Endocr (2011) 39:199–204
DOI 10.1007/s12020-011-9452-7

REVIEW

Cinacalcet as alternative treatment for primary hyperparathyroidism: achievements and prospects

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Received: 22 February 2011 / Accepted: 26 February 2011 / Published online: 26 March 2011

Abstract Primary hyperparathyroidism (pHPT), which most frequently occurs asymptomatically, is a common endocrine disease associated with increased morbidity and mortality. The newly introduced management guidelines as well as the recent availability of the first calcimimetic offer a highly promising therapeutic option for patients with pHPT. Cinacalcet, the first available calcimimetic, increases the sensitivity of the calcium-sensing receptor (CaR) to circulating serum calcium, thereby safely reducing serum calcium and PTH concentrations in patients with mild-to-moderate pHPT, intractable disease, and also parathyroid carcinoma. Cinacalcet has proved efficient in short- and long-term controls of hypercalcemia and, though bone mineral density was not improved, the available data point to cinacalcet as the treatment of choice in non-operable patients with pHPT. These results encompass a wide spectrum of disease severity. Results are pending as to whether cinacalcet decreases mortality and morbidity in pHPT, confirmation of which would conclusively recommend this drug as a valid alternative to surgery.

Keywords Cinacalcet · Calcimimetics · Calcium-sensing receptor · Primary hyperparathyroidism

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Introduction

Primary hyperparathyroidism (pHPT) is an endocrinopathy characterized by overproduction of parathormone (PTH) due to a solitary adenoma (80%) or to multiple adenomas (5%), to hyperplasia (15%) and, rarely, (<1%) to carcinoma of the parathyroid glands [1]. It is the third most common endocrine disorder, with a prevalence of 3 per 1,000 in the general population, typically affecting elderly women.

pHPT is marked by overproduction of parathormone (PTH), hypercalcemia induced by increased bone calcium (Ca) mobilization, enhanced intestinal Ca absorption, and renal tubular Ca reabsorption. The increased PTH activity results in augmentation of osteoclasts, whose heightened activity may lead to subperiostal resorption slacunes and acroosteolysis in the hands and feet. The most frequent manifestations are nephrolithiasis (calciumphosphate or -oxalate), bone disease, and gastrointestinal symptoms. The introduction in the 1970s of automated serum calcium measurement in the routine biochemical screening enabled the diagnosis of "asymptomatic patients" and increased by about fivefold the reported incidence of pHPT [2]. Based on this development, the term asymptomatic hyperparathyroidism, defined as pHPT without symptoms and signs of renal and bone disease, was established. Most patients with asymptomatic pHPT do well, as only 25 percent exhibit signs of progressive disease, including hypercalcemia and deterioration of bone mineral density [1]. Those younger than 50 years are approximately three times more prone to present with progression of their disease. Although osteodystrophia cystica generalisata von Recklinghausen (braun tumors) was once regularly observed, this is today becoming extremely rare, and most patients (about 80%) are in fact asymptomatic, so that the disease

Table 1 Symptoms most frequently reported by "asymptomatic patients"

Nephrolithiasis
Osteoporosis
Neuromuscular weakness
Intellectual weariness
Fatigue
Mood changes
Depression

now constitutes a routine clinical problem [3]. However, asymptomatic is not a precise term as patients often complain at the time of presentation of various non-specific symptoms, of which they are relieved after surgery (Table 1) [1, 4]. Discussion concerning the provision of guidelines in the usage of diagnostic tests for optimal identification of this condition was the aim of an International Meeting held in 2008, the results of which have been widely circulated among the participating societies [5, 6].

Diagnosis of pHPT is based on the detection of increased serum Ca concentration, high intact PTH combined with low serum phosphate, high urine Ca and phosphate excretion, and increased serum alkaline phosphatase, the extent of impairment of these parameters being highly dependent on kidney function and vitamin D status [7]. However, a serum Ca of above 2.6 mmol/l (5.2 mval/l = 10.5 mg/dl) with concomitantly normal kidney function and total plasma proteins and increased serum intact-PTH suggest pHPT, at a rate of 95% CI. Localization of disease is made via sonography, ^{99m}Tc-MIBI (technetium sestamibi) scintigraphy occasionally combined with SPECT, spiral-CT and MRI.

