An Update on Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

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New Strategies in the Management of Glucocorticoid-Induced Osteoporosis (GIOP)

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THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
2010 ACR Recommendations for the Prevention and Treatment of Glucocorticoid Induced Osteoporosis (GIOP)

Arthritis Care & Research
Vol. 62, No. 11, November 2010, pp 1515–1526
GIOP 2011

New Treatment Strategies

- How is osteoporosis risk best assessed?
- What can be done to prevent and treat GIOP?
- What is being done?
- How can we improve quality?
GIOP Pathophysiology

Glucocorticoids

Bone

OSTEOCYTE
- Function ↓
- Apoptosis ↑

OSTEOBLAST
- Differentiation ↓
- Function ↓
- Apoptosis ↑

↓ bone formation

↓ Bone Quality

↓ Bone Mass

Increased risk of fracture

Canalis E. Osteoporosis Int 2007;18:1319
GIOP Pathophysiology

Glucocorticoids

BONE

OSTEOCYTE
- Function ↓
- Apoptosis ↑

OSTEOBLAST
- Differentiation ↓
- Function ↓
- Apoptosis ↑

OSTEOCLAST
- Genesis ↑
- Apoptosis ↓

- Bone formation ↓
- bone resorption ↑

Bone Quality ↓

Bone Mass ↓

Increased risk of fracture

Canalis E. Osteoporosis Int 2007;18:1319
GIOP Pathophysiology

Glucocorticoids

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↑ Genesis
↓ Apoptosis

Bone formation
↓ Bone resorption

↓ Bone Formation
↓ Bone Mass

Bone Quality

Increased risk of fracture

Neuroendocrine

Calcium Metabolism

Glucocorticoids

RANKL
CSF

↓ intestinal absorption
↑ Renal excretion

↓ sex steroids

GH/IGF-I

↓ negative calcium balance

Canalis E. Osteoporosis Int 2007;18:1319
GIOP Pathophysiology

Glucocorticoids

BONE

OSTEOCYTES
- Function
  - Apoptosis

OSTEOBLASTS
- Function
  - Apoptosis

OSTEOCLASTS
- Genesis
  - Apoptosis

RANKL

CSF

Bone formation
- BONE

Bone resorption
- Bone Mass

Bone Quality
- Bone Mass

Bone Quality
- Increased risk of fracture

Neuroendocrine

Calcium Metabolism

Muscle

Increased risk of fracture
- Risk of falls
  - Muscle weakness

- intestinal absorption
  - Renal excretion

Proteolysis of myofibrils

- Fibrils

- negative calcium balance

Negative calcium balance
- sex steroids

- GH/IGF-I

- Proteolysis of myofibrils

- Fibrils

- Myopathy

Canalis E. Osteoporosis Int 2007;18:1319
Adjusted Relative Rate of Non-vertebral fracture
Fracture Incidence (%) of Lumbar Spine T-Score

Fracture Risk by Spine BMD is Different in Post Menopausal Oral Glucocorticoid Users vs Non-Users

56 postmenopausal patients in PBO arm of Risedronate GIO trials compared to 1899 postmenopausal women from PMO trials for fracture incidence at 1 year at specific BMDs (RR=5.67)

Steroids alter the BMD Fracture Threshold

# Prevalence and the RR of fracture for age, sex, risk factors in GIOP (not included in 2001 recommendations)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence</th>
<th>Clinical osteoporotic fracture RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (for each 10 years of age)</td>
<td></td>
<td>1.63 (1.60–1.66)</td>
</tr>
<tr>
<td>Sex, Male</td>
<td>39.8%</td>
<td>0.51 (0.49–0.54)</td>
</tr>
<tr>
<td>BMI &lt;20</td>
<td>4.8%</td>
<td>1.48 (1.34–1.62)</td>
</tr>
<tr>
<td>BMI &gt;26</td>
<td>43.5%</td>
<td>0.84 (0.78–0.89)</td>
</tr>
<tr>
<td>History of fall in prior 6 m</td>
<td>1.6%</td>
<td>2.57 (2.30–2.86)</td>
</tr>
</tbody>
</table>

Van Staa, Q J Med, 2005
Screening by bone mass measurement and prescription of non-estrogen therapies for the prevention of GIOP in 2001-2003

Curtis JR et al. Arthritis Rheum Vol.52, 8: 2485-2494
Updating the Recommendations

