Glucocorticoid-Induced Osteoporosis (GIOP) Past, Present and Future

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Division of Clinical Immunology and Rheumatology
Department of Medicine

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Disclosures

- Sources of Research Funding:
  - NIAMS, NCMRR, NCATS, AHRQ, PCORI
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- Immediate Past President, Board of Trustees, National Osteoporosis Foundation

- Secretary, American College of Rheumatology

- Consultant: Amgen, Lilly, Radius, Roche
GIOP 2019

• 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?
GIOP 2019

- 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?
Historical Trends in Glucocorticoid Use

- Glucocorticoids (GCs) first proposed by Hench for RA
- Initial enthusiasm dampened by long-term toxicities
- Despite innovative steroid-sparing therapies, GCs used commonly in 2018 for many acute and chronic diseases

Glucocorticoid Use in the U.K. and U.S.

- Glucocorticoids used chronically by 0.5% of population\(^1\)
- Aetna managed care members beginning long-term (>3 mo.) steroid therapy \((n = 6756)\)\(^2\)

- Rheumatoid arthritis (21%)
- Emphysema (16%)
- Asthma (15%)
- Lupus (7%)
- Inflammatory bowel disease (7%)
- Polymyalgia rheumatica (5%)

Physicians Prescribing Glucocorticoids (n=792)

- Internal Medicine (n=311) - 39%
- Rheumatology (n=129) - 16%
- Gastroenterology (n=53) - 7%
- Pulmonary Medicine (n=23) - 3%
- All others (n=153) - 19%

- GP / FP (n=123) - 16%
Use of Glucocorticoids in US Medicaid Population for Rheumatoid Arthritis (RA)

Girjavala C. *Rheumatology* 2008;47:1061
Changing Glucocorticoid Use

- **United Kingdom**\(^1\)
  - 3% prevalence women 80 to 90
  - 34% increase in long-term use from ‘89 to ’08
- **Denmark**\(^2\)
  - 3% use of at least one prescription per year
  - 10% use among elderly
  - Slight increase in systemic use from ‘99 to ‘15

2. Laugesen K. *BMJ Open* 2017;7:e015237
Rapid Bone Mineral Density (BMD) Decline Associated with Glucocorticoids in Rheumatoid Arthritis (RA)

% Change Lumbar Trabecular Bone Mineral Density (BMD)

Placebo (n = 17)

Prednisone (n = 13)

Laan R. *Ann Intern Med* 1993;119:966,
## Annual Incidence of Fractures on Glucocorticoids

Meta-regression of Control Arms of GIOP Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>Vertebral</th>
<th>Non-Vertebral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucocorticoid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiating</td>
<td>5.1 % (95 % CrI = 2.8–8.2)</td>
<td>2.5 % (95 % CrI = 1.2-4.2)</td>
</tr>
<tr>
<td>Continuing</td>
<td>3.2 % (95 % CrI = 1.8–5.0)</td>
<td>3.0 % (95 % CrI = 0.8–5.9)</td>
</tr>
</tbody>
</table>

Amiche M. *Osteop Int* 2016;27:1709
Increased Risk of Fracture
Is There a Safe Dose?

• U.K. General Research Practice Database
• Steroid users matched by age, gender and clinical practice to non-users (n = 244,235 in each arm)
• ~60% women, mean age 57 yrs

van Staa TP. *JBMR* 2000;15:993
Effect of Daily Glucocorticoid Dose on Non-Vertebral Fractures

No Fully Safe Dose For Bone

Adjusted Relative Rate of Fracture (and 95% CIs)

van Staa T. Rheumatology 2000;39:1383
Dose-Response of Glucocorticoid Impact on Fracture Risk Observed among RA Patients
US Marketscan Claims Data (n = 42K)

Incidence rates* (95% CI)
Systemic Glucocorticoid Exposure
Spine Fracture
Daily Cumulative

Dose-Response of Glucocorticoid Impact on Fracture Risk Observed among RA Patients
US Marketscan Claims Data (n = 42K)

