Safety of Bisphosphonates
For Whom and For How long

A Critical Review of the Literature
In relation to the Bisphosphonate Therapies

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Disclosure Stefan Goemaere

- **Consulting fees:**
  - GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Proctor & Gamble, Roche

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  - GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Proctor & Gamble, Roche

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Safety Questions for Bisphosphonates

- **For Whom?**
  - Which patients presents contraindications for BP treatment or how to circumvent problems?

- **For how Long?**
  - Is time revealing BP specific toxicity?
Bisphosphonates: Pharmacokinetics

- Oral
- IV

Short plasma half-life
No circulating metabolites

Papapoulos 2005
Safety Agenda of Bisphosphonates

- Renal Safety
- Hypocalcemia
- Acute-Phase Reaction
- Impact on Bone Remodeling and Quality
- Osteonecrosis of the Jaw (ONJ)
- Cardiovascular concerns
- Conclusions
Both phosphonate groups act as a "bone hook" and are essential both for binding to hydroxyapatite and biochemical mechanism of action.

When $R^1$ is an OH group, binding to bone is enhanced.

$R^2$ site determines anti-resorptive potency and affects binding to hydroxyapatite.

Intracellular BPResorption pit

Side view

Courtesy of Dr Fraser Coxon, University of Aberdeen
Biochemical Mechanism of Action of Nitrogen-Containing Bisphosphonates

HMG-CoA → Mevalonate → Geranyl pyrophosphate → FPP synthase → FPP → Geranylgeranyl pyrophosphate (GGPP)

N-BPs inhibit FPP synthase, thus blocking the prenylation of small GTPase signaling proteins essential for cell function and survival.

Statins inhibit FPP synthase, thus blocking the prenylation of small GTPase signaling proteins essential for cell function and survival.

Ras

Rho

Rab
Effects of Bisphosphonates on Osteoclast Function

Normal Osteoclast

Osteoclast Following Uptake of Bisphosphonate

- Cytoskeletal disorganization
- Altered vesicular trafficking
- Loss of ruffled border


Cell death by apoptosis
Bisphosphonates
Key Pharmacological Characteristics

- High binding affinity for bone
  - Maximizes attachment
  - Minimizes detachment
- Potent FPP synthase inhibition
  - Maximizes antiresorptive potential
  - Minimizes total amount of drug required
  - Allows single administration of total annual dose

Proposed Mechanism of Local Recycling of Bisphosphonates in Bone

- **Low Affinity BP**
  - Weak uptake
  - High desorption
  - Low reattachment
  - More diffusion in bone

- **High Affinity BP**
  - Avid uptake
  - Low desorption
  - High reattachment
  - Less diffusion in bone
Not all bisphosphonates are the same

- In terms of action / activity
  - Preferences?

- In terms of side effects?
  - Are there differences?
Bisphosphonates’ Clinical Indications

Clinical Role of bisphosphonates

- Cancer
- Osteoporosis
- Paget’s disease of bone
Renal Safety
Renal Safety of Bisphosphonates

- Bisphosphonates are excreted through the kidney and may affect tubular function, resulting in transient renal toxicity.

- The risk for renal toxicity increases with dose and short infusion times.

- No significant renal toxicity has been observed in oral or IV BP treatment schedules for Osteoporosis and Paget’s disease.

- However, BP are not recommended for patients with severe renal impairment (creatinine clearance <30 mL/min) due to lack of adequate clinical experience in this population.

- Ensure patients are appropriately hydrated prior to infusion.
**Increase From Pre-Infusion in Serum Creatinine >0.5 mg/dL by 9-11 Days After Infusion (Overall)**

<table>
<thead>
<tr>
<th>Visit/Lab Test</th>
<th>Pre-infusion Creatinine Clearance Level (mL/min)</th>
<th>ZOL 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n (%)</td>
<td>N</td>
</tr>
<tr>
<td>Increase in serum creatinine &gt;0.5 mg/dL</td>
<td>&lt;30</td>
<td>0 (0.0)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>≥30 – ≤35</td>
<td>47 (10.6)</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>≥35 – ≤40</td>
<td>84 (2.4)</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>≥40 – ≤50</td>
<td>372 (1.9)</td>
<td>358</td>
</tr>
<tr>
<td></td>
<td>&gt;50 – &lt;60</td>
<td>550 (0.7)</td>
<td>513</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>1267 (1.0)</td>
<td>1304</td>
</tr>
<tr>
<td>All patients</td>
<td>2320</td>
<td>31 (1.3)</td>
<td>2338</td>
</tr>
</tbody>
</table>

- 27/31 (87%) of patients in the ZOL 5 mg group and 8/10 (80%) in the placebo group reported a recovery (to within <0.5 mg/dL of their pre-dose value) within 1 month of their serum creatinine levels within 12 months.

