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Effets du cinacalcet après transplantation rénale pédiatrique : étude rétrospective basée sur les données du registre CERTAIN

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**Effets du cinacalcet après transplantation rénale pédiatrique :
Étude rétrospective basée sur les données du registre CERTAIN**

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RESUME

Contexte

L'hyperparathyroïdie secondaire (SHPT) peut persister après la transplantation rénale (RTx), se traduisant par une hypophosphatémie et une hypercalcémie qui empêchent l'utilisation des analogues de la vitamine D. Au décours d'essais randomisés chez l'adulte, le calcimimétique cinacalcet, utilisé en post-transplantation rénale, corrige la calcémie et le taux de PTH. Il existe peu de données pédiatriques disponibles.

Méthodes

Au cours de cette étude rétrospective, nous avons analysé 20 patients pédiatriques du Registre Cooperative European Paediatric Renal TransplAnt INitiative (CERTAIN) qui ont reçu du cinacalcet en post-transplantation rénale. Les données ont été recueillies dans la base de données CERTAIN. Les résultats sont présentés comme médiane (min-max).

Résultats

À 13,0 (4,3-20,9) ans, 20 patients pédiatriques ont bénéficié d'une RTx ; trois d'entre eux avaient déjà été traités par cinacalcet avant la RTx. Le cinacalcet a été introduit à 0,4 (0,1 à 6,4) ans après la transplantation. Le débit de filtration glomérulaire était estimé (DFG) à 50 (15-102) mL/min/1,73 m² ; le calcium plasmatique à 2,61 (2,20-3,15) mmol/L ; le phosphore standardisé par rapport à l'âge (z-score) à -1,7 (-5,1-0,4) et la PTH à 136 (84-896) ng/L. La dose d'initiation du cinacalcet était de 0,5 (0,1-1,5) mg/kg par jour, avec une dose maximale de 1,1 (0,2-3,1) mg/kg par jour. Après un suivi de 3,0 (0,2-10,8) années de traitement par cinacalcet, le DFG reste stable. Le taux plasmatique de PTH a diminué de façon significative à 79 (37-1272) ng/L au dernier suivi (p=0,01). Un patient a présenté un épisode d'hypocalcémie (1,8 mmol/L). Le cinacalcet a été arrêté chez trois patients (hypocalcémie, parathyroïdectomie, inobservance). Aucune néphrocalcinose n'a été rapportée.

Conclusions

L'utilisation hors AMM du cinacalcet pour traiter l'hyperparathyroïdie secondaire est efficace et sûre en post-transplantation rénale chez l'enfant.

Efficacy and safety of cinacalcet after pediatric renal transplantation: An international CERTAIN Registry study

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ABSTRACT

Background

Secondary hyperparathyroidism (SHPT) may persist after renal transplantation (RTx), inducing hypophosphatemia and hypercalcemia that precludes the use of vitamin D analogs. The calcimimetic cinacalcet improved plasma calcium and parathyroid hormone (PTH) levels in randomized controlled trials in adults after RTx. Pediatric data are missing.

Methods

In this retrospective study, we analyzed 20 pediatric patients from the Cooperative European Paediatric Renal TransplAnt Initiative (CERTAIN) Registry who received cinacalcet after RTx. Data were collected in the CERTAIN database. The results are presented as median (min-max).

Results

At 13.0 (4.3-20.9) years of age, 20 pediatric patients received RTx, among them three received cinacalcet already before RTx. Cinacalcet was introduced at 0.4 (0.1 to 6.4) years post-transplant at an estimated glomerular filtration rate (eGFR) of 50 (15 to 102) mL/min/1.73 m², plasma calcium of 2.61 (2.20 to 3.15) mmol/L, age-standardized (z-score) phosphate of -1.7 (-5.1 to 0.4) and PTH of 136 (84 to 896) ng/L. The starting dose of cinacalcet was 0.5 (0.1 to 1.5) mg/kg per day, with a maximum dose of 1.1 (0.2-3.1) mg/kg per day. With a follow-up of 3.0 (0.2 to 10.8) years on cinacalcet therapy, eGFR remained stable; PTH levels significantly decreased to 79 (37 to 1272) ng/L at the last follow-up (p=0.01). One patient displayed hypocalcemia (1.8 mmol/L). Cinacalcet was withdrawn in three patients (hypocalcemia, parathyroidectomy, non-compliance). Nephrocalcinosis of the graft was not reported.

Conclusions

The off-label use of cinacalcet for SHPT after pediatric RTx is effective in controlling post-transplant SHPT and well tolerated.

Key words:

Secondary hyperparathyroidism; calcimimetic; renal transplantation; children

INTRODUCTION

Secondary hyperparathyroidism (SHPT) is an important and frequent complication of advanced chronic kidney disease (CKD) [1], resulting from global disturbances in mineral metabolism, notably hypocalcemia, hyperphosphatemia and decreased 1,25 [OH]₂ vitamin D (1,25-D) levels, contributing to the complex CKD associated-mineral and bone disorders (CKD-MBD) including renal osteodystrophy, ectopic and vascular calcifications, and leading to increased over-all morbidity and mortality [2].

Calcimimetic agents, such as cinacalcet or the new-generation etelcalcetide, inhibit parathyroid hormone (PTH) synthesis through sensitization of the parathyroid Calcium-Sensing Receptor by enhancing signal transduction. Calcimimetics are widely used against SHPT in adults receiving dialysis, as a first-line therapy or in combination with vitamin D analogs, as recommended in the 2017 K-DIGO guidelines [3]. Cinacalcet was recently licensed in Europe in children for SHPT in children receiving dialysis, with an initial single daily dose of 0.2 mg/kg [4]; a European consensus statement from the European Society of Paediatric Nephrology has just been published, delineating the use of this compound in pediatric dialysis [5].

After renal transplantation (RTx), SHPT may persist, and is responsible for hypercalcemia and hypophosphatemia, on a kidney with usually near-normal renal function. In this setting, the use of vitamin D analogs is difficult because of the prevalent hypercalcemia, and it remains debated among nephrologists whether phosphate supplementation should be proposed. The management of such post-transplant SHPT is a daily challenge for nephrologists, sometimes requiring parathyroidectomy. To date, 41 papers reported the use of cinacalcet after RTx in adults: some are case reports, several retrospective [6–20] and prospective studies [21–43], but most of them were small series. Two Randomized Controls Trials (RCTs) in patients with post-transplant SHPT [37, 39], demonstrate beneficial effects of cinacalcet therapy, at least on

calcium and PTH levels. The use of cinacalcet after RTx may avoid parathyroidectomy. However, some reports highlighted a potential risk of nephrocalcinosis on the renal graft, but this criterion was not a primary outcome in RCTs. In pediatrics, only one case-report of a 7-year-old child reported the efficacy of cinacalcet after RTx [44].