* Incidence rates per 1000 person years

Balasubramanian A. Osteop Int 2016;27:3239
Oral GC & Hip Fx Risk in Danish NHS
Daily (DD) vs. Cumulative Dose (CD)

<table>
<thead>
<tr>
<th>Category</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never GC use (reference)</td>
<td>1.06 (1.03-1.10)</td>
<td>0.97 (0.93-1.01)</td>
</tr>
<tr>
<td>Distant past GC use</td>
<td>1.21 (1.12-1.31)</td>
<td>1.04 (0.96-1.14)</td>
</tr>
<tr>
<td>Past GC use</td>
<td>1.37 (1.26-1.49)</td>
<td>1.19 (1.08-1.30)</td>
</tr>
<tr>
<td>Recent GC use</td>
<td>1.88 (1.80-1.98)</td>
<td>1.56 (1.48-1.65)</td>
</tr>
<tr>
<td>Current GC use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By DD mg:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7.5</td>
<td>1.63 (1.53-1.73)</td>
<td>1.37 (1.28-1.47)</td>
</tr>
<tr>
<td>7.5-14.9</td>
<td>1.87 (1.72-2.03)</td>
<td>1.53 (1.39-1.68)</td>
</tr>
<tr>
<td>≥15</td>
<td>3.16 (2.80-3.57)</td>
<td>2.50 (2.19-2.85)</td>
</tr>
<tr>
<td>By CD g:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1.39 (1.25-1.55)</td>
<td>1.28 (1.14-1.44)</td>
</tr>
<tr>
<td>≥1</td>
<td>2.02 (1.91-2.12)</td>
<td>1.64 (1.54-1.74)</td>
</tr>
<tr>
<td>≥5</td>
<td>2.06 (1.92-2.20)</td>
<td>1.61 (1.50-1.74)</td>
</tr>
<tr>
<td>≥10</td>
<td>2.06 (1.89-2.25)</td>
<td>1.57 (1.42-1.73)</td>
</tr>
<tr>
<td>1-4.9</td>
<td>1.96 (1.81-2.12)</td>
<td>1.67 (1.53-1.83)</td>
</tr>
<tr>
<td>5-9.9</td>
<td>2.05 (1.85-2.27)</td>
<td>1.67 (1.49-1.86)</td>
</tr>
</tbody>
</table>

Amiche M. Archives Osteop 2018;13:30
Oral GC & Hip Fx Risk in Danish NHS
Combining Daily and Cumulative Dose

Amiche M. Archives Osteop 2018;13:30
Fractures Are the Most Common Serious Glucocorticoid (GC) Adverse Event Among RA Patients

<table>
<thead>
<tr>
<th>Adverse Events (AEs)</th>
<th>GC User (112)</th>
<th>GC Nonuser (112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fracture</td>
<td>21 (19%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Serious Infection</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>GI Bleed or Ulcer</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Diabetic Complication</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Stroke</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Time to the Development of the First Adverse Event (AE)

- No Prednisone (n=112)
- Prednisone Dose < 5 mg (n=41)
- Prednisone Dose 5-10 mg (n=62)
- Prednisone Dose > 10-15 mg (n=9)

Probability of Remaining “AE Free” (Survival)

Years of Prednisone (Cases) or Follow-up (Controls)

## Risk Factors for the First AE Among RA Patients

<table>
<thead>
<tr>
<th>Final Model Variables</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average prednisone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10-15 mg/d</td>
<td>32.3</td>
<td>4.6, 220</td>
<td>0.0004</td>
</tr>
<tr>
<td>5-10 mg/d</td>
<td>4.5</td>
<td>2.1, 9.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>&gt; 0- &lt;5 mg/d</td>
<td>1.9</td>
<td>0.8, 4.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>3.9</td>
<td>1.9, 8.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>Bony erosions</td>
<td>2.4</td>
<td>1.2, 4.7</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Job: farmer/laborer</td>
<td>2.4</td>
<td>1.1, 5.6</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>GI protective drugs</td>
<td>0.6</td>
<td>0.4, 0.9</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>
Glucocorticoid Induced Osteoporosis (GIOP) and Rheumatoid Arthritis

Is it Steroids or RA?

