Effects of Rofecoxib or Naproxen vs Placebo on Alzheimer Disease Progression
A Randomized Controlled Trial

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Context Laboratory evidence that inflammatory mechanisms contribute to neuronal injury in Alzheimer disease (AD), along with epidemiological evidence, suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) may favorably influence the course of the disease.

Objective To determine whether treatment with a selective cyclooxygenase (COX) -2 inhibitor (rofecoxib) or a traditional nonselective NSAID (naproxen) slows cognitive decline in patients with mild-to-moderate AD.

Design Multicenter, randomized, double-blind, placebo-controlled, parallel group trial, with 1-year exposure to study medications.

Setting Forty ambulatory treatment centers affiliated with the Alzheimer’s Disease Cooperative Study consortium.

Participants Participants with mild-to-moderate AD (Mini-Mental State Examination score of 13-26) were recruited from December 1999 to November 2000 using clinic populations, referrals from community physicians, and local advertising. Stable use of cholinesterase inhibitors, estrogen, low-dose aspirin, and vitamin E was allowed. Participants with inflammatory diseases that might respond to the study medications were excluded. Of 474 participants screened, 351 were enrolled.

Interventions Once-daily rofecoxib, 25 mg, or twice-daily naproxen sodium, 220 mg, or placebo.

Main Outcome Measures The primary outcome measure was the 1-year change in the Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) subscale score. Secondary outcome measures included the Clinical Dementia Rating scale sum-of-boxes, the Neuropsychiatric Inventory, the Quality of Life-AD, and the time to attainment of significant end points (4-point decline from baseline ADAS-Cog score, 1-step worsening on the global Clinical Dementia Rating scale, 15-point decline on the ADCS activities of daily living inventory, institutionalization, or death).

Results The 1-year mean (SD) change in ADAS-Cog scores in participants treated with naproxen (5.8 [8.0]) or rofecoxib (7.6 [7.7]) was not significantly different from the change in participants treated with placebo (5.7 [8.2]). Results of secondary analyses showed no consistent benefit of either treatment. Fatigue, dizziness, and hypertension were more commonly reported in the active drug groups, and more serious adverse events were found in the active treatment group than in the placebo group.

Conclusion The results of this study indicate that rofecoxib or low-dose naproxen does not slow cognitive decline in patients with mild-to-moderate AD.

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(NSAID) efficacy in the treatment of AD have been encouraging. One report indicated a stabilizing effect of indomethacin treatment for 6 months, while a follow-up study showed a trend toward benefit with diclofenac treatment for 25 weeks. Neither study showed conclusive results, and the patients with AD showed poor tolerability of both drugs. Larger studies with better tolerated treatment regimens, such as low-dose prednisone for 1 year and hydroxychloroquine for 18 months, failed to demonstrate benefit in the treatment of AD.

Recent studies have provided strong support for the testing of efficacy of NSAIDs in the prevention of AD. A large epidemiologic study using computerized medical records to accurately indicate drug use corroborates earlier work, with evidence that use of NSAIDs sharply reduces AD risk. In transgenic mice with AD-type amyloid deposition, the NSAID ibuprofen reduced brain inflammation and levels of soluble and insoluble amyloid peptide, and improved behavior.

In this trial, we tested the hypothesis that NSAID treatment would slow the rate of cognitive decline in participants with mild-to-moderate AD. Selection of treatment regimens was based on consideration of the appropriate target in AD brain, as well as medication tolerability. Results of studies in cell culture systems, rodents, and humans indicate that neuronal up-regulation of cyclooxygenase (COX) 2 may contribute to neurodegeneration in AD. However, the epidemiologic data support the efficacy of long-term use of low doses of nonselective NSAIDs that inhibit COX-1 and COX-2, and microglial COX-1 may be an important target. Long-term treatment with full doses of nonselective NSAIDs has been associated with a substantial risk of serious gastrointestinal tract toxicity. Therefore, we used a standard dose of the selective COX-2 inhibitor rofecoxib and a low-dose of the nonselective NSAID naproxen. We chose a treatment period of 1 year based on evidence from a pilot study of NSAID efficacy with short-term treatment and the concern about the risk of long-term exposure in individuals with AD.

**METHODS**

**Study Design**

The study used a randomized, double-blind, 3-group parallel design to compare rofecoxib or naproxen with placebo. The treatment period was 12 months, followed by a 2-month washout. Forty ambulatory treatment centers affiliated with the Alzheimer’s Disease Cooperative Study (ADCS) consortium participated in this trial after obtaining approval from their local institutional review boards. Written informed consent was obtained from participants and/or legally authorized representatives, according to local guidelines.

