Chapter 3

“Real world” use of cinacalcet for the management of secondary hyperparathyroidism in The Netherlands: Analysis of data from the European ECHO observational study

Marc G Vervloet, Peggy WG du Buf-Vereijken, Bert-Jan Potter van Loon, Nick Manamley, Louis JM Reichert, Peter JH Smak Gregoor

Submitted
Chapter 3: Cinacalcet use in The Netherlands

Abstract

Background. ECHO was a pan-European observational study that investigated the use and effectiveness of cinacalcet in the treatment of severely uncontrolled secondary hyperparathyroidism (SHPT) in "real-world" clinical dialysis practice. Here we report data for the Dutch cohort of this study.

Methods. All Dutch participants in the pan-European ECHO study were included in this study. All patients who initiated cinacalcet based on clinical judgement were observed from 6 months prior to start of treatment up to 12 month after the start of treatment. Biochemical, pharmacological and clinical data were collected over this observation period.

Results. 144 dialysis patients with a mean age of 59 years were enrolled from 13 sites. Of these, nearly 80 were on hemodialysis, with a median dialysis vintage of 52 months. Median peritoneal dialysis vintage was 32 months. On initiation of cinacalcet, median (IQ ranges) biochemical values improved for parathyroid hormone (PTH), calcium, and phosphate levels from 88 pmol/l (55-127) to 39.4 (21-79), 2.6 mmol/l (2.5-2.7) to 2.3 (2.25-2.55), and 1.8 mmol/l (1.5-2.1) to 1.7 (1.2-2.1) respectively. On initiation of cinacalcet, attainment of prevailing KDOQI targets increased from 8% to 17% for PTH, from 14% to 41% for calcium, and from 45% to 49% for phosphate. The median percentage change from baseline for PTH was -34%, -49%, and – 58% for month 3, 6 and 12 respectively. The use of active vitamin D compounds and phosphate binder therapy remained stable during the observation period. Median dose at month 12 was 60 mg; cinacalcet was well tolerated.

Conclusion. Initiation of cinacalcet in Dutch dialysis patients with severely uncontrolled SHPT leads to substantial improvements in both absolute PTH and calcium levels and the attainment of target levels as recommended in the prevailing guidelines.
Chapter 3: Cinacalcet use in The Netherlands

Introduction

Secondary hyperparathyroidism (SHPT) is a frequent complication of chronic kidney disease (CKD)\(^1\). It is caused by vitamin D deficiency, chronic hyperphosphataemia, and decreased expression of the vitamin D receptor, the calcium sensing receptor and klotho\(^2\)\(^-\)\(^9\). The latter impairs the inhibitory effects of FGF23 on the parathyroid. The presence of SHPT is associated with dismal outcome in several epidemiological studies\(^10\)\(^-\)\(^13\). National (www.nefro.nl) and international guidelines (KDOQI, recently replaced by KDIGO [Kidney Disease: Improving Global Outcomes] at www.kdigo.org) advocate controlling this complication with dietary and pharmacological interventions. Consistent achievement of treatment targets for levels of calcium, phosphate and PTH is linked to improved outcome. However, only a minority of patients with CKD stage 5 reach all KDOQI targets simultaneously\(^14\).

The therapeutic options treating the laboratory abnormalities of CKD- mineral and bone disease (CKD-MBD) traditionally consisted of several classes of phosphate binders and vitamin D analogues. Although being effective in treating some aspects of CKD-MBD, these agents, especially calcium-containing phosphate binders and vitamin D analogues have been associated with increased calcium loading and hyperphosphataemia respectively\(^15\)\(^,\)^16. These two effects are thought to play a role in soft tissue and vascular calcification.