• RA, NOT steroids, causes bone loss¹
• Independent effects on hip fx of both RA and steroids²
• Dutch RCT - increased fx in steroid arm³

1. Verhoven A. J Rheum 1997; 24:1495
2. Cooper C. Ann Rheum Dis 1995; 54:50

Gravellese EM. Arthritis Res 2001; 3:6
Madsen OR. Ann Rheum Dis 2002; 61:325
GIOP and Pulmonary Disease

Are inhaled steroids safe?

- Cohorts of “pure” inhaled user have bone loss\(^1,2\)
- Respiratory disease activity/severity confounds steroid-fracture association\(^3\)
- Fluticasone greater systemic bioactivity than other inhaled agents\(^4\)
- Inhaled safer to bone than systemic steroids\(^5\)

1. Israel E. *NEJM* 2001;345:941
4. Lipworth BJ. *Arch Int Med* 199;159:941
5. van Staa TP. *JBMR* 2001;16:581

73 yo WM with COPD inhaled and oral steroids x 10 yrs
Risk of fracture in SLE Patients vs Matched Controls

Bultink IEM. *Osteoporos Int* 2014;25:1275
GIOP 2019

• 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?
Glucocorticoids alter the BMD Fracture Threshold

van Staa T. *Arth Rheum* 2003; 48: 3224
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. *J Clin Dens* 2011;14:212
McCloskey E. *Osteo Int* 2011;22:809
## Adjustments to 10 yr FRAX by Glucocorticoid Dose

<table>
<thead>
<tr>
<th>Fracture Site and Dose</th>
<th>Prednisone Equivalent Mg/dl</th>
<th>% adjustment in fracture risk over all ages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hip Fracture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 2.5</td>
<td>- 35</td>
</tr>
<tr>
<td>Medium</td>
<td>2.5 to 7.5</td>
<td>referent</td>
</tr>
<tr>
<td>High</td>
<td>≥ 7.5</td>
<td>+ 20</td>
</tr>
<tr>
<td><strong>Major Osteoporotic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 2.5</td>
<td>- 20</td>
</tr>
<tr>
<td>Medium</td>
<td>2.5 to 7.5</td>
<td>referent</td>
</tr>
<tr>
<td>High</td>
<td>≥ 7.5</td>
<td>+ 15</td>
</tr>
</tbody>
</table>

Kanis JA. *Osteoporos Int* 2011;22:809
Trabecular Bone Score (TBS)

Prior fracture after 50
TBS (per SD)
BMD Total Hip
Ever use of systemic corticosteroids
Rheumatoid arthritis
Parental history of hip fracture
BMD spine (per SD)
Alcohol intake >2 units daily
Current smoking
BMI (20 vs 25 kg/m²)
BMI (30 vs 25 kg/m²)

Relative Risk of Fracture

Bousson V. Osteo Int 2012;23:1489
Hans D. J Clin Dens 2011;doi10.1016
Trabecular Bone Score (TBS) Differs from BMD in GIOP Trial

* p<0.05 from baseline; ° p<0.05 between groups

Saag K. *Arth Rheum* 2016;68:2122
Bone Tissue Properties Measurement by Reference Point Indentation

Mellibovsky L. *JBMR* 2015;30:1651-1656
Micro-Indentation in GIOP
Variation by Therapeutic Agent

Time (weeks)

BMSi variation (% vs baseline)

Teriparatide
Denosumab
Risedronate
Calcium + Vit D

Mellibovsky L. JBMR 2015;30:1651
Teriparatide vs. Risedronate in GIOP HRQCT Finite Element Analysis

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

Glüer CC. JBMR 2013;28:1355
GIOP 2019

• 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?
Glucocorticoid Therapy

- PPARγ2 upregulated
- Sclerostin upregulated
- Wnt signaling downregulated
- BMPs downregulated

