# Clinical Trial to Evaluate Omega-3 Fatty Acids and Alternate Day Prednisone in Patients with IgA Nephropathy: Report from the Southwest Pediatric Nephrology Study Group

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**This randomized, placebo-controlled, double-blind trial evaluated the role of prednisone and omega 3 fatty acids (O3FA) in patients with IgA nephropathy. Entry criteria were (*1*) biopsy-proven IgA nephropathy, (*2*) estimated GFR ≥50 ml/min per 1.73 m$^2$, and (*3*) moderate to severe proteinuria. Thirty-three patients were randomly assigned to receive prednisone 60 mg/m$^2$ every other day for 3 mo, then 40 mg/m$^2$ every other day for 9 mo, then 30 mg/m$^2$ every other day for 12 mo (prednisone group); 32 were randomly assigned to receive O3FA 4 g/d for 2 yr (1.88 g eicosapentaenoic acid, 1.48 g docosahexaenoic acid; O3FA group); and 31 were randomly assigned to receive placebo (placebo group). Most (73%) patients completed 2 yr of treatment. Randomly assigned patients who were hypertensive were given enalapril 2.5 to 40 mg/d. The primary end point was time to failure, defined as estimated GFR <60% of baseline. An overall significance level of 0.10 was used. The three groups were comparable at baseline except that the O3FA group had higher urine protein to creatinine (UP/C) ratios than the placebo group ($P = 0.003$). Neither treatment group showed benefit over the placebo group with respect to time to failure, with 14 patient failures overall (two in the prednisone group, eight in the O3FA group, and four in the placebo group). The primary factor associated with time to failure was higher baseline UP/C ratios ($P = 0.009$). Superiority of prednisone or O3FA over placebo in slowing progression of renal disease was not demonstrated in this study. However, the relatively short follow-up period, inequality of baseline UP/C ratios, and small numbers of patients precludes definitive conclusions.**

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Recent studies have shown that IgA nephropathy (IgAN) leads to kidney failure in up to 40% of patients (1–7). Proposed therapies include corticosteroids (8–20), fish oil (21–31), and angiotensin-converting enzyme (ACE) inhibitors (32,33). Although some studies of corticosteroids and omega-3 fatty acids (O3FA) have reported significant benefit, others showed no apparent benefit. The studies that evaluated corticosteroids used a wide variety of protocols (8,10,18). Possible explanations for the variable outcomes in patients who were treated with fish oil supplements include differences in the patient populations and variations in the dose or composition of the fish oil used. ACE inhibitors have been helpful in patients with a wide assortment of glomerulopathies, including patients with IgAN (32,33). This study was designed to evaluate whether a 2-yr course of alternate-day prednisone or of daily O3FA on a background of ACE inhibitor therapy in hypertension patients provides an effective means of preventing deterioration of GFR in young patients with IgAN.

## Materials and Methods

This placebo-controlled, double-blind, prospective clinical trial was set up with the administrative coordinating center in the central offices of the Southwest Pediatric Nephrology Study Group in Dallas, TX; the Data Coordinating Center was established in Birmingham at the University of Alabama. A network of 37 adult and pediatric nephrology centers recruited patients for the trial, which was conducted with the support of the National Institutes of Health. Informed consent forms were approved by the Institutional Review Board at each of the centers.

Entry criteria were (*1*) age ≤40 yr at the time of entry; (*2*) a renal biopsy showing IgAN (there was no time limitation set as to when the diagnostic biopsy was obtained); (*3*) estimated GFR (eGFR) ≥50 ml/min per 1.73 m$^2$ using an age-appropriate formula (Schwartz equation [34,35] or Cockcroft-Gault equation [36]); and (*4*) proteinuria/biopsy

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findings of (*a*) persistent severe proteinuria, *i.e.*, first morning urine protein to creatinine (UP/C) ratio ≥1.0 or (*b*) moderate proteinuria, *i.e.*, UP/C ratio ≥0.5 plus renal biopsy changes indicating risk for progression, *i.e.*, areas of glomerulosclerosis or proliferation. Exclusion criteria were (*1*) systemic lupus erythematosus; (*2*) Henoch-Schönlein purpura; (*3*) abnormal liver function; (*4*) diabetes, cataracts, aseptic necrosis of any bone, or other conditions that potentially are exacerbated by prednisone; (*5*) prednisone or other immunosuppression and/or fish oils for >3 mo.

