A Randomized Trial of High-Dose Compared with Low-Dose Omega-3 Fatty Acids in Severe IgA Nephropathy

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Abstract. Tested was the hypothesis that high-dose omega (ω)-3 fatty acids will be more effective than low-dose ω-3 fatty acids in preserving renal function in patients with severe IgA nephropathy in a randomized, open-label, parallel-group clinical trial. Patients were assigned to receive either high-dose fatty acids (EPA 3.76 g and DHA 2.94 g) or low-dose fatty acids (EPA 1.88 g and DHA 1.47 g), both given daily in a highly purified ethyl ester concentrate (Omacor). Patients were treated for a minimum of 2 yr in the absence of a treatment failure or until study closure (January 2000). Seventy-three patients were enrolled in the trial with two ranges of elevated serum creatinine (SC): 63 patients (86%) with a range of 1.5 to 2.9 mg/dl and 10 patients (14%) with a range of 3.0 to 4.9 mg/dl. The primary end point, within-patient rates of change in SC (2-yr minimum), showed an annualized median increase in SC of 0.08 mg/dl per yr in the low-dose group and 0.10 mg/dl per yr in the high-dose group (P = 0.51). Patients in the lower entry SC range had lower SC slopes (P = 0.02) and less end-stage renal disease (ESRD) (P < 0.001) compared with those in the higher entry SC range. No patient died, and 18 patients developed ESRD: 10 in the low-dose group and 8 in the high-dose group (P = 0.56). SC slopes were significantly lower, and survival free of ESRD was significantly higher (both, P = 0.04) in the 63 Omacor-treated patients compared with the 22 placebo-treated patients from our previously reported clinical trial in which both groups had a similar level of renal impairment. Patient compliance was excellent, and no serious adverse events were noted. Low-dose and high-dose ω-3 fatty acids were similar in slowing the rate of renal function loss in high-risk patients with IgA nephropathy, particularly those with moderately advanced disease.

We previously reported that omega (ω)-3 polyunsaturated fatty acids significantly reduced renal disease progression in patients with idiopathic IgA nephropathy in a multicenter, placebo-controlled, randomized, 2-yr clinical trial (1). In a follow-up observational study extending beyond the 2-yr trial, long-term treatment with ω-3 fatty acids retarded renal progression consistent with the findings in the 2-yr trial (2). Both the primary end point—an increase in serum creatinine of 50% or more—and end-stage renal disease (ESRD) were substantially lower in the fatty acid–treated group in observations extending 6.4 yr from randomization to last follow-up. Despite these encouraging results, in large cohort studies of patients with IgA nephropathy as many as 30 to 50% develop ESRD over a 20-yr period after diagnosis (3–5). More progressive disease relates to higher prevalence rates of well-recognized clinical markers of disease progression in patients with hypertension, reduced renal function and abnormal proteinuria at diagnosis, and high glomerular histopathologic scores in their renal biopsy specimens (5). In 1995, in a new study, we proposed the hypothesis that high-dose ω-3 fatty acids will be more effective than low-dose ω-3 fatty acids in preserving renal function in patients with IgA nephropathy who are at high risk for developing progressive renal disease. We designed a prospective, randomized, comparative two-dose study of ω-3 fatty acids using a highly purified ethyl ester concentrate of ω-3 fatty acids, and we report here the effects of treatment on the renal outcome of patients with severe IgA nephropathy who participated in the trial.

Materials and Methods

Study Design

The study was a randomized, open-label, parallel-group comparison of treatment for 2 yr with high-dose and low-dose ω-3 fatty acids. As this was an open-label study, patients who completed a minimum of 2 yr of treatment (in the absence of failure) were continued on their same regimens, either low dose or high dose, until study closure (January 2000). The quantities of ω-3 fatty acids we chose for the low-dose group approximated the amounts of C20:5ω3 (EPA) and C22:6ω3 (DHA) that were given to patients in the clinical trial (1) and extended observational study (2). In these earlier studies, patients were given 1.68 to 1.87 g/d EPA and 0.97 to 1.36 g/d DHA. In the present study, patients in the low-dose group received 1.88 g/d EPA and 1.47 g/d DHA; in the high-dose group, patients received 2× this

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dietary sodium restriction limited to 90 mmol/d was advised. Hypertensive drugs were added at the physician's discretion. Mild
When the target BP of 140/85 mmHg was not achieved, other anti-
treated with the angiotensin-converting enzyme inhibitor enalapril
sules once a day ingested with a meal. Patients with hypertension were
low-dose group. Dosing instruction was eight capsules or four cap-
4 g/d given as four 1-g soft gelatin capsules containing 1.88 g of EPA and 2.94 g of DHA for a total of 6.7 g of
3 fatty acid–treated patients compared with 33% in the placebo group in
the analyses.

