Cinacalcet therapy in dialysis patients: Results of the German REACT trial

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INTRODUCTION

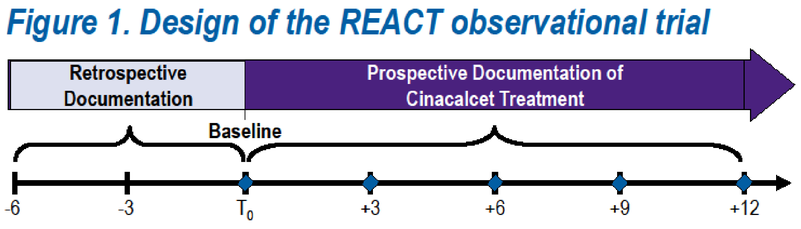
- The calcium-sensing receptor agonist cinacalcet is utilized for therapy of secondary hyperparathyroidism (SHPT) in dialysis patients.
- The efficacy of cinacalcet in SHPT was demonstrated in several studies[1-4].
- In this study, the usage pattern of cinacalcet under routine clinical conditions was documented both for the NKF-K/DOQI™ [5] and KDIGO® [6] eras.

OBJECTIVE

- The aim of the observational trial REACT (**RE**garding the SHPT treatment goal fulfilments under the treatment with Mimp**A**ra® in view of **C**linically relevan**T** subgroups) was to assess intact parathyroid hormone (iPTH) target range achievement with cinacalcet therapy in German dialysis patients with SHPT in accordance with both the NKF-K/DOQI™ and KDIGO® guidelines.

METHODS

Figure 1. Design of the REACT observational trial



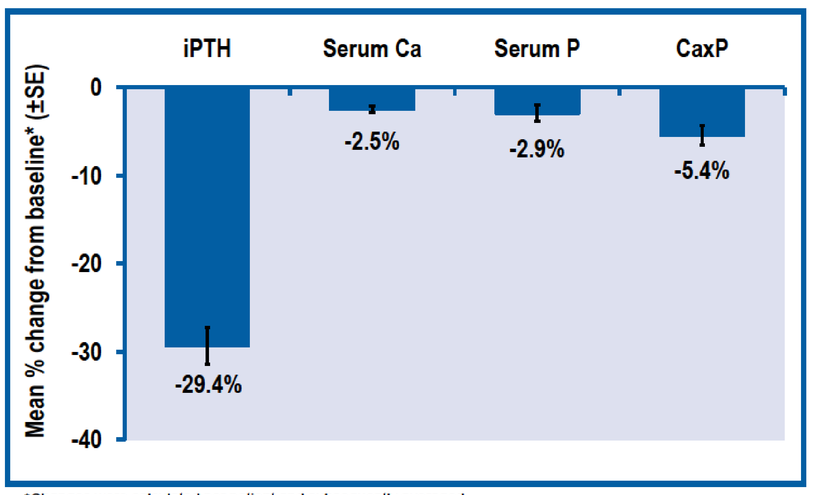
- Design: Multicenter observational trial with 6 months retrospective and 12 months prospective data collection
- Patients: 1,180 chronic dialysis patients with SHPT from 124 German sites
- Eligibility criteria: CKD patients with SHPT in whom cinacalcet treatment was initiated no more than 4 weeks before inclusion
- Primary endpoint: Relative (percentage) change in iPTH from baseline to month 9-12.
- Secondary endpoints:
  - Changes in iPTH after 6 and 12 months of cinacalcet treatment
  - Percentage of patients with an iPTH reduction of at least 30% from baseline
  - Range and frequency of cinacalcet dose titration steps as recommended according to the OPTIMA algorithm[4]
  - Impact of concomitant medication (vitamin D, phosphate binders) and cofactors (e.g. CKD stage) on achieving the NKF-K/DOQI™ targets for both, iPTH and calcium-phosphorus product (Ca x P)
  - Absolute and relative changes in iPTH, Ca, P and Ca x P at the intervals month -6 to -3, month -3 to T_0 (baseline), month T_0 to month 6, month 6 to 12
- Statistics: iPTH levels were summarized in 3-month periods before and after initiation of cinacalcet; FAS (Full Analysis Set)=1,180 patients. The primary analysis of efficacy is based on the FAS. Influence of cofactors on primary endpoint was analyzed using logistic regression methods. An interim analysis covered 6 months cinacalcet treatment of the first 432 patients who started treatment with cinacalcet during the NKF-K/DOQI™ era. *Post hoc* analysis of the FAS led to subgroup comparison regarding efficacy in patients enrolled before and after KDIGO® guidelines publication.
- Here, we report on the final analysis of all enrolled patienst pre- and post KDIGO® publication.