Therefore, the main objectives of the current study were to evaluate the use of cinacalcet after RTx in pediatric patients included in the CERTAIN Registry, and to evaluate its indications, safety and efficacy.

PATIENTS AND METHODS

Patients and study design

The CERTAIN Registry aims to provide pertinent information on the short- and long-term outcome of pediatric renal allograft recipients for clinical research and quality assurance in order to improve patient care (www.certain-registry.eu) and has already been detailed in previous papers [45]. To avoid redundant data input, CERTAIN has set up data exchange interfaces with Eurotransplant, Collaborative Transplant Study (CTS) and the registry of the European Society of Pediatric Nephrology (ESPN) and European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) (ESPN/ERA-EDTA registry). For research purposes, an analysis of the multinational dataset requires approval of the predefined study protocol by the CERTAIN Registry Steering Committee. This registry is kept in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. This retrospective study was performed by data extraction of the CERTAIN database. Inclusion criteria were pediatric patients below the age of 21 years with persistent SHPT, having received cinacalcet after RTx, exclusion criteria were subtotal or total parathyroidectomy either before

or after RTx. Twenty patients were identified from five different countries and nine different centers, as follow: Heidelberg (n=10), Hamburg (n=2), Lyon (n=2), Jena (n=1), Essen (n=1), Samsun (n=1), Roma (n=1), Zurich (n=1), and Tübingen (n=1).

Laboratory analyses

We collected data for plasma total calcium, phosphate, PTH, creatinine and 25-OH vitamin D levels. Due to the physiological evolution of plasma phosphate during childhood, phosphate levels were normalized and expressed as Z-score for age [46]. Glomerular filtration rate was estimated using the 2009 Schwartz formula [47]. Calcium (Ca), phosphate (Ph), creatinine and 25-OH vitamin D levels were locally measured by standard methods. Since plasma PTH assessment was a crucial key parameter in this study, we double-checked with each center all the PTH data, asking the physicians to validate both the level of PTH at the different time points and the local assay used for routine assessment of PTH. As summarized in **Table 1**, different kits were used in the centers with different normal ranges. However, the upper limit was not that different among centers. We therefore have not corrected PTH levels and present “raw data” of PTH levels along the manuscript. When available, 24-hour urinary excretion rates of calcium were recorded and expressed as mmol/kg per day, the upper normal limit being 0.15 in children, 0.12 in teenagers and 0.1 in adults [48]. These laboratory parameters were analyzed at six different time points during follow up, namely at the time of transplant surgery, 4 weeks post-transplant, at cinacalcet initiation, at the first documented visit under cinacalcet, at the visit under the maximum cinacalcet dose and at the last visit under cinacalcet.

Statistical analysis

Non-parametric tests were performed, and *p*-values below 0.05 were considered statistically significant. Results are presented as median (minimum-maximum). Wilcoxon matched-pairs

signed rank test was used to compare the differences between follow-up points for eGFR, PTH, calcium, phosphate z-score and 25-D. All analyses were performed using GraphPad software.

RESULTS

Baseline characteristics

Relevant demographic, clinical and biochemical features of the patients at time of RTx are presented in **Table 2**. At a median age of 13.0 (4.3-20.9) years, a total of twenty patients (15 males) were included (fifteen after a first RTx and five after a second RTx). Ten patients had Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). The median time spent on dialysis was 1.9 (0.3-12.8) years.

Before cinacalcet introduction, thirteen patients received phosphate supplementation; four received native vitamin D and one received active vitamin D. With cinacalcet therapy, eleven patients received phosphate supplementation; ten received native vitamin D and three received active vitamin D.

Cinacalcet post-transplant

Thirteen of 20 patients (65%) had a history of SHPT before RTx, data were not available for 7 patients. Three patients received cinacalcet before RTx at a median dose of 0.4 (0.3-1.1) mg/kg perday. Three patients stopped cinacalcet during the post-transplant period of observation (parathyroidectomy; severe hypocalcemia; non-compliance). Cinacalcet was introduced 0.4 (0.1-6.4) years after RTx. The starting daily dose was 0.5 (0.1-1.5) mg/kg per day. According to therapeutic responses, the maximum dose was 1.1 (0.2-3.1) mg/kg perday, 1.5 (0.3-6.5) years post-transplant. eGFR was decreased when cinacalcet was introduced one year and half after

RTx ($p=0.002$) (**Figure 1A**). There was no statistically significant difference between the maximal dose whether cinacalcet was introduced during or after the one year and a half post-transplant ($p=NS$) (**Figure 1B**). There was no statistical difference about PTH levels when cinacalcet was begun before or after one year and half post-transplant (data nonpublished). The median follow-up under cinacalcet therapy was 3.0 (0.2-10.8) years. For 55% of cases, follow-up with cinacalcet therapy of more than 3 years.

Evolution of PTH and calcium in response to cinacalcet initiation

The evolution of the main biochemical parameters at different time-points under cinacalcet therapy are given in **Table 3**. Graft function remained stable with no statistically significant difference between cinacalcet initiation and the last visit under treatment ($p=NS$), as illustrated in **Figure 2A**. We observed a 21% decrease in median PTH levels between cinacalcet initiation and the first visit under treatment ($p=0.005$) and nearly a 40% decrease at the last visit ($p=0.01$), as shown in **Figure 2B**. Calcium levels decreased from 2.61 (2.20-3.15) mmol/L to 2.47 (1.80-2.70), by an average of 0.14 mmol/L ($p=0.01$) over the course of the study. The decrease in calcium levels reached a maximum of 0.18 mmol/L ($p=0.04$) at the time-point during which the daily dose of cinacalcet was maximal, after a period of 1.5 (0.3-6.5) years under cinacalcet therapy. This evolution is summarized in **Figure 2C**.

Evolution of phosphate, 25-OH-vitamin D and total alkaline phosphatase in response to cinacalcet

As illustrated respectively in **Figures 3A, 3B** and **3C**, there were no significant changes in plasma phosphate, 25-OH-vitamin D and total ALP before and after initiation of cinacalcet therapy throughout the observation period. However, as expected, a significant decrease of phosphate was observed between the time point of transplant surgery and the time point of 4

weeks post-transplant because of increased renal function on one hand and persistent SHPT on the other hand. ALP data were available in 6 patients.

Adverse effects

During the entire follow-up, no side effects of cinacalcet were reported by the different centers. Tolerance was reported to be good in all centers. However, one patient presented an episode of acute and severe hypocalcemia (1.80 mmol/L) in a context of suppressed PTH of 7ng/L, with no clinical symptoms, at an eGFR of 16.5 mL/min/1.73m², 6.5 years post-transplant and 3.5 years after cinacalcet initiation, at a daily dose of 1.9 mg/kg per day, thus leading to cinacalcet withdrawal. The previous serum calcium before hypocalcemia was 2.0mmol/L, 6 years to RTx (PTH levels: 23 ng/L). For one patient, SHPT persisted with parathyroid adenoma: cinacalcet was stopped and subtotal parathyroidectomy was performed. Eventually, for the third patient, cinacalcet was stopped because therapeutic adherence was poor. 24-hour urine calcium excretion was measured on all along the study in only 2 patients. All patients underwent regular follow-up by ultrasound of their graft (usually on a yearly basis), and no nephrocalcinosis was reported during different follow-ups.