- Systematically developed statements to assist both practitioners’ and patients’ decisions about appropriate health care for specific clinical situations. This was an update to the prior 2001 recommendations from the ACR

- Since 2001
  - New osteoporosis medications
  - Expanded data on existing therapies
  - New methodology of fracture risk assessment
  - Refined methodology of developing guidelines
Groups responsible for each component of guideline development:

**Core Executive Panel (CEP)**
- Review of existing GIOP guidelines
- Perform systematic review
- Development of evidence report and clinical scenarios
- Draft and grade recommendations
- Finalize recommendations

**Expert Advisory Panel (EAP)**
- Development of proposed domains for the updated GIOP guidelines
- Teleconferences and face to face meeting to refine domains of the guidelines and develop definitions of low, medium, and high risk patients
- Review of evidence report and first round voting on clinical scenarios
- Face to face meeting to review preliminary ratings, discuss areas of disagreement, and re-vote on case scenarios using the RAND/UCLA Appropriateness Method
- Review and edit recommendations

**Task Force Panel (TFP)**
- Review and approve recommendations

*American College of Rheumatology Quality of Care Committee and Board of Directors*
Core Executive Panel

UCLA
- Jennifer Grossman, MD
- Daniel E. Furst, MD
- Rebecca Gordon, MD
- Maureen McMahon, MD
- Veena Ranganath, MD
- Elizabeth Volkmann, MD
- Weiling Chen, MA
- Diane Tan, BA
- Rikke Ogawa

UAB/U of Colorado
- Kenneth Saag MD, MSc
- Jeffrey Curtis MD, MPH
- Nivedita Patkar MD, MSPH
- Kathy Parham
- Liron Caplan, MD
Expert Advisory Panel

- Marc Hochberg, MD
- Nancy Lane, MD
- Johannes Bijlsma, MD
- Willem Lems, MD
- Chad Deal, MD
- Catherine MacLean, MD, PhD
Task Force Panel

- Ted Hahn, MD
- Robert Adler, MD
- Cathleen Colon-Emeric, MD
- Michael Maricic, MD
- Anthony Sebba, MD
- Stuart Silverman, MD
- Gary Bryant, MD
- Chad Deal, MD
- Joseph Flood, MD
- Amye Leong
Refining the Scope

- No childhood GIOP
- No transplant GIOP
- No inhaled steroids only
- No IV pulse steroids only
- Limited to medications approved by FDA, Canada, or EU used to treat osteoporosis
- Refine scope of project given number of variables that can affect fracture risk
What is FRAX®

- A tool to calculate 10-year probability of fracture
  - hip fracture
  - major osteoporotic fracture
    - clinical spine, hip, forearm, humerus
- Uses patient derived intuitive clinical risk factors
- Can calculate with or without femoral neck BMD
- Intended to provide information to clinicians and patients on fracture risk that adds to that provided by BMD alone
- http://www.shef.ac.uk/FRAX
FRAX® makes use of independent risk factors

Adapted from Kanis et al., Osteoporos Int. 2005
Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: 55
   Date of birth: Y: [-] M: [-] D: [-]

2. Sex
   - Male
   - Female

3. Weight (kg)
   65

4. Height (cm)
   165

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)
    Select DXA
    [ ]

BMI 23.9
The ten year probability of fracture (%)
without BMD
- Major osteoporotic
  12
- Hip fracture
  1.4

www.sheffield.ac.uk/FRAX/
Caucasian Women

Low Risk- FRAX
<10% for 10 yr major OP fracture

Medium Risk- FRAX
10-20% for 10 yr major OP fracture

High Risk- FRAX
>20% for 10 yr major OP fracture

Major OP fractures are hip, clinical spine, wrist and humerus fractures
Limitations of Frax

- Does not incorporate all known risk factors (ie falls)
- Lacks dose response effects (corticosteroids, tobacco, alcohol, severity of rheumatoid arthritis, number of previous fractures)
- Uses only BMD of the hip
- Does not account for non-hip fractures in parents
- Relevant only for untreated patients
How Good is FRAX In Accounting for Steroid Use?