**Statistical Analyses**

Univariate baseline comparisons between the two dose groups were
done using the rank-sum (continuous data) or χ² (nominal data). Continuous factors were summarized using means and SD. Distribu-
tions that were particularly skewed or that had severe outliers (urine
protein, triglycerides, serum creatinine slopes) were summarized using
medians and the estimated interquartile range (25th, 75th percentiles).
For patients who developed ESRD, only laboratory values taken
before starting dialysis or receiving a renal transplant are included in
the analyses.

The primary end point for the study was rate of change in serum
creatinine. Changes in serum creatinine over time were estimated in
two ways. First, simple linear regression analysis (Y \(=\) serum crea-
tinine, X = years since start of Omacor) was used to estimate annu-
alized rates of change (slopes) in serum creatinine and reciprocal
serum creatinine for each patient. Although reciprocal serum creati-
nine values were more linear over time than direct values, both
measurements are presented as the interpretation of the direct changes
is more familiar to readers. The rank-sum test was then used to
compare dose groups with respect to serum creatinine slopes. Anal-
yses followed intent-to-treat principles, with every attempt made to
include all randomized patients in the analysis. However, one patient,
randomized to high-dose Omacor, left the study before beginning
treatment and was excluded from this analysis as only a single
baseline serum creatinine reading was available.

**Study End Points**

The primary end point of the study was the estimated annual
within-patient slope in serum creatinine, a determinant of change in
renal function, over the entire time in study for each patient (2-yr
minimum). Secondary end points were time to ESRD (defined as
chronic, repetitive dialysis or receiving a renal transplant) and time to
treatment failure, defined as the first occurrence of any of the follow-
ing: (1) the development of ESRD, (2) a serious side effect leading to
the inability to continue study medicines and death from any cause, and
(3) refusal to continue participation (noncompliance). For non-
compliant patients, we attempted to obtain follow-up information on
subsequent renal failure and vital status following the intent-to-treat
principle. Other variables monitored included changes in BP and 24-h
urine total protein and changes in serum lipid profiles, peripheral
blood counts, and serum potassium for safety.

**Patient Monitoring**

At study entry, complete medical histories were taken and physical
examinations were performed for all patients. Initial clinical and
laboratory results were sent to the coordinating center. Follow-up
patient examinations and measurements of serum creatinine; total,
high-density lipoprotein, and low-density lipoprotein cholesterol; trig-
llycerides; and 24-h urine total protein were scheduled after 1.5, 6, 12,
18, and 24 mo of treatment. Patients who remained at risk for a renal
failure event after 24 mo of treatment were continued on the same
dose regimens to which they were originally assigned, and they had
scheduled visits and the above named laboratory tests performed at
6-mo intervals until study closure (January 2000). Also, first morning
urinalysis, hemoglobin, hematocrit, peripheral blood leukocytes,
platelets, and serum potassium were collected and analyzed at the
local center at each scheduled visit. All clinical and laboratory results
were recorded on case report forms, forwarded to the coordinating
center, and entered for data processing. To reduce variability, we
analyzed each sample for serum creatinine and lipids and 24-h urine
total protein at the Mayo Medical Laboratories (Rochester, MN) using
standard methods. Patient compliance was ascertained by measuring
the plasma phospholipid fatty acids—EPA, DHA, and C20:4o6
( AA)—at 6 wk and 6 mo versus baseline within and between the two
Omacor-supplemented groups. The EPA/AA ratio, a particularly sen-
sitive indicator of compliance, was also calculated. The fatty acid
composition including ω-6 and ω-3 fatty acids of plasma phospholipid
was measured by capillary gas-liquid chromatography (8,9).

**Patient Selection and Treatment**

Patients aged 18 yr and older with a baseline serum creatinine of
1.5 to 4.9 mg/dl were eligible for the study if they had renal biopsy-
proven IgA nephropathy. The diagnosis of IgA nephropathy was
based on histologic assessment of renal biopsy tissue performed by
one investigator (J.P.G.) and was confirmed by immunofluorescence
studies showing predominant or co-dominant mesangial deposition of
IgA (5,6). Histopathologic assessment of renal injury was done by a
semi-quantitative scoring system, as described previously (5). In a
previous study of 148 patients with IgA nephropathy, total glomerular
score, derived from extent of mesangial cell proliferation, matrix
increase, capillary loop narrowing or disruption, glomerular sclerosis,
cellular crescents, and fibrous adhesions, was an independent predic-
tor of adverse outcome (5). Therefore, total glomerular score at time
of renal biopsy was assessed in this study.

