Cardiovascular Outcomes in the J-DAVID Based on Alkaline Phosphatase: A Post-hoc Analysis of a Randomized Controlled Trial

Tatsufumi Oka

Osaka University

Yusuke Sakaguchi (✉ sakaguchi@kid.med.osaka-u.ac.jp)

Osaka University

Yoshitaka Isaka

Osaka University

Haruka Ishii

Osaka City University

Daijiro Kabata

Osaka City University

Ayumi Shintani

Osaka City University

Shinya Nakatani

Osaka City University

Tomoaki Morioka

Osaka City University

Katsuhito Mori

Osaka City University

Masaaki Inaba

Osaka City University

Masanori Emoto

Osaka City University

Tetsuo Shoji

Osaka City University

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Abstract

In the Japan Dialysis Active Vitamin D (J-DAVID) trial, oral alfacalcidol numerically, but not significantly, increased the risk of cardiovascular events among patients undergoing hemodialysis. Because the cardiovascular effect of alfacalcidol could be modulated by bone turnover status, this post-hoc analysis of the J-DAVID examined how alkaline phosphatase (ALP), a more precise marker of bone turnover than parathyroid hormone (PTH), modifies the impact of alfacalcidol. The J-DAVID was a 48-month, open-label, randomized controlled trial comparing oral alfacalcidol with no vitamin D receptor activators (VDRAs) use in terms of cardiovascular events among 976 hemodialysis patients without secondary hyperparathyroidism. This post-hoc analysis included 959 patients with available data on baseline ALP. The median [25–75th percentile] baseline ALP level was 234 [183–296] U/L. In a Cox proportional hazards model, ALP did not significantly modify the effect of alfacalcidol on the rate of cardiovascular events or all-cause death (P for effect modification=0.54 and 0.74, respectively). The effect of alfacalcidol on time-series changes in calcium, phosphate, and intact PTH were similar across ALP subgroups. In conclusion, oral alfacalcidol did not significantly affect cardiovascular outcomes irrespective of bone turnover status.

Introduction

Vitamin D receptor activators (VDRAs) have long been the mainstay of treatment for secondary hyperparathyroidism in patients undergoing hemodialysis.¹ In addition to its primary role in mineral and skeletal homeostasis, basic studies have shown a variety of pleiotropic effects of vitamin D, including cardiovascular (CV) protection,² anti-inflammatory effects,³ immunomodulation,⁴ and antitumor immunity.⁵ Through these actions, VDRAs may improve the prognosis of hemodialysis patients, who have the substantial risk of CV events, infection, and malignancy⁶, independently of secondary hyperparathyroidism. Indeed, a cohort study of Italian patients undergoing hemodialysis found a significant association between VDRA use and better survival even among those with low intact parathyroid hormone (PTH) levels (≤ 150 pg/mL).⁷

The Japan Dialysis Active Vitamin D (J-DAVID) trial was the first randomized controlled trial (RCT) to examine the efficacy of oral alfacalcidol for CV events and mortality among hemodialysis patients without overt hyperparathyroidism (intact PTH ≤ 180 pg/mL).⁸ Unexpectedly, the hazard ratio for the primary outcome, fatal and non-fatal CV events, was numerically higher in the alfacalcidol group than in the control group, although the difference was not significant (hazard ratio 1.25; 95% confidence interval, 0.94–1.67; $P=0.13$). This finding raised a concern that VDRAs might exert a detrimental CV effect through accelerating vascular calcification by enhancing the intestinal absorption of calcium and phosphate, especially among those with low bone turnover that impairs mineral buffering capacity.^{9–11} In other words, the balance between the benefits and harms of VDRAs might depend on the status of bone turnover. Notably, PTH is a much poorer marker for low bone turnover than other markers, particularly alkaline phosphatase (ALP).¹² Thus, patients in the J-DAVID could be heterogeneous in terms of bone

turnover. In this post-hoc analysis of the J-DAVID, we explored how ALP modulates the effect of alfacalcidol on CV outcomes.