When surgical treatment is indicated, eclectic surgery of the parathyroid adenoma is the treatment of choice and cures the patient [8]. Surgery may also be beneficial for some patients with asymptomatic pHPT, who, however, fulfill the criteria for surgery according to the Guidelines for the management of asymptomatic pHPT issued by the third International Workshop [9]. The aforementioned surgery Guidelines are depicted in Table 2. Nevertheless, in those cases where surgery is contraindicated, when the patient refuses surgical intervention or when the current Guidelines are not met, an alternative medical therapy targeting hypercalcemia and/or osteoporosis should be considered [9, 10]. There are currently two main groups of drugs for the treatment of pHPT: (1) antiresorptive drugs that inhibit the increased bone turnover, and (2) calcimimetics which lower calcium secretion by interacting with PTH secretion.

Table 2 Guideline indications for surgery in asymptomatic primary hyperparathyroidism

Measurement	2008
Serum calcium (>upper limit of normal)	1.0 mg/dl (0.25 mmol/l)
24 hour urine for calcium	Not indicated
Creatinine clearance (calculated)	Reduced to <60 ml/min
BMD	T-score < −2.5 at any site and/or previous fracture fragility
Age (years)	<50

Modified from Ref. 9

This review focuses on the alternative treatment modalities for pHPT, with special emphasis on cinacalcet, a novel calcimimetic compound which may be used in those instances when surgery is contraindicated, when patients refuse the operation or even when the Guidelines contraindicate surgery.

Antiresorptive drugs

Diphosphonates in pHPT

Diphosphonates have been applied for the past two decades in the management of asymptomatic patients with pHPT, in inoperable cases of pHPT, in the management of pseudohyperparathyroidism as well as in patients with pHPT complicated by hypercalcemia crisis. Diphosphonates act by inhibiting bone resorption, this being documented by the reported decrease of urinary hydroxyproline and urinary calcium excretion, while serum calcium remains unchanged or decreases [11].

In a randomized, double-blind, placebo-controlled trial with alendronate 10 mg daily conducted over 2 years in 44 patients with asymptomatic pHPT, the alendronate-treated group registered a 3.67% ($P = 0.038$ vs. baseline) gain in bone density at the femoral neck site, while the placebo group, when crossed over to active treatment, showed a 4.1% gain in the LS ($P = 0.003$) and 1.7% at the hip site ($P = 0.009$), respectively [12]. However, serum calcium and PTH concentrations were not modified.

Comparable results have recently been reported in men with pHPT treated with alendronate for 1 year [12]. Relative to baseline, alendronate treatment induced a significant gain of 4.4% in BMD at the lumbar spine, and a 2.95% gain in hip BMD, whereas bone specific alkaline phosphatase decreased up to 47% [13]. There is thus good evidence showing that diphosphonates, and particularly alendronate, provide skeletal protection for men and women with pHPT.

In another recent study conducted over 10 days, intravenously administered diphosphonates, such as pamindronate, ibandronate, and zolendronic acid, were used in 14 patients with pHPT complicated by hypercalcemia crisis and significantly decreased serum Ca, from 3.50 to 2.85 mmol/l [14]. The decrease of Ca was related to

baseline levels and was observed to be more pronounced in patients with adenomas or hyperplasia than in those with parathyroid carcinoma.

Diphosphonates represent an alternative to surgery in pHPT patients. However, duration of this treatment is at present limited to a period of up to 2 years, the constraint being due to the necessity for a longer study period to allow evaluation of their efficacy and safety levels in this category of patients. Moreover, the recent warning disseminated by national regulatory agencies regarding the use over extended time periods of diphosphonates in patients with osteoporosis highlights the need for considerable caution whenever their administration in pHPT patients is scheduled [15].

Selective estrogen receptor modulators in pHPT

Selective estrogen receptor modulators (SERMs) have been used in pHPT due to their antiresorptive action. The fact that SERMs have not been associated with breast cancer or with cardiovascular disease renders them more attractive than estrogen containing compounds [16]. Raloxifene is at present the only available SERM which has been used in pHPT. While it is well tolerated, some cases of thrombophlebitis and deep vein thrombosis, although reported in a small number of instances, underscore the need for vigilance as well as for further investigation [15]. In a short-term study conducted over 8 weeks in 18 postmenopausal patients with asymptomatic pHPT, raloxifene significantly decreased calcium, by about 0.4 mg/dl, as well as markers of resorption and formation [17]. Calcium decrease was achieved to a similar degree as that would be induced with estrogens. PTH was not affected by raloxifene. Another study reported a decrease of calcium up to 1 mg/dl after 12 months of treatment with raloxifene in postmenopausal women with pHPT [18]. It is remarkable that although PTH decreased after 6 months, it returned to baseline concentrations after 12 months of treatment.