### *Treatment Arms*

**Prednisone Group.** The prednisone group received 2 yr of treatment with a tapering regimen of alternate-day prednisone tablets (Deltasone, provided by Upjohn and Pharmacia, Kalamazoo, MI). For the first 3 mo, they received 60 mg/m$^2$ every other day (80 mg maximum), followed by 9 mo at 40 mg/m$^2$ every other day (60 mg maximum), and then 12 mo at 30 mg/m$^2$ every other day (40 mg maximum).

**O3FA Group.** The O3FA group received 2 yr of treatment with Omacor, a purified preparation of O3FA, provided by Pronova Biocare (Lysaker, Norway). This preparation is a formulation that consists of 84% highly purified ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The administration of 4 g of this product provided each patient with 1.88 g/d EPA and 1.48 g/d DHA.

**Placebo Group.** Patients in the placebo group received 2 yr of treatment with placebo. Half of this group received prednisone placebo tablets; the other half received O3FA placebo capsules. The placebo capsules contained corn oil.

In addition to the study medications, all patients with hypertension were given enalapril (provided by Merck & Co., West Point, PA) at doses that were individualized to normalize their BP readings. Hypertension was defined as either systolic BP >140 mmHg or diastolic >90 mmHg in adults and >95th percentile for age in children and adolescents.

Randomization of patients was performed using block randomization within each stratum to ensure that the treatments were evenly allocated. The patient groups were stratified on the basis of the presence or absence of hypertension.

### *Outcome Criterion*

Time to failure was defined as the interval until the eGFR fell to <60% of baseline value. This was confirmed with a repeat GFR.

### *Laboratory Studies*

Specimens were sent to Laboratory Corporation of American (LabCorp, Dallas, TX) for routine studies and urinary protein concentration (using the QuanT7test Total Protein Assay System [#40-02/87; Hawthorne, CA], which has an intra-assay coefficient of variation <9.5% for urine). Urine and serum creatinine concentrations were determined using isocratic (succinic acid-mobile phase) ion-exchange HPLC with ultraviolet detection. This method is sensitive and free from drug interference and the effect of noncreatinine chromogens in serum and provides results that range from 97 to 102% of those obtained using stable isotope mass spectrometry (37,38). Urine protein and creatinine concentrations were measured on first morning urine specimens.

### *Renal Biopsy Studies*

Before a patient's acceptance into the study, the pathology report from each patient's diagnostic renal biopsy was evaluated by the core pathologists (C.J. and R.S.) to ensure that the histologic entry criteria were met. At the end of the study, the pathologists reviewed the biopsy slides and photographs of the electron microscopy studies from each patient. The pathologists were blinded with respect to therapy. They both reviewed (and scored) the individual biopsies in all patients and then held a face-to-face meeting in Dallas to resolve any discrepancies. A standardized score sheet was developed and used for defining the severity of renal histopathology in each patient.

### *Safety Monitoring*

An External Advisory Committee was established by the National Institute of Diabetes and Digestive and Kidney Diseases to review reports of adverse events and rates of deterioration of enrolled patients.

### *Measurement of Plasma Phospholipid Fatty Acid Profiles*

Complete plasma phospholipid fatty acid profiles were measured in 36 patients who had received capsules for 21 to 24 mo of the study (in 23 patients who received Omacor capsules and 13 patients who received placebo capsules). The assay methods that were used have been described previously (39). Coded specimens were sent in a frozen state, and the laboratory personnel were blinded as to which of the specimens were from patients who were taking Omacor and which were from patients who received placebo capsules. The code was broken after all of the clinical data and laboratory results were available.

