SURVIVAL BENEFITS WITH ACTIVE VITAMIN D THERAPY

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Timeline of various treatments for CKD-MBD

1970s
Aluminum
Calcium acetate
Calcium carbonate

1980s
Lanthanum carbonate
Sevelamer hydrochloride

1990s
Magnesium-based compounds*
Trivalent iron compounds*
Niacin (inhibitors of intestinal mucosal phosphate transport)*

2000s
Calcitriol
Doxercalciferol
Paricalcitol
22-oxacalcitriol**
1 alpha-hydroxyvitamin D3**


*Not approved as phosphate binder
**Not approved in the US
<table>
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<th>Treatment</th>
<th>Comparator</th>
<th>Design</th>
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<td>calcitriol</td>
<td>Baseline Cox models; as-treated analyses.</td>
<td>As treated analysis (not ITT). Selection bias and residual confounding.</td>
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<td>Selection bias and residual confounding.</td>
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<td>Tentori 2006</td>
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<td>no treatment; each other</td>
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<td>Selection bias and residual confounding.</td>
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<tr>
<td>Melamed 2006</td>
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<td>no treatment</td>
<td>Baseline and time-dependent Cox models.</td>
<td>Selection bias and residual confounding.</td>
</tr>
<tr>
<td>Naves-Diaz 2008</td>
<td>oral calcitriol or alfacalcidol</td>
<td>no treatment</td>
<td>Time-dependent Cox models. Used propensity scores.</td>
<td>Selection bias and residual confounding.</td>
</tr>
<tr>
<td>Shinaberger 2008</td>
<td>paricalcitol</td>
<td>no treatment</td>
<td>Baseline Cox models.</td>
<td>Selection bias and residual confounding.</td>
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<tr>
<td>Tentori 2009</td>
<td>calcitriol, paricalcitol or doxercalciferol</td>
<td>no treatment; each other</td>
<td>Baseline and time-varying Cox models, MSM, IV.</td>
<td>Appropriateness of IV questionable.</td>
</tr>
</tbody>
</table>
Survival of Patients Undergoing Hemodialysis with Paricalcitol or Calcitriol Therapy

Ming Teng, M.D., Myles Wolf, M.D., M.M.Sc., Edmund Lowrie, M.D., Norma Orlohm, Ph.D., J. Michael Lazarus, M.D., and Ravi Thadhani, M.D., M.P.H.

BACKGROUND

elevated calcium and phosphorus levels after therapy with injectable vitamin D for secondary hyperparathyroidism may accelerate vascular disease and hasten death in patients undergoing long-term hemodialysis. Paricalcitol, a new vitamin D analogue, appears to lessen the elevations in serum calcium and phosphorus levels, as compared with calcitriol, the standard form of injectable vitamin D.

METHODS

We conducted a historical cohort study to compare the 36-month survival rate among patients undergoing long-term hemodialysis who started to receive treatment with paricalcitol (iable 29,021 patients) or calcitriol (38,178 patients) between 1995 and 2001. Crude and adjusted survival rates were calculated and stratified analyses were performed. A subgroup of 16,483 patients who switched regimens was also evaluated.

RESULTS

The mortality rate among patients receiving paricalcitol was 3417 per 19,931 person-years (0.180 per person-year), as compared with 6805 per 30,471 person-years (0.223 per person-year) among those receiving calcitriol (P<0.001). The difference in survival was significant at 12 months and increased with time (P<0.001). In the adjusted analysis, the mortality rate was 16 percent lower (95 percent confidence interval, 10 to 21 percent) among paricalcitol-treated patients than among calcitriol-treated patients. A significant survival benefit was evident in 28 of 42 strata examined, and in no stratum was calcitriol favored. At 12 months, calcium and phosphorus levels had increased by 6.7 and 11.9 percent, respectively, in the paricalcitol group, as compared with 8.2 and 13.9 percent, respectively, in the calcitriol group (P<0.001). The two-year survival rate among patients who switched from calcitriol to paricalcitol was 75 percent, as compared with 64 percent among those who switched from paricalcitol to calcitriol (P<0.004).

