

Original Article

Combined treatment with renin–angiotensin system blockers and polyunsaturated fatty acids in proteinuric IgA nephropathy: a randomized controlled trial

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Abstract

Background. Currently, several therapeutic protocols exist for IgA nephropathy (IgAN); results in slowing the progression to end-stage renal disease (ESRD) are variable, but ~30–40% of patients require replacement therapy (dialysis or renal transplantation) by 20 years from the onset. The adverse effects brought by the chronic assumption of drugs can be a potential limit. Actually, the most used therapies for IgAN are renin–angiotensin system blockers (RASB), glucocorticoids and immunosuppressive agents. Trials with polyunsaturated fatty acids (PUFA) in IgAN have been done since the first successful attempt by Hamazaki in 1984, resulting in alternate answers, but no trials have ever been done testing the efficacy of combined therapy with RASB and PUFA.

Methods. We tested the effect of a 6-month course of PUFA (3 grams/day) in a group of 30 patients with biopsy-proven IgAN and proteinuria already treated with RASB randomized to receive PUFA supplementation or to continue their standard therapy. The primary end-point was the percent reduction of proteinuria from the baseline. Secondary end-points were modifications in glomerular filtration rate (GFR), blood pressure, serum triglycerides and erythrocyturia.

Results. At the end of the 6-month trial, the percent reduction of proteinuria was 72.9% in the PUFA group and 11.3% in the RASB group ($P < 0.001$). A reduction of $\geq 50\%$ of baseline proteinuria was achieved in 80.0% of PUFA patients and 20.0% of RASB patients ($P = 0.002$). Erythrocyturia was significantly lower in the PUFA group ($P = 0.031$). No significant changes in renal function, blood pressure and triglycerides were observed.

Conclusions. PUFA associated with RASB reduced proteinuria in patients with IgAN more than RASB alone.

Keywords: IgA nephropathy; kidney diseases; polyunsaturated fatty acids; proteinuria; renin–angiotensin system blockers

Introduction

IgA nephropathy (IgAN) is the most common primary glomerulonephritis throughout the world [1]; end-stage renal disease (ESRD) occurs in ~40% of patients by 20 years from the onset [2]. Risk factors associated with a poorer outcome are impaired renal function at diagnosis, high blood pressure (BP) and entity of urinary protein excretion [3]. Proteinuria has proven to be the most important predictor of renal failure, and therapeutic efforts have been focused on its reduction [4,5]. Drugs used to slow the progression of disease are steroids [6–8], renin–angiotensin system blockers (RASB), including angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB) [9,10] and immunosuppressive agents such as azathioprine [11], mofetil mycophenolate [12] and cyclophosphamide [13].

Polyunsaturated fatty acids (PUFA) are substrates for the acids of the α -linolenic series; studies in animal models of kidney disease showed that high levels of PUFA cause a shift of eicosanoid production from the α -linoleic fatty acids to molecules with a lower ability to activate inflammatory response, vascular permeability and chemotaxis. As a result, a broad immunomodulation occurs with reduction in cell-mediated cytotoxicity and antigen presenting activity. In these preclinical studies, PUFA administration has been associated with a reduction in transforming growth factor beta [14], urinary protein excretion and proliferation of mesangial cells [15,16]. These evidences provide the physiopathological basis for PUFA administration in IgAN [17].

Since the first, successful report by Hamazaki *et al.* [18] more than 20 years ago, however, clinical trials designed to investigate the role of PUFA in IgAN patients showed

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inconsistent findings [19–27]. As pointed out by a meta-analysis on this subject [23], a possible cause for the unclear outcomes observed in clinical trials may be the differences in inclusion criteria adopted (resulting in different study populations), dose or composition of the fish oil used and duration of treatment. Recently, two of the investigators reviewed their data and found a relation between size-adjusted dose of PUFA and proteinuria reduction [28] or kidney function [29].

In the majority of the studies, PUFA were administered as a high-dosage ‘rescue therapy’ to aggressively treat IgAN patients refractory to first-line treatments with deteriorating renal function. Less data are available to verify the efficacy and safety of PUFA as an addition to classic first-line therapies like ACE inhibitors and ARB in mild to moderate IgAN. In fact, to the best of our knowledge, there are no trials performed to test the effects of PUFA in association with RASB in IgAN. We designed this controlled study to evaluate the effect of an oral supplementation of PUFA to both ACE inhibitors and ARB for 6 months in proteinuric patients with IgAN.

