Update on Treatment of Glucocorticoid-induced Osteoporosis

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March 10, 2012
Objectives

- Discuss Mechanisms of Glucocorticoid-induced Osteoporosis
- Discuss Guideline Recommendations for treatment of Glucocorticoid-induced Osteoporosis
Case 1: JV 1/23/2009

- 52 y.o. man referred by GI for GIOP management
- PMH: ulcerative colitis dx 2002
- Meds: prednisone since 2005, currently 7.5 mg qd, (difficulty weaning), Pentasa, Proctofoam
- No personal or parental h/o fragility fracture
- No height loss, 5’ 5 ¾”, 150.4 lbs
- Low calcium diet

<table>
<thead>
<tr>
<th></th>
<th>L1-4</th>
<th>LFN</th>
<th>LTH</th>
<th>RFN</th>
<th>RTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/2/08</td>
<td>-3.8</td>
<td>-2.2</td>
<td>-1.4</td>
<td>-2.4</td>
<td>-1.8</td>
</tr>
</tbody>
</table>
Case 1: Initial tests

- Ca 9.2, alb 4.3
- PO4 3.5
- ALP 54
- Total testosterone 344 ng/dl
- intact PTH 49.8 pg/ml
- 25-hydroxy vitamin D 16.3 ng/ml
- urinary Ca 353 mg/24 hr (5.0 mg/kg/24 hr), Cr 1.54 g/24 hr, and vol 1223 ml
- Spine x-rays: age-indeterminate T8 anterior wedge compression fracture
Is this patient at high risk for fracture?
Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: [52]  Date of birth: [Y: ] [M: ] [D: ]

2. Sex  ☐ Male ☐ Female

3. Weight (kg)  [68.22]

4. Height (cm)  [165.1]

5. Previous fracture  ☐ No ☐ Yes

6. Parent fractured hip  ☐ No ☐ Yes

7. Current smoking  ☐ No ☐ Yes

8. Glucocorticoids  ☐ No ☐ Yes

9. Rheumatoid arthritis  ☐ No ☐ Yes

10. Secondary osteoporosis  ☐ No ☐ Yes

11. Alcohol 3 or more units per day  ☐ No ☐ Yes

12. Femoral neck BMD (g/cm²)
   T-Score [2.4]
   Clear  Calculate

BMI 25.0
The ten year probability of fracture (%)

- Major osteoporotic  21
- Hip fracture  7.9
TPTD in GIOP

- More costly, SQ administration, other agents
- $T$-score $\leq -3.5$ without fracture
- $T$-score $\leq -2.5$ with fracture
- Unable to tolerate oral BIS: e.g. active upper GI symptoms, upper GI symptoms on oral BIS, achalasia, esophageal stricture, ring, web, Barrett’s
- Unable to tolerate IV Bisphosphonate
- Failed other therapy: fracture with loss of BMD despite good adherence
TPTD vs. ALE in GIOP

Saag K.G. NEJM 2007;357:2028-39
Saag K.G. Arth & Rheum 2009;3346-55
# TPTD vs. ALE: Fracture Data

<table>
<thead>
<tr>
<th>Fracture</th>
<th>TPTD</th>
<th>ALE</th>
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</thead>
<tbody>
<tr>
<td>Morphometric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebral Month 18</td>
<td>1/171 (0.6%)*</td>
<td>10/165 (6.1%)*</td>
</tr>
<tr>
<td></td>
<td>Month 36</td>
<td>Month 36</td>
</tr>
<tr>
<td></td>
<td>3/173 (1.7%)**</td>
<td>13/169 (7.7%)**</td>
</tr>
<tr>
<td>Nonvertebral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 18</td>
<td>12/214 (5.6%)</td>
<td>8/214 (3.7%)</td>
</tr>
<tr>
<td></td>
<td>Month 36</td>
<td>Month 36</td>
</tr>
<tr>
<td></td>
<td>16/214 (7.5%)</td>
<td>15/214 (7.0%)</td>
</tr>
</tbody>
</table>

* P=0.004
** P=0.007

Saag K.G. NEJM 2007;357:2028-39
Saag K.G. Arth & Rheum 2009;3346-55
Case 1: Follow Up

