Rofecoxib did not slow progression of dementia in patients with established Alzheimer’s disease


Clinical impact ratings Neurology ★★★★★ Geriatrics ★★★★★

In patients with established Alzheimer’s disease (AD), does rofecoxib slow progression of dementia?

**METHODS**

**Design:** randomised controlled trial.

**Allocation:** (concealed*).†

**Blinding:** blinded [patients, clinicians, data collectors, outcome assessors, and data analysts]*

**Follow up period:** 12 months.

**Setting:** 31 sites in the US.

**Patients:** 692 patients who were ≥50 years of age (mean age 76 y, 53% women), met standard research criteria for possible or probable AD, had mild or moderate dementia (Mini-Mental State Examination [MMSE] score 14–26 and a Clinical Dementia Rating [CDR] global score no worse than moderate dementia), and had a reliable informant or caregiver to accompany them to clinic visits and ensure that they took the test medication. Exclusion criteria: history of angina or congestive heart failure with symptoms at rest; uncontrolled hypertension; myocardial infarction, coronary artery bypass, angioplasty, or stent replacement in the previous year; stroke, multiple lacunar infarcts, or transient ischaemic events in the previous 2 years; gastrointestinal bleeding in the previous 3 months; and long term use of non-steroidal anti-inflammatory drugs (>7 d/mo in the previous 2 mo).

**Intervention:** rofecoxib, 25 mg, once daily (n = 346) or placebo (n = 346) for 12 months.

**Outcomes:** change in scores on the cognitive subscale of the AD Assessment Scale (ADAS-cog) and the Clinician’s Interview Based Impression of Change with caregiver input (CIBIC+).

**Patient follow up:** 648 patients (94%) were included in the intention to treat analysis (ie, patients with baseline data and >1 post-randomisation measure up to 12 months).

*See glossary.
†Information provided by author.

**MAIN RESULTS**

Patients in the rofecoxib and placebo groups did not differ for mean change in ADAS-cog and CIBIC+ scores from baseline to 12 months (table).

**CONCLUSION**

In patients with established Alzheimer’s disease, 12 months of rofecoxib did not slow the progression of dementia compared with placebo.

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**Rofecoxib v placebo in patients with Alzheimer’s disease**

<table>
<thead>
<tr>
<th>Outcomes (mean change from baseline to 12 mo)</th>
<th>Rofecoxib</th>
<th>Placebo</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-cog†</td>
<td>4.84</td>
<td>5.44</td>
<td>−0.60 (−1.90 to 0.70)</td>
</tr>
<tr>
<td>CIBIC+‡</td>
<td>0.90</td>
<td>0.87</td>
<td>0.03 (−0.12 to 0.18)</td>
</tr>
</tbody>
</table>

*Higher change scores indicate greater declines regardless of sign.
†ADAS-cog = AD Assessment Scale – cognitive subscale. Total scores range from 0–70 errors.
‡CIBIC+ = Clinician’s Interview Based Impression of Change with caregiver input, a 7 point scale ranging from 1 = very much improved to 7 = very much worse. Reported values are change from a default score of 4 at baseline (no change); increase of approximately 1 point corresponds to “minimal worsening.”

**Commentary**

Should patients with AD be treated with non-steroidal anti-inflammatory drugs (NSAIDS)? The study by Reines et al adds to the evidence suggesting that selective cyclooxygenase (COX)-2 inhibition with rofecoxib does not modify the course of mild to moderate AD, at least over a 12 month period. Similar negative results were found in a previous randomised trial comparing rofecoxib, naproxen, and placebo, which suggests that non-selective NSAIDS also do not slow cognitive decline.1 Although most adverse events were not severe, gastrointestinal adverse effects were higher in the treatment groups than in the placebo groups. These negative trials occurred despite compelling animal data that nonsteroidal anti-inflammatory drugs might contribute to the pathophysiology of AD and epidemiological data that NSAIDS might modify the course of clinical progression.

This study will not be the last we hear of anti-inflammatory drugs for AD. Longer duration trials (>2 years) may be required to show meaningful benefits, although this seems unlikely. Different patient groups need further attention, specifically patients with severe dementia and those at risk of dementia. Large trials are under way to see whether prophylactic NSAID or COX-2 treatment in at risk elderly patients will alter the incidence of AD.

In the absence of clear benefits, however, a treatment with greater risk of adverse effects (including increased admissions for heart failure†?) and cost cannot be justified. Until further studies are available, there is no evidence to support the routine use of NSAIDS in the treatment or prevention of AD.

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