Average Dose Captured by FRAX is ~2.5 to 7.5 mg/day prednisone

- Fracture probability under-estimated if prednisone dose > 7.5 mg/d and over-estimated if < 2.5 mg/d
- Frequent intermittent high dose steroids increases fracture risk; FRAX can not capture this
- FRAX may underestimate fracture risk in users of high dose inhaled steroids
- Appropriate glucocorticoid replacement in individuals with adrenal insufficiency should not be included in FRAX

Leib E, JCD, 2011
Recommended Adjustment to FRAX Based on Glucocorticoid Dose

Green = Hip Fracture Adjustment
Pink = Major Osteoporosis Fracture Adjustment

McCloskey E. OI 2011:22;809
GIOP 2011

New Treatment Strategies

- How is osteoporosis risk best assessed?
- What can be done to prevent and treat GIOP?
- What is being done?
- How can we improve quality?
Alendronate GIOP Prevention and Treatment

Saag KG. *NEJM* 1998; 339:292
Effect of Risedronate on BMD in Patients on Long-Term Corticosteroid Therapy

% Change in BMD From Baseline at 12 Months

- Lumbar Spine
- Femoral Neck
- Trochanter

Control
Risedronate 2.5 mg
Risedronate 5 mg

*P < 0.05 vs control.

Reid DM. *J BMR* 2000; 15: 1006
Zoledronic Acid vs. Risedronate in GIO Lumbar Spine BMD

Treatment sub-population

Prevention sub-population

N = 249

N = 275

N = 129

N = 136

% Change From Baseline

Time (months)

% Change From Baseline

Time (months)

[1.04*]

[1.36*]

N = 249

N = 275

[1.72*]

[1.96*]

N = 129

N = 136

* p-value < 0.01

Reid D, Lancet 2009; 373: 1253
Raloxifene for GIOP

(n = 117 PM Women)

Mok CC. Ann Rheum Dis 2011 70:778
Teriparatide vs. ALN: Lumbar Spine

BMD

Percent Change in BMD
Mean ± SE

Months

Alendronate n= 195 184 173 159 148 131 112 195
Teriparatide n= 198 183 178 170 156 136 123 198

* P<0.05; ‡ P<0.001 Teriparatide vs. Alendronate

BMD = bone mineral density, g/cm²

Saag K, *NEJM* 2007;357:2
Saag K. *Arth Rheum*, 2009
# Teriparatide vs. ALN

## New Vertebral Fractures

<table>
<thead>
<tr>
<th></th>
<th>Alendronate (n=169)*</th>
<th>Teriparatide (n=173)*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vertebral radiographic</strong></td>
<td>13 (7.7%)</td>
<td>3 (1.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Clinical vertebral</strong></td>
<td>4 (2.4%)</td>
<td>0</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*Number (%) of patients with paired baseline and post-baseline spinal radiographs

**Radiographically confirmed vertebral fracture(s) associated with symptoms such as back pain; vertebrae graded individually for compression deformity using semiquantitative criteria
TPTD vs. Risedronate in GIOP

Change in vBMD in Men (n=77)

<table>
<thead>
<tr>
<th></th>
<th>Month 6</th>
<th>Month 18 (primary endpoint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teriparatide</td>
<td>5.7%</td>
<td>16.3%</td>
</tr>
<tr>
<td>Risedronate</td>
<td>3.3%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>

* p=0.004 for the between-treatment comparison (MMRM model)

Note: Percentages reflect the % change from baseline, from the MMRM model.

Glüer CC et al. ASBMR 2011 (Plenary Poster FR0413)
TPTD vs. Risedronate
Finite Element Analysis - Strength

* P ≤ 0.015 for the between-treatment comparison (MMRM model)

Glüer CC et al. ASBMR 2011 (Plenary Poster FR0413)
Risk Category Modifiers

- Higher daily dose of glucocorticoids
- Higher cumulative dose of glucocorticoids
- Declining bone mineral density
- Low body mass
- Parental history of hip fracture
- Current smoking
- More than 2 alcoholic drinks daily
- A diagnosis of rheumatoid arthritis
- Secondary osteoporosis (other than GIOP)

If using risk charts and not calculating the actual FRAX score
# Recommendations - Counseling

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>weight bearing activities</td>
</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>fall risk assessment</td>
</tr>
<tr>
<td>baseline DXA</td>
</tr>
<tr>
<td>serum 25-OH vitamin D level</td>
</tr>
<tr>
<td>baseline height</td>
</tr>
</tbody>
</table>
## Recommendations - Counseling