### *Sample Size Estimation*

Sample size estimation was based on comparing the outcome of the O3FA and prednisone arms with the placebo arm with respect to time to failure. The following assumptions were made: (*1*) Time to failure is exponentially distributed, (*2*) the cumulative proportion of failures at 3 yr would be 5% for the O3FA and prednisone arms and 20% for placebo, (*3*) the accrual period would be 2 yr with a minimum follow-up of 5 yr or until failure, and (*4*) the dropout rate would be 10%. The sample size estimate used a power of 0.75 to try to obtain a sample size that could be achieved in a reasonable time frame. The overall significance level of 0.10 was used to compare the three groups. There were two comparisons of interest (prednisone therapy *versus* placebo, and O3FA *versus* placebo), and the Bonferroni significance level of 0.05 was used for these individual pairwise comparisons. A total of 123 patients divided equally among the three treatment arms were required to test each comparison with power of 0.75.

### *Statistical Analyses*

The product limit method was used to describe the distribution of time to failure and to estimate the cumulative proportion of failures at 3 yr in the three treatment arms. The log-rank test was used to compare the O3FA and prednisone arms with the placebo group with respect to time to failure. The proportional hazards model was used to determine the relationship between time to failure and demographic characteristics, hypertensive status, and protein excretion at baseline. $\chi^2$ analyses were used to compare the three treatment arms with respect to categorical variables. When a significant difference was detected, Fisher exact test was used to compare the placebo arm with each of the other arms. Two-way ANOVA were used to evaluate the effects of treatment arm, time (baseline and 6, 12, and 24 mo), and hypertensive status on UP/C ratio and GFR and on changes from baseline in these measures. Interim analyses were performed using the Lan-DeMets stopping rule (40) with the O'Brien-Fleming stopping rule (41) for superiority and futility (42). An intention-to-treat analysis was performed with all randomly assigned patients.

## Results

### *Patients*

A total of 168 patients were identified as potential trial patients, and 96 were randomly assigned. The other 72 patients

were ineligible for a variety of reasons: 23 were unwilling to be randomly assigned, 33 had UP/C ratios or an eGFR that was too low, and 16 had various other reasons. Of the 96 patients who were randomly assigned (33 to prednisone, 32 to O3FA, and 31 to placebo), 72 completed 2 yr of trial drugs and 18 patients exited prematurely. Six patients opted out of the trial after randomization but before the start of study drugs. Forty-eight of the randomly assigned patients were placed on enalapril at the time of entry because of hypertension.

*Patient Characteristics*

Clinical and laboratory features in the three groups of patients at the time of entry into the study are shown in Table 1. Age, race, and gender were comparable in the three arms. Hypertension was equally distributed in the three arms of patients as a result of patient stratification on the basis of BP status. eGFR also was comparable in the three arms. The UP/C ratio was significantly less ($P = 0.003$) in the placebo arm ($1.4 \pm 1.2$) than in the O3FA treatment arm ($2.1 \pm 1.3$) and tended to be lower than in the prednisone arm ($2.2 \pm 2.5$), although this was not statistically significant.

*Renal Biopsy Findings*

The standardized scores of the renal biopsy lesions were comparable in the three groups of patients. Selected histopathologic features are provided in Table 2. These represent most of the features that have been identified as potential prognostic indicators in previous studies of patients with IgAN. The percentage of glomeruli with endocapillary hypercellularity was slightly higher in the placebo group (44%) than in the prednisone group (26%; $P = 0.04$), but all the indices of chronicity were comparable in the three groups.