- Forteo 20 mcg SQ qd starts 2/2009 ($30/copay)
- Colectomy 12/2009, d/c prednisone 1/2010
- Thiazide to treat hypercalciuria?
- Repeat urinary Ca 167 mg/24 hr (prior 353 mg/24 hr)

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<td>-2.2</td>
<td>-1.4</td>
<td>-2.4</td>
<td>-1.8</td>
</tr>
<tr>
<td>2/19/10</td>
<td>-2.9</td>
<td>-2.3</td>
<td>-1.5</td>
<td>-2.4</td>
<td>-1.8</td>
</tr>
<tr>
<td></td>
<td>(+14.4%)</td>
<td>(-1.7%)</td>
<td></td>
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</tbody>
</table>
Case 1: Follow Up

- Completed 24 months of Forteo (2/2009-2/2011)
- Consolidated with ALE 70 mg weekly 2/2011
- No adverse effects, good adherence, no clinical fractures

<table>
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<th>RFN</th>
<th>RTH</th>
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</thead>
<tbody>
<tr>
<td>12/2/2008</td>
<td>-3.8</td>
<td>-2.2</td>
<td>-1.4</td>
<td>-2.4</td>
<td>-1.8</td>
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<tr>
<td>2/19/2010</td>
<td>-2.9 (:+14.4%)</td>
<td>-2.3</td>
<td>-1.5 (-1.7%)</td>
<td>-2.4</td>
<td>-1.8 (-1.2%)</td>
</tr>
<tr>
<td>3/2/2012</td>
<td>-1.3 (+22.8%)</td>
<td>-1.9</td>
<td>-0.9 (+9.9%)</td>
<td>-1.9</td>
<td>-1.2 (+11.0%)</td>
</tr>
</tbody>
</table>

+40.4% vs. ‘08
Case 2: MW, 3/2/2012

- 62 woman PMH asthma
- Budesonide/formoterol 80-4.5 mcg 2 puffs qhs, occasional courses oral steroid (none over >1 yr)
- DXA T-scores: LS -1.3, LFN -1.7
- Menarche 16, regular menses, menopause 52, no HRT
- 2 servings dairy daily, citracal petites 1 tab bid
- PMH: +Zencker’s diverticulum
- Meds: Singulair, Astelin, Pepcid
- Soc Hx: No cigarettes or alcohol
- Fam Hx: No parental fragility fractures
- Height loss 5’7 → 5’4”, 188 lb, BMI 32
- Plan to limit Symbicort during tree/grass pollen season
Fracture Risk Factors in Glucocorticoid Therapy

- Advanced age
- Low BMI (<24)
- Underlying disease
  - RA, PMR, IBD, COPD, Transplantation
- Greater steroid exposure: ↑ dose, ↑ duration
- Prevalent fracture
- Family history of fracture
- Cigarettes
- Excess alcohol

Arthritis Care & Research 2010;62(11):1515-1526
ACR Guidelines (11/2010) (Level of Evidence)

- Calcium (food + supplement) 1200-1500 mg qd (A)
- Vitamin D ≥ 800 IU qd (A)
- Weight-bearing exercise (C)
- Baseline DXA (C)
- Fall risk assessment (C)
- Measure height (C)
- Assess prevalent fragility fracture (C)
- Consider spine x-rays or VFA (C)
- Smoking cessation (C)
- Avoidance of excessive alcohol (>2 drinks/day) (C)
Case 2: Test results

- Ca 9.4, alb 4.4
- Phos 3.8
- Cr 0.84
- 25 OH vitamin D 23.1 ng/ml
- Intact PTH 64.7 pg/ml (14-72)
- Spinal X-rays: no fracture, + multilevel disc disease thoracic & lumbar spine, anterolisthesis L4 on L5
**Questionnaire:**

1. Age (between 40-90 years) or Date of birth
   - Age: 62
   - Date of birth: Y: _, M: _, D: _

2. Sex
   - Male

3. Weight (kg): 85.5

4. Height (cm): 162.6

5. Previous fracture
   - No

6. Parent fractured hip
   - No

7. Current smoking
   - No

8. Glucocorticoids
   - No

9. Rheumatoid arthritis
   - No

10. Secondary osteoporosis
    - No

11. Alcohol 3 or more units per day
    - No

12. Femoral neck BMD (g/cm²)
    - GE-Lunar: 0.805
    - T-score: -1.7

**BMI 32.3**

The ten year probability of fracture (%)