<table>
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<tr>
<th>Recommendation</th>
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<td>serum 25-OH vitamin D level</td>
<td></td>
</tr>
<tr>
<td>baseline height</td>
<td></td>
</tr>
<tr>
<td>assessment of prevalent fragility fractures</td>
<td></td>
</tr>
<tr>
<td>Vitamin D supplementation</td>
<td></td>
</tr>
<tr>
<td>Calcium intake (supplement plus oral intake) of 1200-1500 mg daily</td>
<td></td>
</tr>
<tr>
<td>Consider radiographic imaging of the spine or VFA</td>
<td></td>
</tr>
</tbody>
</table>
Vertebral Fracture Assessment (VFA)

- Prevalent vertebral fractures (VF) predict future risk
  - The relative risk associated with a history of fractures was 1.92 (95% CI 1.81-2.03) for clinical osteoporotic fracture,
  - 1.68 (95% CI 1.52-1.87) for femur/hip fracture
  - 2.04 (95% CI 0.92-1.30) for clinical vertebral fracture (Van Staa et al)

- Only approximately 25-33% of all VF are clinically apparent

- Many patients with VF have T scores that would not be in the osteoporosis range and might not be offered therapy

- Can be done using DXA scan.

- Grade 2 and 3 have good specificity for vertebral fracture while more research is needed to improve the specificity of grade 1 fractures
T12 Fracture

X-ray

VFA
Height Measurement

- Historical height loss (HHL) (the patient’s tallest recalled height minus the current measured height) exceeding 4 cm has been associated with:
  - an odds ratio for VF of 2.8 (95% CI 2.2-3.6) in the Study of Osteoporotic Fractures
  - 2.9 (95% CI 2.6-3.3) for women who screened for the Fracture Intervention Trial

- In the placebo arm of the Vertebral Efficacy with Risedronate Therapy studies, height loss over three years of > 4.0 cm (1.57 inches) had an odds ratio of 20.6 for incident vertebral fractures (95% CI 9, 45.8) while >2 cm (~0.8 inch) height loss had sensitivity of 35.5% for picking up new VF and specificity of 93.6%.

Meta-Analysis Effect of Calcium Supplementation on Myocardial Infarction

Hazard ratio 1.31 (95% CI 1.02 to 1.67), P=0.035

No at risk
Calcium 4097 3870 3539 2670 1294 373
Placebo 4054 3865 3588 2728 1320 388

Study
Baron 1999
Grant 2005
Grant 2005 VIt D
Prince 2006
Reid 2006
Lappe 2007
Reid 2008
Total

Relative risk of myocardial infarction (95% CI) Weight (%)
1.27 (1.01 to 1.59) 13
1.27 (1.01 to 1.59) 29
1.27 (1.01 to 1.59) 26
1.27 (1.01 to 1.59) 17
1.27 (1.01 to 1.59) 1
1.27 (1.01 to 1.59) 1

Test for heterogeneity:
I^2=0% P=0.96

Bolland M J et al. BMJ 2010;341
## Recommendations - Monitoring

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider serial bone mineral density testing</td>
</tr>
<tr>
<td>Consider annual serum 25OH vitamin D measurements</td>
</tr>
<tr>
<td>Assessment of incident fragility fracture</td>
</tr>
<tr>
<td>Annual height measurement</td>
</tr>
<tr>
<td>Assessment of medication compliance</td>
</tr>
</tbody>
</table>
LOW RISK Postmenopausal women and men ≥50 years:
Pharmacologic Recommendations

- alendronate for 7.5 mg or more prednisone daily
  OR
- risedronate for 7.5 mg or more prednisone daily
  OR
- Zoledronic acid for 7.5 mg or more prednisone daily

starting glucocorticoid therapy with an anticipated duration of ≥3 months
OR
prevalent glucocorticoid therapy of ≥3 months duration

Low risk -FRAX 10 year major osteoporotic fracture risk <10%
MEDIUM RISK Postmenopausal women and men ≥50 years

Pharmacologic Recommendations

- alendronate for any dose of glucocorticoids
- risedronate for any dose of glucocorticoids
- zoledronic acid for 7.5mg or more prednisone daily

Medium risk - FRAX 10 year major osteoporotic fracture risk 10-20%
HIGH RISK Postmenopausal women and men ≥50 years
Pharmacologic Recommendations

- alendronate for any dose of glucocorticoids
- risedronate for any dose of glucocorticoids
- zoledronic acid for any dose of glucocorticoids
- teriparatide for any dose of glucocorticoids

duration > 1 month

For high risk patients- any anticipated duration justifies initiating prescription therapy; for prednisone duration < 1 month, teriparatide recommended for 5 mg daily and higher