Methods

Ethical Considerations

The J-DAVID trial was conducted in accordance with the principles of the Declaration of Helsinki. The protocol of the J-DAVID was approved by the ethics committee at the Osaka City University Graduate School of Medicine in Japan (approval numbers 1227, 1297, 1385, and 1525) and by the relevant ethics committees or institutional review boards at the study sites. All participants gave written informed consent before the study enrollment. The protocol of this post-hoc analysis was approved by the Osaka City University Graduate School of Medicine (approval number 4420)

Study design and participants

This was a post-hoc analysis of the J-DAVID trial. Details of the J-DAVID have been described elsewhere.⁸ Briefly, the J-DAVID was a 48-month, open-label, blinded endpoint randomized controlled trial that compared oral alfacalcidol with no VDRA use in terms of CV events and mortality among 976 hemodialysis patients without overt secondary hyperparathyroidism from 108 dialysis centers in Japan. The key inclusion criteria were as follows: 1) patients on maintenance hemodialysis for ≥ 90 days, 2) aged 20–80 years, 3) serum calcium levels ≤ 10.0 mg/dL, 4) serum phosphate levels ≤ 6.0 mg/dL, 5) intact PTH levels ≤ 180 pg/mL, and 6) no treatment with VDRA within 4 weeks prior to randomization. Patients with abnormal liver function tests exceeding x3 upper normal limits were excluded. The complete inclusion and exclusion criteria are presented in Supplementary Table 1.

Participants were randomly assigned to the oral alfacalcidol or control group in a 1:1 ratio using a computer-generated random sequence with a block randomization method. The initial dose of oral alfacalcidol was 0.5 μ g/day, which was subsequently adjusted within a range of 0.25–7 μ g/week to avoid hypercalcemia (serum corrected calcium levels ≥ 10.5 mg/dL) and hyperphosphatemia (serum phosphate levels ≥ 7 mg/dL) if these were not sufficiently managed by dietary therapy and/or dose adjustment of calcium carbonate, sevelamer hydrochloride, and other medications. Patients in the control group received usual care without alfacalcidol or any other VDRA but were permitted to receive them if necessary.

The primary outcome was fatal and non-fatal CV events, including acute myocardial infarction, coronary artery diseases requiring percutaneous coronary interventions and/or coronary artery bypass grafting, hospitalization for congestive heart failure, stroke, aortic dissection/rupture, sudden cardiac death, and endovascular treatment and/or amputation for limb ischemia. The secondary outcome was all-cause mortality. All clinical events were adjudicated independently by an event evaluation committee who was blinded to the treatment assignment. The detail definitions of CV events are presented in Supplementary Table 2.

In this *post-hoc* analysis, we also assessed the composite of CV events and all-cause mortality. We analyzed the time-series changes in serum corrected calcium, serum phosphate, and intact PTH levels after stratifying patients based on tertiles of baseline ALP levels. These laboratory values were measured at 0, 3, 6, 12, 18, 24, 30, 36, 42, and 48 months following randomization.

Statistical analysis

To examine whether the effect of oral alfacalcidol varied depending on the baseline ALP levels, we used multivariable Cox proportional hazard regression models considering cross-product terms between the treatment assignment and the baseline ALP levels. The models were adjusted for the baseline age, sex, body mass index, systolic blood pressure, dialysis vintage, diabetes mellitus, prior history of CV events, C-reactive protein, serum albumin, serum phosphate, serum corrected calcium, intact PTH, high-density lipoprotein cholesterol, hemoglobin, and use of erythropoiesis-stimulating agents and intravenous iron therapy. The analysis was performed using the full analysis set which consists of 964 randomized participants.⁸ A potentially non-linear effect of ALP on the study outcomes was depicted using a restricted-cubic-spline curve.

Furthermore, we compared the time-series alterations in the corrected calcium, phosphate, and intact PTH levels during the observation period between the alfacalcidol and control groups using multivariable linear regression models. In these analyses, we assumed that the trends of these variables differed according to the baseline ALP levels and then divided the patients into three subgroups according to the ALP tertiles. Then, we considered three- and two-way cross-product terms between the ALP subgroup variable, month of measurement, and the treatment assignment in the multivariable linear regression models. The variance estimators of these regression models were adjusted using Huber-White method, considering the correlation between repeated measurements within a single patient. Finally, the covariates were adjusted similarly to the multivariable Cox proportional hazard regression models described above.

Results

A diagram of participant flow has been reported previously (8). Among 964 patients in the full analysis set, 5 patients were excluded due to missing ALP data. The distribution of baseline ALP levels among 959 patients is shown in Figure 1. The median [25–75th percentile] baseline ALP was 234 [183–296] U/L. Figure 2 illustrates the time-series changes in serum corrected calcium, serum phosphate, and intact PTH levels during the 48-month study period. In the multivariable linear regression models, there were no significant coefficients of the three-way cross-product term among the treatment assignment, ALP, and time for calcium, phosphate, and intact PTH (P for effect modification=0.21, 0.55, and 0.29, respectively), indicating that between-group differences in time-series changes in these laboratory data were not significantly altered by ALP.

