The VITAL trial
Randomized trial of vitamin D3 to prevent worsening of musculoskeletal symptoms and fatigue in women with breast cancer starting adjuvant letrozole.

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Musculoskeletal Symptoms & Fatigue on Aromatase Inhibitors

- New or worsening musculoskeletal pain reported by ~ 50% of women taking adjuvant Aromatase Inhibitors (AIs) for breast cancer
- 18 - 30% women report fatigue
- Symptoms a major cause of premature discontinuation of these important agents

Crew JCO 2007, Hershman JCO 2010
Estrogen Deprivation: Underlying Cause of AI Induced Musculoskeletal Symptoms

- Estrogen has tissue-specific effects on inflammatory cytokines
- Lack of estrogen may result in inflammation and enhanced pain sensitivity (nociception)
- Women on AIs have MRI findings of tenosynovitis suggestive of local inflammation
Clinical Rationale for Vitamin D in AI Associated Musculoskeletal Symptoms

• A syndrome similar to AI induced musculoskeletal pain is seen in subjects with severe vitamin D deficiency

• Vitamin D deficiency is prevalent in women with breast cancer who have musculoskeletal symptoms

• And in women with breast cancer undergoing adjuvant chemotherapy despite supplementation

Crew KD et al. JCO 2009
Proposed Mechanism of Vitamin D Benefit in AI Induced Musculoskeletal Symptoms

Locally produced $1,25(\text{OH})_2\text{D}$ (from $25(\text{OH})\text{D}$ in macrophages) limits joint inflammation.

Higher dose $25(\text{OH})\text{D}$ would provide substrate for increased local production of $1,25(\text{OH})_2\text{D}$.

AI induced estrogen deprivation reduces tissue production of $1,25(\text{OH})_2\text{D}$ increasing inflammation.
Pilot Trial of Benefit of Vitamin D in Women with AI Induced Musculoskeletal Symptoms

- A pilot trial of vitamin D in women starting adjuvant AIs for breast cancer
- 25(OH)D levels of less than 40 ng/ml
- 50,000 IU of vitamin D3 weekly for 12 weeks
- Women with higher than median 25(OH)D had less disability from joint pain

**Vitamin D – Optimal Levels**

- Optimal level of serum 25-hydroxyvitamin D – the best indicator of vitamin D stores unclear
- < 20 ng/ml is considered deficient for bone health
- 40 ng/ml optimal for musculoskeletal function

<table>
<thead>
<tr>
<th>Serum 25(OHD) levels (ng/ml)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Deficient</strong></td>
<td>&lt;20</td>
</tr>
<tr>
<td><strong>Insufficient</strong></td>
<td>20-30</td>
</tr>
<tr>
<td><strong>Sufficient</strong></td>
<td>&gt;30</td>
</tr>
<tr>
<td><strong>Preferred range</strong></td>
<td>30-60</td>
</tr>
<tr>
<td><strong>Toxic</strong></td>
<td>&gt;150</td>
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</tbody>
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*Bischoff-Ferrari AJCN 2006, Holick NEJM 2007*
VITAL: VITamin D for Arthralgias from Letrozole

2 arm, randomized, double-blind, placebo-controlled

KU (university) and CCK Wichita (community practice)

Postmenopausal stage I-III breast cancer starting adjuvant Letrozole
25(OH)D levels 40 ng/ml or less

Stratification: Use of chemotherapy

Letrozole 2.5 mg daily
Vit D3 30,000 IU weekly
RDA of Ca + D

24 wks

Letrozole 2.5 mg daily
Matching placebo weekly
RDA of Ca + D

RDA = Recommended Daily Allowance

All agents provided by the study
Eligibility

• Post-menopausal women with Stage I-III hormone receptor positive invasive breast cancer about to start an adjuvant aromatase inhibitor

• Completed local treatment and adjuvant chemotherapy

• Serum 25(OH)D level of 40 ng/ml or less

• No severe or debilitating musculoskeletal pain

• No history of renal stones

• No history of hypercalcemia or hyperparathyroidism
Sample Size Calculation

• Primary hypothesis: vitamin D3 prevents worsening of musculoskeletal symptoms from AIs

• Sample size calculation: 60 patient pilot study at KU

• To detect a difference of joint pain worsening of 20% in vitamin D arm and 50% in placebo 144 subjects were needed with 90% power and type 1 error of 1%

• With 10% expected dropout rate accrual goal was set at 160 subjects, 80 in each arm
Trial Assessment Timeline

Baseline

- 25(OH)D levels
- CBC and CMP
- Symptoms tools
  - MS pain
  - disability
  - fatigue

12 weeks

- 25(OH)D levels
- CBC and CMP
- Symptoms tools
  - MS pain
  - disability
  - fatigue