CONCLUSIONS

Patients who receive paricalcitol while undergoing long-term hemodialysis appear to have a significant survival advantage over those who receive calcitriol. A prospective, randomized study is critical to confirm these findings.
Paricalcitol vs. Calcitriol in ESRD

- 67,399 prevalent ESRD patients from 1999 to 2001
- Paricalcitol vs. Calcitriol
- Follow-up maximum 36 months
- Outcome: All-cause deaths
- Patients censored when switching treatment ("as-treated analysis")
- Patients switching treatment analyzed separately
- Baseline Cox models

Paricalcitol vs. Calcitriol in ESRD

Paricalcitol vs. Calcitriol in ESRD\(^1\): Questions It Left Open

- Did not examine vitamin D vs. no vitamin D
- Unclear if observed advantage of paricalcitol present when compared to agents other than calcitriol
- Unclear if findings can be extended to non-ESRD populations
- Baseline Cox models do not account for temporal changes in covariates
- As-treated analysis vs. Intention-to-Treat (ITT)
- No dose-response effect examined
- Potential for selection bias
- Potential for residual confounding

\(^1\)Teng et al, N England J Med 2003
Vitamin D vs. no Vitamin D in ESRD

Vitamin D vs. no Vitamin D in ESRD

- 51,037 prevalent ESRD patients from 1996 to 1999
- Paricalcitol or Calcitriol vs. No treatment
- Follow-up maximum 24 months
- Outcome: All-cause deaths
- Intention-to-Treat analyses
- Time-dependent Cox models (primary)
- Marginal structural models, facility-level matching (secondary)

Teng et al, J Am Soc Nephrol 2005
Vitamin D vs. no Vitamin D in ESRD

Results

- Adjusted 2-y survival advantage of 20% for IV vitamin D use
- Benefit of IV vitamin D use seen in most strata, even in patients with low iPTH and elevated Ca and P

Teng et al, J Am Soc Nephrol 2005
Associated Mortality Risk by Level of Serum P, Ca, and PTH in Patients on Hemodialysis With and Without IV Vitamin D Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ca (mg/dL)</th>
<th>Hazard Ratio</th>
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<tr>
<td></td>
<td>≤8.1</td>
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<tr>
<td></td>
<td>8.2-8.4</td>
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<tr>
<td></td>
<td>8.5-8.7</td>
<td></td>
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<tr>
<td></td>
<td>8.8-9.1</td>
<td></td>
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<tr>
<td></td>
<td>&gt;9.1</td>
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<tr>
<td>P (mg/dL)</td>
<td>≤4.2</td>
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<tr>
<td></td>
<td>4.3-4.9</td>
<td></td>
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<tr>
<td></td>
<td>5.0-5.5</td>
<td></td>
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<tr>
<td></td>
<td>5.6-6.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;6.4</td>
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<tr>
<td>PTH (pg/mL)</td>
<td>≤96.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>96.8-173.9</td>
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<tr>
<td></td>
<td>174.0-271.6</td>
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<tr>
<td></td>
<td>271.7-443.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;443.2</td>
<td></td>
</tr>
</tbody>
</table>

Favors Vitamin D | Hazards Ratio
Favors No Vitamin D

Paricalcitol vs. Calcitriol in ESRD\(^1\): Questions Answered

- Did not examine vitamin D vs. no vitamin D
- Unclear if observed advantage of paricalcitol present when compared to other agents
- Unclear if findings can be extended to non-ESRD populations
- Baseline Cox models do not account for temporal changes in covariates
- As-treated analysis vs. Intention-to-Treat (ITT)
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- Potential for selection bias
- Potential for residual confounding

\(^1\)Teng et al, NEJM 2003
Outcomes Associated with Different Types of Active Vitamin D

- 14,586 prevalent ESRD patients from 1999 to 2004
- Paricalcitol vs. Doxercalciferol vs. Calcitriol vs. No treatment
- Outcome: All-cause and cardiovascular deaths
- As Treated and Intention-to-Treat analyses
- Baseline and Time-dependent Cox models

Outcomes associated with different types of Active Vitamin D

- **Unadjusted mortality** was identical in patients on doxercalciferol and paricalcitol and higher in patients on calcitriol.
- **Adjusted mortality** was identical in the three vitamin D treated arms.
- **Adjusted mortality** was higher for patients who did not receive vitamin D vs. those who did.

