Primary Hyperparathyroidism: Issues in Current Management

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UCSF Advances in Endo & Metab 2009
Disclosures

✓ Grant support, PI on Amgen-sponsored trials in primary HPTH

✓ Discuss FDA-unapproved uses – cinacalcet, alendronate - primary HPTH
CASE 1

40 yo male with h/o HIV (CD4 449) referred for hypercalcemia

• **ROS:** + HTN, low energy, body & muscle aching, remote h/o kidney stone (>10 yrs prior); NO fractures
• **Meds:** protonix, prazosin, atenolol, losartan, kaletra, truvada; **NO** Ca, MVI, vitamin D, HCTZ
• **FH:** neg
• **PE:** wnl

*S-Ca 10.3 (8.5-10.5)  alb 4.0  PTH 105 (12-65)*
CASE 2

75 yo Af Am female ref in 10/2007 for hypercalcemia

• DX (2004): plasma cell dyscrasia
  – Anemia
  – +SPEP w/ IgA kappa M spike 2.5, depressed IgM & IgG
  – +UPEP 91 mg kappa light chain
  – Marrow: 15% plasma cells
  – creat 1.3
  – Bone survey -- diffuse osteopenia

PMH: CAD, severe LVH, mild AI, MR with severe pulmonary HTN, mod-severe TR, atrial flutter, pacer, neurofibromatosis type 1, emphysema (? - d/t NF) O₂-dependent, HTN, hyperlipidemia
CASE 2 - cont’d

- **FH:** + NF-1, neg endocrinopathy
- **ROS:** + weight loss, weak, very low energy
- **Meds:** zometa q mo (starting 2004), coumadin, amiodarone, dilt, lasix, lisinopril, simva
- **PE:** wheelchair-bound, cachectic, slow speech  Wt 112 lbs  ++++ café au lait spots, neurofibromas, 3/6 SEM

Ca 11.1  P 2.2  PTH 118 (nl 11-79)  creat 1.3
Objectives

- Recent trials & observational studies –
  - *Natural history* – outcomes of surgery vs medical followup for primary HPTH

- Efficacy of *medical therapy* in controlling biochemical & skeletal complications of primary HPTH

- 2008 *Guidelines* on Disease Management & Monitoring
  - 5/2008 Workshop on Asymptomatic Primary HPTH  
    (JCEM 2/2009)
ASYMPTOMATIC PRIMARY HPTH: 15 YEARS OF FOLLOWUP (Rubin et al, JCEM, 2008)

116 pts (99 asx, 17 sx) (85%/15%)

- Surgery in 59 (51%)
  - 50 asx, 9 sx
  - 100% normalized biochem, improved BMD

- No surgery in 57 (49%)
  - 49 asx (20 surg crit, 29 no) 8 sx
  - Disease progressed in 26 (18 asx - 37% of total, 8 sx - 100% of total)
  - Stable disease in 31 (31 asx)
<table>
<thead>
<tr>
<th></th>
<th>No surgery (57)</th>
<th>Surgery (59)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>57 ± 2</td>
<td>55 ± 2</td>
<td></td>
</tr>
<tr>
<td><strong>Sex (F/M)</strong></td>
<td>45/8</td>
<td>46/9</td>
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<tr>
<td><strong>Postmenop</strong></td>
<td>32</td>
<td>34</td>
<td></td>
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<tr>
<td><strong>Stones</strong></td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td><strong>S-Ca</strong></td>
<td>10.5 ± 0.1</td>
<td>10.8 ± 0.1</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>S-PTH</strong></td>
<td>116 ± 7</td>
<td>144 ± 13</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>U-Ca (mg/G)</strong></td>
<td>236 ± 17</td>
<td>262 ± 17</td>
<td>(&lt;300)</td>
</tr>
<tr>
<td><strong>Alk phos</strong></td>
<td>98 ± 6</td>
<td>98 ± 6</td>
<td></td>
</tr>
<tr>
<td><strong>S-25-OH D</strong></td>
<td>21 ± 1</td>
<td>21 ± 1</td>
<td>(9-52)</td>
</tr>
<tr>
<td><strong>1,25- D</strong></td>
<td>57 ± 2</td>
<td>58 ± 3</td>
<td>(15-60)</td>
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<td><strong>BMD Z scores:</strong></td>
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<tr>
<td><strong>LS</strong></td>
<td>-0.03 ± 0.2</td>
<td>-0.80 ± 0.2</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>fem neck</strong></td>
<td>-0.63 ± 0.1</td>
<td>-1.22 ± 0.1</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>distal 1/3 rad</strong></td>
<td>-0.98 ± 0.2</td>
<td>-1.30 ± 0.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Rubin et al, JCEM, 2008*
15 Years FOLLOWUP - Medical Observation Group (N=57)