Mean Changes in Calculated Creatinine Clearance From Baseline Comparable for Zoledronic Acid vs Placebo Over Time

Zoledronic Acid
Renal Safety — Oncology Experience

- Infusion time for IV ZOL must not be less than 15 min

- In patients with preexisting renal compromise (e.g., myeloma, prostate cancer), infusion of zoledronic acid has been associated with temporary increases in serum creatinine

- Severe renal impairment (National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3–4) developed in <2% of patients with bone metastases (breast cancer or myeloma) treated with IV Zoledronate

ZOL = zoledronic acid
Zometa prescribing information.
Hypocalcemia
Regulation of calcium homeostasis

Calcium Homeostasis, Bone Resorption, and Bone Formation

ZOL = zoledronic acid
Illustration by Seward Hung
Hypocalcemia: Low Incidence and Asymptomatic with Zoledronic Acid

<table>
<thead>
<tr>
<th>Visit</th>
<th>ZOL 5 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-11 day post infusion 1</td>
<td>2114</td>
<td>2129</td>
</tr>
<tr>
<td>n (%)</td>
<td>49 (2.3)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>9-11 day post infusion 2</td>
<td>1663</td>
<td>1721</td>
</tr>
<tr>
<td>n (%)</td>
<td>2 (0.1)</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>9-11 day post infusion 3</td>
<td>1559</td>
<td>1601</td>
</tr>
<tr>
<td>n (%)</td>
<td>5 (0.3)</td>
<td>1 (&lt;0.1)</td>
</tr>
</tbody>
</table>

- Laboratory defined hypocalcemia (serum calcium <2.075 mmol/L) occurred more frequently after the first infusion of ZOL 5 mg
- All cases were asymptomatic and transient
- After second infusion, incidence of asymptomatic hypocalcemia similar in the ZOL 5 mg and placebo groups

Data on file, Novartis
Acute Phase Reactions
# Most Common (>2%) Adverse Events Occurring Within 3 Days After Infusion

<table>
<thead>
<tr>
<th>Event</th>
<th>≤3 Days After Infusion</th>
<th>&gt;3 Days After Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZOL 5 mg (n = 3862) n (%)</td>
<td>Placebo (n = 3852) n (%)</td>
</tr>
<tr>
<td>Total patients with any AE</td>
<td>1983 (51.3)</td>
<td>1013 (26.3)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>621 (16.1)</td>
<td>79 (2.1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>365 (9.5)</td>
<td>66 (1.7)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>301 (7.8)</td>
<td>61 (1.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>273 (7.1)</td>
<td>90 (2.3)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>245 (6.3)</td>
<td>76 (1.9)</td>
</tr>
<tr>
<td>Chills</td>
<td>188 (4.9)</td>
<td>27 (0.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>180 (4.7)</td>
<td>52 (1.3)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>175 (4.5)</td>
<td>40 (1.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>160 (4.1)</td>
<td>85 (2.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>135 (3.5)</td>
<td>55 (1.4)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>107 (2.8)</td>
<td>35 (0.9)</td>
</tr>
<tr>
<td>Pain</td>
<td>89 (2.3)</td>
<td>24 (0.6)</td>
</tr>
</tbody>
</table>

Common (≥5% in ZOL) Post-Dose Symptoms Occurring Within 3 Days After Infusion

- Pyrexia: 15%
- Myalgia: 8%
- Flu-like illness: 7%
- Headache: 6%
- Arthralgia: 5%

N-BPs and Acute Phase Reaction

PBMC

N-BPs

HMG Co-A
Mevalonate
Isopentenyl-PP
Farnesyl-PP
Geranylgeranyl-PP

R
(γ,δ) T cell

Activation, Proliferation
IFN-γ, TNF-α
IL-6

Flu-like
Fever
Lymph
CRP
IL-6
Transient

Modified from Thompson & Rogers JBMR 2004; 19:275
Bone Safety
Bone Remodeling: Key Features

- Life-long, continuous balance or unbalanced process
  - Old bone removed by osteoclastic resorption
  - Replacement bone created through osteoblastic formation
- Why?
  - Contributes to functional adaptation to mechanical stress
  - Repairs microdamage in bone
  - Contributes to calcium homeostasis
Ostecyte networks in normal /osteoporotic bone

Normal  Osteoporosis  Severe osteoporosis
Bone Remodeling: How to Investigate?