*Outcome Analysis*

There were 14 events in which the GFR level fell to ≤60% of baseline: Two patients in the prednisone group, eight in O3FA group, and four in the placebo group. The cumulative proportion of failures in these three groups at 3 yr were estimated as 9.2, 18.8, and 8.7% on prednisone, O3FA, and placebo, respectively. There was no significant difference between the placebo group and either the prednisone group ($P = 0.496$) or the O3FA group ($P = 0.232$) with respect to time to failure. Seven failures occurred in patients who were receiving long-term ACE inhibitors, and four occurred in those who did not take ACE inhibitors. When the UP/C ratio was added to the model, its hazard ratio was found to be significantly different from 1.0, and the upper bounds of the confidence intervals for the treatment hazard ratios decreased markedly (Table 3).

Baseline UP/C levels differed from all other time points but did not vary after treatment started. GFR levels were significantly associated with hypertensive status ($P \leq 0.001$). Changes in UP/C from baseline varied by treatment ($P = 0.10$) and time ($P = 0.015$). The difference between patients in the prednisone group and the placebo group and between 6 and 36 mo was statistically significant. None of the factors analyzed (treatment, time, and hypertensive status) was significantly associated with change in GFR. Baseline proteinuria was significantly associated with time to failure ($P = 0.009$).

Because of the association of time to failure with baseline proteinuria, a subset analysis of failure was performed on 52 patients who had baseline UP/C ratios between 1 and 3: 16 (48%) patients in the prednisone group, 23 (72%) in the O3FA group, and 13 (39%) in the placebo group ($P = 0.025$). In this subgroup, there were nine events—one, six, and two, respectively, in the three groups—and the cumulative proportion of events at 3 yr was 5.6, 23.7, and 16.4%, respectively. There was no significant difference between the placebo group and either the prednisone group ($P = 0.303$) or the O3FA group ($P = 0.683$) with respect to time to failure in this subgroup of patients.

To evaluate the impact of persistent proteinuria on patient outcome, we used two measures: The percentage of visits in each treatment arm for patients for whom the UP/C ratio was >1 and the percentage of visits in each arm for patients for whom the UP/C ratio was >50% of baseline (Table 4). There was no significant difference between treatment arms with respect to percentage of visits at which the UP/C ratio was >1; however, there was a significant difference between treatment arms with respect to the proportion of patients who had UP/C ratios >1 at >50% of their visits. There were no significant differences between treatment

*Table 1.* Baseline features of patients in the IgAN trial[a]

| | Prednisone Group | O3FA Group | Placebo Group | *P* |
|---|---|---|---|---|
| Age (yr) | 24 ± 10 | 20 ± 10 | 21 ± 10 | 0.19 |
| White (%) | 59 | 72 | 84 | 0.07 |
| Male (%) | 70 | 66 | 65 | 0.90 |
| Hypertensive (%) | 55 | 53 | 48 | 0.88 |
| Systolic BP | 127 ± 12 | 127 ± 15 | 124 ± 16 | 0.41 |
| Diastolic BP | 79 ± 14 | 75 ± 13 | 78 ± 11 | 0.35 |
| eGFR (ml/min per 1.73 $m^2$) | 109 ± 39 | 117 ± 43 | 118 ± 47 | 0.68 |
| UP/C ratio | 2.2 ± 2.5 | 2.1 ± 1.3 | 1.4 ± 1.2 | 0.02 |

[a]Data are mean ± 1 SD except where indicated. eGFR, estimated GFR; IgAN, IgA nephropathy; O3FA, omega 3 fatty acids; UP/C, urinary protein/creatinine.