Individuals with probable AD recruited from December 1999 to November 2000 using clinic populations, referrals from community physicians, and local advertising were eligible if they did not have comorbid conditions that increased the risk of adverse events associated with NSAID treatment (hypersensitivity to aspirin or NSAIDs, active peptic ulcer disease within 5 years, renal insufficiency, diabetes, congestive heart failure, or bleeding disorder). Individuals were excluded if they had comorbid conditions that might respond to NSAIDs (eg, inflammatory arthritis). Individual visits were excluded if within the prior 2 months they had regularly used anti-inflammatory medications (aspirin at a daily dose $\leq 325$ mg was allowed), neuroleptics, antidepressants, sedatives, anti-Parkinsonian medications, or any investigational treatment for AD. Inclusion criteria included age older than 50 years and Mini-Mental State Examination (MMSE) score within the range of 13 to 26. Stable use of cholinesterase inhibitors was allowed.

Rofecoxib tablets, 25 mg, were overencapsulated to allow preparation of an identical placebo capsule. Naproxen sodium tablets, 220 mg, and identical placebo tablets were supplied by Bayer Consumer, Inc (Morristown, NJ). Each participant received 2 bottles of study medication with coded labels at baseline and at the 3-, 6-, and 9-month visits: 1 bottle containing rofecoxib or identical placebo capsules, to be taken once daily; and 1 bottle of naproxen or identical placebo capsules, to be taken twice daily.

The randomization process used a permuted block design with block size of 3 stratified by site. The randomization sequence was generated by the ADCS data center. Scratch-off codebreakers were used so that instances of unblinding would be documented; all codebreakers were collected at the end of the trial. Adequacy of masking was assessed by questionnaires completed by participants, caregivers, psychometrists, and site investigators.

Safety assessments, including vital signs, physical examination, urinalysis, and hematology and chemistry blood tests, were performed at each visit. Cognitive and behavioral assessments were performed at baseline and at months 1, 3, 6, 9, 12, and 14.

**Outcome Measures**

The primary outcome measure for this trial was the 1-year change score on the Alzheimer Disease Assessment Scale-Cognitive (ADAS–Cog) subscale, an instrument that evaluates memory, attention, reasoning, language, orientation, and praxis. We considered a significant benefit in the active group to be a 50% reduction in cognitive decline as indicated by change in ADAS-Cog score compared with the placebo group. Data from a small pilot study have supported the hypothesis that an effect of this magnitude might be seen, and we considered that a smaller effect might not justify the risk of long-term NSAID therapy in the AD participants. Using longitudinal ADAS-Cog data from an earlier multicenter trial, we estimated that 100 participants were required in each treatment group (naproxen, rofecoxib, and placebo) for a power of 0.8. An overall drop-out rate of 20% was anticipated. Since we ex-
expected more drop-outs from adverse drug effects in the active drug groups, fewer participants were randomly assigned to the placebo group (participants were randomly assigned using a ratio of 1.2 [naproxen]:1.2 [rofecoxib]: 1.1 [placebo]).

Secondary outcome measures included the Clinical Dementia Rating sum-of-boxes (CDR-SOB),18 Alzheimer’s Disease Cooperative Study activities of daily living (ADCS-ADL) scale,20 the Neuropsychiatric Inventory (NPI),21 the Quality of Life-AD (QOL-AD),22 and the time to attainment of significant end points (4-point decline from baseline ADAS-Cog score, 1-step worsening on the global CDR scale, 15-point decline on the ADCS-ADL, institutionalization, or death).

**Statistical Analysis**

The primary analysis was a comparison of the change in ADAS-Cog score between the naproxen and rofecoxib groups and the placebo group using analysis of covariance (ANCOVA), with the baseline ADAS-Cog score as a covariate. The statistical plan included assessment of the treatment groups for significant imbalance in age, sex, or apolipoprotein E genotype that might influence outcome; if an imbalance was present (P<.15) and the factor influenced ADAS-Cog change scores (P<.10), it would be included in the ANCOVA model.

The primary analysis was conducted on an intent-to-treat basis (ie, including all randomized participants). Because AD is a disease of progressive cognitive deterioration, the protocol specified an alternative imputation scheme rather than last-observation-carried-forward (LOCF) analysis. (LOCF analysis would overestimate a treatment effect if an excess of dropouts occurred in the active drug group due to adverse effects.) To impute a participant’s missing score at week 52, an estimate of change in ADAS-Cog score was applied to the participant’s last observed score. A linear rate of progression was not assumed. We also conducted secondary analyses of change in ADAS-Cog scores using the LOCF imputation, and an analysis of completers only (ie, those who completed the week 52 visit). In addition, we conducted a longitudinal regression analysis using the method of generalized estimating equations.23 For this analysis, a pair-wise comparison of the naproxen group vs the placebo group and the rofecoxib group vs the placebo group, the outcome was the ADAS-Cog score clustered by the baseline, 3-, 6-, 9-, and 12-month visits.

