Effectiveness of cinacalcet in patients with recurrent/persistent secondary hyperparathyroidism following parathyroidectomy: results of the ECHO study

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Abstract

Background. Progressive secondary hyperparathyroidism (sHPT) is characterized by parathyroid gland hyperplasia which may ultimately require parathyroidectomy (PTX). Although PTX is generally a successful treatment for those patients subjected to surgery, a significant proportion develops recurrent sHPT following PTX. ECHO was a pan-European observational study which evaluated the achievement of KDOQITM treatment targets with cinacalcet use in patients on dialysis. Previously published results showed that cinacalcet plus flexible vitamin D therapy lowered serum PTH, phosphorus and calcium in the clinical practice with similar efficacy as seen in phase III trials.

Methods. This subgroup analysis of ECHO describes the real-world cinacalcet treatment effect in patients with recurrent or persistent sHPT after PTX (n = 153) compared to sHPT patients without prior history of PTX (n = 1696).

Results. Both groups of patients had substantially elevated serum PTH with comparable sHPT severity at baseline. After 12 months of cinacalcet treatment, 20.3% (26/128) of patients with prior PTX and 18.2% (253/1388) of patients without prior PTX achieved serum PTH and Ca × P values within the recommended KDOQITM target ranges.

Conclusions. Our data support the successful use of cinacalcet in patients with recurrent/persistent sHPT after PTX.

Introduction

Secondary hyperparathyroidism (sHPT) is part of the mineral metabolism and bone disorder observed in patients with chronic kidney disease (CKD-MBD) and usually coupled with alterations in calcium (Ca) and phosphorus (P) metabolism. sHPT is characterized by abnormally elevated levels of parathyroid hormone (PTH) and is associated with an increased risk of cardiovascular morbidity and mortality in patients on dialysis [1–6]. Consistent control of these biochemical parameters has been shown to improve survival [7] and reduce the risk of cardiovascular and all-cause mortality [6]. Persistently increased serum PTH levels >800 pg/mL (88.0 pmol/L) in the presence of hypercalcaemia or hyperphosphataemia refractory to medical therapy are an indication for surgery [8]. Subtotal and total parathyroidectomy (PTX) with forearm autograft arose as a treatment option in the 1990s [9], and PTX continues to be a primary therapeutic option for refractory sHPT in both Europe and the USA. Rates of PTX increased for US patients on haemodialysis from 1998 to 2002 despite an increase in therapeutic options [10]. The frequency of PTX across Europe has remained relatively stable since the mid-1980s [11] and is lower in older patients [12].

PTX offers the highest percentage cure for sHPT, compared to all other medical and surgical treatments. However, recurrent hyperparathyroidism can be observed in 10–70% of patients dependent on follow-up time [13–15]. What remains unclear is whether the optimal level or target range of serum PTH for patients with prior PTX is equivalent to that of uraemic patients without prior PTX [16]. Uraemic patients with sHPT with or without prior PTX have reduced vitamin D receptor (VDR), Ca-sensing receptor (CaSR), Klotho and FGFR1 expression in hyperplastic parathyroid tissue [9,17–19]. This complicates the control of PTH secretion. Due to the surgical limitations and difficulties of re-PTX, a pharmacological approach to the treatment of recurrent sHPT seems to be
a good alternative to control and possibly prevent its systemic impact. Calculimetics are allosteric modulators of the CaSR that sensitize the receptor to extracellular Ca. This results in reduced PTH secretion and inhibited parathyroid cell proliferation [20,21]. This decrease in serum PTH is accompanied by control of serum Ca and P levels in patients with shPT as well as a halt or regression of parathyroid gland hyperplasia [22]. Inhibited parathyroid gland growth slows disease progression and reduces the risk of PTX [23,24]. This achievement is in line with the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF-K/DOQITM) treatment goals for shPT [8].

Very limited data exist evaluating the use of cinacalcet in patients with prior PTX who show persistent shPT or develop recurrent shPT [25]. ECHO is the first pan-European observational study to focus on cinacalcet usage in daily clinical practice in patients with and without prior PTX. In this subgroup analysis, the effect of cinacalcet treatment is compared in patients with shPT with and without prior PTX.