DISCUSSION

This is the first case series on the use of cinacalcet in pediatric renal transplant recipients. Our data show that cinacalcet for SHPT after pediatric RTx is effective in controlling post-transplant SHPT with acceptable tolerability.

In adults, the incidence of post-transplant SHPT varies from 10 to 75%, and usually appears during the first year after RTx [16]. In a cohort of 100 adults undergoing RTx, 31% of them

had SHPT with subsequent hypercalcemia within one year after transplantation [49]. Cinacalcet administration before RTx and the plasma calcium level at the time of RTx were independent risk factors [49]. Only four studies have reported long term follow-up (i.e., more than 3 years) under this treatment [14, 15, 38, 40]. The main manifestation of post-transplant SHPT is hypercalcemia and its incidence varies widely from 9% to 65%. In 2014, a RCT comparing cinacalcet to placebo in 114 adult patients with persistent SHPT post-transplant concluded to a significant beneficial effect of cinacalcet on hypercalcemia and hypophosphatemia, and the absence of safety signals [14]. Nephrocalcinosis was not reported and good cinacalcet tolerance was observed [36]. However, a prospective observational cohort study including 303 incident renal transplant recipients with or without cinacalcet at the time of RTx reported an increased incidence of both nephrocalcinosis (i.e. 45% at month 3 versus 33% in controls, p=NS) and parathyroidectomy (i.e. 29% versus 7.2% in controls, p=0.02), with no differences in renal function [35]. In a retrospective study, cinacalcet treatment was not associated with a decline in eGFR or renal graft calcium deposition on renal biopsies in the first year following RTx, despite sustained and marked hypercalciuria induced by cinacalcet [13].

In children, CKD-MBD may persist after RTx and worsen allograft prognosis [50]. CKD-MBD has also been associated with impaired longitudinal growth, fractures, anemia, left ventricular hypertrophy, and increased mortality [1] and it frequently persists after RTx and the severe sequelae progress. Recently licensed in hemodialysis patients [4], off-used label cinacalcet could be used to control SHPT after RTx.

Only one case of cinacalcet use in children after RTx has been reported to date. In this 7-year-old child cinacalcet decreased PTH levels from 529 ng/L to 294 ng/L after 3 months treatment [44]. The present study is the first pediatric case series comprising 20 patients treated with cinacalcet after RTx. Despite the high prevalence of SHPT after RTx of 26-41% [50, 51] and

the proven efficacy of cinacalcet in dialysis patients, pediatric nephrologists are reluctant with off-label cinacalcet use after RTx. Only 20 out of a total of 2272 children monitored in the CERTAIN registry received cinacalcet. Routine management of SHPT after pediatric RTx can combine active vitamin D analogs, provided there is no overt hypercalcemia, as well as phosphate supplementation (so as to avoid the bone effects on mineralization of chronic hypophosphatemia), even though the benefit of the later is debated. In this cohort, despite the use of cinacalcet and phosphate supplementation in 10 patients, hypophosphatemia was not completely corrected.

Following RTx, mineral metabolism remains compromised for an extended period of time [52]: in addition to SHPT, FGF23 levels remain elevated for weeks to several months after RTx, both resulting in significant phosphaturia and subsequent hypophosphatemia in the post-transplant period [52]. FGF23 levels were not available in the CERTAIN Registry, the relative contribution as compared to the SHPT remains to be shown. In 2018, increased PTH levels before RTx were defined such as risk factors for persistent hyperparathyroidism in children after RTx [51]. In 19 out of the 20 children treated with cinacalcet pre-transplant data on SHPT was available; all these children had history of pre-transplant hyperparathyroidism. Pre-transplant cinacalcet use predicts the use of cinacalcet post-transplant in adults (ref). The three children receiving cinacalcet before RTx; also had severe SHPT post Tx and cinacalcet was resumed.

For the first time, our data obtained in 20 children, demonstrates that treatment of children with cinacalcet post RTx significantly reduces serum PTH, and calcium. 60 % of hypercalcemic patients normalized serum calcium with cinacalcet.

The CERTAIN registry was not designed to assess cinacalcet therapy post RTx. We therefore contacted all contributing centers. Beyond one episode of hypocalcemia, no adverse effect

signal was reported. An increased occurrence of nephrocalcinosis of the graft was reported in one study in adults [35]. Limited urinary calcium excretion data were available in our patients as well as yearly renal ultrasound findings in all our patients, with no signs of nephrocalcinosis or nephrolithiasis despite a follow-up with cinacalcet therapy of more than 3 years in 55% of cases. Altogether our observational data suggest that cinacalcet therapy after pediatric RTx may be a useful tool to correct SHPT and hypercalcemia with good tolerability.

One episode of severe hypocalcemia occurred in one out of the 20 patients who was followed with cinacalcet treatment for a total of 3.5 years. This is significantly less than in pediatric trials in dialysis [4, 5]. The risk of hypocalcemia should be lower in patients after RTx with SHPT and normal or near-normal renal function, due to the resulting calcium levels within the upper normal range or even above. On the other hand, physicians tended to apply relatively high doses of cinacalcet, which increases the risk of hypocalcemia. The median starting dose of cinacalcet of 0.5 mg/kg per day and the median maximum dose of 3.1 mg/kg per day were above the doses meanwhile recommended doses in the European consensus of ≤ 0.2 mg/kg perday for the starting dose and 2 mg/kg per day for the maximal dose [5]. Two different populations could be distinguished in our patient cohort: 55% of patients received cinacalcet for an early manifestation or persistence of SHPT with only slightly reduced renal allograft function, while 45% presented SHPT because of advanced CKD because of allograft dysfunction which has developed beyond the first 18 months post-transplant. Median and maximal cinacalcet doses, PTH and calcium reduction were similar in both sub-groups.

This retrospective uncontrolled single-arm descriptive pilot study is the first step to delineate the use of cinacalcet for SHPT after pediatric renal transplantation. The strengths of this study are based on the CERTAIN database, which allowed identification of 20 pediatric patients treated with cinacalcet in a large patient cohort. Data were collected prospectively in CERTAIN

registry. On the other hand, the registry was not specifically designed to answer the role of cinacalcet after RTx. However, we were able to double-check the results with all centers and obtain additional information. The next step could be a close, prospective monitoring of all pediatric patients treated with cinacalcet after RTx to specifically assess therapeutic effects but also the array of potential adverse effects, including clinical symptoms, transplant function, urinary electrolyte excretion, biomarkers of bone metabolism, and potential interactions with other drugs. A randomized controlled trial would provide the highest evidence on the use of cinacalcet after RTx, but it requires major efforts and respective financial support. As such, as summarized in **Figure 4**, taking into account the current data and the recent European consensus [5], we propose a therapeutic protocol for the use of cinacalcet after pediatric RTx. Long-term aims would be to identify predictive factors of the response to cinacalcet, to correlate the evolution of SPHT pre-transplant and post-transplant in order to provide adequate pediatric data for a rationale use of cinacalcet in children after RTx with minimization of associated therapeutic risks.