High risk -FRAX 10 year major osteoporotic fracture risk >20% or prevalent fracture
Premenopausal Patients

- The panel felt that there was limited data on premenopausal patients
- Following recommendations are for those with a history of prevalent fracture

Absence of recommendation does not equal no treatment for this population
Premenopausal non-child-bearing potential women and men <50 years with history of fragility fracture

- Anticipated duration glucocorticoid >1 month and < 3 months
  - alendronate if prednisone 5 mg daily or more
  - risedronate if prednisone 5 mg daily or more
  - zoledronic acid if prednisone 7.5 mg daily or more

- Anticipated duration glucocorticoid ≥ 3 months
  - alendronate
  - risedronate
  - zoledronic acid
  - teriparatide
Premenopausal women of child-bearing potential with prior fragility fracture

For those with an anticipated duration of >3 months or ≥3 months of prevalent glucocorticoid use

- alendronate if prednisone 7.5 mg daily or more
- or
- risedronate if prednisone 7.5 mg daily or more
- or
- teriparatide if prednisone 7.5 mg daily or more
Teriparatide or Alendronate in Glucocorticoid Induced Osteoporosis

- 428 men and women age 22-89 (ave 57 yr)
- 80% women, 70% Caucasian
- Randomized to 20 mcg daily teriparatide or alendronate 10 mg daily
- Prednisone 5 mg/d for at least 3 months immediately prior to the start of the study (median dose about 7.5/duration 1.2-1.5 years)
- T score of -2.0 at hip or spine or T-1.0 and a fragility fracture
- 75% with rheumatologic disorders, 14% with respiratory

Saag KG et al. NEngJMed 2007;357:2028-2039
Percent Change in Mean Bone Mineral Density at the Lumbar Spine and Total Hip from Baseline to 18 Months or the Last Measurement

At 18 months, 10 new VF in the ALN arm vs 1 in the Teriparatide (p=0.004)

Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON)

- 833 men and women
- 7.5 mg daily of prednisolone with anticipated duration of at least 12 months
- Treatment (n=545) and prevention subgroups (n=288)
- 68% female (approx 66% postmenopausal)
- BMD treatment group T -1.37, prevention T -0.93
- Mostly rheumatologic disorders (41% RA)
Zoledronic acid vs Risedronate

Reid et al; Lancet 2009
Bone Resorption is Dependent on RANK Ligand, the Primary Mediator of Osteoclast Activity

RANK Ligand is Essential for Osteoclast Formation, Function and Survival


CFU-M = colony forming unit macrophage
Proposed Mechanism of Action for Denosumab

Growth Factors, Hormones, Cytokines

- RANKL
- RANK
- OPG
- Denosumab

Growth Factors

Bone

- Osteoblast Lineage
- CFU-M = colony forming unit macrophage

Osteoclast

- Pre-Fusion Osteoclast
- Multinucleated Osteoclast
- Osteoclast

RANK

CFU-M
Percent Changes in Bone Mineral Density

### Table 3. Adverse Events.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Denosumab (N = 3886)</th>
<th>Placebo (N = 3876)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>3605 (92.8)</td>
<td>3607 (93.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Serious</td>
<td>1004 (25.8)</td>
<td>972 (25.1)</td>
<td>0.61</td>
</tr>
<tr>
<td>Fatal</td>
<td>70 (1.8)</td>
<td>90 (2.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Leading to study discontinuation</td>
<td>93 (2.4)</td>
<td>81 (2.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>Leading to discontinuation of a study drug</td>
<td>192 (4.9)</td>
<td>202 (5.2)</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>2055 (52.9)</td>
<td>2108 (54.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>Cancer</td>
<td>187 (4.8)</td>
<td>166 (4.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>0 (0.0)</td>
<td>3 (0.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>144 (3.7)</td>
<td>125 (3.2)</td>
<td>0.28</td>
</tr>
<tr>
<td>Infection</td>
<td>159 (4.1)</td>
<td>133 (3.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>186 (4.8)</td>
<td>178 (4.6)</td>
<td>0.74</td>
</tr>
<tr>
<td>Stroke</td>
<td>56 (1.4)</td>
<td>54 (1.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>47 (1.2)</td>
<td>39 (1.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>31 (0.8)</td>
<td>30 (0.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29 (0.7)</td>
<td>29 (0.7)</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Adverse events occurring in at least 2% of subjects‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eczema</td>
<td>118 (3.0)</td>
<td>65 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Falling§</td>
<td>175 (4.5)</td>
<td>219 (5.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Flatulence</td>
<td>84 (2.2)</td>
<td>53 (1.4)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Serious adverse events occurring in at least 0.1% of subjects¶</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis (including erysipelas)</td>
<td>12 (0.3)</td>
<td>1 (&lt;0.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Concussion</td>
<td>1 (&lt;0.1)</td>
<td>11 (0.3)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Differences from 2001 to 2010