*Calcitriol: n=3212
Paricalcitol: n=2087
Doxercalciferol: n=2432*

*p<0.001*

Comparing Teng 2003 with Tentori 2006

- **Teng 2003**
  - Advantages
    - Much larger sample size
  - Disadvantages
    - Used only baseline Cox models
    - Used as-treated analysis

- **Tentori 2006**
  - Advantages
    - Used time-dependent Cox models
    - Used intention-to-treat analysis
  - Disadvantages
    - Smaller sample size

Differences could also be due to other factors:
- Different population
- Different era
Paricalcitol vs. Calcitriol in ESRD¹: Questions Answered

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- Potential for residual confounding

¹Teng et al, NEJM 2003
Vitamin D vs. no Vitamin D: Dose-Response Effect

- 58,058 prevalent ESRD patients from 2001 to 2003
- Paricalcitol (different doses) vs. No treatment
- Follow-up maximum 24 months
- Outcome: All-cause deaths
- As-treated analyses
- Baseline and Time-dependent Cox models

Vitamin D vs. no Vitamin D: Dose-Effect Relationship

Did NOT Receive Paricalcitol

Received Paricalcitol

All-Cause Death Hazard Ratio

Administered Paricalcitol Dose (µg/week)

Vitamin D vs. no Vitamin D: Dose-Effect Relationship

- 34,307 prevalent ESRD patients from 2001
- Paricalcitol index = weekly paricalcitol dose (mcg/week)/PTH (pg/ml) *1000
- Follow-up maximum 30 months
- Outcome: All-cause deaths
- As-treated analyses
- Baseline Cox models

Shinaberger et al, CJASN 2008
Vitamin D Dose-Effect: The Role of PTH

Shinaberger et al, CJASN 2008
Paricalcitol vs. Calcitriol in ESRD\textsuperscript{1}: Questions Answered

- Did not examine vitamin D vs. no vitamin D
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- Unclear if findings can be extended to non-ESRD populations
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- No dose-response effect examined
- Potential for selection bias
- Potential for residual confounding

\textsuperscript{1}Teng et al, NEJM 2003
Outcomes associated with VDRA use in non-ESRD populations

- 520 male US veterans between 1990-2005
- Oral calcitriol vs. no treatment
- Follow-up median 2 years
- Outcomes:
  - All-cause pre-dialysis mortality
  - ESRD incidence
- Fixed-covariate (baseline) Cox models
- Intention-to-treat analyses

Kovesdy et al., Arch Intern Med, 2008
Analysis time (years)

Proportion of patients alive

No Calcitriol
Calcitriol

p=0.0005

Kovesdy et al., Arch Intern Med, 2008
Paricalcitol vs. Calcitriol in ESRD\textsuperscript{1}: Questions Answered

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\textsuperscript{1}Teng et al, NEJM 2003
Vitamin D and Residual Confounding

- Methods applied by previous studies cannot address this
- An Instrumental Variable (IV) can be used in observational studies to address residual confounding
What Is an Instrumental Variable?

IV → VDRA → Mortality

Confounder
Conditions for a *Valid* Instrumental Variable

1. IV affects VDRA
2. IV affects outcome (mortality) only through VDRA
3. IV and outcome (mortality) share no common causes
Examples of Valid Instrumental Variables

- **Randomized treatment assignment**
  - Unsuccessful randomization and non-compliance with assigned treatment can render IV invalid

- **Mendelian randomization (natural experiments)**

- **Instruments not assigned by researchers (or by nature)**
  - Always open to skepticism regarding their validity
Vitamin D and mortality in DOPPS