CONCLUSION

In summary, we provide the first pediatric data suggesting that the use of cinacalcet for SHPT after RTx is effective in controlling post-transplant SHPT with acceptable tolerability. The potential risk of hypercalciuria and nephrocalcinosis previously suggested in adult RTx patients and cinacalcet treatment mandates close follow-up in children, too.

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FIGURE LEGENDS

Figure 1

A: Comparison of eGFR when cinacalcet was introduced before or after the one year and a half of RTx

Each dot on the graph represents median with 95% CI (confidence interval) per different follow-up biological parameters before and after one and half year of RTx. Statistical analyses were performed with non-parametric tests: * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$) (Man Whitney test).

B: Comparison of maximum dose when cinacalcet was introduced before or after the one year and a half of RTx

Each dot on the graph represents median with 95% CI (confidence interval) per different follow-up maximum dose parameters before and after one and half year of RTx. Statistical analyses were performed with non-parametric paired tests: $p = \text{NS}$ (Man Whitney test).

Figure 2: Evolution of eGFR (A), PTH (B), and Calcium (C) Levels during cinacalcet therapy

Each dot on the graph represents median with 95% CI per different follow-up biological parameters. Statistical analyses were performed with non-parametric paired tests: * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ (Wilcoxon matched-pairs signed rank test).

Figure 3: Evolution of phosphate expressed as SDS for age (A), 25-OH vitamin D (B), and total alkaline phosphatase (C) levels during cinacalcet therapy

Each dot on the graph represents median with 95% CI per different follow-up biological parameters. ALP data were available in 6 patients. Statistical analyses were performed with non-parametric paired tests: ** $p < 0.01$ (Wilcoxon matched-pairs signed rank test).

Figure 4: Therapeutic protocol for the use of cinacalcet after RTx based on recent European consensus Tables

TABLES

Table 1: Assays used for routine assessment of plasma PTH levels in the contributing CERTAIN centers

Commercial kit	Center	Assay	Normal range
Roche on a Cobas analyser	Essen, Samsun, Roma, Zürich, Lyon	Electro-CLIA	15-65 ng/L
PTH Siemens Analyser Centaur®	Heidelberg, Tübingen	Two-side CLIA	12.3-71.7 ng/L
NA	Hamburg	Two-side CLIA	17-84 ng/L
NA	Jena	NA	NA

Abbreviations : NA : Not available ; CLIA : Chemi-Luminiscence-Immuno Assay

Table 2: Patient characteristics at time of renal transplantation

No	Sex	Age (years)	Graft Number	Donor	Time spent on dialysis (years)*	Primary renal disease	PTH at time of RTx (ng/L)
1	M	18.8	1	Living related	Preemptive Tx	CAKUT	126
2	M	11.1	1	Deceased	2.8	CNS	NA
3	M	17.9	1	Living related	0.5	Watson syndrome	NA
4	M	16.8	1	Living related	1.1	IgA nephropathy	245
5	M	10.7	2	Deceased	1.5	CAKUT	NA
6	M	15.0	2	Deceased	1.9	CAKUT	451
7	F	19.6	1	Deceased	5.5	HUS	264
8	F	12.3	1	Living related	0.3	CAKUT	284
9	F	15.5	1	Deceased	0.6	CAKUT	NA
10	M	4.3	2	Deceased	0.9	CNS	354
11	M	16.5	1	Deceased	12.8	CNS	327
12	F	12.3	1	Deceased	2.5	CAKUT	173
13	M	6.6	1	Deceased	0.8	Tubulointerstitial nephritis	NA
14	M	20.9	2	Deceased	3.2	Uncertain etiology	NA
15	F	14.2	1	Deceased	4.4	Glomerulonephritis	530
16	M	12.7	2	Living related	Preemptive Tx	CAKUT	NA
17	M	12.9	1	Deceased	10.6	HUS	84
18	M	5.2	1	Deceased	3.0	CAKUT	61
19	M	13.1	1	Deceased	0.9	CAKUT	NA
20	M	6.3	1	Living related	Preemptive Tx	CAKUT	120

Abbreviations: No: number; M: male; F: female; Tx: transplantation; eGFR: Estimated Glomerular Filtration Rate; CAKUT: Congenital Anomalies of the Kidney and Urinary Tract; CNS: Congenital Nephrotic Syndrome; HUS: Hemolytic Uremic Syndrome; NA: not available

*In patients with the 2nd transplant, the time spent on dialysis was calculated only for the 2nd transplant