Bone Histomorphometry
- Invasive, expensive
- After Double Tetracycline labeling
- Variability of normal data

Alendronate

Teriparatide
Bone Remodeling: Who to Investigate

Biochemical markers of bone turnover

- Non-invasive by standardized blood/urine sampling
- Validated for groups evaluations
- Lack of validation for use in individual patients
What Is the Optimal level of Bone Turnover?

**Insufficient turnover**
- Accumulation of microdamage
- Increased brittleness due to excessive mineralization

**Excessive turnover**
- Increase in stress risers (weak zones)
- Increase in perforations
- Loss of connectivity

Adapted from Weinstein RS, *J Bone Miner Res* 2000; 15 621.
Oversuppression bone turnover?

Insufficient turnover?

- Accumulation of microdamage
- Increased brittleness due to excessive mineralization
- Pathologic fractures
- Adynamic bone disease

Zoledronic Acid Maintains Mean Serum β-CTX Over Time

Mean Serum β-CTX (ng/mL)

Months

ZOL n = 257  237  201  136  191  190  174
PBO n = 260  248  214  156  196  197  170

Zoledronic Acid 's Bone Safety

- Histomorphometry evaluable in 152 bone biopsies
  - Label seen in all but 1 specimen = ongoing bone remodeling

- On average, turnover markers maintained in pre-menopausal reference range over 36 months

- Normal Fracture healing: Non-union: 2 in ZOL 5 mg, 1 in placebo

- No abnormal or unusual fractures reported

- Avascular necrosis (hip or knee): 4 in ZOL, 3 in placebo

- Osteonecrosis of the jaw?  

Osteonecrosis of the jaw

No uniform diagnostic criteria was accepted previously

"if you think you’ve discovered a new disease, you probably haven’t reviewed the literature thoroughly enough"

- Anonymous -
ONJ: Clinical Description

Clinical Features of Confirmed or Suspected BP-associated ONJ

- Exposed bone in maxillofacial area that occurs in association with dental surgery or occurs spontaneously, with no evidence of healing*

Working Diagnosis of ONJ

- No evidence of healing after 8 weeks of appropriate evaluation and dental care
- No evidence of metastatic disease in the jaw or osteoradionecrosis

*Refer for appropriate dental evaluation and care as soon as possible
Osteonecrosis of the jaw (ONJ) is spontaneously occurring.

ONJ is primarily reported in patients with advanced malignancies and skeletal metastases receiving treatment regimens including bisphosphonates (BP).

However, a causal relationship between BP and ONJ has not been established.

ONJ has not been observed in the Paget’s disease or osteoporosis clinical studies with BP.
Osteonecrosis of the jaw: Background

Etiology and pathogenesis poorly characterized:

- Mucosal damage
  - preceding events & delayed epithelialisation
- Alterations in angiogenesis
- Alterations in bone turnover
- Infection
- Multiple contributing factors
Osteonecrosis of the jaw: Background

Relative contribution of multiple factors?

- >> associated with dental procedures!
  - Tooth extractions (dominating event!)
  - Peridontal disease
  - Dental implant procedures
  - Exostosis and ill-fitting dentures
BP-induced vs BP-associated
Osteonecrosis of the Jaw