At study entry, patients were randomized within strata determined by (1)
two ranges of elevated serum creatinine concentrations (1.5 to
2.9 mg/dl and 3.0 to 4.9 mg/dl), (2) previous treatment with ω-3 fatty
acids, and (3) previous treatment with corticosteroids. One patient
who had a central laboratory baseline serum creatinine of 1.4 mg/dl
was randomized to low-dose Omacor (Pronova Biocare, Oslo, Nor-
way). This patient’s initial serum creatinine was 1.5 mg/dl measured
1 mo before in her local laboratory. We elected to include the patient
in all analyses (in the 1.5 to 2.9 serum creatinine group). Omacor soft
gelatin capsules, the study medicine used in this study, contain 1 g of
a long-chain polyunsaturated ω-3 fatty acid ethyl ester concentrate
including 4 mg of α-tocopherol, which is added as an antioxidant.
The concentrate is produced from high-quality fish oil and contains 47%
EPA, 37% DHA, and 5 to 10% of other ω-3 fatty acids. In the
manufacturing process, impurities, cholesterol, vitamins A and D, and
potentially toxic compounds such as heavy metals, dioxins, and pes-
ticides are removed below detection limits (7). The patients were
randomized to high-dose Omacor, left the study before beginning
the week before starting dialysis or receiving a renal transplant) and time to
treatment failure, defined as the first occurrence of any of the follow-
ing: (1) the development of ESRD, (2) a serious side effect leading to
the inability to continue study medicines and death from any cause, and
(3) refusal to continue participation (noncompliance). For non-
compliant patients, we attempted to obtain follow-up information on
subsequent renal failure and vital status following the intent-to-treat
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include all randomized patients in the analysis. However, one patient,
randomized to high-dose Omacor, left the study before beginning
treatment and was excluded from this analysis as only a single
baseline serum creatinine reading was available.
Second, generalized estimating equations were used to assess the average change over time in serum creatinine readings taken from low-dose versus high-dose Omacor-treated patients (10). In contrast to the first approach, this method eliminates the need first to estimate within patient slopes, while taking into account not only the repeated nature of the data but also the variable number of readings per patient. Furthermore, all patients contributed to the analysis. The dependent variable was serum creatinine (and also reciprocal serum creatinine). Predictor variables were Omacor dose group, time since start of therapy, and dose by time interaction. As readings within patients tend to be correlated, patient was used as a clustering factor. Both an autoregressive reading (correlations between readings within a patient assumed to decrease with time) and an exchangeable reading (correlations between readings within a patient assumed constant across time) were used.

Secondary endpoints included time from start of therapy to development of ESRD and time to either development of ESRD or discontinuation of treatment as a result of an adverse event or noncompliance (refusal to continue). The cumulative percentage of patients who were free of these events was estimated using the Kaplan-Meier method. Dose groups were compared using the log-rank test. All randomized patients were included in these comparisons. The one patient who dropped out before beginning therapy was censored with 0 follow-up for the ESRD end point and counted as an event with 0 follow-up for the ESRD or discontinuation of treatment end point.

Within-dose group 1-yr and 2-yr changes in BP, urine protein, serum lipids, peripheral blood counts, and serum potassium were tested using the sign-rank test. All tests were two-sided with \( \alpha \)-level 0.05.

**Results**

Between October 1995 and January 1998, 103 patients with IgA nephropathy were screened for study. Seventy-three patients met the clinical criteria for eligibility and were willing to continue participation (8 patients), moving away from a study center (2 patients), lack of follow-up (1 patient), or sustaining an adverse event (2 patients). Of the two patients who withdrew from the study early because of an adverse event, one patient had gastrointestinal intolerance (indigestion) after the patient had taken Omacor 8 g/d for 18 mo. The symptom resolved promptly after the drug was stopped. The second patient, with a history of Barrett’s esophagus, discontinued medication (4 g/d) approximately 6 wk after study entry as a result of an exacerbation of reflux esophagitis.