The calcimimetic cinacalcet hydrochloride (Mimpara\(^\text{®}\), Amgen Inc, Thousand Oaks, CA, USA) was released in the Netherlands in 2005 for the treatment of SHPT in patients CKD stage 5. This new class of drugs acts by modulating the calcium-sensing receptor, increasing its sensitivity to actual calcium levels\(^17\)\(^,\)^18. In phase III clinical trials, cinacalcet has been shown to improve the likelihood of achieving target levels for the metabolic abnormalities of CKD-MBD\(^19\)\(^-\)\(^21\). As the controlled situation of prospective clinical trials can differ substantially from every-day clinical practice, it was encouraging that similar levels of improvement in calcium, phosphate and especially PTH were achieved in the recently published ECHO-study (Evaluation of the Clinical Use of Mimpara\(^\text{®}\) in Hemodialysis and Peritoneal Dialysis Patients, an Observational Study)\(^22\). In the ECHO study, the efficacy of cinacalcet was studied in “real-world” situations in 187 sites across 12 countries throughout Europe. Cinacalcet was initiated as clinically indicated, as judged by the treating physician, rather than by using a study algorithm, and as such better reflects every day practice. Independent of baseline levels of PTH, a substantial and sustained improvement over 12 months was noticed for PTH,
Chapter 3: Cinacalcet use in The Netherlands

calcium and phosphate. A subsequent analysis of the ECHO-data demonstrated important differences across participating countries with regard to the timing of initiation of cinacalcet, use of concomitant medication and response to therapy. In the current paper the results for the Dutch participants of the ECHO-study are presented.

Methods

Patients

The ECHO study evaluated the use and effectiveness of cinacalcet in almost 2000 dialysis patients with SHPT in a real-world clinical practice setting in 12 European countries. In the current study, only patients enrolled in the Netherlands are analysed. Detailed descriptions of the methodology used have been published previously. In short, all dialysis patients, either hemodialysis or peritoneal dialysis, in participating centers, that were prescribed cinacalcet at the decision of their treating physician were eligible for inclusion in the analysis. Data 6 months prior to enrolment were collected retrospectively, data after start of cinacalcet were collected primarily prospectively for up to 12 months. No treatment algorithm was provided, no additional visits to the clinic were required, and no additional laboratory testing was performed. Participants provided informed consent. Using case report forms, data regarding medical history, comorbidities, laboratory parameters, and medication use were collected.

Parameters and statistical analysis

Key parameters for the ECHO study were the percentages of patients attaining KDOQI-targets for PTH, calcium, phosphate and Ca x P product. During the study period KDOQI targets, rather than the more recent KDIGO guidelines were the accepted treatment guidelines. Also the absolute and percentage changes for these parameters were recorded. Laboratory data were collected 6 month prior to, at start of cinacalcet, and 3, 6 and 12 month after initiation of cinacalcet treatment. Only laboratory values within a prespecified time frame of these time points were analysed; ± 6 weeks for PTH and ± 2 weeks for Ca and P of these time points were analysed. For the treatment initiation timepoint, only values prior to actual start of cinacalcet were used. To study the impact of baseline severity of SHPT, a subsequent analysis was performed for achievement of KDOQI treatment guidelines.
Chapter 3: Cinacalcet use in The Netherlands

and absolute and percentage change in PTH, according to baseline values of PTH (mild: 32-<52 pmol/l; moderate: 53-85 pmol/l; severe: >85 pmol/l).

Observed data from all enrolled patients who started cinacalcet were analysed (full data set), with percentages calculated according to the total number of patients with no missing data. Analyses were descriptive and are presented for continuous and categorical variables: no formal statistical comparisons were conducted. Intact PTH levels, as other laboratory parameters were analysed locally. No laboratory tested bio intact PTH, and laboratory technique was unchanged during the study period. The value of albumin-corrected calcium was used instead of actual calcium, using the formula: Total calcium (mmol/l) + 0.2(40 – albumin (g/l)).

Results

Patients

From the total of 1865 patients in the entire European cohort, 144 patients were enrolled from 13 sites in The Netherlands. Of these 109 patients (75.7%) completed the study. The reasons for withdrawal from study were death (17 patients, 11.8%), patients transfer to another clinic (10 patients, 6.9%) or non-specified reason in the remaining 8 patients. 84 patients (58.3) were still on cinacalcet treatment at month 12. Reasons for discontinuation of cinacalcet were PTH over suppression (5 pts), nausea and vomiting (5 pts), hypocalcaemia (4 pts), other adverse reaction ( 5 pts), parathyroidectomy (5 pts), renal transplantation (8 pts), poor response (2 pts) or other reason (22 pts). For 4 patients the reason for discontinuation was not recorded.