Calcitonin also has an antiresorptive action but of short duration, and it has not been considered in this review article.

Calcimimetics

Calcimimetics constitute a new category of drugs that, as reflected by their name, mimic the effect of calcium on calcium receptor [19]. The calcium-sensing receptor (CasR) is a G-protein coupled receptor which was first identified on parathyroid cells but is also located on cells of other organs thyroid C cells [20, 21]. CasR is activated when extracellular calcium rises, resulting in activation of phospholipase C through recruitment of the Gαq/11 protein and generation of the second messengers, diacylglycerol (DAG), and inositol triphosphate, which consequently diffuses to the cell cytosol and releases Ca stored in the endoplasmic reticulum [22] (Fig. 1). The intracellular Ca then decreases the PTH secretion from the parathyroid cells [22].

Calcimimetics, which activate the extracellular CasR in the parathyroid and other organs, regulate calcium

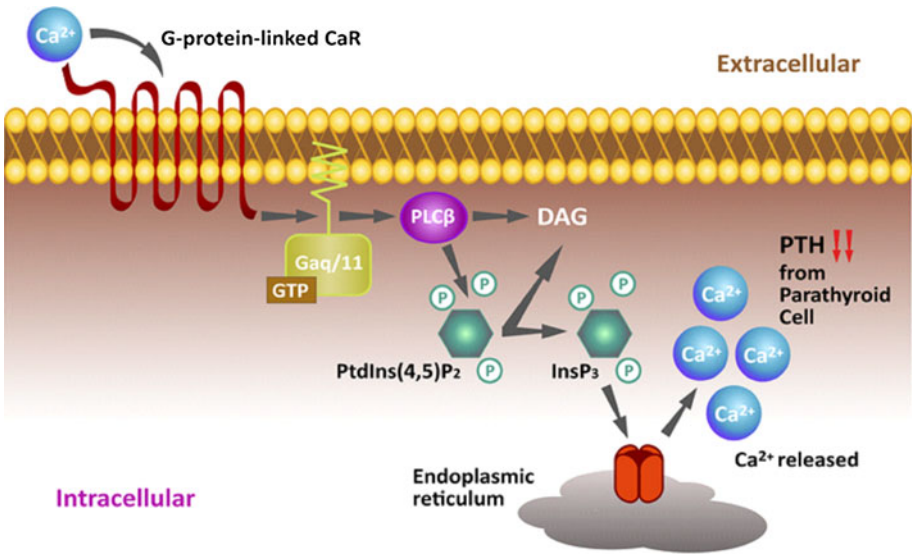

Fig. 1 : The calcium-sensing receptor (CasR) consists of seven hydrophobic helices. The large extracellular domain interacts with the extracellular Ca concentration, at which point it increases, then being categorized as the "first messenger." The interaction of Ca with the CasR activates Phospholipase C, which hydrolyses membrane bound phosphatidylinositol-4,5-diphosphate (PtdIns [4, 5] P_2 to inositol-1,4,5-triphosphate ($InsP_3$) and diacylglycerol (DAG). $InsP_3$ diffuses to cytosol and releases the intracellular Ca, the "second messenger," from the endoplasmic reticulum, which inhibits the secretion of PTH

homeostasis [23]. Two mechanistically distinct classes have been identified: type I full agonists of the parathyroid Ca^{2+} receptor, including Ca and other inorganic and organic actions, and type II, phenylalkylamine compounds, which in a stereoselective manner augment the sensitivity of CasR to extracellular Ca [24]. In test systems, cinacalcet elevated the concentration of cytoplasmatic Ca in embryonic kidney and decreased PTH secretion in the presence of 0.5 mM extracellular Ca [25]. Furthermore, cinacalcet stimulates calcitonin levels in a dose-dependent manner, whereas the compound was 30-fold more potent in decreasing serum PTH than in increasing calcitonin levels [25].

Currently, cinacalcet hydrochloride, the first allostheric activator of a G-protein-coupled receptor, is the only calcimimetic approved for therapeutic administration in humans [26].

Clinical studies with cinacalcet in pHPT

Clinical trials in patients with pHPT have demonstrated an improvement of metabolic profile and suppression of Ca as well as PTH secretion by cinacalcet application [27].