Materials and methods
ECHO [Evaluation of the Clinical Use of Cinacalcet (Mimpara®)] in Haemodialysis and Peritoneal Dialysis Patients: an observational study] was a pan-European, multi-centre, open-label, part retrospective/part prospective observational study to evaluate cinacalcet use in the clinical setting. Details of the ECHO study methodology have been published elsewhere [26]. The results describe data collected for 1865 patients >18 years of age receiving dialysis who had been prescribed cinacalcet at the decision of their treating physician. Patients signed an informed consent where required by local regulations. No treatment algorithm was provided, and no additional clinic visits or laboratory/diagnostic tests were performed for the purposes of this study. Intact PTH (iPTH), P and Ca data were collected at 6 months prior to the initiation of cinacalcet (retrospective data), at cinacalcet initiation (baseline) and at 6 and 12 months of cinacalcet use (retrospective or prospective data). Patients’ biomarker data, medical histories, comorbidities, concurrent medication and history of PTX (yes/no) were recorded using case report forms. Patients with unknown PTX history at baseline were excluded from this analysis. iPTH values were not adjusted and were recorded as measured.

Serious adverse drug reactions (ADRs) were defined as per protocol attributed to the use of cinacalcet and were recorded from cinacalcet initiation to the end of the study at 12 months. Non-serious ADRs (e.g. nausea, vomiting, diarhoea, dyspepsia, hypocalcaemia, abdominal pain) were any which did not meet the protocol criteria for being categorized as serious by the investigator. A list of hypocalcaemia events of interest has been described previously [26]: blood Ca decreased, Ca deficiency, ionized Ca decreased, blood Ca abnormal, ionized Ca abnormal, hypocalcaemia and tetany.

Statistical methods
Descriptive statistics were used to define baseline patient characteristics. These included the number of participants, mean (SD), median, 25th and 75th percentiles. Minimum and maximum values were presented for continuous variables. For categorical variables, the number and percentage of participants that fit each category are reported. Biomarker variables measured longitudinally are summarized graphically by plotting the median with 25th and 75th percentiles as described previously [26].

Results
Of the 1865 patients enrolled, 16 patients were excluded from this analysis because of unknown PTX status at baseline. One hundred and fifty-three patients (mean age ± SD: 57 ± 14 years) had PTX prior to baseline, the remaining 1696 patients (mean age ± SD: 58 ± 15 years) had no history of PTX (Table 1).

At baseline, in the PTX group, 5.3% (8/151) of patients had iPTH within the KDOQITM target range versus 3.4% (57/1671) of patients in the non-PTX group. Median iPTH was 856 (479, 1293) pg/mL and 717 (509, 1037) pg/mL, respectively. Median P and Ca levels at baseline were similar in both groups (Table 1).

Following 12 months of cinacalcet therapy, iPTH, P and Ca levels were reduced from baseline in both groups (Table 2; Figure 1A–C). In the group without PTX, 28.2% (401/1424) of patients reached KDOQITM targets for iPTH, 50.3% (667/1327) for Ca and 47.7% (704/1476) for P. Similarly, 32.1% (42/131) of patients with prior PTX reached treatment targets for iPTH, 53.2% (66/124) for Ca and 45.7% (64/140) for P. Serum PTH and Ca × P values within the recommended KDOQITM target ranges were achieved in 20.3% (26/128) of patients with prior PTX and in 18.2% (253/1388) of patients without prior PTX.

The median dose of cinacalcet was 30 mg/day at baseline, and 6 and 12 months after initiation of treatment in both groups. At baseline, 19.3% of patients without PTX and 14.4% of patients with PTX received calcitriol intravenously or orally. Concerning calcitriol dose, its use remained stable over time in the non-PTX group (median dose intravenously: 3 μg/week; orally: 1.75 μg/week), while it was numerically reduced in the PTX group after 12 months of cinacalcet therapy (median dose intravenously: 4 μg/week at baseline, 1.5 μg/week at month 12; orally: 2 μg/week at baseline, 1.75 μg/week at month 12). The proportion of patients receiving calcitriol at 12 months was 17.2% and 16.4%, respectively, in the two groups. From baseline to month 12, the use of sevelamer decreased by 17% in patients with PTX (daily median dose of 4800 mg at both time points) and by 13% in patients without PTX (same daily median dose as in patients with PTX), whereas the use of Ca-based phosphate binders increased by 11% (daily median dose of 1800 mg at baseline, 2000 mg at month 12) in the PTX group and 5% (daily median dose of 1500 mg at both time points) in the non-PTX group.

