Managing Medication Issues

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Steven T Harris MD FACP FASBMR
Clinical Professor of Medicine
University of California, San Francisco
steve.harris@ucsf.edu
Disclosure and Conflicts of Interest
Steven T Harris MD 2020-2021

- Speakers Bureaus and Consulting
  - Amgen
  - Radius Health
Bisphosphonates and Denosumab
Duration of Therapy

• Optimal duration of therapy
  – “Drug holiday” is a notion that applies only to the bisphosphonates
  – The benefits and risks of both continuation and discontinuation must be considered
    • One might consider a “drug holiday” if continued therapy is not associated with any greater benefit
    • One might also consider a “drug holiday” if continued therapy is associated with an increased risk of adverse events
Two Common Management Problems

Problem #1

• Is it necessary to stop bisphosphonate therapy after a certain number of years?
  – If so, how might patients be monitored to decide whether to restart therapy?
    • BMD changes? Biochemical markers? Clinical progress? All of the above?
Two Common Management Problems

Problem #2

- Is it necessary to stop denosumab therapy after a certain number of years?
  - No. At least based on the 10-year FREEDOM extension trial
  - Stopping denosumab is associated with relatively rapid bone loss and a risk of multiple vertebral fractures ("MVF")
Challenges of Osteoporosis Treatment

- Success has been defined as the absence of fracture—which from a patient perspective is not very “exciting”
- Economic cost of treatment
- Other costs of treatment: nuisance value of taking another medication, reminder of illness, worry about consequences of therapy
- Side effects of treatment
“Relative Risk” vs “Absolute Risk”

- The media will almost always cover medical issues—both risks and benefits—with numbers related to “relative risk”
  - If you do “this,” you will double your risk of “that” (something undesirable)
  - Alternatively, if you do “this other thing,” you will reduce your risk of “that” in half (“by 50%”)

The next question must be:

“What is the risk to begin with?”
“Relative Risk” vs “Absolute Risk”

- For example, imagine that the risk of “badness” is 1% (1 out of 100)
  - If you do something that doubles your risk, the risk is now 2% (2 out of 100)
    - The harm (absolute risk) is 1% (1 out of 100)
  - On the other hand, if you do something that will reduce your risk in half (“by 50%”), then the risk is now 0.5% (1 out of 200)
    - The benefit (absolute benefit) is 0.5% (1 out of 200)
“Relative Risk” vs “Absolute Risk”

• For example, imagine that the risk of “badness” is 20% (20 out of 100)
  – If you do something that doubles your risk, the risk is now 40% (40 out of 100)
    • The harm (absolute risk) is 20% (20 out of 100)
  – On the other hand, if you do something that will reduce your risk in half (“by 50%”), then the risk is now 10% (10 out of 100)
    • The benefit (absolute benefit) is 10% (10 of out 100)
Bisphosphonates: Current Uses and Challenges

• Efficacy
  – “Short-term” efficacy usually established on the basis of fracture risk reduction over 3 years
  – “Long-term” efficacy (Is treatment “forever?”)

• Safety
  – “Short-term” concerns
  – “Long-term” concerns that have been raised
    • Osteonecrosis of the jaw (ONJ)
    • Atrial fibrillation
    • Abnormal bone quality/atypical fractures
    • Esophageal cancer
FIT Long-Term Extension (FLEX)

- Women previously on alendronate for 3-6 years were randomly assigned to 5 years of alendronate (5 or 10 mg daily) or placebo

- Alendronate vs placebo
  - Clinical spine fracture: RR=0.45 (0.23, 0.84)
  - Morphometric spine fracture: RR=0.87 (0.61, 1.25)
  - Nonspine fracture: RR=1.00 (0.76, 1.32)

FLEX: % Change in Femoral Neck BMD

FIT
3 to 4.5 years

Time Between FIT and FLEX
1 to 2 years

FLEX
5 years

Mean Percent Change
From FIT Baseline, %

1.9%
P<0.001

△ = ALN/Placebo (n = 437)
▼ = ALN/ALN (pooled 5-mg and 10-mg groups: n = 662)

FLEX: Incidence of Fractures

**Relative Risk Reduction = 55%**

ARR = 2.9%

\[ P = 0.013 \]

**RR = 0.45**

CI (0.2, 0.8)

**RR = 0.9**

CI (0.6, 1.2)

**RR = 1.0**

CI (0.8, 1.4)

Fracture Incidence, %

- **5.3%**
- **2.4%**
- **11.3%**
- **9.8%**
- **19.0%**
- **18.9%**

**ALN/PLB (n = 437)**

**ALN/ALN (n = 662)**

**Clinical Vertebral**

**Vertebral Morphometric**

**Non-Vertebral**

FLEX Summary and Conclusions

• Over 10 years (FIT and FLEX), continuous alendronate treatment:
  – Prevented bone loss at the total hip and increased BMD at the femoral neck and lumbar spine
  – Maintained biochemical markers of bone turnover at levels similar to FLEX baseline
  – Reduced the relative risk of clinical vertebral fracture by 55% (ARR 2.9%)
  – Resulted in normal bone histology