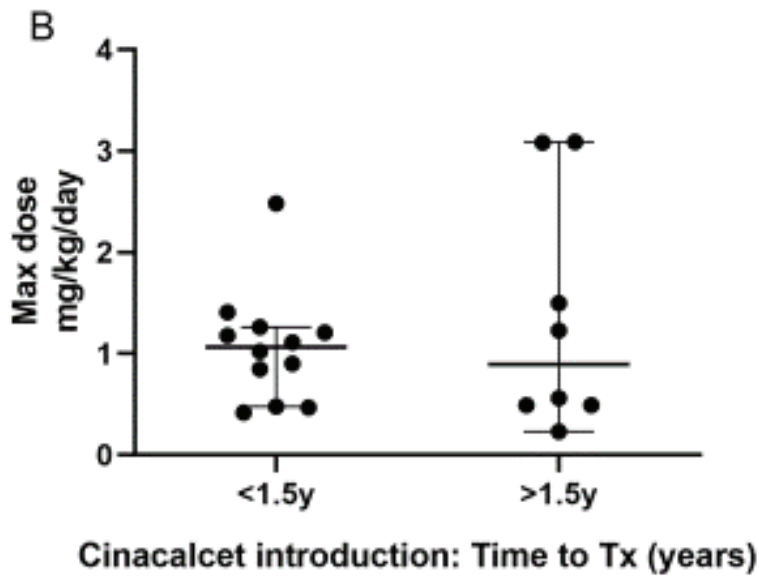
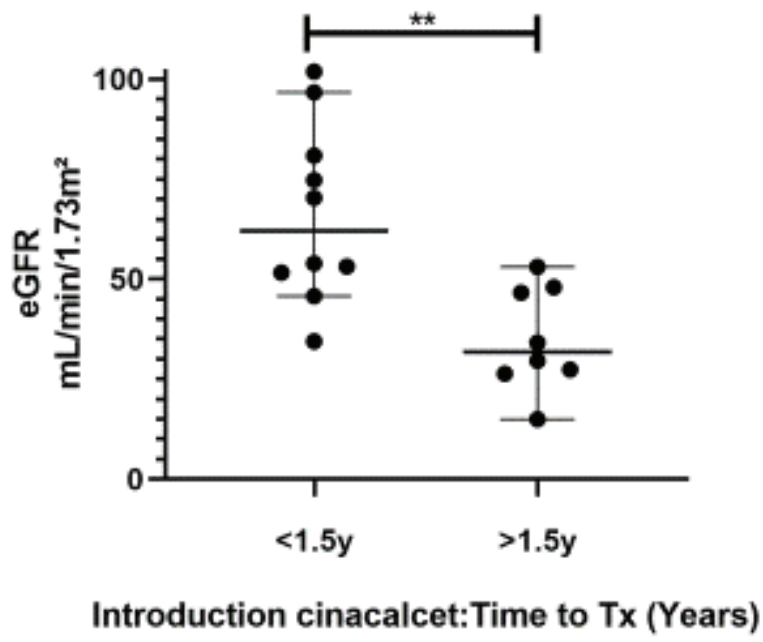
	eGFR mL/min/1.73m²	PTH ng/L	Calcium mmol/L	Vitamin D nmol/L	Phosphate mmol/L	Phosphate SDS	ALP U/L	24h urine Ca mmol/kg/day
At RTx	9 (4-24) n=20	255 (61-530) n=12	2.44 (1.77-2.74) n=17	60 (35-65) n=3	1.54 (0.71-3.12) n=16	0.3 (-3.4-9.6) n=16	154 (52-613) n=10	0.15 (0.03-0.18) n=3
4 weeks post-RTx	65 (32-140) n=20	152 (80-425) n=11	2.57 (2.38-3.00) n=17	39 (34-59) n=3	0.81 (0.52-1.47) n=17	-3.5 (-5.1-0.4) n=17	170 (41-443) n=9	0.12 (0.04-0.43) n=5
Cinacalcet initiation 0.4 years post-Tx (0.1-6.4)	50 (15-102) n=18	136 (84-896) n=13	2.61 (2.20-3.15) n=18	89 (21-115) n=6	1.17 (0.51-1.84) n=18	-1.7 (-5.1-1.6) n=18	272 (176-861) n=5	0.03 (0.01-0.05) n=2
First visit under cinacalcet 0.5 years post-Tx (0.2-6.5)	55 (11-139) n=19	107 (35-160) n=14	2.54 (2.05-2.89) n=18	78 (29-104) n=6	1.00 (0.52-1.65) n=17	-2.3 (-4.4-0.9) n=17	219 (78-852) n=6	0.05 n=1
Maximal dose cinacalcet 1.5 years post-Tx (0.3-6.5)	53 (15-112) n=19	113 (90-714) n=19	2.43 (2.10-2.83) n=18	74 (21-104) n=6	1.13 (0.67-1.65) n=17	-1.2 (-3.6-0.6) n=17	237 (60-356) n=6	NA
Last visit under cinacalcet 4.5 years post-Tx (0.5-11)	46 (11-117) n=20	68 (7-1272) n=14	2.46 (1.80-2.70) n=18	106 (98-136) n=4	1.25 (0.81-1.70) n=17	-1.4 (-2.9-2.4) n=17	222 (57-340) n=5	0.04 n=1

Table 3: Biochemical data of patients treated with cinacalcet at different follow-up

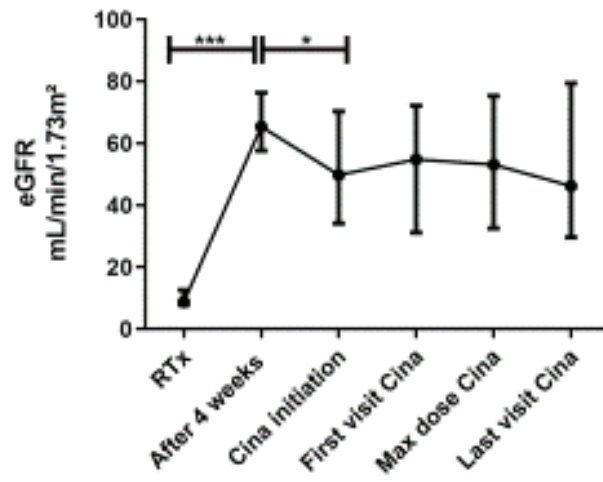
Abbreviations: RTx: Renal Transplantation; eGFR: Estimated Glomerular Filtration Rate; ALP: Alkaline Phosphatase.; Ca: calcium; NA: not available; Grey cellules were statistical data between cinacalcet initiation and different follow-ups after this initiation for biological results