*Table 2.* Comparison of selected renal biopsy features in the three groups of patients

| Histopathologic Feature | Prednisone Group | O3FA Group | Placebo Group | *P* Difference |
|---|---|---|---|---|
| No. of patients | 29 | 31 | 29 | |
| Time interval between renal biopsy and study entry (mo) | 14 ± 19 | 16 ± 27 | 9 ± 13 | 0.60,[a] 0.45[b] |
| No. of glomeruli (%) | 20 ± 9 | 19 ± 26 | 17 ± 9 | 0.72,[a] 0.77[b] |
| Endocapillary hypercellularity (%) | 26 ± 22 | 37 ± 29 | 44 ± 25 | 0.04,[a] 0.59[b] |
| Cellular or fibrocellular crescents (%) | 5 ± 6 | 6 ± 9 | 9 ± 9 | 0.17,[a] 0.45[b] |
| Fibrotic crescents (%) | 9 ± 9 | 10 ± 12 | 13 ± 15 | 0.60,[a] 0.71[b] |
| Segmental glomerulosclerosis (%) | 23 ± 14 | 27 ± 19 | 30 ± 18 | 0.35,[a] 0.89[b] |
| Interstitial fibrosis (grades 1 to 4) | 1.4 ± 0.9 | 1.4 ± 0.8 | 1.2 ± 0.7 | 0.42,[a] 0.53[b] |

[a]Prednisone group *versus* placebo group.
[b]O3FA group *versus* placebo group.

*Table 3.* Proportional hazards model for time to failure

| Effect | Hazard Ratio | 95% Confidence Interval |
|---|---|---|
| Analysis of treatment | | |
| prednisone group | 0.551 | (0.101 to 3.009) |
| O3FA group | 2.031 | (0.611 to 6.751) |
| Analysis of treatment and proteinuria | | |
| prednisone group | 0.308 | (0.053 to 1.798) |
| O3FA group | 1.348 | (0.400 to 4.546) |
| UP/C ratio | 2.694 | (1.299 to 5.586) |

*Table 4.* Number of patients in each group with UP/C <1 and <50% baseline in >50% of clinic visits

| Group | Patients with UP/C >1 in >50% of Visits | Patients with UP/C >50% of Baseline in >50% of Visits |
|---|---|---|
| Prednisone group | 4 (15%) | 3 (12%) |
| O3FA group | 14 (50%) | 8 (29%) |
| Placebo group | 8 (29%) | 6 (21%) |
| Total | 26 (32%) | 17 (21%) |

arms with respect to the percentage of visits with UP/C ratio >50% or the proportion of patients whose UP/C ratio was >50% of baseline at more than half of their visits.

There was a significant difference between treatment arms with respect to serum albumin levels at baseline ($P = 0.018$). Significant treatment differences with respect to changes from baseline were detected for AST ($P = 0.041$), triglyceride ($P = 0.041$), and white blood cell levels ($P = 0.005$). Other laboratory studies were comparable in the three groups and over time (Table 5).

Phospholipid fatty acid profiles that were obtained in 23 patients who received O3FA and 13 who received placebo capsules are shown in the Figure 1. This figure shows a clear difference between these two groups with respect to omega 3/omega 6, EPA/AA (arachidonic acid), and DHA/AA ratios and confirms the marked effect of the O3FA on the phospholipid fatty acid profile in the treated patients.

### *Adverse Events*

There was a significant difference between the prednisone group and the placebo group with respect to the incidence of heartburn (48 *versus* 16%; $P = 0.018$) and increased appetite (73 *versus* 32%; $P < 0.001$). Although weight gain (67 *versus* 42%) and anxiety tended to be more frequently reported in the prednisone group, this was not statistically significant.

## Discussion

The results in this trial do not support the hypothesis that patients with IgAN derive significant benefit from the use of either prednisone or O3FA. However, interpretation of the effects of a 2-yr course of each of these study drugs was affected by the fact that the level of proteinuria in patients who were randomly assigned to receive placebo was less than that in patients who received one of the study drugs. In addition, our inability to enroll an adequate sample size resulted in the power for each comparison of active treatment with placebo to be only 0.63. Furthermore, the observed cumulative proportion of treatment failures after 3 yr of follow-up was not significantly different than the postulated rates of 5% for each treatment group and 20% for the placebo group. Finally, it is important to note that five of the 14 treatment failures that were observed in our trial occurred after 36 mo of follow-up, which indicates that the rate of progression is not constant over time. As a result of these concerns, we propose that further studies be conducted to evaluate the response to corticosteroids and O3FA in a larger number of patients over a more prolonged period before definite conclusions can be drawn. The design of future studies should incorporate considerations that reflect the variability of the rate of progression over time (43).