In a short-term cinacalcet treatment conducted to define the dose achieving the normalization of serum calcium and PTH in patients with pHPT ($n = 22$), cinacalcet normalized the serum calcium after the second dose on day 1, while PTH decreased by 50% at 2–4 h following cinacalcet administration [28]. The fasting and 24-h urine calcium to creatinine ratios were not changed.

In a 1-year multicenter, randomized, placebo-controlled trial including 78 patients, cinacalcet achieved normocalcemia in 73% of the patients, while PTH decreased by 7.6%. These effects were maintained with long-term treatment, while no clinically significant differences in bone mineral density were observed [29].

Forty-five of the patients participating in the 1-year trial were titrated during a period of 12 weeks with cinacalcet 50 mg twice daily if serum calcium levels were 10.3 mg/dl or higher; they were subsequently monitored for a period of 4.5 years [30]. PTH levels were progressively decreased (by 1–21%) throughout the study, without however reaching normal levels. Serum calcium levels were normalized within a month of initiating cinacalcet and remained within the normal range throughout the investigation period [30]. There was no improvement in the BMD at the spine, wrist and femoral neck. The therapy profile was favorable as regards both safety and efficacy in this long-term investigation. In a recent pooled analysis of data investigating the efficacy of the drug in reducing Ca, cinacalcet proved to be effective in patients with pHPT across a wide spectrum of disease severity [31].

In an open-label study with the aim of assessing the ability of cinacalcet to lower serum calcium levels in patients with intractable pHPT (calcium >12.5 mg/dl), cinacalcet 30 mg twice daily, titrated up to a maximum dose of 90 mg four times daily, led to decreases of serum calcium >1 mg/dl in 15 of 17 patients and improvement of health-related quality of life [32], although the strength of this finding was low due to the lack of controls [33]. These results opened the way to approval by EMEA of cinacalcet [34].

In a retrospective study whose objective was investigation of the efficacy of cinacalcet in reducing serum calcium and PTH levels in patients ($n = 18$) with pHPT, while cinacalcet normalized serum calcium in 94% of the patients and ionized calcium in 81%, PTH was reduced in only 25% of subjects [35].

Recently, in an open-label, single-arm study, cinacalcet was administered in 29 patients with parathyroid carcinoma. Cinacalcet was applied, titrating the doses (30 mg twice daily to 90 mg four times daily) until serum calcium was less than 10 mg/dl. At the end of a 16-week period, serum calcium was reduced by at least 1 mg/dl in 62% of the patients [36]. Of importance, it was observed that the higher the baseline calcium levels, the greater the calcium reduction. The results of this study indicate that the capability of cinacalcet to reduce hypercalcemia offers an efficacious therapeutic option for these patients. It remains to be clarified whether pre-surgery short-term cinacalcet administration renders beneficial results by diminishing blood supply and thus rendering the tumor more amenable to extirpation.

The compound could also be a suggested as an alternative in patients with persistent hypercalcemia after unsuccessful surgical interventions [37]. The study of the acute and chronic effects of cinacalcet on serum calcium and PTH levels in patients with persistent pHPT after unsuccessful parathyroidectomies documented a fall of PTH by 13–86.7% after acute application and by 5% at 12 months of treatment while calcium decrement amounted to 10.2% [38].

Cinacalcet may be applied as a short, interim solution before surgery when co-morbidities and other risk factors require optimal control. For instance, cinacalcet administration could be beneficial in patients with osteitis fibrosa cystica accompanied by hypercalcaemia, high PTH and decreased 1,25 $(OH)_2$ D levels, and, in whom, normalization of serum calcium before surgery leading to increased vitamin D levels might be necessary [39].

Patients with multiple endocrine neoplasia type 1 (MEN 1)-associated hyperparathyroidism are characterized by recurrence and increased surgical morbidity, caused by multiple neck explorations [40]. Cinacalcet proved its effectiveness in a study recruiting eight patients with MEN

Table 3 Indications for medical treatment of primary hyperparathyroidism with cinacalcet

Short-term indication
Interim solution before surgery
Long-term indications
Intractable pHPT
Patients with pHPT whom surgery is inappropriate
Inoperable thyroid carcinoma
MEN1associated hyperparathyroidism

1, as the subjects exhibited significant reductions in serum calcium and PTH for a duration of 10–35 months; two out of eight received cinacalcet as primary treatment, and the remaining six after having various neck operations [40]. Furthermore, in a case report, a 30-year-old woman with recurrent MEN 1-associated hyperparathyroidism, who refused further surgical interventions, was successfully treated with cinacalcet. Serum calcium and PTH levels were normalized within a month of treatment [41].