• Discontinuation of alendronate treatment in FLEX:
  – Resulted in a loss of total hip and femoral neck BMD
  – Led to a rise in biochemical markers of bone turnover
  – Resulted in more clinical vertebral fractures—but had no effect on morphometric vertebral fractures or non-vertebral fractures in the entire study group

FLEX: NVF Risk with Extended Alendronate Therapy Stratified by Baseline Femoral Neck BMD

- 1099 patients enrolled in FLEX
- 723 with no vertebral fracture at FLEX baseline

<table>
<thead>
<tr>
<th>Baseline FN BMD</th>
<th>Risk Difference</th>
<th>Relative Risk</th>
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<tbody>
<tr>
<td>T-score &gt; -2</td>
<td>4.01%</td>
<td>1.41 (0.75, 2.66)</td>
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<tr>
<td>T-score ≤ -2.5</td>
<td>-13.32%</td>
<td>0.50 (0.26, 0.96)</td>
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Risedronate 7-year Experience

Lumbar Spine BMD

Abstract: European Calcified Tissue Society meeting, May 2003
Vertebral Fractures Over 7 Years of Risedronate Therapy

VERT-MN: Radiographic Vertebral Fracture*

*Annualized fracture incidence represents the percentage of patients experiencing any new vertebral fracture divided by the number of years in the observed interval.
NTx Change After Risedronate Treatment

VERT-NA Extension Cohort

Watts NB, et al. ISCD 2004

* p<0.05 from baseline
# p<0.05 from placebo
Zoledronic Acid: Long-Term Therapy

Change in Lumbar Spine BMD over 6 years
6 years of therapy vs 3 years of therapy

Continuing treatment for 6 years reduced morphometric vertebral fractures, without an effect on clinical vertebral fractures or non-vertebral fractures

Zoledronic Acid: Long-Term Therapy

Change in Total Hip BMD over 9 years
9 years of therapy vs 6 years of therapy

Continuing treatment for 9 years had no significant effect on fracture rates--but the statistical power was limited

Long-term Treatment and Discontinuation

• FLEX Trial
  – Compared the effects of discontinuing alendronate treatment after 5 years vs. continuing for 10 years
  – Switching to placebo for 5 years resulted in declines in BMD and increases in biochemical markers of bone turnover, but not to pretreatment levels
  – Incidence of all clinical fractures and nonvertebral fractures similar in both groups, but lower risk of clinical vertebral fractures in those who continued therapy
  – Post hoc analyses suggested that continuation was associated with lower risk of nonvertebral fractures in women with femoral neck T-score ≤ -2.5

• VERT-NA Extension Study
  – After treatment with risedronate for 3 years and discontinuation for 1 year:
    • Spine and hip BMDs decreased significantly and biochemical markers of bone turnover increased to placebo levels
    • The risk of new vertebral fractures was reduced by 46% in the former risedronate users compared with the former placebo patients in the year off of treatment

Long-term Treatment and Discontinuation

- HORIZON Pivotal Fracture Trial Extension Study
  - Compared the effects of discontinuing zoledronic acid treatment after 3 years vs. continuing for an additional 3 years
  - Femoral neck BMD remained constant in the continuation group and showed a small decrease in the discontinuation group
  - Significantly fewer morphometric vertebral fractures occurred in the continuation group than in the discontinuation group; no difference in nonvertebral, clinical vertebral, or hip fractures

Long-term Treatment and Discontinuation

Based on these findings, continued BP therapy beyond 3 years with ZOL and beyond 5 years with ALN may be an option in high-risk individuals, based on evidence for reductions in the risk of vertebral fractures only. In lower-risk patients and in light of lack of evidence for fracture reduction with long-term therapy, discontinuation of treatment beyond 3 to 5 years, with monitoring, may be considered with periodic reassessment of fracture risk.

Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research
Adler RA et al. J Bone Miner Res 2016:31(1)16-35
Bisphosphonate Drug Holidays

• Optimal duration of therapy
  – “Drug holiday” is a notion that applies only to the bisphosphonates
  – The benefits and risks of both continuation and discontinuation must be considered
    • One might consider a “drug holiday” if continued therapy is not associated with any greater benefit
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High-Profile Adverse Events

- Osteonecrosis of the jaw (ONJ)
  - Risk factors:
    - Cancer and anti-cancer therapy
    - Poor oral hygiene
  - Prevalence of 1/10,000 to ≤1/100,000 patient-years in patients treated for osteoporosis
- Atypical femur fractures
  - Associated with bisphosphonates - low absolute risk
  - Causality not established
  - Pathophysiology unknown - low bone turnover leading to impaired remodeling and accumulation of microdamage?