Methods

Patients and measurements

The study started in November 2004 at the Renal Unit of the Catholic University of Rome, after approval by the local ethics committee. We decided to consider eligible for enrolment patients with biopsy-proven IgAN and persistent proteinuria (>200 mg/day) despite treatment with ACE inhibitors and/or ARB. Exclusion criteria were dialysis or kidney transplantation, diabetes mellitus, Henoch–Schoenlein purpura, systemic lupus erythematosus and an active or recent (<1 year) treatment with immunosuppressors and/or PUFA.

Patients with histologic diagnosis of IgAN from the database of renal biopsies performed in our centre were contacted (if not already followed in our facility). Of 78 IgAN patients, 2 were dead, 9 were on ESRD (dialysis or transplantation), 4 had a diagnosis of diabetes mellitus, 10 had a history of recent immunosuppressive treatment, 1 did not give his consent. In the remaining 52 patients, after written informed consent was given, three determinations of 24-h proteinuria were performed on different days. Only the patients with at least two positive determinations were recruited.

Thirty proteinuric patients were recruited, and during a 3-week run-in period, their RASB therapy was standardized (ramipril 10 mg/day and irbesartan 300 mg/day), BP and body weight recorded and specimens of blood and urine taken for serum creatinine, triglycerides and erythrocyturia assays. We considered as baseline 24-h proteinuria a mean of the positive measurements obtained before the run-in period, to avoid the effect of RASB titration. The estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) equation [30]. Erythrocyturia was classified as follows: 1 (5–10 red blood cells [rbc]/high power field [hpf]), 2 (11–20 rbc/hpf) or 3 (21–30 rbc/hpf).

Patients were also categorized into high proteinuria (HP) or low proteinuria (LP) subgroups; the cut-off point (1000 mg/day), actually accepted as an independent risk factor for progression of nephropathy, was set based on the MDRD study [31].

After the run-in period, patients were randomly assigned to continue RASB alone (control group) or to add 3 g/day of PUFA (85% eicosapentaenoic acid + docosahexaenoic acid) in the form of three 1-gram soft capsules. Randomization was performed by a random number generator included in the statistical software. No immunosuppressive treatment was allowed during the study period; other anti-hypertensive drugs could be administered to control BP, but the doses of RASB and PUFA could not be changed.

Patients were visited monthly in our outpatient facility to evaluate BP, blood and urine parameters and possible adverse effects. During these visits, PUFA patients were given their monthly supply of fish oil and were asked to bring back the remaining capsules for compliance assessment, calculated as percent of the prescribed drug effectively taken.

The last patient completed the study in February 2006.

End-points

The primary end-point was the percent reduction of proteinuria from baseline after 6 months. Secondary end-points were percent changes in eGFR, erythrocyturia, BP and serum triglycerides from the baseline.

Statistics

Baseline and outcome data were presented as mean \pm SD or total number (percentual frequency) as appropriate and analysed for significant differences using paired and unpaired *t*-tests for continuous variables (after check for normal distribution by the Shapiro–Wilk test), the chi-square test and Fisher’s exact test for categorical variables. Relations between variables were analysed by univariate regression and included in stepwise multivariate models for $P < 0.25$. For predictors of dichotomous variables, logistic regression was performed; the obtained odds ratio (OR) was converted in adjusted relative risk (RR) using the model proposed by Zhang *J et al.* [32].

The accepted level for a two-tailed significant difference was $P < 0.05$.

Statistics were performed using SPSS version 13.0 (Statistical Product and Services Solutions, SPSS Inc., Chicago, IL, USA). Figures were obtained with GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA).