A planned secondary analysis of time to reach clinically significant end points was performed using a Cox proportional hazards model. Intent-to-treat analysis of secondary measures were conducted using both the slope imputation strategy described above and LOCF for missing week 52 values. No interim analysis was performed. Statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC).

**RESULTS**

The flow of participants through the study protocol is shown in Figure 1. From a total of 474 participants screened, 351 met the study criteria and were randomly assigned to 1 of the 3 treatment groups (rofecoxib, naproxen, or placebo). Considering the likelihood that more participants in the active groups would drop out due to adverse effects, more participants were randomly assigned to rofecoxib (n=122) and naproxen (n=118) than to the placebo group (n=111).

The primary outcome measure (change in ADAS-Cog score at week 52) was obtained for study completers: 90 (76%) participants in the naproxen group, 89 (73%) in the rofecoxib group, and 88 (79%) in the placebo group. The predominant reasons for early study discontinuation were caregiver issues (rofecoxib, n=12; naproxen, n=11; and placebo, n=10) and adverse events (rofecoxib, n=14; naproxen, n=11; and placebo, n=9).

The demographic and clinical characteristics of the treatment groups at baseline are shown in Table I. No significant differences were found between the groups on any of the demographic or baseline characteristics. Eighty-seven participants (25%) were using low-dose aspirin during the trial: 33 (27%) in the rofecoxib group, 30 (25%) in the naproxen group, and 24 (22%) in the placebo group. Aspirin use

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did not show a significant effect on ADAS-Cog scores for all groups or for the individual treatment groups.

Baseline characteristics were compared between participants who discontinued early and those who completed the study in the naproxen group, participants who discontinued early had lower mean (SD) MMSE scores (19.6 [3.3] vs 21.0 [3.6]; \( P = .04 \)) using Wilcoxon rank sum test and higher mean (SD) CDR-SOBC scores (7.2 [3.4] vs 6.0 [2.9]; \( P = .26 \)). ADAS-Cog scores for all groups or for the group treated with rofecoxib showed a trend toward greater cognitive decline compared with the other groups. For the comparison of naproxen with placebo, the SE of the difference between change scores was 1.07 (95% confidence interval for the difference in the change scores, \(-0.1 +/- 2.14\)); therefore, it is highly unlikely that naproxen treatment reduces the 1-year decline in ADAS-Cog score by more than 2.04/5.7, or 36%. For the comparison of rofecoxib with placebo, the SE of the difference between change scores was 1.03; a similar calculation indicates it is highly unlikely that rofecoxib reduces the decline in ADAS-Cog score by more than 15%.

When LOCF imputation of the change in ADAS-Cog score was substituted for the primary imputation scheme, the result was similar to the primary analysis (mean [SD] ADAS-Cog change in score in the placebo group, 4.9 [8.2]; rofecoxib group, 5.9 [7.7], \( P = .52 \); and naproxen group, 5.0 [7.9], \( P = .94 \)). Analysis of participants taking study medication who completed the 52-week visit yielded similar results, with no significant difference in rate of decline for the mean (SD) ADAS-Cog score (placebo, 5.3 [8.5], \( n = 79 \); rofecoxib, 6.8 [7.7], \( n = 78 , P = .47 \); naproxen, 5.3 [7.9], \( n = 80 , P = .9 \)).

### Secondary Outcome Measures

The intent-to-treat analysis using the primary imputation scheme for missing values revealed no significant difference in decline for the CDR-SOB scores across all the groups (Table 2). Other analyses, using LOCF imputation or assessing completers only, showed similar results (data not shown). The ADCS-ADL scores showed a trend toward a beneficial effect with use of rofecoxib. However, none of the secondary analyses were adjusted for multiple comparisons because this was not specified in the original protocol. In the slope imputation analysis, use of rofecoxib reduced the decline in ADCS-ADL score by 22% (unadjusted \( P = .09 \)); in the LOCF analysis, use of rofecoxib reduced the decline in ADCS-ADL score by 33% (unadjusted \( P = .04 \)). In an analysis of study completers only, rofecoxib reduced the decline in ADCS-ADL score by 27% (unadjusted \( P = .09 \)). Treatment with rofecoxib or naproxen had no effect on the NPI or QOL-AD scores.