Bisphosphonate-Related ONJ: Incidence

The Background Incidence in the General Population is Not Known

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<thead>
<tr>
<th></th>
<th>Underlying Malignancy</th>
<th>Osteoporosis Paget’s Disease</th>
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<tbody>
<tr>
<td>IV</td>
<td>1% to 10%</td>
<td>Rate not published</td>
</tr>
<tr>
<td>PO</td>
<td>Rate not published</td>
<td>1/10,000 to &lt;1/100,000 patient-treatment-years</td>
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Khosla S, et al. *J Bone Miner Res* 2007;22;1479-1491
• 310 reported cases
• Age range 36-92
• Mostly women
• Duration of bisphosphonate treatment 1.3-17 years, median duration 7 years

Benefit/Risk Estimates

- If you treat 1000 women with bisphosphonates for 5 years
  - Fracture risk similar to Fracture Intervention Trial (FIT), the pivotal clinical trial of alendronate
  - Femoral neck T-score ≤ -1.5, with or without prevalent vertebral fractures
- You would prevent 35-50 non-vertebral fractures
- You would prevent 50-115 vertebral fractures
- You might cause as many as 5 atypical femur fractures (AFF)
- The risk of an AFF is low compared to the risk of common osteoporotic fractures

Atypical Femoral Fracture
Observational Data in Kaiser Southern California

Atypical Femoral Fracture
Observational Data in Kaiser Southern California

Bisphosphonate Drug Holidays

• For oral bisphosphonates, consider a bisphosphonate holiday after 5 years of treatment if fracture risk is no longer high (such as when the T-score is greater than -2.5, or the patient has remained fracture free), but continue treatment up to an additional 5 years if fracture risk remains high (Grade B)

• For oral bisphosphonates, consider a bisphosphonate holiday after 6 to 10 years of stability in patients with very high fracture risk (Grade B)

Camacho PM et al; AACE Clinical Practice Guidelines; *Endocr Pract* 2020;26(Suppl 1):1-46
Bisphosphonate Drug Holidays

• For zoledronate, consider a bisphosphonate holiday after 3 years in high-risk patients or until fracture risk is no longer high, and continue for up to 6 years in very-high-risk patients (Grade A)

• The ending of a bisphosphonate holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in bone mineral density beyond the least significant change (LSC) of the dual-energy X-ray absorptiometry (DXA) machine, or an increase in bone turnover markers (Grade A)

Camacho PM et al; AACE Clinical Practice Guidelines; Endocr Pract 2020;26(Suppl 1):1-46
Denosumab

- Monoclonal antibody to RANKL
- 60 mg subcutaneous injection every 6 months
- 9% increase in spinal BMD after 3 years in the pivotal FREEDOM trial; 4%-5% increase in hip BMD
- Reduction in fracture risk after 3 years:
  - 68% decrease in new vertebral fractures
  - 40% decrease in hip fractures
  - 20% decrease in nonvertebral fractures
- 10-year data: continued increase BMD, reduced bone turnover

Denosumab: Long-Term Extension

Bone HG et al. *Lancet Diabetes Endocrinol* 2017;513-23
Denosumab: Long-Term Extension

Bone HG et al. *Lancet Diabetes Endocrinol* 2017;513-23
Denosumab Long-Term Extension Adverse Events

- Osteonecrosis of the jaw occurred in 5.8 cases per 10,000 patient years

- Atypical femoral fracture occurred in 0.8 case per 10,000 patient years

Bone HG et al. *Lancet Diabetes Endocrinol* 2017;513-23
Change after Stopping Denosumab

Serum CTx (C-telopeptide)  Spine BMD

Zoledronic Acid after Denosumab

Zoledronic acid administered at the time of the next scheduled denosumab injection—or 3 months later

Spine BMD

Solling AG et al. J Bone Miner Res 2020;35(10):1858-1870
Change after Stopping Denosumab

• Stopping denosumab is associated with a brisk increase in bone resorption and a corresponding decrease in BMD

• That increase in bone remodeling after stopping has been associated with an increased risk of multiple vertebral fractures (“MVF”)

• Switching to another antiresorptive agent does not fully protect against that increased bone resorption
  – That is true even if zoledronic acid is administered when the next denosumab injection is due—or after a delay of 3 months
Two Common Management Problems

Problem #1

- Is it necessary to stop bisphosphonate therapy after a certain number of years?
- The risk of ONJ is not clearly time-related, but the risk of AFF does appear to increase over time—and the absolute risks remain relatively small.
- Because the bisphosphonates “stick” to bone, there is continued fracture reduction even after treatment is discontinued. As such, it is probably appropriate to consider a drug holiday after years of bisphosphonate therapy.

ST Harris, personal opinion
Two Common Management Problems

Problem #2

- Is it necessary to stop denosumab therapy after a certain number of years?
  - Probably not. Extended therapy is associated with persistently-low fracture rates, even after a decade.

- Treatment is associated with AFF and ONJ, but the absolute risks again appear to be relatively small.

- If treatment is to be discontinued, it appears to be best to transition to another antiresorptive therapy—but the optimal way to do so is a matter of active ongoing clinical investigation.

ST Harris, personal opinion