• 11/57 died
  Did not correlate with higher S-Ca @ baseline, but did correlate with higher PTH.
• 5/57 - lost to f/u
• 20/57 went to surgery
  ▪ 1 - symptomatic @ baseline - elected surgery
  ▪ 6 - met criteria @ baseline for surgery - but declined & then accepted
  ▪ 6 - disease progression
  ▪ 7 - wanted surgery
• Biochemically -- pts followed showed **NO deterioration** in PTH, creat, U-Ca, 25 OH D or 1,25 OH D

  ▪ **BUT in those pts who completed >10 yrs of medical follow-up -- serum Ca rose significantly in yrs 13 & 15 vs baseline**
15 YEARS FOLLOWUP

<table>
<thead>
<tr>
<th>Year</th>
<th>Serum Ca</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.5 +/- 0.1</td>
<td></td>
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<tr>
<td></td>
<td>(N=49)</td>
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<tr>
<td>Year 5</td>
<td>10.7 +/- 0.1</td>
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<tr>
<td></td>
<td>(N=25)</td>
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<tr>
<td>Year 10</td>
<td>10.8 +/- 0.2</td>
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<tr>
<td></td>
<td>(N=11)</td>
<td></td>
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<tr>
<td>Year 13</td>
<td>11.0 +/- 0.2p &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(N=9)</td>
<td></td>
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<tr>
<td>Year 15</td>
<td>11.1 +/- 0.1p &lt; 0.01</td>
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<td></td>
<td>(N=6)</td>
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</tbody>
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*PTH, U-Ca, 25 D, 1,25 D, S-creat - all stable*

Rubin et al, JCEM, 2008
BMD changes (%)

WHOLE COHORT - 15 YEARS

COHORT Followed X 10 YEARS (N=11)

Rubin et al, JCEM, 2008
BMD changes

Cohort (N=6 pts) followed for 15 years

Rubin et al, JCEM, 2008
Patients Who Had Parathyroidectomy: BMD

- Started with 46 pts at yr 1 and ended with 15 pts at yr 15.

Gains in BMD are consistent & persist over F/U

Rubin et al, JCEM, 2008
SUMMARY - 1

• 29/49 ASYMPTOMATIC pts had >10% declines in BMD by DXA over 15 yrs of followup
• Declines were in cortical sites
  ▪ Different outcome from 1999 NEJM 10-yr report on this cohort
• ~37% developed an indication for surgery over 15 yrs f/u
  ▪ Nothing at baseline was predictive of who

Is it safe to follow beyond 10 years?
SUMMARY - 2

• 8 pts with nephrolithiasis in follow-up group (declined surgery)
  ▪ 6 had recurrent stones
  ▪ 1 had fracture
  ▪ 1 had marked hypercalcemia

• 9 pts in surgical group with stones
  ▪ No subsequent stones/15 years
  ▪ S-Ca 9.8 +/- 0.2
  ▪ S-PTH 31 +/- 21
  ▪ U-Ca 138 +/- 36

****Reinforces benefit of surgery in stone-formers
3 Other Studies - Natural History *

- RCT of surgery vs no surgery in 53 pts
  Rao et al, JCEM, 2004

- RCT of PTX or no PTX in 50 pts
  Ambrogini et al, JCEM, 2007

- Medical observation vs PTX in 191 pts with asymptomatic pHPTH
  Bollerslev et al al, JCEM, 2007

* 1 or 2 yrs data
RCT of Surgery vs No Surgery: 53 pts  
Rao et al, JCEM, 2004

*PTX in 25 pts & medical monitoring in 28 pts*

• BMD, biochemistries, QoL assessed

**24 mo follow-up:**

– Pts were cured biochemically by surgery & **BMD increased at spine, FN, hip, forearm**
– Pts FOLLOWED -stable biochemical indices but **lost BMD at total hip**
– **QoL by SF36** -- **significant declines** in *5/9* domains in pts followed medically - BUT- decline in **only 1/9** domains in pts who had PTX

…and suggestive, unblinded, no controls
Randomized Trial of PTX vs No PTX: 50 Pts

Ambrogini et al, JCEM, 2007

*PTX in 24 pts & medical monitoring in 26 pts*

- BMD, biochemistries, ECHO, QoL & psychol eval at 6 & 12 mos

**Follow-up - 12 mos:**

- 23/24 pts cured by surgery
- Pts FOLLOWED - 4 deteriorated
  - 3 showed marked hypercalciuria (>400 mg)
  - S-Ca rose to >11.2 mg/dl in 1 pt
- PTX pts - **modest improvements in 4 QoL measures** vs medical F/U group & **BMD improved signif vs baseline at LS & total hip (6, 12 mos)**
- ECHO’s - NO changes - either group
Medical Observation vs PTX: 191 Pts with Asymptomatic HPTH  Bollerslev et al, JCEM, 2007