At least one non-serious ADR was reported in 11.1% (189/1696) of patients without PTX; nausea (4.7%) and vomiting (2.8%) were most commonly reported. All other ADRs occurred in <1% of patients: diarrhoea (0.9%), dyspepsia (0.7%) and hypocalcaemia (0.6%). Five patients (0.3%) had serious ADRs: angina pectoris (0.1%), increased blood potassium (0.1%), convulsion (0.1%), gastric ulcer haemorrhage (0.1%) and hypocalcaemia (0.1%).

At least one non-serious ADR was reported in 13.1% (20/153) of patients with PTX; vomiting (5.2%), nausea (3.3%) and upper abdominal pain (1.3%) were most commonly reported. All other ADRs occurred in <1% of patients: anorexia (0.7%), asthenia (0.7%) and hypocalcaemia (0.7%). One patient (0.7%) had a serious ADR of gastric ulcer haemorrhage. Both groups did not differ concerning treatment persistence. In the group of patients with PTX (n = 153), a total of 34 patients (22%) had dis-
continued the use of cinacalcet by day 330, with a mean time (±SD) to discontinuation of 181 (±96) days. The main reasons for discontinuation of cinacalcet were PTX (n = 7, 4.6%), renal transplantation (n = 6, 3.9%), PTH oversuppression (n = 5, 3.3%), nausea and vomiting (n = 4, 2.6%), hypocalcaemia (n = 2, 1.3%), poor response (n = 1, 0.7%), other ADRs (n = 1, 0.7%) and others (n = 6, 3.9%). In the group of patients without prior PTX (n = 1696), a comparable number of patients (n = 415, 24.5%) had discontinued the use of cinacalcet by day 330, with a very similar mean time (±SD) to discontinuation of 178 (±91) days. The main reasons for discontinuation in this group were renal transplantation (n = 90, 5.3%), PTH oversuppression (n = 62, 3.7%), nausea and vomiting (n = 45, 2.7%), non-compliance (n = 24, 1.4%), other ADRs (n = 18, 1.1%), PTX (n = 13, 0.8%), hypocalcaemia (n = 9, 0.5%), poor response (n = 7, 0.4%) and others (n = 122, 7.2%). In the group with prior PTX, 15 patients (10%) withdrew from the study, compared to 235 patients (14%) in the group without prior PTX. Key reasons for withdrawal were death (n = 3, 2%) and others (n = 11, 7.2%) in the PTX group, and death (n = 96, 5.7%), end of treatment at study centre (n = 54, 3.2%) and others (n = 78, 4.6%) in the non-PTX group.

**Discussion**

This study evaluated the efficacy of cinacalcet in real-world clinical practice to treat recurrent/persistent sHPT and showed comparable effectiveness irrespective of prior PTX.

Baseline levels of iPTH were similarly high for patients with PTX and without prior PTX. Following treatment with cinacalcet, median iPTH, P and Ca values were reduced to recommended KDOQI™ target ranges. The effectiveness of cinacalcet was comparable between patients with recurrent/persistent sHPT after PTX and dialysis patients with sHPT who had not previously undergone PTX.

Classical indications for PTX are based on biochemical parameters, i.e. uncontrollable and persistently elevated iPTH >800 pg/mL associated with therapy-resistant hypercalcemia and hyperphosphataemia [8], and on clinical presentation, e.g. fractures, severe high bone turnover, progressive ectopic calcification and calciphylaxis [27,28].

