosphorus and coronary artery calcification in ESRD patients [24].

The reductions in serum calcium and phosphorus in patients administered AMG 073 observed in this study are similar to those in patients following parathyroidectomy. One explanation for these reductions is a decrease in mineral efflux from the bone caused by a reduction in plasma PTH levels. As PTH may indirectly stimulate RANKL-mediated osteoclast maturation and activity [25], reductions in PTH could diminish bone resorption. Positive correlations were observed between changes in phosphorus and calcium x phosphorus with changes in PTH over the maintenance phase of the study. Phosphate binder and vitamin D sterol doses were stable in this study and therefore do not appear to be responsible for the reductions in serum calcium and phosphorus levels. As an extracellular calcium-sensing receptor appears to be expressed in human osteoblasts [26], an alternative hypothesis to explain the observed reductions in serum calcium and phosphorus levels proposes that the mineral flux between bone and plasma may be influenced by calcimimetic agents.

In summary, the calcimimetic agent AMG 073 may offer an advantage over current therapies for the treatment of secondary hyperparathyroidism. As a result of

its unique mechanism of action, AMG 073 potentially provides a novel means to lower both PTH and calcium x phosphorus in dialysis patients with secondary hyperparathyroidism. Ongoing studies at daily doses of AMG 073 higher than 50 mg are assessing the long-term effects of this calcimimetic on PTH, serum calcium, phosphorus, and calcium x phosphorus. These studies will also assess the long-term safety of AMG 073. In addition, ongoing studies are assessing the effect of AMG 073 on bone histomorphometry.

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