- 38,066 prevalent ESRD patients from 1996 onward (DOPPS I through III)
- Any Vitamin D vs. No treatment; also compared different agents
- Outcome: All-cause deaths
- Follow-up median 1.3 years
- As-treated and ITT analyses
- Baseline and Time-dependent Cox, MSM and IV methods
- IV was the adjusted percentage of Vitamin D administration in any given HD unit

Tentori et al, Nephrol Dial Transplant 2009
Vitamin D and mortality in DOPPS

- Vitamin D associated with lower mortality in time-varying Cox [RR = 0.92 (0.87–0.96)], and in baseline [(RR =0.84 (0.78–0.98)] and time-varying MSM [RR = 0.78 (0.73–0.84)]

- No association in adjusted baseline Cox [RR =0.98 (0.93–1.02)]

- No association in IV models [RR for facilities in 75th versus 25th percentile of vitamin D prescription: 0.99 (0.94–1.04)]

- No difference in paricalcitol vs. calcitriol or in doxercalciferol vs. calcitriol.
How an Instrumental Variable Can Be Invalid

- Is it possible that HD units with a higher percentage of VDRA prescriptions provide different care in other ways?
The Path of Discovery

Observation → Confirmation → Biologic plausibility
Cellular Action of Calcitriol and the Vitamin D Receptor

VDR=vitamin D receptor; RXR = retinoid x receptor; VDRE = vitamin D response element

Myocardial contractility
LVH
Myocardial fibrosis
Valvular calcification

Vasodilatation
Vascular calcification
Insulin sensitivity
Lipid metabolism
Bone marrow fibrosis
Erythrophoiesis

Immune function

Cardiac
Vascular
Metabolic
Hematologic
Immunologic

Cardiac hypertrophy,
HTN

Renin-angiotensin
Atrial natriuretic peptide
Endothelin

Atherosclerosis
Vascular calcification

Matrix GLA protein
Runx2/Cbfa1
BMP2
BMP4
Type 1 collagen

Platelet aggregation
Tissue factor
Antithrombin III
Thrombomodulin

Thrombosis

Cathelicidine

Hypercalcemia
Hyperphosphatemia

Tumorigenesis

VDR activation

PTH

Kovesdy & Kalantar-Zadeh, Kidney Int 2008
Dose-dependent vascular calcification with VDRA
The Path of Discovery

Observation ➔ Confirmation ➔ Biologic plausibility ➔ Experimentation

Cannot prove causality
Prospective Mortality Trial with Paricalcitol and Calcitriol

• Phase 4, prospective, randomized, active-controlled, double-blind, double-dummy, multicenter study to evaluate the survival benefits of IV paricalcitol compared with IV calcitriol in Stage 5 CKD patients on HD

• 2200 patients to receive paricalcitol or calcitriol (1:1)
• Enrollment initiated July 2003 at 53 US sites. By 2006, only 21 active sites remained and only 220 subjects (10% of target) randomized
• Study terminated in June 2006

Fishbane S et al. World Congress of Nephrology 2009. M642
Other outcome trials with Vitamin D

• No other trial in progress examining mortality as outcome

• Multiple trials examining surrogate outcomes
  – LVH (NCT00796679, NCT00497146)
  – CAC (NCT00752102)
  – Inflammation (NCT01012414, NCT00656032, NCT00294866)
  – Proteinuria (VITAL, others)
What is the optimal dose of Vitamin D?

- Current methods for monitoring effects (PTH, Ca, PO$_4$) of active vitamin D may not be adequate when considering clinical outcomes

- Possible solutions
  - Restrict VDRA administration to low doses
    - Prevents adverse effects
    - But: may not offer maximum benefit
  - Use alternative means to monitor biologic effects: Tumor necrosis factor-α Converting Enzyme (TACE)$^1$

$^1$Dusso et al, J Steroid Biochem Mol Biol 2010
Vitamin D and Mortality: Summary

- Large amount of observational data suggests lowering of mortality
- Some observational data suggests benefits on renal function
- Complex biological actions
  - Positive
  - Negative
- Conclusions hindered by limited clinical trial data
  - Surrogate end point data (proteinuria) promising
- Optimal implementation hampered by limited ability to determine optimal dose