The patients mean age was 59 years at start of cinacalcet (range 19-90), as shown in table 1. The majority (80%) were on hemodialysis with a median dialysis vintage of 51.8 month (interquartile range 23.7 – 95 month), and 30 had a previous renal transplantation. Most patients were using active vitamin D (72.9%) and 95.1% was using phosphate binder therapy. All patients had severely uncontrolled SHPT with median PTH of 87.1 pmol/l (IQR 54.8 – 126.0). Other baseline data are shown in table 1.
Chapter 3: Cinacalcet use in The Netherlands

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), median (range)</td>
<td>59 (19 - 90)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>79 (54.9)</td>
</tr>
<tr>
<td>Hemodialysis, n (%)</td>
<td>115 (79.9)</td>
</tr>
<tr>
<td>Duration of HD (months), median (Q1, Q3)</td>
<td>51.8 (23.7, 95.0)</td>
</tr>
<tr>
<td>Peritoneal dialysis, n (%)</td>
<td>28 (19.4)</td>
</tr>
<tr>
<td>Duration of PD (months), median (Q1, Q3)</td>
<td>31.6 (16.6, 48.7)</td>
</tr>
<tr>
<td>Previous renal transplant, n (%)</td>
<td>30 (20.8)</td>
</tr>
<tr>
<td>Awaiting renal transplantation, n (%)</td>
<td>35 (24.3)</td>
</tr>
<tr>
<td>Previous parathyroidectomy, n (%)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Any vitamin D treatment, n (%)</td>
<td>105 (72.9)</td>
</tr>
<tr>
<td>Any phosphate binder, n (%)</td>
<td>137 (95.1)</td>
</tr>
<tr>
<td>PTH, (pmol/l) median (Q1, Q3)</td>
<td>87.9 (55.2, 127.2)</td>
</tr>
<tr>
<td>Phosphate, (mmol/l), median (Q1, Q3)</td>
<td>1.8 (1.5, 2.1)</td>
</tr>
<tr>
<td>Calcium, (mmol/l), median (Q1, Q3)</td>
<td>2.6 (2.5, 2.7)</td>
</tr>
<tr>
<td>Ca x P (mmol2/l2), median (Q1, Q3)</td>
<td>4.6 (3.9, 5.5)</td>
</tr>
</tbody>
</table>

Table 1: Baseline characteristics at initiation of cinacalcet treatment.

Achievement of KDOQI treatment target and changes in laboratory values

The proportion of patients achieving KDOQI guideline suggested values increased for all four laboratory target ranges: from 8% to 17% for PTH, from 45% to 49% for phosphate, from 14% to 41% for calcium, and from 41% to 60% for Ca x P product (fig 1). The median (IQR ranges) percentage change from baseline for PTH was -34% (-59, -7%), -49% (-70, -13%), and -58% (-76, -22%) for month 3, 6 and 12 respectively (fig 2a). The absolute and percentage changes from baseline for values of calcium, phosphate and Ca x P product are shown in fig 2b-2d.

Substantial improvement in attaining KDOQI™ targets for calcium was achieved for of all tertiles of baseline PTH-levels, while for PTH targets especially the lowest and highest baseline PTH tertile most frequently reached these targets, as shown in figure 3. Figure 4 demonstrates that the pattern of absolute and percentage change of PTH for the three subgroups was similar, at all time points.
Chapter 3: Cinacalcet use in The Netherlands

**Fig 1:** Proportions of patients (observed cases) achieving Kidney Disease Outcomes Quality Initiative (KDOQI™) recommended targets at baseline, 6 months and 12 months. Ca, calcium; Ca x P, calcium–phosphorus product; IPTH, intact parathyroid hormone; P, phosphorus.

**Cinacalcet dose, and use of vitamin D and phosphate binders**

All but one patient started on a dose of 30 mg cinacalcet per day. For those that remained on treatment by month 12 the mean daily dose was 68.6 mg (standard deviation (SD) 34.4).

