Impact of cinacalcet introduction on MBD management: the MBD-5D study in Japan

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Chronic kidney disease-mineral and bone disorder (CKD-MBD) has recently attracted attention in light of its association with clinical outcomes, such as fracture, cardiovascular disease, and mortality. Management of CKD-MBD has therefore come to have a central role in dialysis practice. Cinacalcet, a newly developed drug, has changed prescription patterns in many centers based on different changes in MBD markers than those observed with active vitamin D derivatives. As physicians require real-world evidence to guide their treatment decisions with respect to MBD management, we conducted the Mineral and Bone Disorder Outcomes Study for Japanese CKD Stage 5D Patients (MBD-5D), a 3-year observational study involving prevalent hemodialysis patients with secondary hyperparathyroidism (SHPT). Here, we review the results from the MBD-5D and discuss issues of MBD management in the cinacalcet era. Three years since the introduction of cinacalcet, 40% of hemodialysis patients with SHPT have come to use cinacalcet, enjoying marked improvement in management of circulating MBD markers, such as intact parathyroid hormone (PTH), phosphorus, and calcium. Combination therapy with cinacalcet and a vitamin D receptor activator (VDRA) may allow physicians to choose more suitable prescription patterns based on patient characteristics and therapeutic purposes. We observed an additive association between 'starting cinacalcet' and 'increased VDRA dose,' with marked improvement in the control of intact PTH levels. Further, the combination pattern of 'starting cinacalcet' and 'decreased VDRA dose' was associated with better achievement of target serum phosphorus and calcium levels. Future studies should examine the effect of different prescription patterns for SHPT treatment on clinical outcomes.

Kidney International Supplements (2013) **3,** 436–441;
doi:10.1038/kisup.2013.91

KEYWORDS: cinacalcet; dialysis patients; mineral and bone disorder

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Chronic kidney disease-mineral and bone disorder (CKD-MBD) involves disturbances of mineral metabolism, bone disease, and vascular calcification. It has attracted attention in light of its association with fracture, cardiovascular disease, and mortality, underscoring the clinical importance of MBD management. A number of risk factors for mortality among hemodialysis patients have been identified. Circulating MBD markers (phosphorus, calcium, and intact parathyroid hormone (PTH)) are known to be modifiable risk factors, and their management has a central role in dialysis practice. A previous study examined the relative impact of dialysis practices (such as anemia management, MBD management, and adequate dialysis) by calculating population-attributable risk fraction.[1] Population-attributable risk fraction of MBD (17.5%) was found to be higher than that of inefficient dialysis (5.1%) or anemia (11.3%), suggesting that MBD management is relatively important for improving clinical outcomes compared with other dialysis practices.

MBD management regimens can change with the introduction of new drugs to the market. Treatment of high intact PTH (iPTH) levels was previously limited to two options: Vitamin D receptor activator (VDRA) and parathyroidectomy. As such, the introduction of cinacalcet, which dramatically reduces iPTH levels, was expected to improve MBD management. In patients with simultaneously high serum levels of iPTH, calcium, and phosphorus, it is often difficult to manage PTH levels with VDRA given the concurrent stimulation of the intestinal absorption of phosphorus and calcium. Because cinacalcet does not increase serum levels of phosphorus or calcium, it may be the 'silver bullet' for treating patients with simultaneously high levels of iPTH, calcium, and phosphorus.

Randomized controlled trials examining the effect of cinacalcet on MBD markers and cardiovascular events in selected dialysis patient populations have been reported recently.[2,3] However, physicians require real-world evidence to guide their treatment decisions on MBD management. We therefore conducted the Mineral and Bone Disorder Outcomes Study for Japanese CKD Stage 5D Patients (MBD-5D),[4] a 3-year case-cohort study involving prevalent

hemodialysis patients with secondary hyperparathyroidism (SHPT) based on the whole cohort of patients initially enrolled (8229 patients) and a sub-cohort of patients randomly selected (3276 patients) from the whole cohort. Here, we review the results from the MBD-5D and discuss the issues of MBD management in the cinacalcet era.