Activation of pro-apoptotic molecules

Osteoblasts

- Decreased osteoblastogenesis
- Decreased osteoblast number

Osteocyes

- Activation of pro-apoptotic molecules
- Reduced osteocyte number

Compston J. *Endocrine* 2018;61:7
Glucocorticoid Therapy

- Increased PPARγ2
- Increased Sclerostin
- Decreased Wnt signaling
- Decreased BMPs
- Activation of pro-apoptotic molecules

**Osteoblasts**
- Decreased osteoblastogenesis
- Decreased osteoblast number

**Osteocytess**
- Reduced osteocyte number

**Decreased formation (long term)**

Compston J. *Endocrine* 2018;61:7
GIOP Pathophysiology

**Glucocorticoid Therapy**

- **↑** PPARγ2
- **↑** Sclerostin
- **↓** Wnt signaling
- **↓** BMPs
- Activation of pro-apoptotic molecules

**Osteoblasts**

- Decreased osteoblastogenesis
- Decreased osteoblast number

**Osteocytes**

- Reduced osteocyte number

**Osteoclasts**

- Increased osteoclastogenesis
- Increased activity

**Decreased formation (long term)**

Compston J. *Endocrine* 2018;61:7
GIOP Pathophysiology

Glucocorticoid Therapy

- ↑ PPARγ2
- ↑ Sclerostin
- ↓ Wnt signaling
- ↓ BMPs
  - Activation of pro-apoptotic molecules

- Osteoblasts
  - Decreased osteoblastogenesis
  - Decreased osteoblast number

- Osteocytes
  - Reduced osteocyte number

- Osteoclasts
  - Increased osteoclastogenesis
  - Increased activity

- Increased resorption (early, transient)
  - Increased formation (long term)

Compston J. *Endocrine* 2018;61:7
Protection From GIOP in the Absence of Sost/Sclerostin

Sato AY. JBMR 2016; 31:1791
Alendronate GIOP Prevention and Treatment

Saag K. NEJM 1998; 339:292
GIOP Bisphosphonate Trials: Fracture Rates

Vertebral Fracture Rate (%)

- Baseline
- Placebo
- Etidronate 400 mg Cyclical
- Risedronate 5 mg
- Alendronate 5 mg, 10 mg
- Alendronate Ext 2.5 mg, 5 mg, 10 mg

1 year:
- Etidronate: 38% risk reduction
- Risedronate: 70%* risk reduction
- Alendronate: 40% risk reduction

1 year:
- Saag 98 NEJM

2 year:
- Adachi 01 Arthritis Rheum: 90%* risk reduction

*P < 0.05
Zoledronic Acid vs. Risedronate in GIOP Lumbar Spine BMD

Treatment sub-population

Prevention sub-population

* p-value < 0.01

Reid D. Lancet 2009; 373: 1253
Ibandronate in GIOP (n = 167)

A

![Graph showing % Change of BMD at L1-L4](image)

B

![Graph showing % Change of BMD at Femur neck](image)

C

![Graph showing % Change of BMD at Total hip](image)

Shin K. Clinical Therapeutics 2017;39:268
Comparison of efficacy of Bisphosphonates in Postmenopausal Osteoporosis (PMO) and GIOP

RR

Vertebral fracture

RR = 0.58 0.48

Non-vertebral fracture

PMO 14,551 14,551
GIOP 500 500

N = 9,681 987

From Kanis J. Health Tech Assess 2007;11:1
Alendronate Reduces Hip Fx in GIOP
Swedish National DB (n = 433K)

Hazard ratio, 0.35 (95% CI, 0.22-0.54);
Log-rank  P<.001

No alendronate use

Alendronate use

Axelsson KF. JAMA. 2017;318:146
Oral Bisphosphonates Reduce Fracture Risk Among Oral Glucocorticoid Users in Canada (3945 Alendronate, 5825 Risedronate, and 8464 Etidronate)