Randomized 96 pts to surgery vs 95 pts to med follow-up (multicenter - Denmark, Norway, Sweden)

1-yr data (119 pts), 2-yr data (99 pts) includes BMD, biochem, QoL & comprehensive psychopath scales

Findings at 2 yrs:

- Medical group - stable biochemically
- Surgical group - cured biochemically
  - Spine BMD - improved significantly in surgical group vs baseline & vs medical group
- Baseline SF-36 LOWER in pHPT pts & more psychol symptoms than gen pop. (of Sweden)
- Longitudinal QoL data … inconsistent
SUMMARY: Natural History

- **Columbia series** -- longest duration of F/U, small #'s of subjects at the end of 15 yrs -- affects strength of conclusions about BMD deterioration

- **Other 3 series** -- reinforce the skeletal benefits of surgical cure -- in mildly affected pts -- **short-term F/U**

- **QoL, psychological functioning** - there may be a benefit -- all short-term, unblinded, no controls

- **Neurocognitive function** - likely to be key parameter in elderly pts you need to follow - NOT examined *(…and cardiovascular)*
MEDICAL THERAPIES

- Bisphosphonates - alendronate * (+others)
- Calcimimetic - cinacalcet **
- Raloxifene
- HRT

4*, 2** trials
ALENDRONATE- 1° HPTH

#1: Randomized **26 women** to 10 mg ALN/d or qod or nothing X 2 yrs
- Baseline FN T scores -3.2, -3.5
- BMD (FN, TB) decreased in controls
- BMD increased in Aln-treated: spine +8.6% total hip +4.8% total body +1.2%
  
  *Rossini et al, JBMR, 2001*

#2: **32 pts** (5 men): 14 pts **assigned to** 10 mg ALN/d vs 18 pts untreated
  - ALN group: FN T score ≤ -2.5 or nonvert fx *(mean -3.8 FN)*
  - Untreated: FN T score > -2.5 *(mean -2.1 FN)*
- ALN-treated pts gained bone @ all sites @ 2 yrs
  - LS + 7.3%
- NO statistical improvement @ cortical sites
  
  *Parker et al, JCEM, 2002*
#3: Randomized 40 women - ALN or placebo X 48 wks
- **Co-morbidities:** age 70, 30% had h/o stones, 13% PUD/GIB, 33% DM, 65% HTN, 18% CAD, osteoporotic @ baseline
- BMD in ALN-treated: FN $+4.2\%$  Spine $+3.8\%$ vs NO change in placebo group
- S-Ca down modestly but significantly w/ALN

*Chow et al, JCEM, 2003*

#4: Randomized 44 asymptomatic pts (9 men) to ALN (10 mg/d) vs placebo
- **2 yrs ALN** on BMD: LS $+6.8\%$  Hip $+4.0\%$
  (significantly > cont)  FN $+3.7\%$  radius 0
- BTM - decreased; S-Ca & PTH were stable

*Khan et al, JCEM, 2004*
SUMMARY--

Alendronate: -
- does **NOT** reverse
  biochemical
  abnormalities of HPTH

- stabilizes & enhances
  BMD -- may be **alternative**
  to protect skeleton -
  vs PTX
Ca-sensing Receptor

- GPCR - critical role in PTH secretion & cell proliferation

- CaSR activation - inhibits PTH secretion & proliferation

- Calcimimetics - CaSR “agonists” -- allosteric modulators -- req EC Ca to work
RCT - Cinacalcet in PHPT

- 78 pts
- Serum [Ca] 10.3 - 12.5 mg/dL
- Intact PTH > 45 pg/mL
- Randomized: (50/50)
  - 30, 40, 50 mg cinacalcet or placebo bid X 1 year
- Followed by 4 yr open-label extension
- Endpoints:
  - Reduction in S-Ca to < 10.3 mg/dL or by > 0.5 mg/dL from baseline
  - Other bioch parameters, hormones, BMD, markers, safety