Cinacalcet thus shows itself to be a valuable therapeutic alternative for patients contraindicated for parathyroidectomy or who have had a failed response to previous parathyroidectomy and have persistent or recurrent pHPT.

The short- and long-term indications for treatment of pHPT with cinacalcet are listed in Table 3.

No economic comparison has been drawn up between surgical intervention and medical therapy with cinacalcet in patients with pHPT. An economic analysis regarding cinacalcet administration in patients with secondary hyperparathyroidism concluded that, since >9 months cinacalcet treatment entailed higher cost than that of surgical procedure, it could, therefore, be proposed as a presurgery interim solution [42]. It is thus advisable that, in patients with pHPT in whom surgery is contraindicated, a cost evaluation be performed between cinacalcet and other treatment modalities, without, however, neglecting the morbidity risk incurred via the respective medical approaches.

Mortality, morbidity in pHPT, and cinacalcet

Mortality and morbidity are clearly high in dialysis patients [43]. Cinacalcet was recently successfully implemented for treatment of secondary hyperparathyroidism in patients receiving haemodialysis [44, 45]. Both mortality and morbidity were also reported increased in mild pHPT in a retrospective population-based observational study [46]. Patients with mild pHPT were found to have an increased risk of developing cardiovascular disease, fatal and non-fatal events, cerebrovascular disease, and other co-morbidities [46, 47]. In studies including over 6,500 European patients, increased mortality was reported, while an analysis of the nationwide Cancer Registry and Causes-of-Death Registry in 10,995 Swedish patients (>20 years of age) demonstrated an increased risk of death following surgical treatment for pHPT [48]. However, overall mortality was not different than in the normal population in those patients who were operated on, between 1985 and 1997, suggesting that modern surgery may annihilate the risk of death from pHPT. By contrast, another population-based study in Rochester, Minnesota, did not reveal a higher overall mortality rate among patients with pHPT, although those with more severe disease, this based on higher calcium levels, exhibited an increased risk of death [49]. The increased cardiovascular morbidity and mortality of mild-to-moderate forms of pHPT is due to persistent arterial hypertension, left ventricular hypertrophy, myocardial and valvular calcifications, altered vascular reactivity and also alterations in carbohydrate metabolism, insulin resistance, and hypercholesterolaemia [50, 51]. By reducing serum levels of calcium and PTH, calcimimetics, and especially cinacalcet, modify with a leftward shift the set point for calcium-regulated PTH secretion [52].

There are as yet no data available as to whether long-term cinacalcet treatment may reduce mortality rate either in patients with pHPT, who do not meet the surgical criteria or who refuse surgery, or in patients with secondary hyperparathyroidism. The results of an ongoing, global, phase 3, double-blind, randomized, placebo-controlled trial (EVOLVE) for the evaluation of whether cinacalcet therapy lowers mortality and cardiovascular events in hemodialysis patients with secondary hyperparathyroidism are therefore very eagerly awaited [53].

Future prospects

Recent research has brought about the functional discovery of the CasR as well as improved knowledge of the molecular background of pHPT. In parallel, realization has been attained that the oncogene cyclin D1, encoding a key regulator of the cell cycle, plays, together with vitamin D, 1,25 (OH)D2, Ca^{2+} and phosphate, the role of regulators of parathyroid cell proliferation, a pivotal role in the pathogenesis of pHPT. The upshot has been the development of calcimimetics. Awaiting determination, one that would be of noteworthy significance, is whether long-term use of calcimimetics may affect PTH-regulating action of p38 mitogen-activated protein kinase in intestinal cells [54], while the fact that PTH enhances enterocyte DNA synthesis in a dose and age-dependent manner is now broadly corroborated. Meanwhile, increasing insight into the molecular pathogenesis of parathyroid tumors has revealed the importance of Wnt signaling and the role that an aberrant regulation of Wnt/beta-catenin signaling may have in tumor development [55], it having been established that

hyperparathyroidism inducing Wnt signaling leads to osteopenia [56]. The outcome of these all-important findings has been ever-growing achievement in the search to identify therapies targeted at these molecular pathways. It is thus evident that combined treatment of calcimimetics with compounds targeting Wnt signaling or suppression of Wnt antagonists provides significant potential for the future of medical treatment of hyperparathyroidism.

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