- Expanded recommendations for counseling and monitoring
- Updated pharmacologic recommendations
- Delineated for postmenopausal women and men over age 50 years, premenopausal women not of childbearing potential and men under the age of 50 years with a history of a fragility fracture, and premenopausal women of childbearing potential with a history of a fragility fracture.
- The newer therapies zoledronic acid and teriparatide are now recommended along with alendronate and risedronate for the treatment of GIOP, while the previously included therapies estrogen replacement and testosterone are no longer endorsed.
- Recommendations now guided by patient’s overall clinical risk instead of T-scores alone
Counsel and assess risk factors those starting or on prevalent glucocorticoid therapy (table 2)

Determine Patient Risk Category (figure 1a-d and table 1)

Low Risk*
- Alendronate, Risedronate or Zoledronic acid for those on ≥7.5 mg daily glucocorticoids

Medium Risk*
- Alendronate and risedronate for any dose glucocorticoids and zoledronic acid for ≥7.5 mg daily glucocorticoids

High Risk-
- Alendronate, risedronate, zoledronic acid for any dose or duration of glucocorticoids, and teriparatide for 5 mg or more prednisone daily duration 1 month or less and for any dose of glucocorticoids with a duration greater than 1 month

Monitor patients on prevalent glucocorticoid therapy (table 3)

* For low and medium risk patients recommendations are for an anticipated or prevalent duration of ≥ 3 months glucocorticoids
Approach to premenopausal women and men under age 50 years starting or on glucocorticoid therapy

- No prevalent fragility fracture
  - Counsel and assess risk factors of those starting or on prevalent glucocorticoid therapy (refer to Table 2)
- Inadequate data for recommendation
- Women (non-childbearing potential) or men age <50 years
  - Glucocorticoids 1-3 months
    - if pred ≥ 5 mg daily alendronate or risendronate
    - OR
    - if pred ≥ 7.5 mg daily zoledronic acid
  - Glucocorticoids ≥ 3 months
    - Alendronate OR
    - Risedronate OR
    - Zoledronic acid OR
    - Teriparatide
- Monitor patients on prevalent glucocorticoid therapy (refer to Table 2)
- Glucocorticoids 1-3 months
  - No Consensus
- Glucocorticoids ≥ 3 months
  - Alendronate if pred ≥ 7.5 mg daily OR
  - Risedronate if pred ≥ 7.5 mg daily OR
  - Zoledronic acid if pred ≥ 7.5 mg daily
  - Pred <7.5 mg daily
  - No consensus

Pred = prednisone
American College of Rheumatology 2010 Recommendations for the Prevention and Treatment of **GLUCOCORTICOID-INDUCED OSTEOPOROSIS**

**CLINICIAN’S GUIDE**

The objective of this guide is to provide a summary of the ACR 2010 Recommendations for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis, which have been reviewed and endorsed by the American Society for Bone and Mineral Research.

**Clinical Issue**

Although glucocorticoids may effectively be used in the management of many inflammatory conditions, their use is associated with significant morbidity and mortality. Osteoporosis, with resultant fractures, constitutes one of these morbid complications and is associated with significant pain and disability. A rapid decline in bone mineral density (BMD) begins within the first 3 months of glucocorticoid use and peaks at 6 months, followed by a slower, steady loss with continued use. An increased risk of both vertebral and nonvertebral fractures has been reported with dosages of prednisolone or equivalent as low as 2.5-7.5 mg daily, and this risk may relate more strongly to daily rather than to cumulative doses of glucocorticoids. However, there has been some controversy regarding the dose at which an increased risk of fracture occurs, as some smaller studies have found no appreciable decline in bone density with mean daily 8.0 mg dosages of prednisone, or prednisone <5 mg/day. In a large meta-analysis, prior and current use of oral glucocorticoids increased the risk of any type of fracture, with no significant difference in relative risk between men and women.