<table>
<thead>
<tr>
<th>Bone Site</th>
<th>Exposed</th>
<th>Unexposed</th>
<th>Hazard Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>131</td>
<td>183</td>
<td>0.71 (0.57 - 0.89)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>323</td>
<td>552</td>
<td>0.58 (0.51 - 0.66)</td>
</tr>
<tr>
<td>Forearm</td>
<td>76</td>
<td>98</td>
<td>0.81 (0.60 - 1.11)</td>
</tr>
<tr>
<td>Humerus</td>
<td>46</td>
<td>56</td>
<td>0.85 (0.60 - 1.21)</td>
</tr>
</tbody>
</table>

Amiche M. JBMR 2018; 33:419
Lumbar Spine BMD in GIOP PTH (teriparatide) vs. ALN

% Change

Months

Teriparatide

Alendronate

‡ P<0.001

Saag K. NEJM 2007;357:2028
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>Vertebral radiographic</td>
<td>13 (7.7%)</td>
<td>3 (1.7%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical vertebral**</td>
<td>4 (2.4%)</td>
<td>0</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*Number (%) of patients with paired baseline and postbaseline spinal radiographs
**Radiographically confirmed vertebral fracture(s) associated with symptoms such as back pain; vertebrae graded individually for compression deformity using semiquantitative criteria

Saag K. *NEJM* 2007;357:20
Raloxifene for GIOP
(n = 117 PM Women)

Mok CC. Ann Rheum Dis 2011 70:778
Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomised, double-blind, active-controlled, double-dummy, non-inferiority study


Saag K. Lancet Diab Endo 2018;6:445
Study Design

Key Inclusion Criteria:

• Women and men ≥ 18 years receiving GC therapy at ≥ 7.5 mg prednisone daily or equivalent prior to screening; stratified for
  - ≥ 3 months (Glucocorticoid-continuing [GC-C])
  - < 3 months (Glucocorticoid-initiating [GC-I])

• All subjects < 50 years required to have a history of osteoporotic fracture

• GC-C subjects ≥ 50 years required to have LS, TH, or FN BMD T-score ≤ –2.0; or T-score ≤ –1.0 with history of osteoporotic fracture

Saag KG. Lancet Diab Endo, 2018;6:445
Tsourdi E. Lancet Diab Endo 2018
Lumbar Spine BMD Percentage Change From Baseline Months 6 and 12

Glucocorticoid-continuing (GC-C)

Glucocorticoid-initiating (GC-I)

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Risedronate n=</th>
<th>Denosumab n=</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>227</td>
<td>224</td>
</tr>
<tr>
<td>6</td>
<td>211</td>
<td>209</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risedronate

Denosumab

n = Number of subjects with observed values at baseline and the time point of interest; *p ≤ 0.002
Total Hip BMD Percentage Change From Baseline Month 12

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Risedronate n=</th>
<th>Denosumab n=</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>215</td>
<td>217</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = Number of subjects with observed values at baseline and the time point of interest; *p ≤ 0.001

**Glucocorticoid-continuing (GC-C)**

**Glucocorticoid-initiating (GC-I)**
Lumbar Spine BMD Change from Baseline Month 24

P-value for denosumab vs risedronate by ANCOVA: * p ≤ 0.05; † p ≤ 0.01; ‡ p ≤ 0.001
n = number of subjects with observed values at baseline and the time point of interest

Saag K, ECTS, 2018
Saag K, in press, Arthritis Rheum
## Clinical and New Vertebral Fractures

<table>
<thead>
<tr>
<th></th>
<th>Risedronate</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical fracture – n / N (%)</strong></td>
<td>15 / 397 (3.8)</td>
<td>19 / 398 (4.8)</td>
</tr>
<tr>
<td><strong>New vertebral fracture – n / N1 (%)</strong></td>
<td>11 / 342 (3.2)</td>
<td>9 / 333 (2.7)</td>
</tr>
</tbody>
</table>

n = Number of subjects with ≥ 1 fracture  
N = Number of subjects randomized  
N1 = Number of subjects randomized with a baseline assessment and ≥ 1 post-baseline assessment of vertebral fracture
# Serious Infections by High Risk Subgroups

## In Denosumab Glucocorticoid-Induced OP Study

### With Concomitant Biologics Medication, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Risedronate</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>With Concomitant Biologics Medication or Immunosuppressants</td>
<td>2 (7.4)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