The multivariable Cox proportional hazard regression models showed that the cross-product term between the treatment assignment and ALP was not significant with respect to the rate of CV events (P

for effect modification=0.54) (Figure 3). Similar results were obtained for the rate of all-cause death and the composite of CV events and all-cause death (P for effect modification=0.74 and 0.50, respectively) (Figure 3).

Discussion

In this *post-hoc* analysis of the J-DAVID, we found that the effect of alfacalcidol on the risk of CV events, all-cause deaths, or their composite was not significantly modified by ALP among hemodialysis patients with baseline intact PTH levels ≤ 180 pg/mL. Similarly, the effects of alfacalcidol on time-series changes in calcium, phosphate, and intact PTH levels were comparable across the baseline ALP categories.

While observational studies have reported an association between the use of VDRAs and better prognosis in hemodialysis patients,^{13,14} the J-DAVID showed a numerically higher risk of CV events in the alfacalcidol group.⁸ This may be owing to a harmful aspect of VDRAs, which might outweigh the benefits of these drugs. When used for patients without hyperparathyroidism, VDRAs could further suppress bone turnover and impair mineral buffering capacity. As a result, elevated calcium and phosphate loads due to enhanced intestinal absorption caused by VDRAs might accelerate vascular calcification.^{9–11} To address this issue in more detail, we used ALP to better specify the patients' bone turnover status. Indeed, the area under the receiver operating characteristic curve (AUC) of the total ALP for discriminating low bone turnover in patients with advanced chronic kidney disease (CKD) is reported to be 0.753, as compared to 0.606 for intact PTH.¹² Given the poor discrimination ability of PTH, participants in the J-DAVID are expected to have various bone turnover status. With a more precise assessment of bone turnover by ALP, we sought to determine how the effect of alfacalcidol was modified by bone turnover.

Contrary to our hypothesis, ALP did not significantly modify the effect of alfacalcidol on CV outcomes. There are two potential explanations for this result. First, the dose of alfacalcidol (initial dose: 0.5 $\mu\text{g}/\text{day}$) might not be enough to modulate the bone-vascular axis. This is suggested by the fact that between-group differences in calcium, phosphate, and PTH levels during the study period were small and not modified by ALP. In the ADVANCE study, which compared VDRAs alone with a combination of cinacalcet and low-dose VDRAs, the former showed greater progression of coronary and valvular calcifications accompanied by remarkable between-group differences in calcium and phosphate; patients in the VDRAs group received 12.6 $\mu\text{g}/\text{week}$ of paricalcitol on average, which is equivalent to nearly 1 $\mu\text{g}/\text{day}$ of oral alfacalcidol.¹⁵ Thus, when used at low doses as in the J-DAVID, the potential harm of VDRAs on CV outcomes may not manifest even among those with low bone turnover.

Second, it has not been formally verified whether low bone turnover *per se* actually predisposes to the progression of vascular calcification and augments CV risks. Although observational studies reported associations between low bone turnover and vascular calcification, they did not prove causation.^{9–11} In a cohort of incident hemodialysis patients, naturally decreasing PTH levels were associated with a much higher risk of mortality than treatment-induced low PTH levels,¹⁶ suggesting that factors contributing to low bone turnover, such as diabetes mellitus, malnutrition, and inflammation, are more directly involved in

CV risks.¹⁷ It is also unclear to what extent calcium load affects the risk of CV events.¹⁸ In a randomized trial of 2,309 patients undergoing hemodialysis, no significant differences were found between calcium carbonate and lanthanum carbonate in terms of the CV events.¹⁹ Notably, the median intact PTH of this trial (107.2–114.0 pg/mL) was similar to that of the J-DAVID (85.1–86.1 pg/mL). Our results suggest that low-dose VDRAs do not aggravate CV risks even among those with pre-existing low bone turnover defined by low ALP.

The Kidney Disease Outcome Quality Initiative guideline recommends withholding VDRAs if intact PTH levels are less than 150 pg/mL.²⁰ Based on the current findings, we propose that discontinuation of VDRAs is not always necessary when bone turnover markers are suppressed given that VDRAs did not significantly increase CV risks and mortality even among those with low bone turnover. It must be recognized, however, that the statistical power of our analysis may not be enough to detect a significant effect modification. Prospective confirmation of the current findings from adequately powered trials is required.