The imbalance in study groups with respect to the severity of proteinuria at the time of study entry is relevant because in recent years, mounting evidence has shown that increasing levels of proteinuria are a harbinger of progressive renal dysfunction and that

*Table 5.* Changes in median laboratory values in the three patient groups

| | Prednisone Group | | O3FA Group | | Placebo Group | |
|---|---|---|---|---|---|---|
| | Start | End | Start | End | Start | End |
| No. of patients | 30 | 20 | 30 | 24 | 29 | 24 |
| Serum creatinine (mg/dl) | 1.0 | 1.0 | 0.9 | 1.1 | 0.8 | 1.1 |
| Blood urea nitrogen (mg/dl) | 15 | 18 | 14 | 15 | 17 | 16 |
| Alkaline phosphatase (IU/L) | 79 | 82 | 84 | 80 | 109 | 104 |
| Albumin (g/d) | 3.9 | 4.1 | 3.6 | 3.9 | 4.0 | 4.2 |
| Total serum protein (g/dl) | 6.8 | 7.1 | 6.6 | 6.9 | 6.8 | 7.2 |
| ALT (IU/L) | 20 | 20 | 15 | 16 | 12 | 18 |
| Serum glucose (mg/dl) | 92 | 85 | 90 | 89 | 90 | 90 |
| Serum cholesterol (mg/dl) | 213 | 207 | 202 | 215 | 210 | 204 |
| Serum triglyceride (mg/dl) | 141 | 200 | 151 | 124 | 144 | 168 |
| Serum LDL cholesterol (mg/dl) | 126 | 123 | 118 | 134 | 121 | 117 |
| Serum HDL cholesterol (mg/dl) | 49 | 51 | 45 | 50 | 45 | 44 |
| Hemoglobin (g/dl) | 14.1 | 13.9 | 13.6 | 13.8 | 13.0 | 14.6 |
| WBC count | 6300 | 9500 | 6600 | 6000 | 6100 | 5800 |

[a]"End" refers to values recorded at 24-mo visit. WBC, white blood cell.

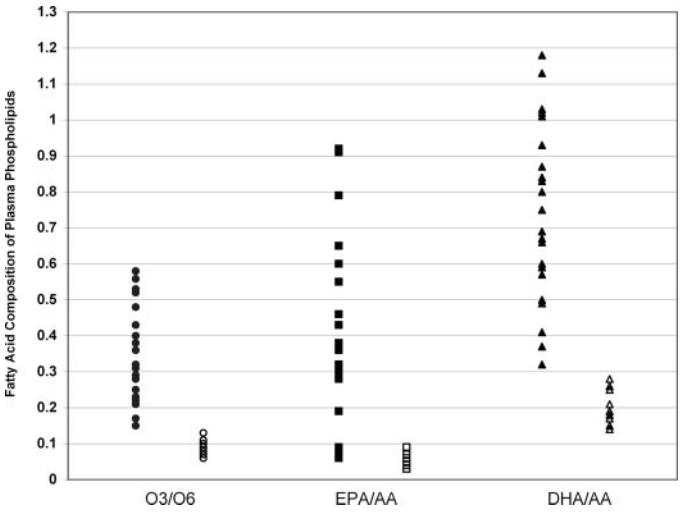


*Figure 1.* Fatty acid composition of plasma phospholipids in patients who received active treatment (filled symbols) *versus* placebo (open symbols). The three sets of data show (*1*) ratio of omega 3/omega 6 fatty acids (O3/O6), (*2*) ratio of eicosapentaenoic acid/arachidonic acid (EPA/AA), and (*3*) ratio of docosahexaenoic acid (DHA/AA).