Alternative Explanations!
ONJ reported in OP and Paget’s disease

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (yrs)</th>
<th>M/F</th>
<th>Disease</th>
<th>Bisphosphonate</th>
<th>Oral site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruggerio et al.</td>
<td>7</td>
<td>59-82</td>
<td>1M/6F</td>
<td>O (7)</td>
<td>A (6), A + Z (1)</td>
<td>Mand (6) Max (1)</td>
</tr>
<tr>
<td>Cheng et al.</td>
<td>8</td>
<td>39-84</td>
<td>4M/4F</td>
<td>O (3) P (5)</td>
<td>A (5), P (2), A + P (1)</td>
<td>Mand (3) Max (5)</td>
</tr>
<tr>
<td>Marx et al.</td>
<td>3</td>
<td></td>
<td></td>
<td>O (3)</td>
<td>A (3)</td>
<td></td>
</tr>
<tr>
<td>Marunick et al.</td>
<td>2</td>
<td>59, 64</td>
<td>2F</td>
<td>O (2)</td>
<td>A (2)</td>
<td>Mand (2)</td>
</tr>
<tr>
<td>Miglioriti et al.</td>
<td>1</td>
<td>61</td>
<td>1F</td>
<td>O (1)</td>
<td>A (1)</td>
<td>Max (1)</td>
</tr>
<tr>
<td>Purcell et al.</td>
<td>1</td>
<td>67</td>
<td>1F</td>
<td>O (1)</td>
<td>A (1)</td>
<td>Max (1)</td>
</tr>
<tr>
<td>Farrugia et al.</td>
<td>5</td>
<td>63-83</td>
<td>1M/4F</td>
<td>O (4) P (1)</td>
<td>A (5)</td>
<td>Mand (3) Max (2)</td>
</tr>
<tr>
<td>Chang et al.</td>
<td>11</td>
<td></td>
<td></td>
<td>O (11)</td>
<td>A (11)</td>
<td></td>
</tr>
<tr>
<td>Mavrokokki et al.</td>
<td>32</td>
<td></td>
<td></td>
<td>O (26) P (6)</td>
<td>A (25), P (2), R (2), A + R (2), A + P (1)</td>
<td>Mand (23) Max (9)</td>
</tr>
<tr>
<td>Starck et al.</td>
<td>1</td>
<td>75</td>
<td>1F</td>
<td>O (1)</td>
<td></td>
<td>Mand (1)</td>
</tr>
<tr>
<td>Hoefert et al.</td>
<td>3</td>
<td></td>
<td></td>
<td>O (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Najm et al.</td>
<td>3</td>
<td>45-84</td>
<td>1M/2F</td>
<td>O (3)</td>
<td>A (2), P + Z (1)</td>
<td>Mand (2) Max (1)</td>
</tr>
<tr>
<td>Carter et al.</td>
<td>3</td>
<td></td>
<td></td>
<td>P (3)</td>
<td>A (1), P (2)</td>
<td>Max (3)</td>
</tr>
<tr>
<td>Pozzi et al.</td>
<td>1</td>
<td></td>
<td></td>
<td>O (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (excluding overlapping cases)</td>
<td>64</td>
<td></td>
<td>O (57) P (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Literature review of bisphosphonate-associated ONJ reports in patients with osteoporosis or Paget’s disease.

Reported Cases of BP-associated ONJ in osteoporosis (n=57) or paget’s disease (n=7)
ONJ identified in cancer patients with longterm BP:

- Multiple myeloma: 5.4%
- Breast cancer: 2.5%
- Prostate cancer: 2.9%

Duration of IV BP treatment: variable

Wang EP, AAOMS 2006
BP-associated ONJ
Recommendations by international societies

General

- Free communication between health care professionals
- Patient information about benefits and risk of BP
- Patient should maintain oral hygiene & regular dental visits
- Education of physician & patients
Patients with non-malignant bone disease

- Inform patient about risk: between $1/10^4$ and $1/10^5$
- Practice good oral hygiene & regular dental visits
- No dental examination needed before start
- If patient is concerned consult dentist
- Precautions for longterm users (oral & IV BP =)
  - Peridonditis treatment: preferable non-surgical management
  - Proper consenting in case of surgical procedure
  - Preferable endodontic treatments
  - Stopping BP before invasive dental procedure ??
Patients with malignancy

- Inform patient about risk: between 1% to 10%
- Dental evaluation before start
- Dental procedure before or at start of BP treatment
- Elective dento-alveolar procedures are not recommended
- Symptomatic teeth:
  - Preferable non-surgical management
  - No peri-apical or peri-dontal surgery recommended
  - Extraction if a region of exposed bone
Cardiac Events
# Data Summary: Most Frequent Cardiovascular or Stroke-Related SAEs

## Most commonly (≥ 0.5%) reported CV/NS SAEs

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>ZOL 5 mg (N = 3862)</th>
<th>PBO (N = 3852)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td>228 (5.9)</td>
<td>192 (5.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>50 (1.3)</td>
<td>20 (0.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>36 (0.9)</td>
<td>37 (1.0)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>28 (0.7)</td>
<td>31 (0.8)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>23 (0.6)</td>
<td>18 (0.5)</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>21 (0.5)</td>
<td>13 (0.3)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>162 (4.2)</td>
<td>175 (4.5)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>39 (1.0)</td>
<td>34 (0.9)</td>
</tr>
</tbody>
</table>