24 weeks

- 25(OH)D levels
- CBC and CMP
- Symptoms tools
  - MS pain
  - disability
  - fatigue

Performed at central lab and results not disclosed

MS = musculoskeletal
Symptom Tools to Track Worsening of Musculoskeletal Pain

Simple Descriptive Pain Intensity Scale

– Women were asked to report any joint pain in the last 24 h, and if present whether the severity was mild, moderate, severe, or disabling

BPI (Brief Pain Inventory Short Form)

– BPI Intensity: Questions to capture intensity of pain
– BPI Interference: Interference with activity due to pain
Symptom Tools to Track Worsening of Disability and Fatigue

• Worsening of Disability from Musculoskeletal Pain
  – HAQ II (Health Assessment Questionnaire)
    • Measures degree of difficulty with common activities
    • A higher score indicates greater disability
    • Change of 0.25 clinically meaningful

• Worsening of Fatigue
  – BFI (Brief Fatigue Inventory)
    • Consists of questions related to intensity of fatigue and impact of fatigue on common activities
Trial Endpoints

• Primary endpoints:
  – Protocol defined: Incidence of a musculoskeletal event – (worsening of pain using Simple Descriptive Pain Intensity Scale, disability using HAQ II, or discontinuation of letrozole due to pain) at 6 months
  – Primary endpoint using quantitative BPI (instead of Simple Descriptive Pain Intensity Scale)

• Secondary endpoints:
  – Incidence of a QOL event (a musculoskeletal event or worsening of fatigue) at 6 months
  – Safety of 30,000 IU weekly vitamin D3 for 6 months
RESULTS
# Demographic and Treatment Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo N = 80</th>
<th>Vit D3 N = 80</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td>62</td>
<td>61</td>
<td>0.71</td>
</tr>
<tr>
<td>Race: Caucasians</td>
<td>75</td>
<td>77</td>
<td>0.56</td>
</tr>
<tr>
<td>Median BMI, Kg/m²</td>
<td>29.6</td>
<td>29.9</td>
<td>0.92</td>
</tr>
<tr>
<td>Median 25(OH)D at Baseline, ng/ml</td>
<td>25.1</td>
<td>22.5</td>
<td>0.29</td>
</tr>
<tr>
<td>Adjuvant Chemotherapy</td>
<td>45</td>
<td>41</td>
<td>0.63</td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>49</td>
<td>48</td>
<td>0.74</td>
</tr>
</tbody>
</table>
Serum 25OHD Levels at 24 weeks (y-axis) as a Function of Baseline Level (x-axis)

- **Vitamin D arm**
- **Placebo arm**

87 ng/ml

Serum 25OHD Level at Baseline, ng/ml
Median 25OHD Levels Over Time

Median values
Interquartile and total ranges

Placebo  VitD

Baseline  12 wks  24 wks

25(OH)D Level, ng/ml

Median 25OHD Levels

P=0.001  P=0.001

24 wks

12 wks

P=0.001
Compliance and Adverse Events

- 13 subjects did not complete the study for reasons unrelated to study agents and/or musculoskeletal symptoms
- This resulted in 147 evaluable subjects for efficacy analysis
- One subject in the placebo arm developed mild hypercalcemia. No other serious adverse events
- Three subjects, all in the placebo arm, discontinued early due to musculoskeletal adverse events
Primary Endpoint (Protocol Defined): Incidence of a MS Event Using Simple Descriptive Pain Intensity Scale*

*Worsening pain (Simple Descriptive Pain Intensity Scale), worsening disability (HAQ II), or discontinuation of letrozole due to musculoskeletal pain
Primary Endpoint: Incidence of a MS Event Using Brief Pain Inventory (BPI)*

*Worsening pain (Brief Pain Inventory, + 1 point), worsening disability (HAQ II + 0.25), or discontinuation of AI due to musculoskeletal pain
Secondary Endpoint: Incidence of an Adverse QOL Event: A Musculoskeletal Event + Worsening of Fatigue

Frequency of QOL event, %

Placebo arm: 72%
VitD3 arm: 42%
P= <0.001
Conclusions

• Six months of vitamin D3, 30,000 IU/week
  – Is safe in women starting an aromatase inhibitor for adjuvant treatment of breast cancer
  – Is associated with less worsening of AI-related musculoskeletal symptoms
  – Is associated with fewer overall adverse quality of life events
Thanks to All Who Helped with the Trial

The Oncologists at Wichita
The Investigational Pharmacists
The Study Coordinators
Jennifer Nydegger
Tracy Hartup
Amanda Brandt

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BTR Group, Inc. (James Grote, M.D.)
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