- Major osteoporotic: 11
- Hip fracture: 2.2
Treatment of GIOP According to Fracture Risk

For postmenopausal women and men >50 years initiating or receiving GC

<table>
<thead>
<tr>
<th>Risk</th>
<th>Major OP Fracture Risk</th>
<th>Treatment (Level of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;10%</td>
<td>Pred &lt;7.5 mg qd: no drug tx (A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pred ≥7.5 mg qd: ALE (A), RIS (A), ZOL (B)</td>
</tr>
<tr>
<td>Medium</td>
<td>10-20%</td>
<td>Pred &lt;7.5 mg qd: ALE (A), RIS (A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pred ≥7.5 mg qd: ALE (A), RIS (A), ZOL (B)</td>
</tr>
<tr>
<td>High</td>
<td>&gt;20%</td>
<td>Pred &lt;5 mg qd x ≤ 1 month: ALE (A), RIS (A), ZOL (B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pred ≥ 5 mg qd x ≤ 1 month or any pred dose &gt; 1 month: ALE (A), RIS (A), ZOL (B), or TPTD (B)</td>
</tr>
</tbody>
</table>

Arthritis Care & Research 2010;62(11):1515-1526
Limitations of ACR Recommendations

- Scope of ACR recommendations excludes:
  - GC in transplant recipients
  - GC in pediatric population
  - Inhaled GC

- FRAX does not incorporate spine BMD

- FRAX does not incorporate GC exposure in dose-response
  - FRAX assumes average risk

- FRAX alone dose cannot replace clinical judgment in fracture risk assessment
  - e.g. declining BMD (exceeding LSC): higher risk
GIOP Tx: Premenopausal Women and Men < 50

- Limited evidence
- Medication safety to fetus not well defined
- FRAX does not apply to persons < 40 years

| GC 1-3 months         | Nonchildbearing potential | ALE for pred ≥ 5 mg qd (A)  
|                       |                           | RIS for pred ≥ 5 mg qd (A)  
|                       |                           | ZOL for pred ≥ 7.5 mg qd (B)  
| Childbearing potential |                           | Inadequate data for recommendation |
| GC ≥ 3 months         | Nonchildbearing potential | ALE for any pred dose (A)  
|                       |                           | RIS for any pred dose (A)  
|                       |                           | ZOL for any pred dose (B)  
|                       |                           | TPTD for any pred dose (B) |
| Childbearing potential |                           | ALE for pred ≥ 7.5 mg qd (A)  
|                       |                           | RIS for pred ≥ 7.5 mg qd (C)  
|                       |                           | TPTD for pred ≥ 7.5 mg qd (C) |
Monitoring in GIOP (Level of Evidence)

- Serial DXA measurement (C)
- Consider annual 25 OH vitamin D measurement (C)
- Annual height measurement (C)
- Assessment of incident fragility fracture (C)
- Assessment of adherence to osteoporosis medication (C)

Arthritis Care & Research 2010;62(11):1515-1526
ZOL vs. RIS in GIOP

Reid, Lancet 2009;373:1253-63
Case 3: MA 9/9/2011

- 62 y.o. woman evaluation for OP
- PMH: well controlled asthma, HTN
- Meds: Advair x 10 years, recently switched to Flovent 110 mcg bid, albuterol prn, HCTX 12.5 mg qd
- No personal or parental fragility fracture
- Menarche 13, normal menses, menopause 52, no HRT
- 2 servings dairy daily + Ca-D 600 mg-400 IU bid
- 5’6” no height loss, 117 lbs, BMI 18.9

<table>
<thead>
<tr>
<th>Date</th>
<th>LS (T, Z-score)</th>
<th>LFN (T, Z-score)</th>
<th>LTH (T, Z-score)</th>
<th>RFN (T, Z-score)</th>
<th>RTH (T, Z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/26/2011</td>
<td>-2.9, -1.3</td>
<td>-3.0, -1.4</td>
<td>-3.8, -2.5</td>
<td>-2.8, -1.3</td>
<td>-3.5, -2.2</td>
</tr>
</tbody>
</table>
**Questionnaire:**