Results

Patients

Table 1 shows baseline demographic, clinical and biochemical characteristics of the two groups. The patients were homogeneous except for haematuria, which was statistically higher in the PUFA group. All patients showed dosable proteinuria ranging from 200 to 4500 mg/day, and were

Table 1. Baseline characteristics of the study population

	PUFA group (n = 15)	Control group (n = 15)	P-value
Age (years)	39.5 ± 15.3	41.5 ± 15.6	0.73
Male sex, no. (%)	7 (46.6)	11 (73.3)	0.13
Months from renal biopsy	31.5 ± 26.8	35.1 ± 29.5	0.73
Systolic BP (mmHg)	125.0 ± 23.9	121.7 ± 20.7	0.68
Diastolic BP (mmHg)	75.3 ± 10.1	76.0 ± 11.4	0.86
Mean BP (mmHg)	91.9 ± 14.3	91.2 ± 13.7	0.89
Body weight (kg)	68.4 ± 13.5	71.2 ± 14.0	0.59
eGFR (ml/min)	90.6 ± 42.3	72.8 ± 37.3	0.23
CE, no. (%)			0.009
1	2 (13.3)	10 (66.7)	
2	8 (53.3)	4 (26.7)	
3	5 (33.3)	1 (6.7)	
UPE (mg/day)	1307 ± 1203	1447 ± 1080	0.74
HP subgroup, no. (%)	8 (53.3)	9 (60.0)	0.71
Triglycerides (mg/dl)	143.1 ± 143.3	170.3 ± 131.6	0.59

Plus-minus values are mean ± SD. PUFA, polyunsaturated fatty acids; BP, blood pressure; eGFR, estimated glomerular filtration rate; CE, class of erythrocyturia; UPE, urinary protein excretion; HP, high proteinuria (≥1000 mg/day).

Table 2. Stepwise multivariate regression model for baseline UPE

	B (SEB)	Beta	Adjusted R ²	P-value
Body weight	32.2 (14.4)	0.39	0.12	0.012
Gender				0.29
Baseline mean BP				0.19

UPE, urinary protein excretion; SEB, standard error of B; BP, blood pressure.

taking ACE inhibitors (*n* = 13), ARB (*n* = 9) or both (*n* = 8) before the run-in period, without substantial differences in the two groups. One PUFA patient and two controls had a history of steroid administration (completed 22, 36 and 28 months before randomization, respectively).

Most of the patients showed preserved kidney function and normal BP with a baseline eGFR <60 ml/min in only nine (30.0%) patients, and baseline BP values >140/90 mmHg in only two (6.6%) patients.

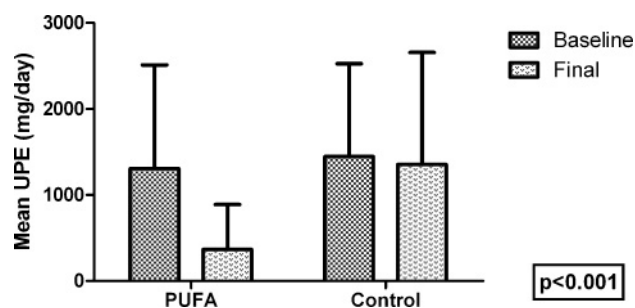
In univariate analysis, baseline proteinuria showed a correlation with baseline triglycerides (*r* = 0.69, *P* < 0.001), body weight (*r* = 0.39, *P* = 0.033) and baseline mean BP (*r* = 0.36, *P* = 0.053), and was higher in males than females (1711 ± 1255 versus 875 ± 668 mg/day, *P* = 0.025). No relations were found between baseline proteinuria and age, months from renal biopsy and baseline eGFR.

In multivariate analysis, entering baseline mean blood pressure, gender and body weight as predictors of baseline proteinuria, only body weight resulted as an independent predictor (*P* = 0.012). Results of multivariate analysis on baseline proteinuria are shown in Table 2.

Proteinuria reduction

Table 3 shows complete results after 6 months.

Patients treated with PUFA showed a significant reduction in proteinuria with a mean percent reduction from the baseline of 72.9%, compared with a mean percent re-

**Fig. 1.** Proteinuria at 6 months. UPE, urinary protein excretion; PUFA, polyunsaturated fatty acids.

duction from the baseline of 11.3% in the control group (*P* < 0.001) (Figure 1).