For the entire population that started cinacalcet at baseline, including 25 patients with interrupted cinacalcet at month 12, mean daily dose by month 12 was 52.6 mg (SD 41.9).

<table>
<thead>
<tr>
<th></th>
<th>alfalcaldiol</th>
<th>calcitriol</th>
<th>paricalcitol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>iv (n=22)</td>
<td>oral (n=59)</td>
<td>iv (n=11)</td>
</tr>
<tr>
<td>month -6</td>
<td>3.7 (2.9)</td>
<td>3.1 (2.2)</td>
<td>5.0 (1.4)</td>
</tr>
<tr>
<td>baseline</td>
<td>4.6 (3.1)</td>
<td>3.2 (2.6)</td>
<td>3.6 (2.1)</td>
</tr>
<tr>
<td>month 6</td>
<td>5.5 (2.7)</td>
<td>3.8 (3.2)</td>
<td>3.5 (2.4)</td>
</tr>
<tr>
<td>month 12</td>
<td>5.4 (2.6)</td>
<td>4.3 (4.0)</td>
<td>3.0 (2.1)</td>
</tr>
</tbody>
</table>

**Table 2:** Mean (SD) weekly dose of active vitamin D throughout the study period. The number at the top of each column depicts the number taking that drug at baseline. Only data are shown for patients for whom dosing data are available
Figure 2a: Changes in serum levels of laboratory parameters over time: intact parathyroid hormone (iPTH, Fig. 2a), phosphate (Fig. 2b), calcium (Fig. 2c), and calcium-phosphorus product (Fig. 2d). The dashed line indicates KDOQI's treatment target. KDOQI, Kidney Disease Outcomes Quality Initiative; Q, quartile.
Chapter 3: Cinacalcet use in The Netherlands

Fig 3a-d: Achievement of Kidney Disease Outcomes Quality Initiative (KDOQI™) recommended targets for PTH (fig 3a), phosphate (fig 3b), calcium (fig 3c), and calcium-phosphate product (fig 3d), according to baseline disease severity (observed cases): mild (baseline intact parathyroid hormone [iPTH] 32–<53 pmol/l), moderate (baseline iPTH 53–85 pmol/l) and severe (baseline iPTH >85 pmol/l). Ca, calcium; Ca x P, calcium–phosphorus product; P, phosphorus
Chapter 3: Cinacalcet use in The Netherlands

![Graph showing median serum PTH levels over time and comparison to KDOQITM recommended targets.]

**Fig 4:** Magnitude of intact PTH reduction according to baseline disease severity: Mild (iPTH 300-500 pg/ml), moderate (iPTH 500-800 pg/ml) and severe (iPH >800 pg/ml)

The majority of patients were on active vitamin D treatment at baseline (72.9% of those for whom these data were available). Dose changes for active vitamin D compounds are shown in table 2.

At baseline, 137 patients (95%) were on phosphate binder therapy (53 on calcium-based binders, 124 on sevelamer, 16 on aluminium-based binders; lanthanum was not available at baseline). The total number of patients using each drug changed only minimal during the observation period (data not shown) Changes in mean dosages for each individual phosphate binder are shown in table 3.

**Safety**

Adverse events were reported by 22 patients (15.3%). One episode of hypocalcemia was reported as serious. The other non-serious AE were nausea and vomiting (7.5%), hypocalcemia (2.1%), abdominal pain, malaise, myalgia (1.4% each), and pruritus, urticaria, paraesthesia, calcnosis, pain in extremity was reported by 1 patient each (0.7%).

---

55
Chapter 3: Cinacalcet use in The Netherlands

<table>
<thead>
<tr>
<th></th>
<th>Ca-based, n=53</th>
<th>Sevelamer, n=124</th>
<th>Lanthanum, n=0 (baseline)</th>
<th>Al-based, n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>month -6</td>
<td>1900 (1477)</td>
<td>7157 (3298)</td>
<td>0</td>
<td>1842 (1345)</td>
</tr>
<tr>
<td>baseline</td>
<td>1740 (1123)</td>
<td>6569 (3411)</td>
<td>0</td>
<td>2163 (1355)</td>
</tr>
<tr>
<td>month 6</td>
<td>2015 (1266)</td>
<td>6637 (3119)</td>
<td>2400</td>
<td>1464 (551)</td>
</tr>
<tr>
<td>month 12</td>
<td>2171 (1465)</td>
<td>6673 (3304)</td>
<td>1768 (1750)</td>
<td>1975 (1704)</td>
</tr>
</tbody>
</table>