FIGURES

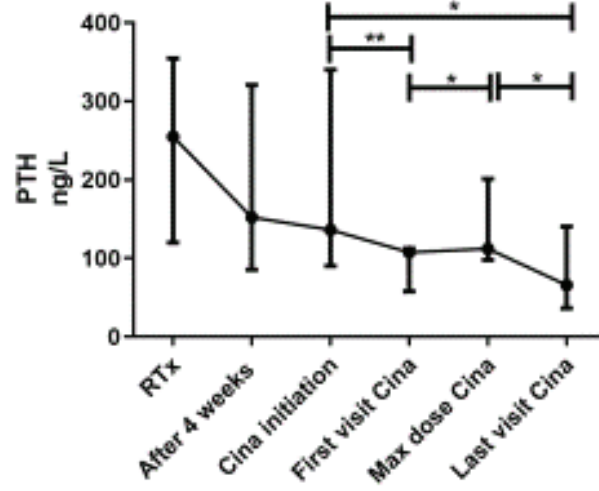
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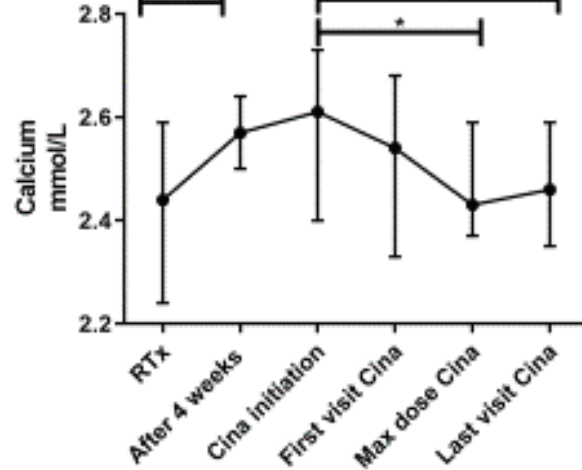
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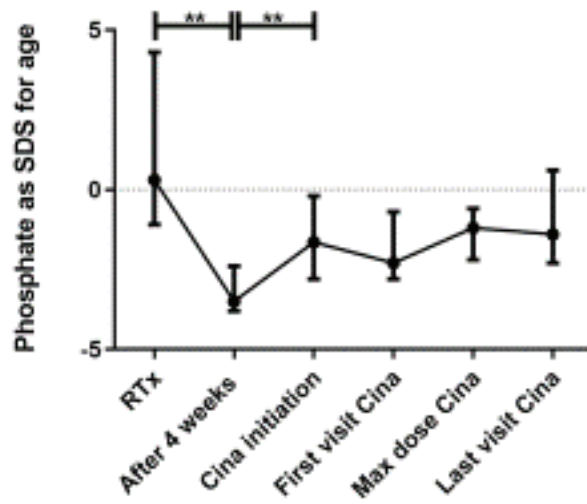
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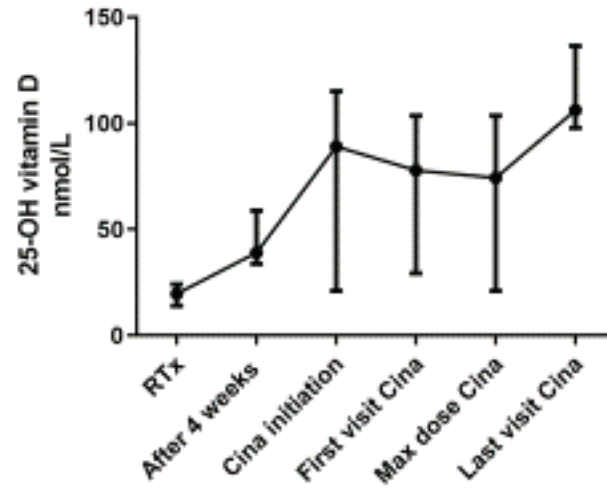
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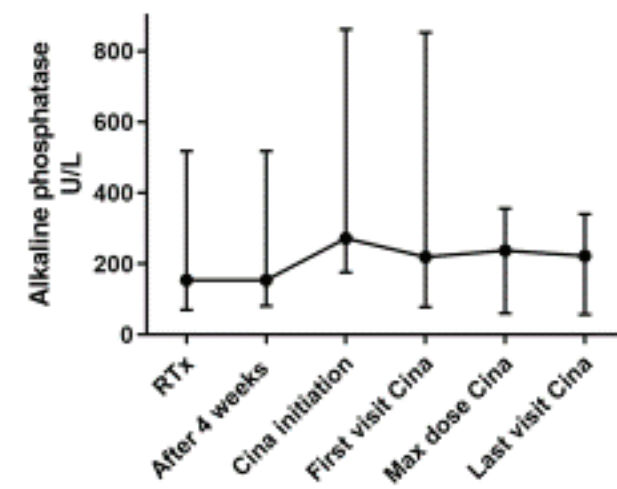
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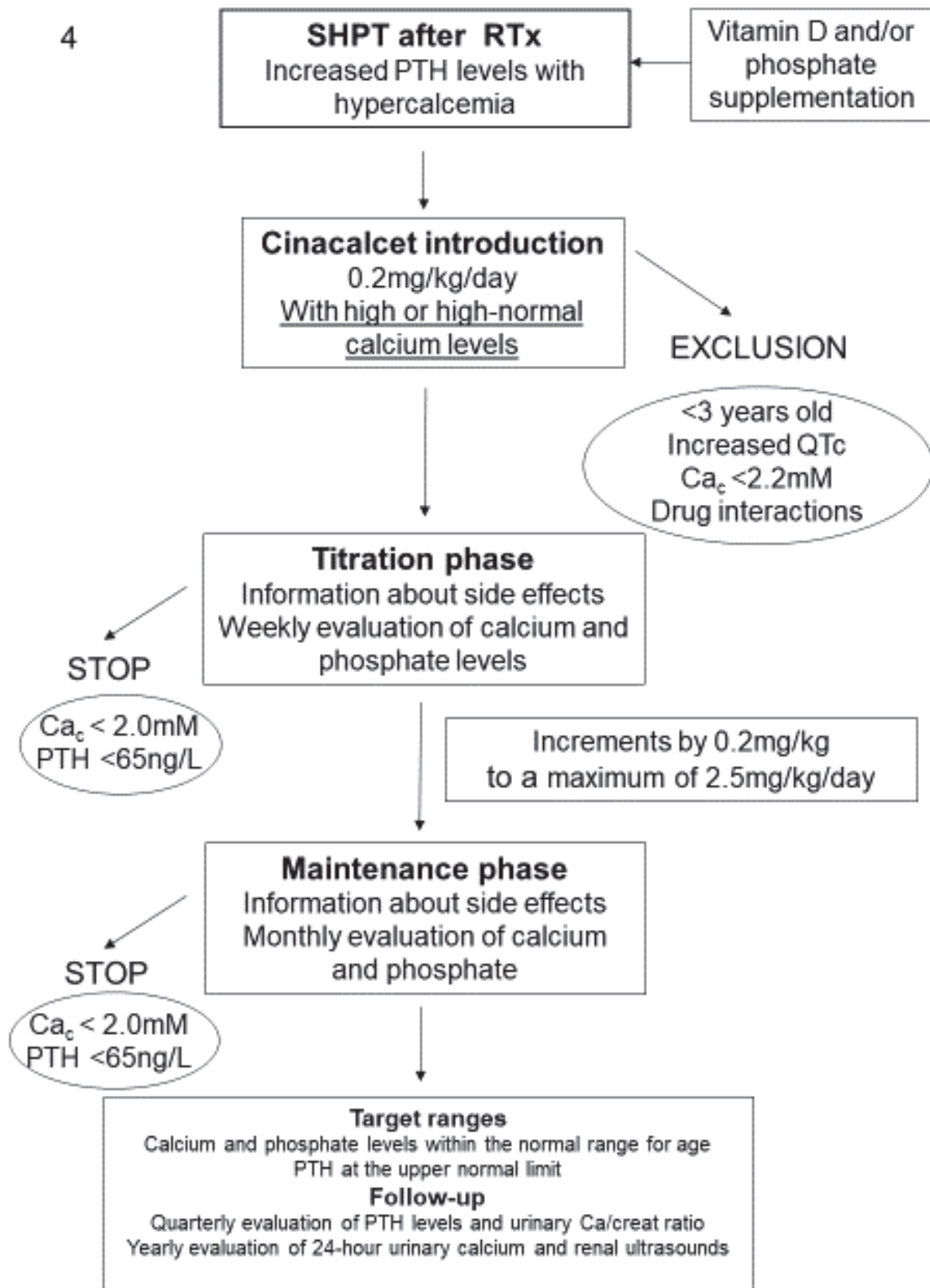
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C