PTX alone significantly decreases Ca and P levels to within KDOQI™ target ranges in the short term. Nevertheless, within 1 year, Ca levels tend to rise resulting in a proportion of fewer than 40% of patients within the target range.
Cinacalcet treatment, all three biochemical markers were maintained within or just above KDOQI™ treatment goals for patients with and without prior PTX. From this, it is obvious that patients with recurrent sHPT still respond to calcimimetics although progressive sHPT is characterized by more nodular hyperplasia and concomitant reduction in cellular expression of CaSR [9]. Furthermore, our data elucidate that a cinacalcet-based therapeutic regime significantly improves biochemical response of mineral metabolism in PTX-naive patients who are therefore less likely to need future PTX. The latter has been confirmed by the combined analysis of safety data from four randomized clinical cinacalcet trials which showed a significantly reduced risk for PTX (relative risk 0.07, 95% CI 0.01–0.55) when randomized to cinacalcet compared to placebo [24]. Finally, whereas PTX has been shown to put patients at risk of permanent hypoparathyroidism [14,16], cinacalcet allows a dose-dependent PTH reduction, which more easily enables achievement of specified target ranges [26].

Interestingly, a numerically stronger effect on iPTH, Ca and P reduction, could be observed in the PTX group. Although it remains speculative, this better response to cinacalcet might be caused by the surgical selection of non-nodular parathyroid tissue during PTX, favouring a more diffuse hyperplasia in the residual tissue. In contrast, in patients with long-standing sHPT, the risk of monoclonal nodular hyperplasia increases with time [29,30]. Nodular hyperplasia results in diminished responsiveness of parathyroid tissue to active vitamin D and cinacalcet treatment [31]. In line with this theory, Meola and colleagues recently found a significant decrease of parathyroid gland volume with cinacalcet in patients with a baseline gland volume <500 mm³ only, while in glands with a baseline volume >500 mm³ (considered to have monoclonal nodular hyperplasia) mean gland volume did not decrease [22].

Besides an improved biochemical response, calcimimetics are also able to reduce parathyroid cell proliferation [32], attenuate progression of parathyroid hyperplasia [33], enhance parathyroid cell apoptosis [34] and decrease parathyroid gland size [22,35]. This putative regression of parathyroid hyperplasia might therefore improve long-term control of sHPT with the use of cinacalcet. Moreover, calcimimetics have been shown experimentally to upregulate VDR and CaSR expression in parathyroid glands [36,37]. These effects may further improve the biochemical response with better achievement of recommended targets. Recently, in a subset analysis of the ACHIEVE study, cinacalcet on top of a fixed low dose vitamin D was found to reduce FGF23 levels in haemodialysis patients compared to dose-escalating vitamin D treatment only [38]. Whether cinacalcet has also a beneficial effect on FGFR1 and Klotho expression in parathyroid hyperplasia, which have both been found to be downregulated and responsible for parathyroid cell resistance to FGF23 [18,39], remains to be clarified in future studies.

Cinacalcet was well tolerated in both groups in our study. The number of hypocalcaemic events was comparable in both groups supporting the safe use of cinacalcet in patients with previous PTX. The more frequent use of Ca-
based phosphate binders (+11% vs +5% increase at month 12) in cinacalcet-treated patients with prior PTX may have reduced the incidence of hypocalcaemic events.

Limitations

Due to the study design, no detailed information is available about the surgical procedure of PTX (subtotal PTX, total PTX with or without autotransplantation), the number of previous PTX, the time period between PTX and recurrent shPT or the percentage of patients with persistent shPT. Nevertheless, the incidence of recurrent shPT has been shown to be comparable between subtotal PTX and total PTX with autotransplantation [14].

Because of the lack of a control group, it is not possible to exclude the possibility that a more attentive conventional therapy could have enabled a similar number of patients to achieve the recommended treatment target ranges. Nevertheless, comparing the ECHO results to those found in the control arm receiving conventional therapy in other studies, a higher number of patients achieved the recommended KDQOI™ target ranges for iPPTH. In total, 32.1% of patients in the PTX group and 28.2% of patients in the group without prior PTX achieved the KDQOI™ treatment targets, whereas, for example, 17% of patients in the study by Messa et al. [40] and 10% of patients in the study by Moe et al. [41] reached this goal using conventional therapy.

Conclusions

The observations from this subgroup analysis of the ECHO study suggest that cinacalcet may be a viable and safe treatment option for recurrent/persistent shPT in patients at risk for PTX.

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