**Outcome: Annual within-Patient Slopes in Serum Creatinine**

Based on within-patient serum creatinine profiles (Figure 1), we estimated within-patient annualized rates of change (slopes) for serum creatinine. These slopes are summarized in Table 2 and Figure 2. Although both groups demonstrated slopes that were significantly different from 0 (4 g, \( P = 0.008 \); 8 g, \( P = 0.001 \) [sign-rank test]), no significant differences were noted between the two Omacor dose groups (\( P = 0.51 \) [rank-sum test]). Additional analyses based on slopes derived from reciprocal serum creatinine profiles also showed no significant differences between Omacor dose groups (\( P = 0.58 \)). Further analyses based on generalized estimating equations (see the Materials and Methods section) also found no significant evidence of an Omacor dose effect on follow-up serum creatinine levels (all \( P \) values \( >0.20 \)). For example, the mean slope in reciprocal serum creatinine was estimated to be \(-0.03 \) dl/mg per yr for the low-dose group compared with \(-0.02 \) dl/mg per yr for the high-dose group (\( P = 0.58 \)). Annualized median change in serum creatinine was not different in previously \( \omega-3 \) fatty acid–treated (0.107 mg/dl per yr) versus non-previously \( \omega-3 \) fatty acid–treated patients (0.064 mg/dl per yr; \( P = 0.36 \) [rank-sum test]) or in reciprocal serum creatinine slopes comparing previously \( \omega-3 \) fatty acid–treated (\(-0.026 \) dl/mg per yr) with non-previously \( \omega-3 \) fatty acid–treated (\(-0.020 \) dl/mg per yr) patients (\( P = 0.71 \) [rank-sum test]).

It is apparent that the majority of patients who had baseline serum creatinines of 1.5 to 2.9 mg/dl at study entry (\( n = 63 \)) had stable renal function in both the low-dose and high-dose Omacor groups (Figure 1). Patients with initial serum creatinine levels of 1.5 to 2.9 mg/dl had significantly lower rates of deterioration in renal function (median creatinine slope = 0.08 versus 1.3 mg/dl per yr [\( P = 0.019 \)]; median reciprocal creatinine slope = \(-0.02 \) versus \(-0.07 \) [\( P = 0.062 \)]) and less ESRD (13 versus 85% at 3 yr; \( P < 0.001 \) [log-rank test]) when compared with those with initial serum creatinines of 3.0 to 4.9 mg/dl. Large serum creatinine slopes (\( >0.5 \) mg/dl per yr) were observed in 14 of 62 patients (23%) with baseline serum creatinines of 1.5 to 2.9 mg/dl compared with 7 of 10 (70%) patients with baseline serum creatinines of 3.0 to 4.9 mg/dl and in 17 of 18 patients who subsequently developed ESRD. Although we recognize that serum creatinine slopes (\( >0.5 \) mg/dl per yr) are nonlinear for expressing changes in GFR, such large slopes have clinical interpretation and correlate with the development of ESRD.
Renal Failure Events
Survival free of ESRD was similar in the two treatment groups (Table 2, Figure 3), and survival without sustaining any event—ESRD, an adverse event leading to discontinuation of treatment, or refusal to continue therapy—was also similar in the low-dose and high-dose Omacor treatment groups (Table 2).

Changes in BP, Proteinuria, Serum Lipids, Peripheral Blood Counts, and Potassium
There were no significant within-dose group time trends in BP, proteinuria, serum lipids, peripheral blood counts, and potassium, with the exception that BP and serum triglycerides were lower in the low-dose Omacor group at 12 mo compared with baseline, and high-density lipoprotein and low-density lipoprotein cholesterol were lower in the high-dose Omacor group at 12 mo compared with baseline (Table 3). Although there was a decline in urine protein excretion over time in the low-dose group compared with no change in the high-dose group, the median annual slopes in proteinuria were not significantly different between treatment groups ($P = 0.17$ [rank-sum test]).

Compliance with Treatment
As a measure of compliance, in 56 patients who were not taking $\omega$-3 fatty acids at study entry, plasma phospholipid fatty acid changes from pretreatment were significant for all studied fatty acids (Table 4). There were significant increases in EPA and DHA and significant reductions in AA levels at 6 wk and 6 mo after supplementation ($P < 0.01$ for all values [paired $t$ test]). With the exception of AA, fatty acid changes from baseline were, in general, higher for the high-dose compared with the low-dose group (Table 4). EPA/AA ratios were also significantly increased in both treatment groups and were higher at both 6 wk ($P = 0.007$, two-tailed $P$ value from rank-sum test) and 6 mo ($P = 0.002$) in the high-dose group (Table 4).