4



ANNEXS

Annex 1: bibliography summary

Author, year	Study design	Number of patients	Results
Zavvos and al. 2018	Single-center prospective study	77	Long-term treatment with cinacalcet during 5 years in renal transplant recipients with secondary hyperparathyroidism controls hypercalcemia and corrects hypophosphatemia, without affecting graft function with being well-tolerated
Cheunschon and Sritippayawan. 2017	Case report	1	Successful treatment with cinacalcet of early allograft dysfunction with extensive calcium phosphate deposition in distal tubules caused by severe hyperparathyroidism after renal transplantation
Mawad and al. 2017	Single-center retrospective study	27	Discontinuing cinacalcet within the first month of renal transplantation often leads to hypercalcemia. Cinacalcet appears to be an effective treatment of hypercalcemic hyperparathyroidism in kidney transplant recipients
Niel and al. 2016	Case report	1	Hypercalcemia associated with secondary hyperparathyroidism can be corrected with Cinacalcet after pediatric renal transplantation
Soliman and al. 2016	Single-center retrospective study	59	Correction of severe hyperparathyroidism was similar in both surgical and cinacalcet groups with the absence of a difference of long-term serum iPTH 1-84 levels between the two groups of renal transplant recipients
Wazna-Jablonska and al. 2016	Single-center retrospective study	30	Cinacalcet administered after renal transplantation seems to be an effective option for the management of persistent hypercalcemia owing to hyperparathyroidism with satisfactory tolerability
Cruzado and al. 2016	Prospective multicenter and randomized study	30	Standard of care subtotal parathyroidectomy is superior to cinacalcet to correct hypercalcemia in renal allograft recipients with persistent hyperparathyroidism during 12 months evaluation.
Thiem and al. 2015	Single-center prospective study	44	Six-week cinacalcet treatment controlled hypercalcemic hyperparathyroidism in renal transplantation recipients in the long-term and increased low inorganic phosphate levels without causing hyperphosphatemia
Evenepoel and al. 2014	Prospective multicenter and randomized study	114	Hypercalcemia and hypophosphatemia were effectively corrected after treatment with cinacalcet (starting dose: 30mg/day) in patients with persistent hyperparathyroidism after renal transplantation. There were 3 phases: dose titration phase (20weeks); efficacy assessment phase (20-26weeks); maintenance phase (weeks 34,42 and 52)
Torregrosa and al. 2014	Retrospective observational multicenter study	32	Cinacalcet improves the control of serum PTH values without causing changes to calcaemia, phosphataemia or kidney function after renal transplantation

Paschoalin and al. 2012	Retrospective observational study	23	Cinacalcet was effective for long-term control of hypercalcemia related to persistent hyperparathyroidism for patients with stable kidney transplantation
Cohen and al. 2012	Meta-analysis of prospective and retrospective studies	21	From nonrandomized studies, Cinacalcet appears to be safe and effective for the treatment of posttransplant hyperparathyroidism
Courbebaisse and al. 2012	Retrospective single center observational study	71	Despite sustained and marked hypercalciuria induced by cinacalcet treatment, cinacalcet does not have adverse effects on GFR or on renal graft calcium deposits in the first year following renal transplantation.
Evenpoel and al. 2012	Prospective observational cohort study	303	Cinacalcet does not affect the course of secondary hyperparathyroidism in patients awaiting kidney transplantation. Biochemical profiles and a high parathyroidectomy rate suggest rebound hyperparathyroidism in renal transplant recipients discontinuing Cinacalcet at the time of transplantation, which may be related to the short exposure time specific to this population. Risk/benefit studies are urgently required to define the role of continued calcimimetic treatment in renal transplant recipients and to determine the optimal treatment of secondary hyperparathyroidism in patients listed for transplantation
Zitt and al. 2011	Prospective controlled single-center cross-over study	10	In the short term, cinacalcet increases the urinary concentration of calcium, magnesium, and sodium. The observed antihypertensive effect might be beneficial in patients with a high cardiovascular risk after renal transplantation
Boulanger and al. 2011	Prospective multicentric study	13	Cinacalcet normalizes total and ionized calcium in renal-transplanted recipients with hypercalcemia secondary to hyperparathyroidism through a mechanism that could be independent of PTH serum level suppression. The increase in bone-specific alkaline phosphatases, biochemical markers of bone accretion and the significant decrease in fasting urine calcium suggest the possibility of a beneficial impact of Cinacalcet on bone remodeling
Pinho and al. 2011	Prospective observational cohort study	18	This preliminary experience suggests that cinacalcet may be useful in the treatment of persistent hyperparathyroidism after renal transplant. In addition, Cinacalcet controlled hypercalcemia, which has well known adverse effects after transplant. This was accomplished with no evidence of declining kidney function or limiting side effects
Henschkowski and al. 2011	Meta-analysis of observational study	115	Cinacalcet treatment was associated with a decline of renal function in kidney transplant recipients with persistent HPT. Our meta-analysis underscores the need for frequent monitoring of creatinine and calcium levels during cinacalcet treatment
Scharz and al. 2011	Prospective observational study	58	Calcium-phosphorus homeostasis in hypercalcemic renal transplant patients normalizes under Cinacalcet and PTH decreases, albeit not to normal. The renal functional decline could be PTH

			mediated, analogous to the effects observed after parathyroidectomy.
Borstnar and al. 2010	Prospective clinical study	11	Cinacalcet seems to be a safe drug with no negative effect on renal function in treating posttransplant hyperparathyroidism
Seikrit and al. 2010	Case report	1	Renal allograft failure in a hyperparathyroid patient following initiation of cinacalcet after renal transplantation
Cho and al. 2010	Observational retrospective single center study	163	Cinacalcet therapy was associated with greater bone mass density increase at the hip over the 36-month posttransplant period. Cinacalcet was well tolerated. Our results suggest that Cinacalcet may have a small but favorable effect on bone density following kidney transplantation.
Aalten and al. 2010	Prospective clinical study	29	Cinacalcet can safely be continued immediately after renal transplantation.
Copley and al. 2010	Multicenter retrospective observational study	41	Cinacalcet may be useful for the treatment of hyperparathyroidism after kidney transplantation
Guerra and al. 2010	Prospective clinical study	17	Calcimimetic agents represent a therapeutic alternative in transplant patients with persistent hyperparathyroidism, as they correct hypercalcemia and reduce PTH levels with no adverse effects on kidney function
Borchhardt and al. 2010	Prospective clinical study	10	While Cinacalcet might decrease bone formation rate, it did not change bone volume, and bone mineral density of the femur increased. Therefore, the use of Cinacalcet in hypercalcemic hyperparathyroidism might be safe with regard to the bone disease present after kidney transplantation.
Lopez and al. 2009	Prospective clinical study	29	Cinacalcet was safe and effective in kidney transplant patients with hypercalcemia secondary to hyperparathyroidism
Carrasco and al. 2009	Prospective single-center study	14	Cinacalcet is an effective treatment for persistent hyperparathyroidism associated with hypercalcemia among renal transplant patients and may be helpful for hypertension control.
Gomez Marques and al. 2009,	Retrospective observational study	48	Treatment with Cinacalcet controlled hyperparathyroidism and hypercalcemia among patients with posttransplant SHP. It was a safe drug, with a low incidence of side effects.
Serra and al. 2008	Open-label prospective uncontrolled study	10	Cinacalcet effectively corrected urinary phosphate wasting in kidney transplant recipients, resulting in normalization of serum phosphorus levels. The phosphatemic effects of Cinacalcet correlated with a marked decrease in the phosphaturic hormone PTH, rather than with a change in FGF-23 levels or acid-base status, highlighting the importance of PTH in post-transplantation hypophosphatemia.
Borchhardt and al. 2008	Prospective single-center study	32	Calcium lowering effect of cinacalcet in patients with persistent hyperparathyroidism after kidney