Peacock et al, JCEM, 2005
## Demographics and Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=40)</th>
<th>Cinacalcet (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>62 ± 13</td>
<td>62 ± 12</td>
</tr>
<tr>
<td>M/F</td>
<td>9/29</td>
<td>12/28</td>
</tr>
<tr>
<td>S-[Ca]</td>
<td>10.7 ± 0.4</td>
<td>10.7 ± 0.5</td>
</tr>
<tr>
<td>PTH</td>
<td>120 ± 54</td>
<td>105 ± 36</td>
</tr>
<tr>
<td>1,25 - D</td>
<td>82 ± 32</td>
<td>81 ± 29</td>
</tr>
<tr>
<td>S-Phos</td>
<td>2.8 ± 0.4</td>
<td>2.7 ± 0.5</td>
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<tr>
<td>24 hr U-Ca (mg/ratio)</td>
<td>0.27 ± 0.10</td>
<td>0.31 ± 0.13</td>
</tr>
<tr>
<td>Fasting U-Ca</td>
<td>0.22 ± 0.10</td>
<td>0.26 ± 0.14</td>
</tr>
<tr>
<td>S-BSAP</td>
<td>20.4 ± 12.2</td>
<td>18.7 ± 7.3</td>
</tr>
<tr>
<td>S-NTX</td>
<td>21.4 ± 10.4</td>
<td>18.2 ± 6.3</td>
</tr>
<tr>
<td>U-NTX</td>
<td>64 ± 53</td>
<td>48 ± 22</td>
</tr>
</tbody>
</table>

*Peacock et al, JCEM, 2005*
Study Year

Pre-dose* Serum Ca: 5 Yrs of Treatment -- 80-90% normalized

Serum Ca (mg/dL)

Placebo  Cinacalcet  Mean ± SE

*12 hrs post-dose, NADIR of drug effect

(N): 24 24 21 21 41 37 34 25 25

Peacock et al, ASBMR, 9/2006
Pre-dose* Plasma iPTH: 5 Yrs of Treatment

p = 0.034

* Underestimate ...

Peacock et al, ASBMR, 9/2006
Pharmacodynamic Responses to Cinacalcet - Week 24

Plasma PTH

Mean (± SE) % Change

Time (Hours Post-dose)

Serum Calcium

Mean (± SE) % Change

Time (Hours Post-dose)

Peacock M et al, JCEM, 2005
Serum Phosphorus: 5 Yrs of Treatment

**Mean ± SE**

*Placebo* | *Cinacalcet* | Mean ± SE
---|---|---

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**Serum Phos (mg/dL)**

- **Cinacalcet vs. Placebo**
- **Open-label Cinacalcet**

- **p < 0.001**

*Peacock et al, ASBMR, 9/2006*
## Other Biochemistries - Year 1

- **No significant changes in:**
  - serum 1,25 OH D
  - 24 hr U-Ca

- **Fasting U-Ca/creat (mg/mg)**

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>Cinacalcet</th>
<th>PBO</th>
<th>Cinacalcet</th>
<th>PBO</th>
<th>Cinacalcet</th>
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<tbody>
<tr>
<td>Fasting U-Ca/creat (mg/mg)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>0.22</td>
<td>0.21</td>
<td>0.25</td>
<td></td>
<td>0.26</td>
<td>0.20</td>
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<tr>
<td></td>
<td>0.20</td>
<td>0.20</td>
<td>0.16</td>
<td>***</td>
<td>0.16</td>
<td>0.16</td>
</tr>
</tbody>
</table>

- **TmP (mg/100 mL GFR)**

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<thead>
<tr>
<th></th>
<th>PBO</th>
<th>Cinacalcet</th>
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<th>Cinacalcet</th>
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<th>Cinacalcet</th>
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<tr>
<td>TmP (mg/100 mL GFR)</td>
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<tr>
<td></td>
<td>2.7</td>
<td>2.8</td>
<td>2.7</td>
<td></td>
<td>2.7</td>
<td>3.7</td>
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<tr>
<td></td>
<td>2.8</td>
<td>3.7</td>
<td>2.7</td>
<td>***</td>
<td>3.5</td>
<td>***</td>
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</tbody>
</table>

*** $p < 0.001$ (C vs P)   *** $p < 0.001$ (baseline vs 52 wk)
## Baseline Bone Mineral Density by DXA

<table>
<thead>
<tr>
<th></th>
<th>T score</th>
<th>Z score</th>
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</thead>
<tbody>
<tr>
<td><strong>Lumbar Spine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>-1.22</td>
<td>-0.10</td>
</tr>
<tr>
<td>cinacalcet</td>
<td>-0.90</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Total Hip</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>-1.32</td>
<td>-0.33</td>
</tr>
<tr>
<td>cinacalcet</td>
<td>-1.20</td>
<td>-0.31</td>
</tr>
<tr>
<td><strong>Distal 1/3 Radius</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>-1.79</td>
<td>-0.31</td>
</tr>
<tr>
<td>cinacalcet</td>
<td>-1.61</td>
<td>-0.46</td>
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</table>