*Table 3: Mean (SD) daily dose (mg) of phosphate binder therapy throughout the study period. Calcium-based drug-dosing is based on elemental calcium content of the binder. One patient used lanthanum at month 6, 2 at month 12.*

**Discussion**

The current analysis of Dutch patient included in the pan-European ECHO study shows, that achievement of KDOQI guideline treatment targets for the management of CKD-MBD has improved after the introduction of cinacalcet, especially for PTH and calcium levels, as shown in figure 1. Its effectiveness is consistent with previous controlled trials. As since data collection from this study, guidelines have changed from KDOQI to KDIGO, important additional information is provided by the absolute and percentage change from baseline of these laboratory markers of deranged mineral metabolism. As evident from the baseline characteristics of this Dutch cohort, these patients had severe and uncontrolled SHPT, reflected by high levels of PTH, despite widespread use of active vitamin D, relatively high levels of calcium, and high use of phosphate binder therapy. Nevertheless, PTH levels declined to over 50% from month 6 on, and this decline was sustained during the subsequent study period. As evident from figure 2, the majority of patients would have reached the more recent KDIGO suggested range for PTH (maximum of up to 9 times the upper limit for the assay). Importantly, the Dutch data confirm previous observations, that a high baseline level of PTH does not predict cinacalcet unresponsiveness (figure 3). Indeed, as shown in figure 4, those with moderate or severe SHPT had an even more pronounced reduction in PTH level, when comparing to the subgroup with mild SHPT. Although this may be the consequence of up titration during follow-up, this appears unlikely for two reasons. First, the most striking reduction in PTH levels was seen already at month 3 in all groups, a moment at which dose optimisation probably had not occurred yet. Second, the mean daily dose of cinacalcet was only 68.6 mg/day (± 34.4 mg) while the majority of patients were grouped in those with moderate or severe SHPT. Therefore it appears likely that the
parathyroid gland remains sensitive to the effects of the calcimimetic cinacalcet, irrespective of stage of disease.

Despite current guidelines, and epidemiological associations linking SHPT with increased mortality and even suggestions that controlled SHPT may improve outcome\(^{14,24}\), this is still a matter of debate\(^{25}\). A recent meta-analysis found no association between level of PTH and various markers of clinical outcome\(^{26}\). ARO group found a U-shaped all cause mortality\(^{27}\). The recent ADVANCE trial showed attenuated vascular and cardiac valve calcifications when SHPT treatment in hemodialysis patients was based on cinacalcet, as compared to a vitamin D based regimen\(^{28}\). Currently, a prospective controlled trial is underway (EVLOLVE), that will address the question whether or nor cinacalcet improves clinical outcome\(^{29}\).

An important additional finding of the current study is that besides improvements in level of PTH, also Ca-levels declined, while the change in phosphate was negligible (fig 2b and 2c). The associated improvement in Ca x P product clearly was due to the parallel changes in both calcium and phosphate levels (fig 2d). As for PTH-response, baseline severity of SHPT did not predict the change in calcium levels after initiation of cinacalcet (fig 3c). The baseline level of calcium, and its subsequent decline after initiation, was higher in the Dutch cohort compared to other European countries\(^{31}\). This is probably caused by more widespread use of active vitamin D compounds in the Netherlands for the treatment of SHPT (72.9%). This finding, together with the highest baseline PTH levels in the Netherlands (together with the UK and Ireland), suggests that cinacalcet was started rather late in the course of development of SHPT, compared to other European countries. The subsequent decline in calcium levels can have several explanations. First, the decline in PTH could have led to a decline in frequency or dosing of active vitamin D compounds. However, as shown in table 2, vitamin D dosing tended to increase. The number of patients being described vitamin D did not change (data not shown). Second, it is possible that the amount of calcium-containing phosphate binders decreased, but again this was not supported by our data (table 3). A final possible explanation of the decline in calcium level is that it is secondary to the lower PTH level, which in turn led to improvement of hyperdynamic bone disease and reduced release of calcium from bone. This hypothesis could have been supported by changes in levels of alkaline phosphatase\(^{30,31}\), but that was not routinely determined, and therefore not captured in the database of the ECHO study. The clinical consequences of the decline in calcium levels could be important. First, as noted above, high calcium levels or intake are thought to be
Chapter 3: Cinacalcet use in The Netherlands
detrimental in dialysis patient\textsuperscript{27,32-35}, although this is still debated and lacks definitive proof\textsuperscript{36,37}. Second, a decline in calcium level may widen the window of opportunity to initiate or continue active vitamin D compounds, which is consistently associated with improved mortality\textsuperscript{38}. In addition a recent observational study found a significant survival benefit associated with cinacalcet prescription in patients receiving i.v. Vitamin D\textsuperscript{34}.