N = Number of subjects who received ≥ 1 dose of IP with or without concomitant biologics medication

### With Concomitant Biologics Medication or Immunosuppressants, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Risedronate</th>
<th>Denosumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>227</td>
<td>208</td>
</tr>
<tr>
<td>9 (4.0)</td>
<td>6 (2.9)</td>
<td></td>
</tr>
</tbody>
</table>

N = Number of subjects who received ≥ 1 dose of IP with or without concomitant biologics medication or immunosuppressants
GIOP RCTs Summary

BMD at Spine and Hip
- ALN, RIS, IBD > PBO
- ZOL, DMAB > RIS
- TPTD > ALN

BMD at Spine
- RAL > PBO

Saag K. *NEJM* 1998; 339:292
Cohen S. *Arth Rheum* 1999;42:2309
Reid D. *J BMR* 2000; 15: 1006
Saag K. *NEJM* 2007;357:2028
Reid D. *Lancet* 2009; 373: 1253
Mok C. *Ann Rheum Dis* 2011 70:778
Shin K. *Clinical Therapeutics* 2017;39:268
Saag K. *Lancet Diab Endo* 2018;6:445
GIOP RCTs Summary

**BMD at Spine and Hip**
- ALN, RIS, IBD > PBO
- ZOL, DMAB > RIS
- TPTD > ALN

**BMD at Spine**
- RAL > PBO

**Vert Fx**
- TPTD > ALN (secondary)
- RIS > PBO (post hoc)
- ALN > PBO (ext only)

---

Saag K. *NEJM* 1998; 339:292
Cohen S. *Arth Rheum* 1999;42:2309
Reid D. *J BMR* 2000; 15: 1006
Saag K, *NEJM* 2007;357:2028
Reid D, *Lancet* 2009; 373: 1253
Mok C. *Ann Rheum Dis* 2011 70:778
Shin K. *Clinical Therapeutics* 2017;39:268
Saag K. *Lancet Diab Endo* 2018;6:445
2017 ACR GIOP Guidelines
Baseline Risk Stratification

Fracture Incidence Rate
- Low
- Moderate
- High

MOF 10 year risk
- 10%
- 20%

What level of risk?

Buckley L. Arthritis Rheum 2017;69:1521
2017 ACR GIOP Guidelines
Fracture Risk Groups

Adults ≥ 40 yrs

• **High Fracture Risk**
  • Prior osteoporotic fracture(s)
  • Men ≥ 50 years and PMP women with a BMD T score ≤ -2.5 at the hip or spine
  • FRAX (GC – adjusted) 10 year risk
    • MOF* ≥20%
    • Hip Fracture ≥3%

• **Moderate Fracture Risk**
  • FRAX (GC – adjusted) 10 year risk
    • MOF* 10-19%
    • Hip Fracture >1% and <3%

• **Low Fracture Risk**
  • FRAX (GC – adjusted) 10 year risk
    • MOF* <10%
    • Hip Fracture ≤1%

Adults < 40 yrs

• **High Fracture Risk**
  – Prior osteoporotic fracture(s)

• **Moderate Fracture Risk**
  – Z score < -3 at hip or spine or
  – Rapid bone loss (≥ 10%/ yr at hip or spine)
And continuing prednisone treatment for
≥ 6 months at ≥ 7.5 mg per day

• **Low Fracture Risk**
  – None of above risk factors other than glucocorticoid treatment

---

*Major Osteoporotic Fracture (MOF): includes fractures of the spine (clinical), hip, wrist, and humerus*
Optimize Calcium and Vitamin D intake and Life Style Modification

Adults:
- Calcium: 1000 – 1200 mg/d
- Vitamin D: 600- 800 IU/d

AND

- Treat Men and Women (not of child bearing potential) < 40 yrs and ≥ 40 yrs at moderate to high fracture risk (in order of preference)
  1. Oral Bisphosphonate*
  2. IV Bisphosphonate
  3. Teriparatide
  4. Denosumab
  5. Raloxifene: for PMP women for whom none of the medications listed above is appropriate