*Peacock et al, JCEM, 2005*
### Mean Changes (+/- SD) in Z Scores: NO Significant Differences

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th>Week 52</th>
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</thead>
<tbody>
<tr>
<td><strong>Lumbar Spine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>0.05 (0.23)</td>
<td>0.03 (0.29)</td>
</tr>
<tr>
<td>cinacalcet</td>
<td>-0.08 (0.20) *</td>
<td>0 (0.21)</td>
</tr>
<tr>
<td><strong>Total Hip</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>0.03 (0.16)</td>
<td>-0.02 (0.18)</td>
</tr>
<tr>
<td>cinacalcet</td>
<td>-0.03 (0.28)</td>
<td>-0.01 (0.22)</td>
</tr>
<tr>
<td><strong>Distal 1/3 Radius</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>0.02 (0.24)</td>
<td>-0.01 (0.36)</td>
</tr>
<tr>
<td>cinacalcet</td>
<td>0.01 (0.17)</td>
<td>-0.05 (0.32)</td>
</tr>
</tbody>
</table>

* P = 0.023 (vs placebo)  

*Peacock et al, JCEM, 2005*
% Change in BMD: Baseline to Week 220

<table>
<thead>
<tr>
<th>Skeletal Site</th>
<th>Placebo (n = 24)</th>
<th>Cinacalcet (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine BMD, %</td>
<td>0.5 ± 1.7</td>
<td>-0.5 ± 2.3</td>
</tr>
<tr>
<td>Femoral neck BMD, %</td>
<td>-4.0 ± 1.3</td>
<td>-5.1 ± 1.5</td>
</tr>
<tr>
<td>1/3 Distal radius BMD</td>
<td>-0.1 ± 3.0</td>
<td>-0.1 ± 2.2</td>
</tr>
<tr>
<td>Total hip BMD, %</td>
<td>-2.8 ± 1.5</td>
<td>-3.5 ± 2.4</td>
</tr>
</tbody>
</table>

Aln
+6-8%
+3-5%

NS difference in trends/time

Peacock et al, ASBMR, 9/2006
Adverse Events

- Mild to moderate, overall well-tolerated

- **Year 1** **nausea** (28% in cinacalcet, 16% placebo) headache (23% cinacalcet, 41% placebo)

- **Withdrawals**: 8 (cinacalcet), 6 (placebo)
  - 3 pts with hypocalcemia (<8.0 mg/dL) in cinacalcet group were withdrawn
  - 2 pts with paresthesias in cinacalcet group (Ca 7.8, 8.1 mg/dL)

- AE’s @5 years similar to year 1

*Peacock et al, JCEM, 2005; unpubl data*
Summary - Cinacalcet in Primary HPT -1

- Normalizes S-Ca in ~80-90% of pts w/mild HPTH x 5 yrs
- Reduces PTH, increases S-phos
- No change in 24 h U-Ca, 1,25 OH D
- Modest decrease in fasting U-Ca & increase in TmP
- BMD Z scores - stable X 5 years

How about “sicker” patients?
Patients with Intractable HPTH * (N=17)

- 8 males, 9 females  
  entry [Ca] > 12.5 mg/dl

- 14/17 prior surgery  
  7/17 renal stones

- 10/17 prior bisphosphonates

**DOSING:** 30 mg cinacalcet BID to 90 QID to get S-Ca to ≤ 10 mg/dl (16 wks titration)

*open-label*  
Marcocci et al, submitted 2008
Patients with Intractable HPTH * (N=17)

- 8 males, 9 females  
  entry [Ca] > 12.5 mg/dl
- 14/17 prior surgery  
  7/17 renal stones
- 10/17 prior bisphosphonates

**DOSING:** 30 mg cinacalcet BID to 90 QID to get S-Ca to < 10 mg/dl (16 wks titration)

<table>
<thead>
<tr>
<th></th>
<th>Baseline (17)</th>
<th>End titration (13)</th>
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<tbody>
<tr>
<td>S-Ca</td>
<td>12.7 +/- 0.8</td>
<td></td>
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<tr>
<td>S-phos</td>
<td>2.2 +/- 0.4</td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>243 +/- 105 pg/ml (nl 10-65)</td>
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<tr>
<td>Median PTH</td>
<td>263</td>
<td></td>
</tr>
</tbody>
</table>

*open-label*  
Marcocci et al, submitted 2008
Patients with Intractable HPTH * (N=17)

- 8 males, 9 females
- entry [Ca] > 12.5 mg/dl
- 14/17 prior surgery
- 7/17 renal stones
- 10/17 prior bisphosphonates