The changes of phosphate levels on initiation of cinacalcet were small (fig 2b). Compared to other European countries P –decline was among the lowest, but baseline level of phosphate was also among the lowest and phosphate binder therapy was the highest in Europe\textsuperscript{23}, possibly explaining the lack of pronounced decline in phosphate level. Remarkable is the observation that phosphate improved most in those patients with highest baseline PTH level (fig 3b), again suggesting that some phosphate originally was bone-derived, and improved on better-controlled SHPT by cinacalcet. However, this hypothesis requires additional studies.

Cinacalcet was generally well tolerated. Of 144 patients that started cinacalcet 56 discontinued its use for several reasons including PTH over suppression in 5, and hypocalcaemia in 4. During the period this study was performed, quite shortly after release of cinacalcet on the Dutch market, dosing titration was generally based on manufacturer provided instruction, but it is possible that some individual patients may require more prudent dosing. Another frequent reason for discontinuation was renal transplantation, because several participating centres did not use cinacalcet off-label post-transplantation. The frequency of adverse drug reactions was low, with gastrointestinal complaints being most frequent.

Our study has several limitations. First, as a consequence of study design, the study population is not well defined, because inclusion depended on clinical judgement on the need to initiate cinacalcet. Despite the fact that the studied patients were selected on the basis of severely uncontrolled SHPT, the one-year mortality rate was rather low (11.8%). This probably reflects some unidentified beneficial selection and precludes unrestricted general applicability. Due to the observational nature of this study and the lack of a comparator group, firm conclusions on efficacy of cinacalcet cannot be drawn from our data. However, strength of our study is its reflection of every day clinical practice, and provided clinicians important information what to expect from this new class of drugs. Also, due to the
multicentre design, included patients likely reflect the average Dutch dialysis patients with uncontrolled SHPT.

We conclude that in uncontrolled SHPT, despite conventional treatment, the addition of cinacalcet leads to substantial improvement in biochemical parameter of CKD-MBD. As such cinacalcet appears to be a welcomed expansion of therapeutic possibilities. While the Dutch patients started relatively late with this drug, this did not jeopardize its efficacy. Whether this new intervention will lead to reduced need for parathyroidectomy, decreased development of vascular calcification and ultimately a decline in cardiovascular morbidity and mortality, both impending hallmarks of uncontrolled CKD-MBD, needs prospective controlled clinical trials.

Acknowledgement:
This study was sponsored by Amgen Europe. Minimal editorial support, funded by Amgen (Europe) GmbH, was provided by Kate Bass on behalf of Bioscript Sterling Ltd.

We would also like to thank the Dutch ECHO-investigators:
EC Hagen, AAMJ Hollander, MAGJ ten Dam, LJ Vleeming, HW van Hamersveld, Dr KW Mui, Dr P Douwes, Dr ML Galli.
Chapter 3: Cinacalcet use in The Netherlands

References


8. Suzuki M. [Control of the secondary hyperparathyroidism by the suppression of plasma phosphate level in chronic renal failure patients]. Clin Calcium 2001; 11: 1335-1339


Chapter 3: Cinacalcet use in The Netherlands