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology are intended to provide guidance for particular patterns of practice and...
GIOP
“The Data-free Zone”

- Indications for Therapy
  - Premenopausal women?
  - Children?

- Surveillance
  - Frequency of DXA?
  - Utility of bone biomarkers?

- Duration of therapy
  - Rx after teriparatide?
  - Persistence of Rx after steroid discontinued?
  - “Drug Holidays”?
Uncertainties in the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

Professional Practice Committee of the American Society for Bone and Mineral Research

“We discuss several patient scenarios for which the new treatment [2010 ACR] guidelines do not apply, or for which our committee interprets existing literature differently and suggests an alternative approach.”

Karen E Hansen, H Alexander Wilson, Carol Zapalowski, Howard A Fink, Salvatore Minisola, and Robert A Adler

# Treatment of Postmenopausal Women and Men Over Age 50

## ASBMR PPC:

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Prednisone &lt;7.5 mg/d: If no therapy given, monitor closely for prevalent fracture and decline in BMD Prednisone ≥7.5 mg/day: Bisphosphonates</td>
</tr>
<tr>
<td>Medium risk</td>
<td>Bisphosphonate</td>
</tr>
<tr>
<td>High risk</td>
<td>Bisphosphonate or teriparatide</td>
</tr>
</tbody>
</table>

## COMPARISON to ACR:

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>ACR Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Agreement zoledronate only in patients taking ≥7.5 mg of prednisone daily</td>
</tr>
<tr>
<td>Medium risk</td>
<td>ACR recommended teriparatide only in patients taking glucocorticoids &gt;1 month, or ≥5 mg daily for &lt;1 month</td>
</tr>
<tr>
<td>High risk</td>
<td>ACR recommended teriparatide only in patients taking glucocorticoids &gt;1 month, or ≥5 mg daily for &lt;1 month</td>
</tr>
</tbody>
</table>

JBMR: 26 (9), 1898-1896 2011
### Treatment of Premenopausal Infertile Women and Men Under Age 50

#### ASBMR PPC:

- **No prevalent fracture**
  - Consider therapy if Z-score $-2.0$ or significant decline in BMD related to glucocorticoid therapy

#### Prevalent fracture

<table>
<thead>
<tr>
<th>Prednisone $\leq$ 3 months</th>
<th>Prednisone $&gt;3$ months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonate</td>
<td>Bisphosphonate or teriparatide</td>
</tr>
</tbody>
</table>

#### COMPARISON to ACR:

- ACR committee found inadequate data for this subgroup
- ACR committee recommended zoledronate only if prednisone dose $\geq 7.5$ mg/d

**Agreement**

---

*JBMR: 26 (9), 1898-1896 2011*
**Treatment of Premenopausal Fertile Women**

**ASBMR PPC:**

<table>
<thead>
<tr>
<th>No prevalent fracture</th>
<th>Prevalent fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone ≤3 months</td>
<td>Prednisone &gt;3 months</td>
</tr>
<tr>
<td>Consider therapy if Z-score $\leq -2.0$ or lower, or significant decline in BMD related to ongoing glucocorticoid therapy</td>
<td>Little data to support therapy</td>
</tr>
<tr>
<td>Agreement</td>
<td>Preference for short-acting drugs like teriparatide or denosumab instead of bisphosphonates</td>
</tr>
</tbody>
</table>

COMPARISON to ACR:

ACR committee found inadequate data for this subgroup

No consensus if prednisone dose $<7.5 \text{ mg/d}$; alendronate, risedronate, or zoledronate (not teriparatide) if prednisone dose $\geq 7.5 \text{ mg/d}$

*JBMR: 26 (9), 1898-1896 2011*
How is osteoporosis risk best assessed?

What can be done to prevent and treat GIOP?

What is being done?