**DOSING:** 30 mg cinacalcet BID to 90 QID to get S-Ca to \(< 10\) mg/dl (16 wks titration)

<table>
<thead>
<tr>
<th></th>
<th>Baseline (17)</th>
<th>End titration (13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Ca</td>
<td>12.7 +/- 0.8</td>
<td>10.4 +/- 0.3 mg/dl</td>
</tr>
<tr>
<td>S-phos</td>
<td>2.2 +/- 0.4</td>
<td>2.8 +/- 0.1 mg/dl</td>
</tr>
<tr>
<td>PTH</td>
<td>243 +/- 105 pg/ml (nl 10-65)</td>
<td>173 pg/ml</td>
</tr>
<tr>
<td>Median PTH</td>
<td>263</td>
<td>173 pg/ml</td>
</tr>
</tbody>
</table>

*open-label*  

Marcocci et al, submitted 2008
• Improvement 3-5 points (deemed significant) -- **7/8 domains improved**

• MOS cognitive function scale - baseline to titration **61.2 --> 74.4**

*average for US pop. 82.4*

Use of cinacalcet may be considered:

- To control hypercalcemia in pts w/symptoms (too sick, decline or failed surgery)

- To aid decision-making regarding surgery in pts w/unclear symptomatology (not evidence-based)

- If long-term use - consider costs ($) -- significant - absence of BMD response
GUIDELINES from 2008 INTERNATIONAL WORKSHOP on the MANAGEMENT of ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM (JCEM, 2/09)

(w/permission of Drs. Bilezikian, Khan, Potts)

**Recommend surgery if** –

<table>
<thead>
<tr>
<th>Condition</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of hypercalcemia</td>
<td>YES</td>
</tr>
<tr>
<td>AGE</td>
<td>&lt; 50</td>
</tr>
<tr>
<td>Serum total calcium</td>
<td>1.0 mg/dL above ULN</td>
</tr>
<tr>
<td>Urine calcium</td>
<td>- not indicated</td>
</tr>
<tr>
<td>Renal function/creat clearance</td>
<td>&lt; 60 ml/min</td>
</tr>
<tr>
<td>BMD by DXA</td>
<td>T score ≤ -2.5 at any DXA site</td>
</tr>
<tr>
<td></td>
<td>(LS, hip or distal 1/3 radius)</td>
</tr>
</tbody>
</table>

**Medical surveillance is neither desired nor possible**
<table>
<thead>
<tr>
<th>Test</th>
<th>1990</th>
<th>2002</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Ca</td>
<td>biannually</td>
<td>biannually</td>
<td><strong>ANNUALLY</strong></td>
</tr>
<tr>
<td>24 h U-Ca</td>
<td>annually</td>
<td>NOT</td>
<td>NOT recommended</td>
</tr>
<tr>
<td>Creat clear</td>
<td>annually</td>
<td>NOT</td>
<td>NOT recommended</td>
</tr>
<tr>
<td>S-creat</td>
<td>annually</td>
<td>annually</td>
<td>annually</td>
</tr>
<tr>
<td>BMD</td>
<td>annually</td>
<td>annually</td>
<td>annually (3 sites)</td>
</tr>
<tr>
<td>Abd xray (+/- U/S)</td>
<td>annually</td>
<td>NOT</td>
<td>NOT recommended</td>
</tr>
</tbody>
</table>

* Khan et al, JCEM, 2/09
CASE 1

40 yo male with h/o HIV (CD4 449) referred for hypercalcemia

- **ROS:** + HTN, *low energy, body & muscle aching, remote h/o kidney stone (>10 yrs prior)*  NO fractures
- **Meds:** protonix, prazosin, atenolol, losartan, kaletra, truvada;  **NO** Ca, MVI, vitamin D, HCTZ
- **FH:** neg
- **PE:** wnl

* S-Ca 10.3 (8.5-10.5)  alb 4.0  PTH 105 (12-65)
Case 1 - cont’d

**WORKUP**  40 yo male

- S-Ca 10.3 (8.5-10.5)  alb 4.0  PTH 105 (12-65)  (rpt Ca 10.5  PTH 117)  creat 1.3

- 24 h urine: creat 2082 mg  Ca 417 mg  
  (100- 250)

- DXA T score LS - 2.8  Fem neck - 2.1
Case 1 - cont’d

**WORKUP**

PT sestamibi: +R lower focus of tracer

Neck U/S: prob enlarged R lower PT gland

Underwent successful surgery with removal of adenoma --> normalization of serum Ca & PTH & urinary Ca;
followup DXA scan in 1 year
CASE 2