Effective proteinuria reduction, intended as a percent reduction from baseline ≥50%, was achieved in 12 (80.0%) PUFA patients, compared to only three (20.0%) controls (RR 4.0, 95% confidence intervals [CI] 1.4–11.3, *P* = 0.002). The difference between the two groups remained significant (RR 4.1, 95% CI 1.8–4.9, *P* = 0.008) after correction for age, months from renal biopsy, gender, baseline values of proteinuria, eGFR and mean BP.

Five (33.3%) PUFA subjects showed a complete negativization of proteinuria, whereas no patient in the control group achieved this goal (*P* = 0.042).

In a further analysis of the HP subgroups, in the PUFA group mean proteinuria fell from 2088 to 588 mg/day with a 68.6% reduction from the baseline, while in the control group proteinuria went from 2022 to 1944 mg/day with only a 5.3% reduction (*P* = 0.004). In 5 (33.3%) PUFA patients and in one (6.6%) control, proteinuria fell below 500 mg/day (*P* = 0.05).

In the PUFA group, HP and LP subgroups were similar with regard to percent reduction (−77.9 ± 29.7 versus −68.6 ± 28.9%, *P* = 0.55) and final values of proteinuria (587 ± 627 versus 114 ± 186 mg/day, *P* = 0.077), whereas final proteinuria remained significantly different in HP and LP controls (1944 ± 1395 versus 467 ± 273 mg/day, *P* = 0.013).

In univariate analysis, none of the continuous variables tested (age, baseline values of proteinuria, eGFR and mean BP, months from renal biopsy, body weight) resulted as significantly associated with percent variation of proteinuria, even if body weight was almost significant (*r* = 0.35, *P* = 0.055). With regard to categorical predictors, proteinuria reduction resulted as significantly smaller in males compared with females (−28.0 ± 45.5 versus −63.2 ± 43.8%, *P* = 0.044).

Variables considered as predictors of proteinuria reduction in multivariate analysis were treatment group, gender and body weight. The prediction model showed that the only factor affecting proteinuria variation was treatment allocation (*P* < 0.001) (Table 4).

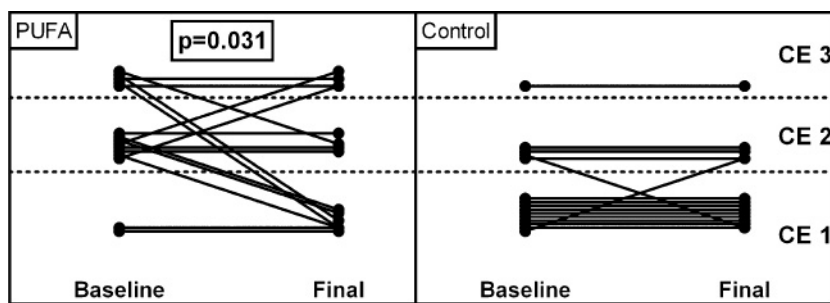
Secondary outcomes

Analysis of eGFR percent variation showed no significant differences in the two groups (*P* = 0.119) and this result did not change after adjustment for baseline eGFR values.

Table 3. Results

	PUFA group (<i>n</i> = 15)		Control group (<i>n</i> = 15)		<i>P</i> -value
	Baseline	Final	Baseline	Final	
UPE (mg/day)	1307 ± 1203	367 ± 520	1447 ± 1080	1353 ± 1304	<0.001
eGFR (ml/min)	90.6 ± 42.3	93.9 ± 35.4	72.8 ± 37.3	67.7 ± 35.0	0.11
CE, no. (%)					0.031
1	2 (13.3)	7 (46.7)	10 (66.7)	10 (66.7)	
2	8 (53.3)	4 (26.7)	4 (26.7)	4 (26.7)	
3	5 (33.3)	4 (26.7)	1 (6.7)	1 (6.7)	
Systolic BP (mmHg)	125.0 ± 23.9	123.0 ± 20.3	121.7 ± 20.7	123.0 ± 19.9	0.36
Diastolic BP (mmHg)	75.3 ± 10.1	75.3 ± 9.3	76.0 ± 11.4	76.7 ± 9.0	0.68
Mean BP (mmHg)	91.9 ± 14.3	91.2 ± 12.8	91.2 ± 13.7	92.1 ± 12.0	0.84
Triglycerides (mg/dl)	143.1 ± 143.3	145.7 ± 143.4	170.3 ± 131.6	184.3 ± 167.3	0.87

Plus-minus values are mean ± SD. Significance values refer to comparison between groups. PUFA, polyunsaturated fatty acids; UPE, urinary protein excretion; eGFR, estimated glomerular filtration rate; CE, class of erythrocyturia; BP, blood pressure.