RESULTS

Table 1. Baseline demographics and disease characteristics

Parameter		N=1,180 patients
Male gender		701 (59%)
Age (years, mean SD)	62.5	14.8 (Range: 17-92)
Mean dialysis vintage (months, mean SD)	45.3	45.5 (Range: 0-407)
Underlying nephrological disease (multiple answers possible)		
Diabetic nephropathy		285 (24%)
Glomerular nephropathy		240 (20%)
Hypertensive nephrosclerosis		148 (13%)
Vascular nephropathy		144 (12%)
Others		397(34%)
No data		14 (1%)
iPTH at baseline >9 times the upper normal limit		426 (42%)

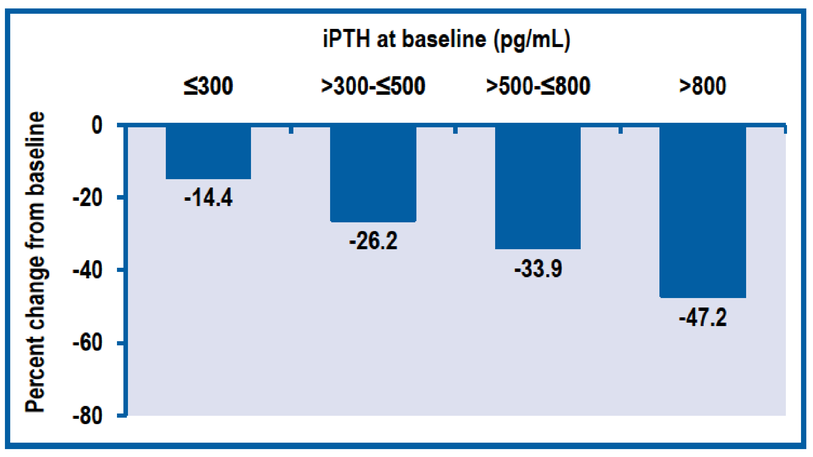
Figure 2. Mean changes in iPTH, Ca, P and Ca x P from baseline to month 9-12



*Changes were calculated per patient and subsequently averaged.

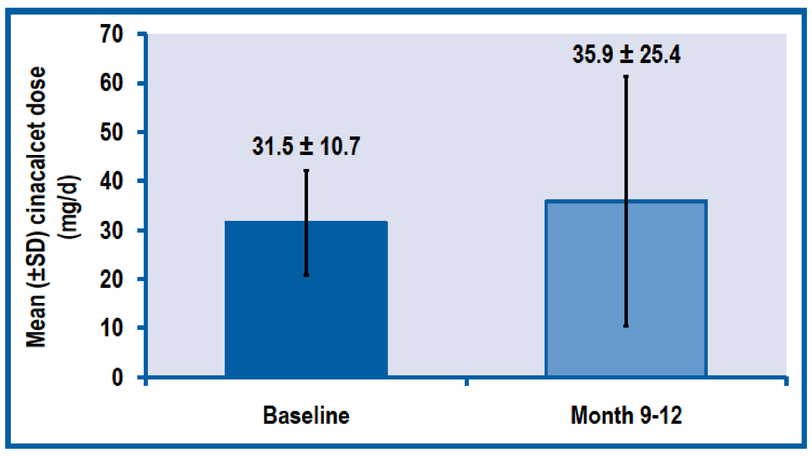
- Mean iPTH (±SD) changed from 616.4 ± 339.3 pg/mL at baseline to 382.1 ± 311.1 pg/mL at month 9-12.
- Phosphorus, calcium and Ca x P also decreased.
- 506 (50%) patients achieved an iPTH reduction of at least 30% from baseline to month 9-12.