The planned survival analysis considered the time interval from the baseline visit to the first among 5 possible end points: death, institutionalization, increase in global CDR score, 15-point decline on the ADCS-ADL scale, or 4-point decline on the ADAS-Cog scale. A total of 242 subjects (69%) reached at least 1 end point (placebo group, \( n = 78 \) [70%]; naproxen group, \( n = 83 \) [70%]; and rofecoxib, \( n = 81 \) [66%]). Rofecoxib (\( P = .63 \)) or naproxen (\( P = .50 \)) vs placebo did not differ in time to first end point. When time to individual end point...
points was examined, the only significant difference was between the rofecoxib and placebo groups for time to institutionalization, favoring the rofecoxib group (P= .03) (data not shown). However, this analysis was based on a small number of events (7 in the placebo group and 1 in the rofecoxib group), and the P value was not adjusted for multiple comparisons.

**Adverse Events**

Treatment emergent adverse events were grouped into categories for analysis. Naproxen and rofecoxib groups had more frequent adverse event reports (P<.10) (Table 3). Dizziness and fatigue were more common in the active drug groups than in the placebo group, and dry mouth was more common in the naproxen group than the placebo group. New cases of hypertension were reported as adverse events in the active drug groups, but none were reported in the placebo group (naproxen [n=6] vs placebo [n=0], P=.03 and rofecoxib [n=9] vs placebo, P=.004).

In addition to adverse events reported on case report forms, study participants were asked about a list of symptoms that might arise with NSAID treatment. When the proportion of each treatment group reporting new symptoms (not present at baseline) was compared, the difference was significant compared with placebo for dry mouth (10% for naproxen vs 2% for placebo; P=.01) and muscle pain (13% for rofecoxib vs 4% for placebo; P=.03). The percentage of participants with new reports of any gastrointestinal tract symptom did not differ among the treatment groups (37% for naproxen, 31% for rofecoxib, and 30% for placebo).

Despite the cases of hypertension noted above, mean blood pressure did not differ significantly by treatment group. The effects of treatment group on mean (SD) change were minimal for hematocrit (placebo [n=87]:−0.3%[2.2]; naproxen [n=88]: −1.0%[2.2] vs placebo, P=.01; and rofecoxib [n=87]: −1.2%[2.2] vs placebo; P=.05) and for serum creatinine (0.02[0.13] mg/dL or 1.8[11.5] µmol/L, n=88; naproxen [n=87]: 0.02[0.13] mg/dL or 1.8[11.5] µmol/L; vs placebo, P=.90; and rofecoxib [n=84]: 0.08[0.16] mg/dL or 7.1[14.1] µmol/L vs placebo, P=.01).

The total number of serious adverse events in each treatment group, along with number of events within specific categories, did not differ significantly (Table 4).

**Success of Blinding**

The randomization code was broken in 1 instance, based on clinical need for the management of an acute medical problem. Study personnel involved in administering assessment tools were shielded from group assignment data in this instance. The results of questionnaires administered at the month 12 visit indicated that the percentage of participants who believed they were taking active study medication also did not differ significantly across the treatment groups (rofecoxib group, 70%; naproxen group, 74%; and placebo group, 73%; P=.82, Fisher exact test), indicating that blinding was adequately maintained.

At the 12-month visit, the percentage of informants who believed that participants were taking active study medication also did not differ across the participants’ treatment group (52% for rofecoxib group, 51% for naproxen group, and 59% for placebo group; P=.10, Fisher exact test). The differences also were not significant for study coordinators (54% for rofecoxib group, 50% for naproxen group, and 43% for placebo group; P=.52, Fisher exact test) and study physicians (56% for rofecoxib group, 40% for naproxen group, 2823
and 40% for placebo group; \( P = .19 \), Fisher exact test).

**COMMENT**

This is the first large-scale trial, to our knowledge, to determine the efficacy of both nonselective and COX-2 selective NSAIDs in the treatment of AD. The result of the primary intent-to-treat analysis of this trial showed that neither naproxen nor rofecoxib slowed the rate of cognitive decline in comparison with placebo in participants with mild-to-moderate AD. Similar results were obtained when an LOCF analysis was substituted for the primary slope method of imputing missing 12-month data and when the data were analyzed using the generalized estimating equations method. The results of an analysis of study completers (those who were able to complete the trial while still taking study medication) also revealed no beneficial treatment effect of the active study drugs in comparison with placebo. Instead, the rofecoxib group showed a trend toward greater cognitive decline compared with placebo.