Adverse Events
A total of nine patients (five at 4 g/d, four at 8 g/d) had adverse events, including the two aforementioned patients who withdrew early as a result of adverse events. Of the remaining seven patients, one patient (4 g/d) had episodes of cryptogenic gastrointestinal bleeding before, during, and after study participation. Omacor was discontinued in this patient 2 yr after

### Table 1. Characteristics of the patients in the low-dose and high-dose Omacor treatment groups at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low [Mean (SD); N = 37]</th>
<th>High [Mean (SD); N = 36]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at randomization (yr)</td>
<td>46 (13)</td>
<td>45 (13)</td>
</tr>
<tr>
<td>Male gender</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td>White race</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>92%</td>
<td>92%</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>139 (16)</td>
<td>136 (16)</td>
</tr>
<tr>
<td>diastolic</td>
<td>84 (10)</td>
<td>82 (9)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>2.1 (0.7)</td>
<td>2.3 (0.7)</td>
</tr>
<tr>
<td>Hematocrit (vol %)</td>
<td>39 (6.2)</td>
<td>38 (5.5)</td>
</tr>
<tr>
<td>Peripheral blood leukocytes ($\times10^{9}$/L)</td>
<td>7.2 (2.5)</td>
<td>7.1 (2.0)</td>
</tr>
<tr>
<td>Platelets ($\times10^{9}$/L)</td>
<td>214 (50)</td>
<td>251 (64)</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>4.8 (0.62)</td>
<td>4.8 (0.47)</td>
</tr>
<tr>
<td>Serum cholesterol (mg/dl)</td>
<td>217 (36)</td>
<td>228 (53)</td>
</tr>
<tr>
<td>HDL</td>
<td>41 (15)</td>
<td>44 (14)</td>
</tr>
<tr>
<td>LDL</td>
<td>135 (28)</td>
<td>146 (47)</td>
</tr>
<tr>
<td>Serum triglycerides (mg/dl)$d$</td>
<td>178 (109, 277)</td>
<td>156 (114, 235)</td>
</tr>
<tr>
<td>24-h urine protein (mg/24 h)$d$</td>
<td>1791 (757, 2569)</td>
<td>1526 (702, 3662)</td>
</tr>
<tr>
<td>Time from biopsy to randomization (yr)$d$</td>
<td>3.7 (2.1, 9.4)</td>
<td>2.6 (0.4, 6.0)</td>
</tr>
<tr>
<td>Total glomerular histopathologic score$e$</td>
<td>5.5 (2.4)</td>
<td>4.9 (2.2)</td>
</tr>
<tr>
<td>scores &gt;5 (%)</td>
<td>57</td>
<td>40</td>
</tr>
</tbody>
</table>

$^a$ HDL, high-density lipoprotein; LDL, low-density lipoprotein.

$^b$ All $P$ values for the comparison between the two groups were >0.05, except for platelets ($P < 0.05$).

$^c$ Hypertension was defined as a systolic pressure $\geq 140$ mmHg or a diastolic pressure $\geq 85$ mmHg or currently being treated for hypertension.

$^d$ Median (25th, 75th percentiles) are presented due to extreme skewness.

$^e$ Total scores based on a semiquantitative scoring system (see Materials and Methods section).
study enrollment during an episode of gastrointestinal bleeding 1 mo before the patient was started on maintenance hemodialysis for ESRD. Another patient (4 g/d) discontinued therapy after development of rectal bleeding from hemorrhoids 48 mo after study entry. This patient had advanced renal failure at the time. Other single adverse events noted during the course of study participation included one episode of diverticulitis (4 g/d), an episode of pneumonitis and possible pancreatitis (8 g/d), development of asymptomatic atrial fibrillation (8 g/d), hyperkalemia (4 g/d) that resolved after discontinuing angiotensin-converting enzyme inhibitor therapy, and development of hemiparesis as a result of ischemic cerebrovascular disease (8 g/d). None of these events was thought to be related directly to study medication.

Discussion
In this multicenter, randomized, 2-yr, comparative two-dose trial, both low-dose and high-dose \( \omega-3 \) fatty acids, given daily...

Figure 1. Serum creatinine profiles in patients who had IgA nephropathy and who were treated with low-dose (A) and high-dose (B) Omcor. The serum creatinines are plotted and connected for each patient and include all readings before renal failure (if present).