proteinuria may be the cause of at least some of this renal injury. The importance of proteinuria in causing progressive renal injury is supported by our findings that baseline proteinuria was significantly associated with time to failure ($P = 0.009$). The relatively low UP/C ratio in our placebo group may provide a partial explanation for the apparent discrepancy between some of our findings and those obtained by Donadio *et al.* (26). The placebo failure rate in their study was 33% in comparison with 13% in our study. If we had observed a similar placebo failure rate of 33%, then our prednisone group would show statistically significant benefit with a failure rate of 6%. In contrast, the O3FA failure rate in our study is 25 *versus* 6% in the Mayo Collaborative Group study.

A potentially important difference between the study population in our study and those studied previously is that many of the participants in our study were younger, with half of them being adolescents. There are several implications of this difference. Because our patients are younger, they may be at an earlier stage of disease and the progression rates over the period of study may be lower for all groups, including placebo. Younger participants may be consuming a more fatty diet, which may reduce the absorption of the fish oil. In addition, compliance among younger patients to the fish oil (which has a distinctive odor and breath odor) may be lower because they are likely to be more image conscious than older patients. Compliance in this population also may be lower as a result of motivational factors inasmuch as it may be more difficult for them to comprehend fully the long-term risk of their IgAN and act on reducing those risks. However, the O3FA-induced changes in our patients were similar to those reported by Donadio *et al.* (26), making this a less likely explanation.

The relatively short duration of follow-up of the patients in our study also is worthy of comment. It is widely known that IgAN often is a very slowly progressive disease and, as a result, that there usually is the need for a prolonged period of evaluation before meaningful conclusions can be drawn with respect to changes in GFR. This is exemplified by the fact that five of the 14 treatment failures in our study occurred after 3 yr of follow-up. Although our goal was to study each patient for at least 5 yr, many of the patients in our trial were followed for shorter periods, thereby reducing the likelihood of detecting a significant difference in GFR.

Recent clinical trials of patients with various glomerular diseases that are associated with proteinuria have shown a positive correlation between persistence of proteinuria and progressive renal insufficiency and have concluded that

changes in the level of proteinuria provide a good surrogate marker for response to therapy. However, the lack of uniformity in the entry levels of proteinuria in the patients in our trial compromised our ability to use raw proteinuria data in this analysis. We therefore assessed this risk factor in two alternative ways (Table 4). The first approach was to determine whether serial measurements of UP/C levels were >1 in >50% of the study visits and whether this differed between the groups. However, this approach also is of questionable value in our study because the initial UP/C levels were not equal across the three groups. The second approach was to determine how often the follow-up UP/C ratios remained at levels ≥50% of the baseline values. This analysis revealed that only 21% of the patients had levels that remained in this range during the course of follow-up. There was no apparent differences between groups, although the prednisone group tended to be lower, *i.e.*, only 12% of the prednisone group maintained UP/C ratios >50% of baseline in >50% of the study visits.

## Conclusion

The final outcome analysis in this trial was limited by a number of factors, some of which must be addressed in future studies of IgAN and other renal diseases that are associated with significant proteinuria. In the meantime, it is not possible to derive any definitive recommendations regarding the use of corticosteroids or fish oil supplements on the basis of the results obtained in this trial.

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## Appendix

*Appendix.* Participating centers/investigators

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| The Nemours Children's Clinic | Jorge Ramirez, MD |
| University of Rochester | Melissa Gregory, MD |
| University of Michigan | Joseph Flynn, MD, and Sean Leavey, MD |
| Carolina's Medical Center, Charlotte | Susan Massengill, MD |
| Gunderson Lutheran/LaCrosse | Philip Dahlberg, MD |

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