In the naproxen group, baseline MMSE and CDR-SOB scores differed between individuals who discontinued study participation early and those who completed the study. This difference raises the possibility that imputation of the data missing from non-completers may have influenced the outcome of the primary analysis. However, the nonsignificant finding of the primary analysis is in agreement with the nonsignificant findings of the LOCF analysis, the completers analysis, the generalized estimating equations regression analysis, and the clinical end points survival analysis, which strongly support its validity.

Secondary analyses of the effect of treatment on a global measure of cognitive decline, behavioral, ADL, and quality of life showed no consistent advantage of either treatment over placebo. Rofecoxib delayed the time to institutionalization, but this result was based on a small number of end points. Adjustment for multiple comparisons would have made this comparison nonsignificant.

In some analyses, there was a trend toward smaller decline in ADL with active treatment, particularly with rofecoxib. The trend toward greater cognitive decline with rofecoxib treatment suggests that the trend toward protection against decline in ADL may be related to an anagletic effect rather than an effect on AD.

Both active treatments were reasonably well tolerated, although participants who dropped out due to adverse events were more commonly from the active drug groups than from the placebo group. Surprisingly, the gastrointestinal tract symptoms were similar in the 3 groups. The small number of serious gastrointestinal tract events (primarily bleeding) in the active drug groups was consistent with expected risks. The occurrence of adverse events likely was reduced by excluding individuals at high risk of NSAID toxicity.

Two important issues must be raised when interpreting the lack of active treatment effect. The first issue concerns selection of drug, dose, and duration of treatment. Naproxen was selected because the epidemiological evidence supports the efficacy of non-selective COX inhibitors, and naproxen has a long half-life (allowing for twice-daily dosing) and is relatively well tolerated. The naproxen dose was low because of concern that full-dose therapy with a nonselective COX inhibitor would be associated with more serious adverse events and a high dropout rate compared with placebo. The nonsignificant results with naproxen could be explained by an insufficient dose; alternatively, other drugs in this same class, such as ibuprofen, may have greater activity in AD mediated by an effect on processing of the amyloid precursor protein. It is also possible that a higher dose is necessary to influence neuronal survival; a high dose of celecoxib, above the standard anti-inflammatory dose, is required to influence neoplastic transformation in the gastrointestinal tract. It is also possible that a period of exposure to anti-inflammatory treatment greater than the 1 year of treatment in this trial is necessary to slow the disease process. Some epidemiological studies of AD prevention suggest that at least 2 years of exposure is necessary to optimally reduce risk of AD.

The second issue concerns the selection of participants. The most compelling epidemiological evidence suggests that long-term exposure to NSAIDs reduces risk of subsequent AD; on the other hand, some studies suggest a stabilizing effect of NSAID therapy in patients with clinically evident disease, supporting the design of the current trial. While COX-2 and other inflammatory mediators are elevated in mild-to-moderate AD brain, it is nonetheless possible that when the disease is clinically apparent, the neuropathology is too advanced to be significantly attenuated by NSAID therapy. The results of this trial do not address the efficacy of NSAIDs in the prevention of AD. A primary prevention trial, in which elderly persons without dementia are randomly assigned to treat-

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**Table 4. Number of Serious Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Naproxen</th>
<th>Rofecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total serious events</td>
<td>15</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Deaths</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal tract event*</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Stroke/transient ischemic attack</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Subdural hematoma</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

*Serious gastrointestinal tract events included 6 cases of gastrointestinal tract bleeding and 1 case of perforated small intestine (the latter occurred in the naproxen group).
ment with an NSAID or placebo, is necessary to test the utility of long-term NSAID therapy in AD risk reduction. Such a trial is now under way. 20 The results of the current study do not support the hypothesis that rofecoxib or naproxen can slow the progression of AD. Considering the risk of serious toxicity, such treatment should not be recommended. In view of evidence from cell culture and animal studies suggesting reduction of β-amyloid generation with other NSAIDs, such as ibuprofen (but not naproxen or selective COX-2 inhibitors), 21 additional treatment trials using other NSAIDs may be warranted. Recommendations regarding risk reduction with long-term NSAID therapy must await the results of a primary prevention trial.

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References

17. Folstein M, Folstein S, Mchugh P. The Mini


The human understanding is no dry light, but receives infusion from the will and affections; whence proceed sciences which may be called “sciences as one would.” For what a man had rather were true he more readily believes. Therefore he rejects difficult things from impatience of research; sober things, because they narrow hope; the deeper things of nature, from superstition; the light of experience, from arrogance and pride; things not commonly believed, out of deference to the opinion of the vulgar. Numberless in short are the ways, and sometimes imperceptible, in which the affections color and infect the understanding.

—Francis Bacon (1561-1626)