Figure 2. Annualized rate of change in renal function in patients who had IgA nephropathy and who were treated with low-dose and high-dose Omcor. The annual rates of change (slopes) for serum creatinine were computed for each patient by linear regression analysis using all results before renal failure (if present). The annualized median change in serum creatinine was 0.08 mg/dl per yr in the low-dose group and 0.10 mg/dl per yr in the high-dose group (\( P = 0.51 \)). +, median.
as a highly purified ethyl ester concentrate of EPA and DHA (Omacor), were equally effective in slowing the rate of loss of renal function in patients who were at high risk for renal progression, all having impaired renal function at the start of treatment. Changes in renal function (serum creatinine) were only 0.08 mg/dl per yr in the low-dose group and 0.10 mg/dl per yr in the high-dose group.

Patients who had the most stable renal course in both the low-dose and high-dose groups were those who had less impaired renal function upon entering the study with a baseline

**Table 2. Results of low-dose versus high-dose Omacor regarding primary and secondary end points**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Omacor Dose</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>slopes in serum creatinine (mg/dl per yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (25th, 75th percentile)</td>
<td>0.08 (−0.03, 0.79)</td>
<td>0.10d (−0.02, 0.70)</td>
</tr>
<tr>
<td>slope &gt;0.5 mg/dl per yr (no.)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of events</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>event-free [% (SEM)]</td>
<td>86 (6.0)</td>
<td>80 (6.9)</td>
</tr>
<tr>
<td>at 2 yr</td>
<td>73 (8.4)</td>
<td>76 (7.6)</td>
</tr>
<tr>
<td>ESRD, adverse event, or noncompliante</td>
<td></td>
<td></td>
</tr>
<tr>
<td>number of events</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>event-free [% (SEM)]</td>
<td>78 (6.9)</td>
<td>72 (7.5)</td>
</tr>
<tr>
<td>at 2 yr</td>
<td>62 (9.2)</td>
<td>65 (8.2)</td>
</tr>
</tbody>
</table>

a ESRD, end-stage renal disease.
b Based on two-sided rank-sum test. Note that similar results obtained when using slopes based on reciprocal serum creatinine (medians = −0.02 low dose, −0.03 high dose; P = 0.58).
c Based on two-sided log-rank test.
d Excludes one patient with a single serum creatinine who dropped out of the study before beginning treatment. This patient is included in the analyses of secondary end points.
e Includes patients with ESRD or an adverse event leading to discontinuation of treatment or refusal to continue therapy.

**Figure 3.** Cumulative percentage of patients who had IgA nephropathy and who were treated with low-dose and high-dose Omacor and did not have renal failure during the treatment period. In the low-dose group, 73% of the patients (SEM = 8.4%) were free of renal failure at 3 yr compared with 76% (7.6) in the high-dose group (P = 0.56). Numbers of patients who were at risk at 3 yr were 12 in the low-dose group and 15 in the high-dose group.
Table 3. Time trends in BP, urine protein, lipids, and CBC by Omacor dose

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Low Omacor Dose</th>
<th>High Omacor Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (Baseline)</td>
<td>12 Mo (n = 32)</td>
</tr>
<tr>
<td></td>
<td>(n = 37)</td>
<td>(n = 36)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>139 (16)</td>
<td>132 (16)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84 (10)</td>
<td>80 (9.4)</td>
</tr>
<tr>
<td>Urine protein (mg/24 h)</td>
<td>1791</td>
<td>1325</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>217 (36)</td>
<td>204 (63)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>41 (15)</td>
<td>40 (15)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>135 (28)</td>
<td>124 (47)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>178</td>
<td>137</td>
</tr>
<tr>
<td>Hgb (g/dl)</td>
<td>13.6 (3.1)</td>
<td>13.4 (2.0)</td>
</tr>
<tr>
<td>Hct (vol %)</td>
<td>39 (6.2)</td>
<td>39 (5.9)</td>
</tr>
<tr>
<td>Erythrocytes (×10³/L)</td>
<td>4.4 (6.6)</td>
<td>4.4 (6.2)</td>
</tr>
<tr>
<td>Leukocytes (×10³/L)</td>
<td>7.2 (2.5)</td>
<td>7.1 (2.3)</td>
</tr>
<tr>
<td>Platelets/1000 (×10³/L)</td>
<td>214 (50)</td>
<td>210 (53)</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.8 (62)</td>
<td>4.7 (65)</td>
</tr>
</tbody>
</table>

* Tabled values are mean (SD). Readings after ESRD (10 patients in low-dose group, 8 patients in high-dose group) are excluded.