Data on file, Novartis
# Data Summary: ECG Substudy

<table>
<thead>
<tr>
<th>ECG Finding</th>
<th>Pre-3rd infusion</th>
<th>9-11 day post 3rd infusion</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZOL 5 mg (N = 276)</td>
<td>PBO (N = 279)</td>
<td>ZOL 5 mg (N = 252)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>31 (11.2)</td>
<td>23 (8.2)</td>
<td>14 (5.6)</td>
</tr>
<tr>
<td>Conduction</td>
<td>55 (19.9)</td>
<td>66 (23.7)</td>
<td>8 (3.2)</td>
</tr>
<tr>
<td>Myocardial</td>
<td>4 (1.5)</td>
<td>3 (1.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rhythm</td>
<td>23 (8.3)</td>
<td>23 (8.2)</td>
<td>13 (5.2)</td>
</tr>
<tr>
<td>ST segment</td>
<td>1 (0.4)</td>
<td>4 (1.4)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>T waves</td>
<td>26 (9.4)</td>
<td>23 (8.2)</td>
<td>14 (5.6)</td>
</tr>
<tr>
<td>U waves</td>
<td>1 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Data on file, Novartis
# Data Summary: Arrhythmic Events

<table>
<thead>
<tr>
<th>Events</th>
<th>ZOL 5 mg (N = 3862)</th>
<th>PBO (N = 3852)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All arrhythmia AEs</td>
<td>284 (7.4)</td>
<td>242 (6.3)</td>
</tr>
<tr>
<td>All arrhythmia SAEs</td>
<td>112 (2.9)</td>
<td>80 (2.1)</td>
</tr>
<tr>
<td>Atrial fibrillation/Atrial Flutter AEs</td>
<td>96 (2.5)</td>
<td>75 (1.9)</td>
</tr>
<tr>
<td>Atrial fibrillation/Atrial Flutter SAEs</td>
<td>51 (1.3)</td>
<td>22 (0.6)</td>
</tr>
<tr>
<td>Adjudicated arrhythmia SAEs</td>
<td>82 (2.1)</td>
<td>48 (1.3)</td>
</tr>
<tr>
<td>Adjudicated atrial fibrillation SAE</td>
<td>50 (1.3)</td>
<td>17 (0.4)</td>
</tr>
</tbody>
</table>

Data on file, Novartis
Investigators commonly report the terminal event which is frequently cardiac as the cause of death and not the primary underlying disease, thus adjudication was performed.

<table>
<thead>
<tr>
<th>Reason of Death</th>
<th>ZOL 5 mg (N = 3862)</th>
<th>PBO (N = 3852)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>131 (3.4)</td>
<td>118 (3.1)</td>
</tr>
<tr>
<td>Due to cardiac</td>
<td>17 (0.4)</td>
<td>18 (0.5)</td>
</tr>
<tr>
<td>Due to cerebrovascular</td>
<td>16 (0.4)</td>
<td>6 (0.2)</td>
</tr>
<tr>
<td>Other</td>
<td>50 (1.3)</td>
<td>55 (1.4)</td>
</tr>
<tr>
<td>Unknown</td>
<td>48 (1.2)</td>
<td>39 (1.0)</td>
</tr>
</tbody>
</table>

Data on file, Novartis
Imbalanced data (SAE due to atrial fibrillation and death due to cerebrovascular accident) is likely a chance finding and not a drug effect:

- Overall incidence of AF and stroke is comparable between groups and substantially lower than what would be expected in a similar population\textsuperscript{1,2}.

- 47/50 (94\%) of atrial fibrillation SAEs in ZOL arm occurred >30 days after dosing (drug no longer in circulation).

- No AF imbalance between groups observed in ECGs of 559 patients taken days 9-11 after 3d infusion.

SAE = serious adverse event

Imbalanced data (SAE due to atrial fibrillation and death due to cerebrovascular accident) is likely a chance finding and not a drug effect:

- Event rate was relatively constant over time in ZOL arm (no increase in risk with increased drug exposure) and unexpectedly declined over time in placebo arm.

- No signal with ZOL in pre-clinical cardiovascular safety screening of 3 different species (hamster, cat, dog) up to 77 weeks after dosing.

- No imbalance noted with Zometa studies (~2-10x higher dose annually) or Aclasta study (RFT after hip #).

SAE = serious adverse event
**A judge for a good balance**

**Effects**
- Decreased
  - Fracture
  - SRE
  - Pain

- Improved
  - QoL
  - Survival

**Bisphosphonates**

**Side-Effects**
- Gasto-intestinal
- Kidney ?
- M-S pain
- Heart ?
- Lung cancer ?
- Uveitis ?
- Bone necrosis ?