75 yo Af Am female ref in 10/2007 for hypercalcemia

• DX (2004): plasma cell dyscrasia
  PMH: CAD, severe LVH, mild AI, MR with severe pulmonary HTN, mod-severe TR, atrial flutter, pacer, neurofibromatosis type 1, emphysema (? - d/t NF) O2 dependent, HTN, hyperlipidemia

• ROS: + weight loss, weak, very low energy

• Meds: zometa q mo (starting 2004), coumadin, amiodarone, dilt, lasix, lisinopril, simva

• PE: wheelchair-bound, cachectic, slow speech
  Wt  112 lbs  ++++ café au lait, neurofibromas, 3/6 SEM

Ca 11.1  P 2.2  PTH  118 (nl 11-79)  creat 1.3
<table>
<thead>
<tr>
<th>Date</th>
<th>Ca</th>
<th>Alb</th>
<th>Phos</th>
<th>PTH*/other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>8.9</td>
<td></td>
<td>3.6</td>
<td></td>
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<td>2000</td>
<td>10.3</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>DX</td>
<td>2004</td>
<td>10.4</td>
<td>3.0</td>
<td>2.5 creat 1.3</td>
</tr>
<tr>
<td>PCD</td>
<td>2004</td>
<td>11.1</td>
<td>3.4</td>
<td>PTH 118*</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td>9.6</td>
<td>3.3</td>
<td>2.0</td>
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</table>

Zometa q mo
# CASE 2 - LABS

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<tr>
<th>Date</th>
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<th>PTH* / other</th>
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<tbody>
<tr>
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<td>8.9</td>
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<td>10.4</td>
<td>3.0</td>
<td>2.5</td>
<td>creat 1.3</td>
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<tr>
<td>2004</td>
<td>11.1</td>
<td>3.4</td>
<td></td>
<td>118* (10-65)</td>
</tr>
<tr>
<td>2005</td>
<td>9.6</td>
<td>3.3</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>6/05-11/07</td>
<td>10.1-11.1</td>
<td>3-3.3</td>
<td>1.6-2.6</td>
<td>CREAT 2.1 PTH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>131* (11-79)</td>
</tr>
</tbody>
</table>

DX  
PCD
<table>
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<tr>
<th>Date</th>
<th>Ca</th>
<th>Alb</th>
<th>Phos</th>
<th>PTH*/other</th>
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<td></td>
</tr>
<tr>
<td>6/05-11/07</td>
<td>10.1-11.1</td>
<td>3-3.3</td>
<td>1.6-2.6</td>
<td>CREAT 2.1 PTH</td>
</tr>
<tr>
<td>1/08 -</td>
<td>8.8</td>
<td>2.9</td>
<td>2.1</td>
<td>PTH 76* (15-88)</td>
</tr>
</tbody>
</table>

**DXA:**

- T score LS -4.8, FN -2.7, HIP -3.1

**DX**

- PCD

**Zometa q mo**

- 118* (10-65)

**Cinacalcet started 30 mg/day**

- 131* (11-79)

**Creat 1.1**
Questions
## Changes in Health-related QOL Scores: End of titration - Baseline

<table>
<thead>
<tr>
<th>Component</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical components</td>
<td>3.1</td>
</tr>
<tr>
<td>Mental components</td>
<td>7.3</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>4.6</td>
</tr>
<tr>
<td>Role limitations - physical</td>
<td>3.3</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>5.1</td>
</tr>
<tr>
<td>General health perception</td>
<td>3.0</td>
</tr>
<tr>
<td>Social functioning</td>
<td>6.9</td>
</tr>
<tr>
<td>Vitality</td>
<td>5.6</td>
</tr>
<tr>
<td>Role limitations - emotional</td>
<td>7.7</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>7.5</td>
</tr>
<tr>
<td>MOS cognitive functioning</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Baseline 61.2 --> 74.4

*(average MOS US pop. 82.4)*

Change of +3-5 deemed significant improvement; no control, open-label

Marcocci et al, submitted 2008
Adverse Events

• **5-year open-label**, most frequent AE’s were -
  – Arthralgia 38%
  – Myalgia 27%
  – Diarrhea 22%
  – Upper respiratory infection 20%
  – Nausea 20%

• Safety chemistries unchanged over 5 years

*Peacock et al, unpublished data*
Baseline BMD Z Scores* of 45 Patients Completing Year 1 and Enrolled in 4-yr Extension