**Fig. 2.** Erythrocyturia at 6 months. CE, class of erythrocyturia; PUFA, polyunsaturated fatty acids.**Table 4.** Stepwise multivariate regression model for UPE reduction

	B (SEB)	Beta	Adjusted <i>R</i> ²	<i>P</i> -value
Treatment group	57.6 (13.2)	0.62	0.46	<0.001
Gender				0.72
Body weight				0.12

UPE, urinary protein excretion; SEB, standard error of B.

Patients treated with PUFA showed a significant improvement of erythrocyturia with six (40.0%) patients reducing the urinary erythrocyte excretion class compared with one (6.7%) control (*P* = 0.031) (Figure 2).

Final values of BP and triglycerides did not differ in the two groups.

Compliance and safety data

Patients treated with PUFA showed a good compliance with their scheduled therapy, with a mean percent of pills taken of 83.7 ± 14.2%. Associated therapy was well tolerated with no adverse effects reported for neither PUFA nor RASB. No hyperkalaemia (serum potassium > 5.5 mEq/l) occurred. We did not experience any dropout during the study period.

Discussion

Despite the available therapeutic options, 35–40% of patients affected by IgAN still develop ESRD and require

dialysis or organ transplantation. Of the known risk factors, the most important and potentially modifiable is proteinuria, whose control has been associated with outcome improvement [5]. A classic strategy adopted in proteinuric patients, especially those with a preserved renal function, is the inhibition of the renin–angiotensin–aldosterone system by means of RASB, but this is not always sufficient to achieve a complete negativization of proteinuria.

With these premises, we tested the hypothesis that in IgAN patients with proteinuria not fully controlled with RASB, an amelioration could be obtained by the anti-inflammatory and immunomodulating properties of PUFA.

Our randomized controlled trial showed an important reduction of proteinuria after 6 months of combined therapy with RASB (ramipril 10 mg/day and irbesartan 300 mg/day) and PUFA (3 g/day) compared to RASB alone in a group of 30 proteinuric IgAN patients already treated with RASB. A reduction of ≥50% of baseline proteinuria levels and final values of proteinuria <500 mg/day have been achieved with a fourfold and fivefold higher frequency in PUFA patients, respectively.

The association of RASB and PUFA was especially effective in patients with proteinuria ≥1000 mg/day, as PUFA patients in the HP subgroup showed final values of proteinuria almost comparable to those of the LP subgroup (*P* = 0.077), whereas it remained substantially different after 6 months in RASB HP and LP patients (*P* = 0.013).

The probable cause of the additional proteinuria reduction achieved by PUFA administration is the anti-inflammatory effect, as suggested by the significant

reduction in haematuria, a known marker of inflammation in IgAN patients, even if not regarded as a prognostic tool.

Final triglycerides values were not different in the two groups, even if PUFA are generally given to reduce triglycerides levels in dyslipidaemic populations [33]. This finding is consistent with other studies of PUFA in IgAN [22] and may be related to the peculiar and not completely known effects of proteinuria on lipid metabolism [34,35].

Our study has two points of weakness. First, we did not use a placebo in the RASB group and the open-label nature of the trial could somehow partially account for the striking results observed. Second, the use of a single randomization list, rather than a list balancing enrolment between subgroups in each group, introduced a distortion between treatment groups, with the control group having lower baseline values of eGFR, higher proteinuria and prevalence of male sex; anyway, these differences were not statistically significant and they were considered as controllers in multivariate analyses when appropriate. Moreover, the eGFR was not a primary outcome and male sex could have played a greater role in a study with a longer follow-up and with renal survival as the primary outcome.

In conclusion, our work defines an effective, well-tolerated and original use for PUFA in association with RASB in IgAN patients with preserved renal function and refractory proteinuria.

Conflict of interest statement. None declared.

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