MBD-5D STUDY DESIGN

The design of the MBD-5D study has been reported in detail previously.[4] The target population was hemodialysis patients with SHPT, defined as patients with serum iPTH 180 pg/ml or receiving intravenous VDRA or oral falecalcitriol. Patients with hemodialysis duration 3 years were included in the MBD-5D study. Settings were relatively large dialysis facilities from nine geographically divided regions of Japan ($N = 86$), with the number of facilities chosen in each region proportional to the number of hemodialysis patients in that region. Because MBD markers are tested for periodically and MBD treatment patterns are often changed based on levels of iPTH, calcium and phosphorus, data directly related to MBD markers and treatments were collected every 3 months,[5] while other data were collected every 6 months. Patient follow-up started in January 2008 and ended in January 2011. The MBD-5D study was conducted as case-cohort study, including the whole cohort ($N = 8229$) and a randomly selected sub-cohort ($N = 3276$). When we used cardiovascular death or death from any cause as our main outcome, the whole cohort was analyzed as a case-cohort study, because that sample size is required to detect meaningful associations among the Japanese hemodialysis patient population with an infrequent incidence of major outcomes.

Several unique characteristics of the MBD-5D study design warrant mention. First, a case-cohort design was used to facilitate efficient analysis of the whole cohort. This study design is useful when study budget and availability of a clinical research coordinator is insufficient to collect data for all patients thoroughly. As such, in the MBD-5D study, thorough data were prospectively collected for only the subcohort patients, not the whole cohort, thereby saving cost and manpower. For those patients making up the rest of the whole cohort ($N = 4953$), only baseline data and the date and occurrence of main outcomes (i.e., death from any cause or cardiovascular death) were collected initially; detailed data were then collected retrospectively for those non-subcohort patients who developed main outcomes. Second, the MBD-5D is a closed cohort that was started before cinacalcet was marketed. We were therefore able to demonstrate the rate at which cinacalcet prescription spread in daily practice. In addition, when examining the association between cinacalcet prescription and hard clinical outcomes, including only new cinacalcet users who had pretreatment, MBD markers might reduce bias with advanced statistical analysis correcting time-varying cinacalcet prescription and confounders, such as when using marginal structural models.[6]

CHANGES IN PRESCRIPTION PATTERNS AFTER CINACALCET INTRODUCTION

Given that the MBD-5D is an observational study that begun just when cinacalcet first became available in Japan (January 2008), we were able to observe the spread of cinacalcet prescription in daily practice. The proportion of patients receiving cinacalcet increased steadily from 0% to 42% over the 3 years following cinacalcet introduction (Figure 1a). In the years since its release, cinacalcet has come to have a major role in managing MBD. This relatively rapid spread of cinacalcet use suggests hope among members of the medical and pharmaceutical communities that cinacalcet will compensate for the shortcomings of traditional MBD treatment, such as VDRA and phosphate binders.

MBD-5D findings demonstrated that cinacalcet users were younger, less likely to have comorbid conditions (such as diabetes and cardiovascular disease), and more likely to have high serum levels of calcium, phosphorus, and iPTH than non-users. This observation suggests that cinacalcet was more likely to be prescribed for relatively healthy dialysis patients who were expected to have improved clinical outcomes via better control of MBD markers.

The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial,[2] which is a randomized controlled trial to examine the effect of cinacalcet on cardiovascular events, reported that only 38% (741 patients) of the intervention group (1948 patients who had been randomized to receive cinacalcet) had continued cinacalcet during the follow-up period (median follow-up time of intervention group, 21 months), with an annual continuing rate of only 73%. As such, the proportion of patients receiving cinacalcet continuously in the EVOLVE study was lower than expected.

Regarding the proportion of patients continuing cinacalcet in a real-world, estimated proportion receiving cinacalcet at the end of the follow-up period in the present study (median follow-up time: 33 months) was 70%, with an annual continuing rate of 89%. Several reasons may explain the observation of a higher proportion of patients receiving cinacalcet continuously in the real-world setting in Japan than in the international randomized controlled trial. First, median dose of cinacalcet in the MBD-5D study was 25 mg/day (interquartile range: 25–50 mg/day), which was lower than that in the EVOLVE study (median dose: 55 mg/day). Although differences in race and stature between Japan and the mostly Caucasian and African-American patient population of EVOLVE may have influenced the metabolism of cinacalcet and discrepant clinical outcome findings, the lower cinacalcet dose used in Japan might also have contributed to relatively higher proportion of patients staying on cinacalcet therapy in this country. Second, patients in the MBD-5D study had lower iPTH levels before cinacalcet administration than those in the EVOLVE study (median levels of iPTH, 265 vs. 693 pg/ml). This also may have contributed to the higher proportion of patients receiving cinacalcet continuously.

Regarding changes in administration of other MBD medications, such as VDRA and phosphate binders, after