How can we improve quality?
Changing Patterns of GIOP Rx - US

HRT + Bone Rx among New Glucocorticoid Users (n = 5,471)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women &lt; 50</th>
<th>Women 50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995-1998</td>
<td>9%</td>
<td>14%</td>
<td>41%</td>
</tr>
<tr>
<td>2001-2003</td>
<td>23%</td>
<td>33%</td>
<td>62%</td>
</tr>
</tbody>
</table>

p < 0.01 for all comparisons

Curtis JR. Arth Rheum 2005;52:2485
## GIOP Treatment Rates by Specialist

**MEDCO (n = 106K steroid users)**

<table>
<thead>
<tr>
<th>Prescriber Specialty</th>
<th>N (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Medicine</td>
<td>5,053 (25.1)</td>
<td>Referent</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>7,726 (32.1)</td>
<td>1.61 (1.54-1.68)</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>685 (18.4)</td>
<td>1.15 (1.04-1.26)</td>
</tr>
<tr>
<td>Nephrology</td>
<td>578 (20.1)</td>
<td>1.36 (1.22-1.50)</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>1,351 (27.7)</td>
<td>1.35 (1.25-1.45)</td>
</tr>
<tr>
<td>Other</td>
<td>5,710 (17.4)</td>
<td>0.78 (0.75-0.82)</td>
</tr>
</tbody>
</table>

Outman R. ASBMR, 2010
GIOP 2011

New Treatment Strategies

- What effects do glucocorticoid patterns of use have on osteoporosis risk?
- How is osteoporosis risk best assessed?
- What **can** be done to prevent and treat GIOP?
- What **is** being done?
- How can we **improve** quality?
UAB GIOP Group RCT Study Design

Control Arm (n = 75)
- Unrelated CME Module
- Follow up DXA Screening and Rx Rate

Intervention Arm (n = 75)
- Internet GIOP Intervention
- Baseline DXA Screening and Rx Rate

Aetna U.S. Healthcare Population

High-risk Steroid Users
- Doctors Prescribing Steroids

Curtis, JR, Arch Int Med 2007; 167:591
GIOP Internet Intervention

- Access via e-mail
- Tailored presentation
- Case-based interactive learning
- Personal data feedback using Achievable Benchmark of Care (ABC™)
- Improvement “toolbox”
- Printable CME certificate
- Continued exposure to combat “decay”

## GIOP Group RCT Results

### % Receipt

<table>
<thead>
<tr>
<th></th>
<th>Intent-To-Treat</th>
<th>Intervention (n = 76 docs)</th>
<th>Control (n = 73 docs)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD</td>
<td>19</td>
<td>21</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Prescription Rx</td>
<td>26</td>
<td>24</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Per Protocol*</td>
<td></td>
<td>(n = 27 docs)</td>
<td>(n = 18 docs)</td>
<td>p-value</td>
</tr>
<tr>
<td>BMD</td>
<td>26</td>
<td>16</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>BisphosphonateRx</td>
<td>24</td>
<td>17</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>BMD or Rx</td>
<td>54</td>
<td>44</td>
<td>0.07</td>
<td></td>
</tr>
</tbody>
</table>

* Completed all 3 modules

Self Scheduling of DXAs
Results From Kaiser NW

Warriner A, ASBMR (Plenary Poster FR0325), 2011
Poor Adherence to Bisphosphonates Among Glucocorticoid Users

Curtis J. *Osteoporosis Int*, 2006; 17:12
Sclerostin

- Sclerostin is a protein
  - produced by osteocytes and functions to inhibit bone formation by binding to LRP5 and inhibiting Wnt signaling
- Sclerosteosis is an autosomal recessive trait resulting from a deficiency of sclerostin which is an inhibitor of Wnt signaling
  - heterozygous carriers have increased bone mass with few sequelae
- Homozygous individuals have high bone mass
  - Z-scores often >+7.0.
- In a study of a monoclonal antibody against sclerostin given to cynomolgus monkeys
  - Increased BMD
  - Increased osteoblast mediated bone formation
  - Doubled skeletal strength

Ominsky et al. JBMR 2010
Odanacatib

- Cathepsin K inhibitor
- CatK, a cysteine protease, is expressed primarily in osteoclasts degrades type I collagen - Inhibits matrix dissolution but not viability of the osteoclast
- 2 year phase IIb study of 399 subjects randomized to placebo or one of 4 doses
- The 50 mg dose was associated with 5.7% increase in LS spine and 4.1% increase in total hip compared to placebo
- Safety profile similar to placebo

Bone et al. JBMR 2010
Building “Designer Steroids”

Crystal structure of GR ligand binding domain discovered

Trans-activation $\approx$ toxicity
Trans-repression $\approx$ anti-inflammatory effects

Glucocorticoid Mimetics (GCM) with attempts to disassociate properties-
- Selected Glucocorticoid Receptors Agonists (SEGRAs)
- Dissociated Glucocorticoid Receptor Agonists (DAGR)

Bledsoe RK, Cell 110:93, 2002