Alfacalcidol did not exhibit a favorable effect on CV outcomes even among patients without low ALP who were likely to have normal or high bone turnover. Although animal studies have reported CV protective effects of VDRAs,^{21,22} previous RCTs in non-dialysis CKD found no beneficial effects of paricalcitol on left ventricular structure and function.^{23,24} A recent meta-analysis has shown a neutral effect of vitamin D supplementation on CV outcomes in both CKD and non-CKD populations.²⁵ Compared to alfacalcidol, calcimimetics have reduced left ventricular mass among hemodialysis patients, which was correlated with a decrease in fibroblast growth factor 23.²⁶ Calcimimetics have also been more effective to attenuate serum calcification propensity, T50, than maxacalcitol.²⁷ In addition, calcimimetics would be preferred to achieve strict phosphate control that was shown to attenuate the progression of coronary artery calcification.²⁸ Taken together, calcimimetics may have an advantage over VDRAs to mitigate CV risks among hemodialysis patients.

The present study had some limitations. First, this was a post-hoc, not pre-planned, analysis of the J-DAVID trial. The study protocol was not specifically designed to test the cross-product between the treatment assignment and ALP. Thus, the statistical power to detect significant effect modifications might be limited. Larger studies are warranted to confirm whether VDRAs neither improve nor worsen the prognosis of hemodialysis patients. Second, because randomization was not stratified by ALP, there could be potential differences in the measured and unmeasured covariates between the study groups in each ALP strata, although extensive adjustment for baseline characteristics in the multivariate models was performed to address this issue. Third, we used total ALP, but not bone-specific ALP. Total ALP could be affected by factors other than bone formation, such as liver diseases although the J-DAVID trial excluded patients with abnormal liver function tests. Fourth, we did not take into account ALP after administration of VDRAs. We believe, however, that pre-treatment values are particularly of importance in deciding the initiation of the drug. Fifth, we did not have information about bone histology which is the

gold standard for the evaluation of bone turnover. Finally, our study was limited to J-DAVID participants, thereby limiting the generalizability to those with overt secondary hyperparathyroidism.

In conclusion, the effect of oral alfacalcidol on the risk of CV events and mortality was not substantially modified by ALP among hemodialysis patients without overt secondary hyperparathyroidism. The present results suggest that low-dose alfacalcidol does not worsen the prognosis of patients with pre-existing low bone turnover, but is unlikely to improve CV outcomes irrespective of the bone turnover status.

Declarations

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Author contributions

T.O., Y.S., and Y.I. conceptualized and designed the study, drafted the manuscript. H.I., D.K. and A.S. performed statistical analysis and revised the manuscript. S.N., T.M., K.M., M.I., M.E., and T.S. offered advice regarding the data interpretation, obtained funding, and provided supervision for the overall project. All of the authors approved the final version to be published.

TO and YS contributed equally to this work.

Data Availability Statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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Conflict of interest statement

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Figures

Figure 1

Figure 1

Histogram of baseline total alkaline phosphatase levels among 976 randomized patients

A total of 495 patients in the alfacalcidol group (blue) and 481 patients in the control group (red). The median [25–75th percentile] baseline alkaline phosphatase level was 234 [183–296] U/L.

Figure 2

Figure 2

Time-series changes in laboratory data during 48-month study period stratified by alkaline phosphatase tertiles

(a) Serum corrected calcium level, (b) serum phosphate level, and (c) intact parathyroid hormone level. There are no significant effect modifications between the treatment assignment, alkaline phosphatase, and time for calcium ($P=0.21$), phosphate ($P=0.55$), and intact parathyroid hormone ($P=0.29$).

Figure 3

Figure 3

Alkaline phosphatase does not modify the effect of alfacalcidol on the cardiovascular outcomes and mortality

Cubic spline curves for the hazard ratios of the alfacalcidol groups vs. the control group in terms of (a) cardiovascular events, (b) all-cause death, and (c) composite of cardiovascular events and all-cause death. The Cox models were adjusted for age, sex, body mass index, systolic blood pressure, dialysis vintage, diabetes mellitus, prior history of cardiovascular events, C-reactive protein, serum albumin, serum phosphate, serum corrected calcium, intact parathyroid hormone, high-density lipoprotein cholesterol, hemoglobin, and use of erythropoiesis-stimulating agents and intravenous iron therapy. The lines and gray zones indicate the hazard ratios and 95% confidence intervals. P-values for the coefficient of the cross-product term between the treatment assignment and alkaline phosphatase were 0.54, 0.74, and 0.50 for cardiovascular events, all-cause death, and composite of cardiovascular events or all-cause death.

Supplementary Files

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