*Strong recommendation if high risk, ≥ 40
2017 ACR GIOP Guidelines
Special Populations: Conditional Recommendations

Adult Women of Child Bearing Potential at Moderate to high FX Risk (Not planning a pregnancy during OP RX)
- Oral Bisphosphonate
- Teriparatide

Solid Organ Transplant (Continuing GC treatment, GFR ≥30)
- Follow adult guidelines with special considerations
- Evaluate for metabolic bone disease if renal transplant
- Avoid denosumab

Children 4-17
- Optimize Calcium/Vitamin D intake
- Oral Bisphosphonate if OP fracture and continuing GC ≥ 0.1 mg/kg for ≥ 3 months

Very high dose GC (≥30 mg prednisone or total dose > 5 gms) and age ≥ 30 yr
- Oral Bisphosphonate
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Spine BMD</th>
<th>Hip BMD</th>
<th>Vertebral fracture</th>
<th>Non-vertebral fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>A</td>
<td>A</td>
<td>B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NAE</td>
</tr>
<tr>
<td>Risedronate</td>
<td>A</td>
<td>A</td>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NAE</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>NAE</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NAE</td>
<td>NAE</td>
</tr>
</tbody>
</table>

A: Grade A recommendation
B: Grade B recommendation
a: comparator study
b: not a primary endpoint
NAE: not adequately evaluated

Compston J. *Arch Osteo* 2017;12:43
How Do NOGG 2017 GIOP Guidelines Differ from ACR?

• Similar approach to risk assessment, but NOGG uses UK intervention FRAX thresholds as basis for making treatment decisions
• Does not include denosumab as treatment option
• Recommends continued GIOP prevention while glucocorticoids on board– **NO** Drug Holiday
COMMENTARY

Should Bisphosphonates Be Used for Long-Term Treatment of Glucocorticoid-Induced Osteoporosis?

Steven L. Teitelbaum, Margaret P. Seton, and Kenneth G. Saag
Future GIOP Study Considerations
### GIOP Clinical Trial Comparisons

#### Study Size and Inclusion Criteria

<table>
<thead>
<tr>
<th></th>
<th>Saag¹</th>
<th>Cohen²</th>
<th>Reid³</th>
<th>Saag⁴</th>
<th>Reid⁵</th>
<th>Reid⁵</th>
<th>Saag⁶</th>
<th>Saag⁶</th>
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<tbody>
<tr>
<td><strong>ALN</strong></td>
<td>561</td>
<td>228</td>
<td>290</td>
<td>428</td>
<td>288</td>
<td>546</td>
<td>290</td>
<td>505</td>
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<tr>
<td><strong>RIS (P)</strong></td>
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<td><strong>RIS (T)</strong></td>
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<tr>
<td><strong>TPTD</strong></td>
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<tr>
<td><strong>ZOL (P)</strong></td>
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<tr>
<td><strong>ZOL (T)</strong></td>
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<td><strong>DEN (P)</strong></td>
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<tr>
<td><strong>DEN (T)</strong></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

| **Study size** | 561   | 228    | 290   | 428   | 288   | 546   | 290   | 505   |
| **Study Sites**| 22    | 28     | 23    | 67    | 54    | 79    |       |       |
| **Study length**| 1 (1 ext) | 1        | 1     | 1.5 (1.5 ext) | 1 | 1 (1 ext) |       |       |

| **Prednisone Dose (mg)** | ≥ 7.5 | ≥ 7.5 | ≥ 7.5 | ≥ 5.0 | ≥ 7.5 | ≥ 7.5 |       |       |

| **BMD (T score)** | NA | NA | NA | -2.0 or -1.0 with fx | NA | NA | -2.0 or -1.0 with fx |       |

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Recruitment/Site Challenges

- Time to get different studies recruited: 3 years +
- Number of sites needed: 50+ and rising
- Quality control of sites with less expertise in osteoporosis clinical trials
## GIOP Studies Retention Challenges