** P < 0.05 for significant change from baseline to 12 mo. There were no significant changes from baseline to 24 mo.

serum creatinine that ranged from 1.5 to 2.9 mg/dl. Sixty-three of the 73 patients (86%) who were enrolled in the trial fell into this category. Patients in this lower entry serum creatinine range had significantly lower serum creatinine slopes and less ESRD when compared with those in the higher entry serum creatinine range. Furthermore, large serum creatinine slopes—>0.5 mg/dl per yr, a widely recognized clinical change in renal function—were observed in 14 of 62 patients (23%) with lower baseline serum creatinine levels compared with 7 of 10 patients (70%) with higher baseline serum creatinines and in 17 of 18 patients who subsequently developed ESRD. This is not a surprising finding because most patients in the late stages of IgA nephropathy develop progressive renal failure despite various therapies that have been tried (11,12).

Survival free of ESRD was also similar in the low-dose and high-dose Omacor treatment groups. An event-free survival rate from ESRD was 75% at 3 yr, representing a favorable outcome in view of the high-risk profile in the cohort of patients in this trial. To expand on this point, we compared both the primary endpoint—changes in renal function by annualized rates of change in serum creatinine—and survival free of ESRD in patients in the present study with patients in a placebo-control group in our previously reported clinical trial (1). Time to ESRD was defined in both study groups as time from start of therapy to the start of chronic, repetitive dialysis or receiving a renal transplant, whichever occurred first. To make the analysis comparable between the two groups, we compared outcomes in the 63 patients in the current trial with 22 patients in the placebo-treated group whose baseline serum creatinine concentrations were in the 1.4 to 2.9 mg/dl range (Table 5). Changes in serum creatinine slopes were significantly lower, and survival free of ESRD was significantly higher in the Omacor-treated patients from the present study compared with the placebo-treated patients from our previous study (1). Although this is not a comparison between patients who were contemporaneously randomized to treatment, it does examine the effects of treatment for patients with similar degrees of renal impairment (median serum creatinine is 1.8 mg/dl for both groups).

That the patients in the present study were at high risk for developing progressive renal disease is evidenced not only by the aforementioned impaired pretreatment renal function that was part of the study design but also by the observations that 92% were hypertensive and that urinary protein excretion was in excess of 1.5 g/24 h at study entry. These clinical variables are important predictors of poor outcome in IgA nephropathy (5,13–17). In addition, total glomerular histopathologic score, a semiquantitative index of renal injury and an independent predictor of renal failure (5), was increased in the renal biopsy specimens of 50% of the patients. In a previous study of 148 patients with IgA nephropathy, we found that total glomerular histopathologic scores greater than 5 were associated with adverse outcome (5).

Patient compliance was excellent as ascertained by the expected enhancement of plasma phospholipid EPA and DHA and suppression of AA after Omacor supplementation (1,18). EPA and DHA levels on treatment were higher in the high-dose group compared with the low-dose group. Yet, as already shown, treatment with high-dose ω-3 fatty acids had no added beneficial effect on preserving renal function.

Omacor was well tolerated as only two patients discontinued treatment as a result of gastrointestinal intolerance. There were no unfavorable effects on serum lipid profiles, hematocrits, peripheral blood leukocytes, or platelets.
Because treatment with high-dose ω-3 fatty acids provided no added benefit, we believe that it is appropriate to recommend low-dose ω-3 fatty acids in the treatment of high-risk patients with IgA nephropathy, including those with moderately advanced renal disease, for example, for those patients whose serum creatinines were in the lower entry range of 1.5 to 2.9 mg/dl. We previously determined that this lower dose of ω-3 fatty acids, composed of 1.9 g of EPA and of 1.4 g DHA, efficiently enhanced the EPA and DHA and total ω-3 polyunsaturated fatty acids of plasma phospholipids (18) and can be recommended on the strength of the present findings. For convenience, the ethyl ester ω-3 fatty acid concentrate Omacor, which provides a concentrated preparation of EPA and DHA and was used in this trial, allowed patients who were in the

Table 4. Fatty acid composition of plasma phospholipid in low-dose and high-dose Omacor-treated patients with IgA nephropathy who were not taking omega-3 fatty acids at study entry