			transplantation is caused, at least in part, by increased urinary calcium excretion
Bergua and al. 2008	Prospective single-center study	9	In renal transplant patients with hypercalcemia secondary to persistent secondary hyperparathyroidism Cinacalcet corrects hypercalcemia and PTH, simultaneously improving bone mineral density
Kamar and al. 2008	Prospective single-center study	11	Once- or twice-daily acute administration of Cinacalcet to kidney-transplant patients has similar efficacy. One-year administration of Cinacalcet, given as two daily doses, is safe and efficient.
Esposito and al. 2007	Case report	1	Hypercalciuria induced by a high dose of Cinacalcet in a renal transplant recipient
Falck and al. 2007	Prospective single-center study	14	Cinacalcet treatment showed a moderate effect on the Tacrolimus, but not Cyclosporine A or mycophenolate, pharmacokinetics after 1-week concomitant treatment. This interaction appears to have minor clinical relevance.
Peng and al. 2007	Case report	1	Cinacalcet-associated graft dysfunction and nephrocalcinosis in a kidney transplant recipient
El-Amm and al. 2007	Retrospective observational study	18	Cinacalcet appears to be an effective drug for the treatment of posttransplant hypercalcemia due to persistent secondary hyperparathyroidism.
Srinivas and al. 2006	Prospective single-center study	11	Cinacalcet lowers serum calcium and raises serum phosphorus in the short term in patients with persistent post-transplantation hyperparathyroidism
Apostolou and al. 2006	Retrospective observational study	7	Cinacalcet offered a better holistic treatment approach to such patients with resistant hyperparathyroidism in renal transplant
Serra and al. 2006	Retrospective observational study	12	Continued treatment with Cinacalcet is required to maintain long-term normocalcaemia and to suppress the enhanced PTH production in renal transplant recipients with persistent hyperparathyroidism
Leca and al. 2006	Retrospective observational study	10	Correction of hyperparathyroidism was not permanent as discontinuing Cinacalcet therapy led to a rapid rise in PTH level
Apostolou and al. 2006	Case report	2	Cinacalcet permits a more integrated and successful treatment of hyperparathyroidism after renal transplantation
Drueke and al. 2006	Case report	1	Therapeutic failure of Cinacalcet in a renal transplant patient
Serra and al. 2005	Retrospective observational study	11	Successful treatment of hypercalcemia with Cinacalcet in renal transplant recipients with persistent hyperparathyroidism
Kruse and al. 2005	Retrospective observational study	7	Cinacalcet normalizes serum calcium in renal transplant patients with persistent hyperparathyroidism

Annex 2: abstract notification



July 23rd, 2019

ABSTRACT ID: IPN11183-85

Abstract title:

Cinacalcet use after pediatric renal transplantation: data from the CERTAIN registry

Dear Dr. BERNARDOR

We are pleased to inform you that the above mentioned abstract has been accepted as a **poster presentation**

for the 18th Congress of the International Pediatric Nephrology Association in Venice. Additional information appears below and in August, will be available on the IPNA Congress website as follows: <http://ipna2019.org/preliminary-program/>

Poster Specifications & Guidelines

Posters size must be 0.70 meter by 1.00 meter high to fit the poster boards that will be at the meeting. The number of the poster board for your presentation(s) will be communicated in September.

Expenses associated with the preparation and presentation of an abstract are the responsibility of the presenter(s)/author(s).

Please do not forget to register for the conference, which is a requirement for presentation.

Registration

Presenters are required to register for the meeting.

Registration with the early registration fee will be available only for oral/poster presenters. Please

click on this link to access presenters registration <<https://services.ipna2019.org/author-registration>>.

Please note that you will be asked to type the abstract code and the submitting author's surname to obtain the early registration fee. There is only one early registration available for each abstract. You are strongly encouraged to register before August 31st 2019 to obtain Early Bird rates. After that date, only regular registration will be available, and no exceptions will be made.

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SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences. Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

RESUME

Contexte

L'hyperparathyroïdie secondaire (SHPT) peut persister après la transplantation rénale (RTx), se traduisant par une hypophosphatémie et une hypercalcémie qui empêchent l'utilisation des analogues de la vitamine D. Au décours d'essais randomisés chez l'adulte, le calcimimétique cinacalcet, utilisé en post-transplantation rénale, corrige la calcémie et le taux de PTH. Il existe peu de données pédiatriques disponibles.

Méthodes

Au cours de cette étude rétrospective, nous avons analysé 20 patients pédiatriques du Registre Cooperative European Paediatric Renal TransplAnt INitiative (CERTAIN) qui ont reçu du cinacalcet en post-transplantation rénale. Les données ont été recueillies dans la base de données CERTAIN. Les résultats sont présentés comme médiane (min-max).

Résultats

À 13,0 (4,3-20,9) ans, 20 patients pédiatriques ont bénéficié d'une RTx ; trois d'entre eux avaient déjà été traités par cinacalcet avant la RTx. Le cinacalcet a été introduit à 0,4 (0,1 à 6,4) ans après la transplantation. Le débit de filtration glomérulaire était estimé (DFG) à 50 (15-102) mL/min/1,73 m² ; le calcium plasmatique à 2,61 (2,20-3,15) mmol/L ; le phosphore standardisé par rapport à l'âge (z-score) à -1,7 (-5,1-0,4) et la PTH à 136 (84-896) ng/L. La dose d'initiation du cinacalcet était de 0,5 (0,1-1,5) mg/kg par jour, avec une dose maximale de 1,1 (0,2-3,1) mg/kg par jour. Après un suivi de 3,0 (0,2-10,8) années de traitement par cinacalcet, le DFG reste stable. Le taux plasmatique de PTH a diminué de façon significative à 79 (37-1272) ng/L au dernier suivi (p=0,01). Un patient a présenté un épisode d'hypocalcémie (1,8 mmol/L). Le cinacalcet a été arrêté chez trois patients (hypocalcémie, parathyroïdectomie, inobservance). Aucune néphrocalcinose n'a été rapportée.

Conclusions

L'utilisation hors AMM du cinacalcet pour traiter l'hyperparathyroïdie secondaire est efficace et sûre en post-transplantation rénale chez l'enfant.

Mots-clés

Cinacalcet, transplantation rénale, hyperparathyroïdie secondaire, enfant.