Figure 3. Mean changes in iPTH from baseline to month 9-12, stratified by iPTH at baseline



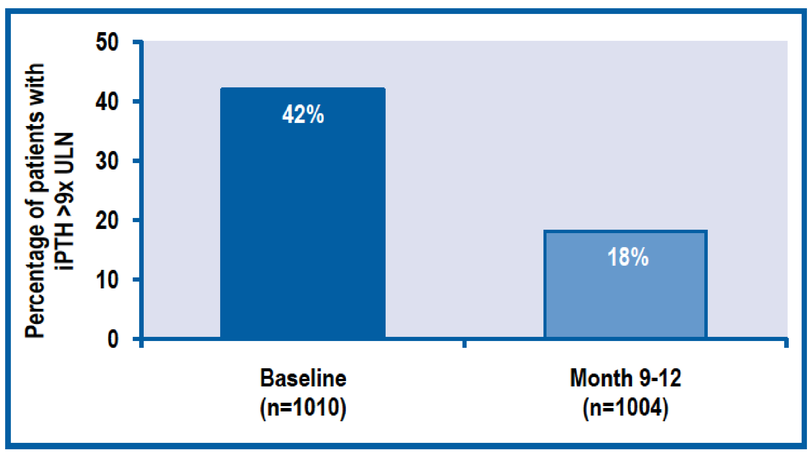
- The reduction in iPTH occurred independently of the iPTH baseline level.

Figure 4. Cinacalcet dose at baseline and month 9-12



- Mean cinacalcet dose increased from 31.5 mg/d at baseline to 35.9 mg/d at month 9-12.
- Cinacalcet doses were unchanged in 43% of patients; 28% of patients required one dose adjustment.
- No relevant changes in the administration of vitamin D and oral phosphate binders were observed.

Figure 5. Achievement of KDIGO® target range for iPTH



- The number of patients outside the recommended KDIGO® target range of >9x upper normal limit (ULN) decreased within 1 year from 42% to 18% (corresponds to a decrease of -56.6%).

Table 2. Cinacalcet initiation before vs. after publication of KDIGO® guidelines in 2009

Parameter	Before publication of KDIGO® guidelines		After publication of KDIGO® guidelines	
N	500 (42%)		680 (58%)	
iPTH at baseline (pg/mL)	627.2	354.3 (532.5)	608.7	328.3 (549.7)
% change baseline to month 9-12	-33.0	47.5 (-44.4)	-26.9	68.3 (-41.0)
≥30% iPTH reduction from baseline	215 (51%)		291 (50%)	
Cinacalcet, overall daily dose (mg)	36.5	25.6 (30.0)	35.4	25.4 (30.0)

Lines 2, 3 and 5 are mean ± SD (median).

- No differences were noted between the two groups with respect to concomitant vitamin D and phosphate binder therapies.

Safety profile

- Overall the reported adverse drug reactions (ADRs) reflected the safety profile mentioned in the Mimpara® "Summary of Product Characteristics" as well as the expected symptoms of the treated patient population. In total, 71 ADRs were observed in 49 patients out of the total 1,180 subjects (4.2%). With 57 ADRs (80.3%), the majority belong to the category "gastrointestinal disorders".

CONCLUSION

- **In this large observational trial, cinacalcet reduced iPTH independently of baseline iPTH.**
- **A large number of patients achieved an iPTH below the upper KDIGO® limit target range during the trial.**
- **No differences in clinical practice were identified when cinacalcet was started before or after publication of KDIGO® guidelines.**
- **The results were achieved with notably low cinacalcet doses and the number of necessary cinacalcet dose adaptions during the study was moderate.**
- **Taken together, the results of this observational trial are consistent with published randomized controlled trials[1,7,8] and further support the use of cinacalcet for the treatment of SHPT in dialysis patients.**

ACKNOWLEDGEMENTS

This study was sponsored by AMGEN. Amgen GmbH Germany provided funds to med:unit GmbH for medical writing support and for graphics support.
This poster was printed by PosterSessionOnline thanks to a grant from ERA-EDTA.

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M) Dialysis. M6) Bone disease in dialysis patients.
Helmut Reichel
DOI: 10.3252/pso.eu.51era.2014
Poster presented at: 51 ERA-EDTA CONGRESS AMSTERDAM 2014
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