<table>
<thead>
<tr>
<th>Skeletal Site</th>
<th>Placebo (n = 24)</th>
<th>Cinacalcet (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>0.3 ± 1.6</td>
<td>0.0 ± 1.4</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-0.4 ± 1.1</td>
<td>-0.7 ± 0.7</td>
</tr>
<tr>
<td>1/3 Distal radius</td>
<td>0.7 ± 0.2</td>
<td>0.7 ± 0.2</td>
</tr>
<tr>
<td>Total hip</td>
<td>-0.4 ± 1.0</td>
<td>-0.5 ± 1.0</td>
</tr>
</tbody>
</table>

* Z Score - c/w age-, gender-matched controls

Peacock et al, ASBMR, 9/2006

NS difference
Pre-Dose* Serum [Ca]
(1st endpoint ~ nl range, 0.5 mg/dL drop)

~88% pts normalized Ca

Peacock M et al, JCEM, 2005

* Peacock M et al, JCEM, 2005

NI: 8.4-10.3

p < 0.001
QoL DATA - tend to favor surgery… -- NOT consistent

Comprehensive Psychopath scores - subtle abnl in HPTH

Bollerslev et al, JCEM, 2007
**Gains in BMD in both osteoporotic and nonosteoporotic patients with PTX**

Ambrogini et al, JCEM, 2007
Mean 1,25-OH₂ Vitamin D - Year 1

AMG 073 = cinacalcet

Placebo (N): 37
AMG 073 (N): 34
Mean 24-hr Urine Ca/Creat (Mg) Ratio - Year 1

Placebo (N): 36
AMG 073 (N): 40

nl, 0.07-0.29
## Bone Markers: Baseline vs 24 vs 52 wks

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cinacalcet</th>
<th>NORMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BSAP</strong></td>
<td>20 → 18 → 21</td>
<td>19 → 23 → 25</td>
<td>7-22</td>
</tr>
<tr>
<td><strong>Serum NTX</strong></td>
<td>21 → 22 → 21</td>
<td>18 → 24 → 23</td>
<td>5-24</td>
</tr>
<tr>
<td><strong>Urine NTX</strong></td>
<td>64 → 59 → 61</td>
<td>48 → 72 → 77</td>
<td>17-188</td>
</tr>
</tbody>
</table>

***Statistically significant (vs placebo at 52 wks), changes in nl range

*Peacock et al, JCEM, 2005*
MEDICAL THERAPIES

# 1: Use of alendronate in elderly women with osteoporosis & mild HPTH X 2 years (Rossini et al, JBMR, 2001)

• Randomized **26 pts** to 10 mg ALN/d or qod, or nothing X 2 yrs
  – FN T scores **-3.2, -3.5**
• Bone markers -- suppressed by ALN
• BMD (FN, TB) decreased in controls
• **BMD - ALN-treated:**
  - LS  + 8.6%
  - TH  + 4.8%
  - TB  + 1.2%
• No consistent biochem changes (S-Ca, S-phos, U-Ca)
# 2: Treatment of pts w/primary HPTH-related osteoporosis for 2 years  (Parker et al, JCEM, 2002)

- **32 pts** (5 men): 14 pts **assigned to** ALN (10 mg/d) vs 18 pts untreated
- ALN group: FN T score $\leq -2.5$ -OR- $\leq -1.0$ and nonvert fracture  *(mean -3.8 FN)*
- Untreated grp: FN T score > -2.5  *(mean -2.1 FN)*
- ALN-treated pts gained bone @ all sites (2 yrs)
  - **LS + 7.3%**  *(only site stat signif)*
- Untreated pts gained BMD at spine (+4.0%) but lost elsewhere

***Did NOT see improvement at cortical sites with ALN***
#3: Effects of ALN on BMD in women with primary HPTH  (Chow et al, JCEM, 2003)

- **DB randomized PCT:** 40 pm women given ALN or placebo X 48 wks
- **Characteristics:** age 70, 30% had h/o stones, 13% PUD/GIB, 33% DM, 65% HTN, 18% CAD
- Osteoporotic @ baseline
- BMD in ALN-treated: FN + 4.2% (significantly > pbo) LS + 3.8%
- BMD - placebo group - no change/48 wks
- S-Ca down modestly but significantly
MEDICAL THERAPIES

#4: DB, randomized PC trial of ALN in primary HPTH
(Khan et al, JCEM, 2004)

• 44 pts (9 men) -- all asymptomatic
• Randomized to ALN (10 mg/d) vs placebo
• After PBO X 12 mo - crossed over to active RX
• 2 yrs ALN on BMD: LS + 6.8% (significantly > cont)
  TH + 4.0%
  FN + 3.7%
  dist radius - no change

• BMD - placebo group - stable X 12 mos
• BTM - came down, S-Ca and PTH were stable

***ALN may be a useful alternative to PTX (all 4 studies)***