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Visit</th>
<th>Low (N=29)</th>
<th>Mean (SD)</th>
<th>High (N=26)</th>
<th>Mean (SD)</th>
<th>Low Versus High P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C20:5ω3 (EPA)</td>
<td>0</td>
<td>0.8 (0.5)</td>
<td>26 0.9 (0.6)</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 wk</td>
<td>3.6 (1.3)</td>
<td>26 4.9 (1.3)</td>
<td>0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>3.1 (1.3)</td>
<td>26 5.2 (1.8)</td>
<td>0.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 wk–0</td>
<td>2.8 (1.2)c</td>
<td>26 4.0 (1.5)c</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo–0</td>
<td>2.3 (1.3)c</td>
<td>26 4.2 (1.9)c</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C22:6ω3 (DHA)</td>
<td>0</td>
<td>3.7 (1.5)</td>
<td>26 3.5 (1.4)</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 wk</td>
<td>6.7 (1.2)</td>
<td>26 7.4 (1.3)</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>6.5 (1.3)</td>
<td>26 7.7 (1.6)</td>
<td>0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 wk–0</td>
<td>2.9 (1.5)c</td>
<td>26 4.0 (1.7)c</td>
<td>0.035</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>6 mo–0</td>
<td>2.9 (1.5)c</td>
<td>26 4.2 (2.0)c</td>
<td>0.020</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C22:4ω6 (AA)</td>
<td>0</td>
<td>10.0 (2.5)</td>
<td>26 9.8 (2.6)</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 wk</td>
<td>8.5 (1.8)</td>
<td>26 8.0 (1.9)</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>8.2 (1.9)</td>
<td>24 7.7 (1.8)</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 wk–0</td>
<td>−1.4 (2.0)c</td>
<td>26 −1.8 (1.8)c</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo–0</td>
<td>−1.9 (2.0)c</td>
<td>24 −2.1 (1.8)c</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPA/AA</td>
<td>0</td>
<td>0.09 (0.07)</td>
<td>26 0.11 (0.08)</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 wk</td>
<td>0.47 (0.29)</td>
<td>26 0.64 (0.22)</td>
<td>0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo</td>
<td>0.45 (0.40)</td>
<td>24 0.71 (0.31)</td>
<td>0.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 wk–0</td>
<td>0.38 (0.26)c</td>
<td>26 0.54 (0.24)c</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 mo–0</td>
<td>0.36 (0.39)c</td>
<td>26 0.60 (0.33)c</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data for each fatty acid are expressed as the weight percentage of total fatty acids and calculated as millimoles per mole divided by 100.

P value from two-sided rank-sum test comparing low-dose versus high-dose Omacor.

P value from two-sided paired t test for within-dose group test of no significant change from pretreatment (visit 0) is ≤0.01.

Because treatment with high-dose ω-3 fatty acids provided no added benefit, we believe that it is appropriate to recommend low-dose ω-3 fatty acids in the treatment of high-risk patients with IgA nephropathy, including those with moderately advanced renal disease, for example, for those patients whose serum creatinines were in the lower entry range of 1.5 to 2.9 mg/dl. We previously determined that this lower dose of ω-3 fatty acids, composed of 1.9 g of EPA and of 1.4 g DHA, efficiently enhanced the EPA and DHA and total ω-3 polyunsaturated fatty acids of plasma phospholipids (18) and can be recommended on the strength of the present findings. For convenience, the ethyl ester ω-3 fatty acid concentrate Omacor, which provides a concentrated preparation of EPA and DHA and was used in this trial, allowed patients who were in the

Table 5. Comparison of renal end points in Omacor- and placebo-treated patients who had pretreatment serum creatinine levels ranging from 1.4- to 2.9 mg/dl

<table>
<thead>
<tr>
<th>End Point</th>
<th>Omacor (n=63)</th>
<th>Placebo (n=22)</th>
<th>Omacor Versus Placebo P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slopes in serum creatinine (mg/dl per yr) median</td>
<td>0.075</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>(25th, 75th percentile)</td>
<td>(−0.22, 0.39)</td>
<td>(0.053, 0.98)</td>
<td>0.04\textsuperscript{a}</td>
</tr>
<tr>
<td>ESRD number of events</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>event-free at 3 yr [% (SE)]</td>
<td>85 (5.1)</td>
<td>64 (11.1)</td>
<td>0.04\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Based on two-sided rank-sum test. One patient from each group did not have sufficient data for a serum creatinine slope.

\textsuperscript{b} Based on a two-sided log-rank test.
low-dose group to consume only four soft gelatin capsules daily. This compares with 12 capsules daily necessary to take in 1.9 g of EPA and 1.4 g of DHA contained in the over-the-counter products that generally are 30% concentrates of \( \omega-3 \) fatty acids. As no other comparative-dose studies have been performed using \( \omega-3 \) fatty acids, we do not know whether a lower dose of \( \omega-3 \) fatty acids might be effective in slowing renal progression for high-risk patients with IgA nephropathy.

Appendix: The Mayo Nephrology Collaborative Group


Acknowledgments

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References


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