### Discontinuation Rates

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Discontinuation Rate (%)</th>
<th>Off Prednisone at study end (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab vs. Risedronate (12 mos)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>13</td>
<td>~8</td>
</tr>
<tr>
<td>Teriparatide vs. Alendronate Ext (36 mo)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>~45</td>
<td>?</td>
</tr>
<tr>
<td>Teriparatide vs. Alendronate (18 mos)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>~30</td>
<td>?</td>
</tr>
<tr>
<td>Zoledronic Acid vs. Risedronate (12 mos)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>7</td>
<td>?</td>
</tr>
<tr>
<td>Risedronate vs. Placebo (12 mos)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>33</td>
<td>?</td>
</tr>
<tr>
<td>Risedronate vs. Placebo (12 mos)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>22</td>
<td>?</td>
</tr>
<tr>
<td>Alendronate vs. Placebo (12 mos)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>15</td>
<td>?</td>
</tr>
</tbody>
</table>

* Or below minimal amount required for inclusion during study period

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<sup>1</sup>Saag K. *Lancet Endo Metab* 2018;6:445  
<sup>2</sup>Saag K. *Arthritis Rheum* 2009;60:3346  
<sup>4</sup>Reid D. *Lancet* 2009;373:1253  
<sup>5</sup>Cohen D. *Arthritis Rheum* 1999;42:2309  
<sup>6</sup>Reid D. *J Bone Miner Res* 2000;15:1006  
Future GIOP Studies
What Patients to Include?

• Prior steroid use
  • < 3 mo - prevention
  • ≥ 3 mo - treatment

• Prednisone dose - ≥ 7.5 mg

• Diseases of interest
  • RA predominate disease in all studies
  • PMR/GCA prevalent in prevention groups

• BMD criteria or NOT?
  • Yes - for treatment study or if drug indication requires it
  • No - if prevention or drug without this indication

• Other “desirable” osteoporosis risk factors that enrich for higher fracture incidence
  • Menopausal status
  • Prior fracture history
How can we possibly study 1000’s of GIOP patients for fractures over an extended period of time?
Pragmatic Clinical Trials (PCT)s?

- Measure “real world” effectiveness (NOT efficacy)
- Large sample size = generalizable results
- Minimal patient eligibility criteria (broad inclusion / exclusion)
- Broad patient population (variably cooperative, less motivated)
- Simpler treatment arms (less complicated design)
- Objective natural endpoints (outcomes)
- Most investigators NOT experienced researchers
What Might a Pragmatic RCT in GIOP Look Like?

- Active comparator with two potent therapies
- Focus on clinical fracture outcomes
- Big, big, sample size
- Extended follow-up
  - Data linkages to electronic database (e.g. billing claims in US, registries in countries with nationalized health systems)
  - Supplemental patient surveys for natural endpoints (fractures)
- Consider direct to patient approaches and/or centralized electronic consent
Other Questions in GIOP

Dmab GIOP Switching Trial

-24 MO
MO 0
DMAB Dose

MO 4
DMAB Dose

MO 6
DMAB Dose

MO 8
DMAB Dose

MO 10
DMAB Dose

MO 12
DMAB Dose

MO 14
DMAB Dose

MO 16
DMAB Dose

MO 18
DMAB Dose

MO 20
DMAB Dose

MO 22
MO 24 End of Study

Up to 24 mo prior DMAB

Randomization to continue DMAB (DMAB Dose) or Switch to Ris

Desired Minimum Duration of DMAB use

MO 18
Final DMAB Dose

Switch to Ris

DMAB

DMAB

DMAB
GIOP Update 2019

- Increasing evidence on glucocorticoid dose and duration effects on fracture risk, risk may vary by fx site
- New RCT data for BMD benefit with denosumab and ibandronate in GIOP
- Observational studies of bisphosphonate show reduced Fx endpoints
- Newer GIOP guidelines from ACR and NOGG
- Quality of GIOP care remains suboptimal and difficult to fix in many international health systems
“C’mon, c’mon—it’s either one or the other.”
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- Nicole Wright, PhD
- Huifeng Yun, BS
- Sophie Zhang, PhD

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