Chemopreventive efficacy of the selective Cox-2 inhibitor, celecoxib, is predicted by expression of Cox-2 and 15-PGDH in adenomas removed during pre-treatment colonoscopy

*contributed equally
Arachidonic Acid

→

PGH₂

→

Prostaglandin Synthases

→

PGD₂, PGI₂, PGF₂α, TXA₂

PGE₂

→


Prostaglandins

Prostaglandin Receptors

Signaling Pathways

Target Genes

Biological Activities

PPARδ

Beta-Catenin

Transcriptional Activity

EGF-R

PI3K/AKT

Cyclin D₁

MMP7

Bcl-2

VEGF

Growth

Migration/Invasion

Anti-Apoptosis

Angiogenesis

NEJM 356:2195, 2007
2035 men and women age 30 or older with large or multiple colorectal adenomas

Randomized to:

- celecoxib 200mg bid N=679
- celecoxib 400mg bid N=685
- placebo bid N=671

*stratified by low-dose aspirin use and clinical center
celecoxib 200mg bid  
N=679

celecoxib 400mg bid  
N=685

placebo bid  
N=671

Core Study: 3 years medication use

Colonoscopy at 1 and 3 years after randomization

Primary Endpoint:
adenoma detected at any post-randomization colonoscopy
Cumulative results: adenoma endpoint

- Placebo bid: 60.7% → 38%
- Celecoxib 200 mg bid: 43.2% → 37.5%
- Celecoxib 400 mg bid: 17.2% → 63%

% of patients with adenomas

% of patients with advanced adenomas
Do pre-treatment adenoma Cox-2 or 15-PGDH levels predict risk of disease recurrence response to celecoxib?

Pre-treatment adenomas removed during study colonoscopies

Cox-2
- low
- high

15-PGDH
- present
- absent

Estimated adenoma PGE$_2$ levels:

<table>
<thead>
<tr>
<th>15-PGDH</th>
<th>Cox-2 High</th>
<th>Cox-2 Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>present</td>
<td>High PGE$_2$</td>
<td>Low PGE$_2$</td>
</tr>
<tr>
<td>absent</td>
<td>High PGE$_2$</td>
<td>High PGE$_2$</td>
</tr>
</tbody>
</table>
Pre-treatment Cox-2 level is not prognostic for adenoma recurrence.

Higher Cox-2 levels predict greater response to celecoxib.

RR 0.64, p < 0.0001, 30.5%

RR 0.37, p = 0.0001, 51.6%

% of patients with adenomas, 3-yr cumulative

Placebo

Celecoxib

Low COX-2

High COX-2
Baseline adenoma marker expression

Total Subjects Randomized N = 2035

Subjects with Endpoints Determined N = 1822

Subjects with Biomarkers Determined N = 1295

Placebo
N = 440
88.2% 15-PGDH absent
6.4% Cox-2 high
90.0% PGE₂ high

Celecoxib
200 mg bid or 400 mg bid
N = 855
89.8% 15-PGDH absent
9.1% Cox-2 high
91.8% PGE₂ high
Pre-Treatment 15-PGDH presence is not prognostic for adenoma recurrence but does predict response to celecoxib

- RR 0.73, p=0.15 ↓ 17.7%
- RR 0.60, p<0.0001 ↓ 33.8%

Bar chart showing:
- % of patients with adenomas, 3-yr cumulative,
- Placebo and Celecoxib conditions.
Estimated Adenoma PGE$_2$ levels yields results consistent with the 15-PGDH analysis.

- RR 0.95, p=0.82 \(\downarrow\) 0%
- RR 0.59, p<0.0001 \(\downarrow\) 34.9%

% of patients with adenomas, 3-yr cumulative

Placebo
Celecoxib
Conclusions

- Patients with higher Cox-2 levels in baseline adenomas achieve the greater response to celecoxib for adenoma prevention (52% reduction vs. 30.5% reduction)

- Subjects whose baseline adenomas retain 15-PGDH expression do not show significant reduction in adenoma recurrence with celecoxib

- A combined biomarker of both Cox-2 and 15-PGDH expression yields results driven by the 15-PGDH alone analysis
Conclusions

- These results suggest that PGE$_2$ is a significant driver of tumorigenesis in the colorectum for many but not all adenoma patients.
Collaborators

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