1. Age (between 40-90 years) or Date of birth
   - Age: 62
   - Date of birth: Y:   M:   D:   
2. Sex  
   - Male  
   - Female
3. Weight (kg)  
   - 53.1
4. Height (cm)  
   - 167.6
5. Previous fracture  
   - No  
   - Yes
6. Parent fractured hip  
   - No  
   - Yes
7. Current smoking  
   - No  
   - Yes
8. Glucocorticoids  
   - No  
   - Yes
9. Rheumatoid arthritis  
   - No  
   - Yes
10. Secondary osteoporosis  
    - No  
    - Yes
11. Alcohol 3 or more units per day  
    - No  
    - Yes
12. Femoral neck BMD (g/cm²)  
   - GE-Lunar  
   - 0.626
   - T-score: -3.0

**BMI 18.9**

The ten year probability of fracture (%)

- Major osteoporotic  
  - 13
- Hip fracture  
  - 4.0
Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 62
   Date of birth: Y: D: M: 

2. Sex
   Male Female

3. Weight (kg)
   53.1

4. Height (cm)
   167.6

5. Previous fracture
   No Yes

6. Parent fractured hip
   No Yes

7. Current smoking
   No Yes

8. Glucocorticoids
   No Yes

9. Rheumatoid arthritis
   No Yes

10. Secondary osteoporosis
    No Yes

11. Alcohol 3 or more units per day
    No Yes

12. Femoral neck BMD (g/cm²)
    GE-Lunar 0.626
    T-score: -3.0
    Clear Calculate

BMI 18.9
The ten year probability of fracture (%)
with BMD
- Major osteoporotic 21
- Hip fracture 7.2
Case 3: Test results

- Ca 9.2
- Phos 3.5
- Cr 0.74
- 25 OH vitamin D 48.3
- iPTH 43.9
- SPEP/UPEP normal
- tTG IgA Ab <3, tTG IgG Ab <3
- 9/12/2012 urinary Ca 288 mg/24 hr (5.3 mg/kg/24 hr), Cr 0.95 g/24 hr, vol 922 ml
Inhaled GC and Fractures

- Retrospective cohort study using GPRD
  - Inhaled GC (170,818) vs. Control (170,818)
  - Vertebral fracture RR 1.51 (1.22-1.85)
  - Hip fracture RR 1.22 (1.04-1.43)
  - Nonvertebral fracture RR 1.15 (1.10-1.20)

- Meta-analysis of RCTs in COPD
  - 14 fluticasone, 2 budesonide, 90 weeks (24-156)
  - OR 1.27 (1.01-1.58)
    - GC fxr 180/9143 (2.0%)
    - Control fxr 141/8370 (1.7%)
  - Number needed to harm = 83 over 3 years

Von Staa JBMR 2001:16:581-8
Loke Thorax doi:10.1136/thx.2011.160028
Case 3: Follow Up

- 2/10/2012 Interim change: Flovent bid → qAM
- Significant improvement in sleep quality
- ? Systemic absorption of inhaled steroid
  - PCP plans to wean off Flovent
- Oral bisphosphonate therapy recommended but patient refused
- Desire to “do things naturally”
  - Plan to repeat DXA 1/2013
Treatment of GIOP: Miscellaneous

- Continue BIS as long as GC tx
  - drug holiday not recommended
  - After GC tx completed, reassess BIS tx

- Diagnosis codes for DXA coverage
  - V58.65 glucocorticoid therapy receiving or expected to receive prednisone 5 mg (or equivalent) x ≥3 months
  - 733.09 Drug-induced osteoporosis
    - E932.0 Glucocorticoids
  - 733.13 vertebral collapse NOS
  - V67.51 completed drug tx for osteoporosis and monitored for response to therapy
  - V45.77 women s/p oophorectomy
  - V58.69 Current tx with drug for osteoporosis/osteopenia
  - V82.81 Special screening for osteoporosis (may be billed on claim but not Medicare necessity)