Therapy of post-renal transplantation hyperlipidaemia: comparative study with simvastatin and fish oil

R. Castro, J. Queirós, I. Fonseca, J. P. S. Pimentel, A. C. Henriques, A. M. Sarmento, S. Guimarães and M. C. Pereira

Transplant Department, Hospital Geral de Santo António, Porto, Portugal

Abstract

Background. Recipients of renal transplantation (RT) exhibit disturbances of serum lipids and apoproteins that may contribute to their cardiovascular morbidity and mortality. In our renal transplant department the hypercholesterolaemia prevalence at the first and fifth year of RT is 70.0% and 81.2%, respectively. Lipid-lowering therapy has been utilized in many Transplant Units. The aim of our study was to evaluate post-RT hyperlipidaemia control with simvastatin or fish oil.

Methods. Forty-three RT patients (26 men and 17 women) with persistent hypercholesterolaemia and stable graft function which were resistant to a lipid-lowering diet (American Heart Association Step Two) were randomized into two groups and treated for 3 months with simvastatin (S) (10 mg/day; n = 25) and fish oil (F) (6 g/day; n = 18). Total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), lipoprotein a (Lp(a)), apolipoprotein A1 (Apo A1), and apolipoprotein B (Apo B) were monitored and at the study baseline they were similar between the two groups.

Results. No side effects were detected after 3 months of therapy. In group S, the concentrations of TC (271 ± 46 mg% vs 228 ± 49 mg%; P < 0.001), TG (180 ± 78 vs 134 ± 45; P < 0.01), LDL-C (177 ± 40 vs 144 ± 43; P < 0.01) and Apo B (96 ± 18 vs 82 ± 16; P < 0.001) were significantly reduced, and Apo A1 concentration had increased (135 ± 24 vs 149 ± 30; P < 0.01). In group F, the concentrations of TC (266 ± 25 vs 240 ± 31; P < 0.001), TG (203 ± 105 vs 156 ± 72; P = 0.02) and HDL-C (63 ± 15 vs 53 ± 12; P < 0.01) were significantly reduced.

Conclusions. We concluded that low-dose simvastatin and fish oil are both effective and safe in correcting post-RT hyperlipidaemia. Further prospective studies with larger follow-up are needed to clarify whether this therapy has an impact on cardiovascular morbidity and mortality in RT patients.

Key words: fish oil; hyperlipidaemia; renal transplantation; simvastatin

Introduction

Atherosclerosis associated with hyperlipidaemia is a major cause of morbidity and mortality after renal transplantation (RT) [1]. About 40% of deaths in RT recipients are attributed to cardiovascular complications [2]. Intensive lipid-lowering therapy can reduce the incidence of cardiovascular events by retarding the progression of coronary artery disease [3]. Chronic rejection is the main cause of graft failure after the first year post-RT and the obstructive changes to the arteries and arterioles represent a main feature of the denominated ‘graft atherosclerosis’ [4].

Several approaches to the treatment of post-RT hyperlipidaemia have been advocated. β-hydroxy-β-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor therapy has been reported to improve lipid abnormalities in RT patients [5]. Low-dose simvastatin (10 mg/day) has been successfully used to improve hyperlipidaemia in RT patients on cyclosporine [6].

Fish oil, containing high concentrations of marine omega-3 polyunsaturated fatty acids such as eicosapentaenoic acid (EPA, C20:5ω3) and docosahexaenoic acid (DHA, C22:6ω3), are known to exert beneficial effects on serum lipid concentrations [7] and mortality from coronary artery disease or cerebrovascular accidents [8]. It has also been associated with a reduced rate of graft function deterioration in RT chronic rejection [9,10].

The objective of our study was to evaluate the efficacy of simvastatin and fish oil in post-RT hyperlipidaemia treatment.

Subjects and methods

Seventy-seven (77) patients ≥1 year post-RT, with stable renal function and persistent hypercholesterolaemia (total cholesterol >200 mg%; mean: 292 ± 48 mg%) were given a
Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Group S (n=25)</th>
<th>Group F (n=18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.6±9.4</td>
<td>43.4±11.7</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (% M/F)</td>
<td>44/56</td>
<td>33/67</td>
<td>ns</td>
</tr>
<tr>
<td>Time of dialysis (months)</td>
<td>67.7±24.2</td>
<td>68.0±26.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Graft follow-up (months)</td>
<td>71.5±21.6</td>
<td>69.2±22.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.4±0.3</td>
<td>1.5±0.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25±4.2</td>
<td>24.8±2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total PRD dose (mg/kg)</td>
<td>388±145</td>
<td>394±179</td>
<td>ns</td>
</tr>
<tr>
<td>CsA dose (mg/kg/day)</td>
<td>3.8±1.2</td>
<td>3.8±1.1</td>
<td>ns</td>
</tr>
<tr>
<td>CsA concentration (ng/ml)</td>
<td>186±38</td>
<td>189±30</td>
<td>ns</td>
</tr>
<tr>
<td>Proteinuria (yes/no)</td>
<td>5/20</td>
<td>7/11</td>
<td>ns</td>
</tr>
<tr>
<td>Proteinuria (mg/24 h)</td>
<td>0 [0–8600]</td>
<td>0 [0–3000]</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>141±17</td>
<td>145±13</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>81±12</td>
<td>86±14</td>
<td>ns</td>
</tr>
<tr>
<td>Anti-hypertensive treatment*</td>
<td>17/8</td>
<td>13/5</td>
<td>ns</td>
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</tbody>
</table>

Values are means±SD except for 24-h proteinuria, where medians and ranges are shown. All values are expressed to the nearest ten.

*Including enalapril (group S: 14, group F: 11), nifedipine (6–5), dihydramine (0–1), minoxidil (0–1), amloidpine (1–0), atenolol (2–2), propranolol (1–1), metildopa (1–1), clonidine (1–0).

cholesterol reduction diet with instruction (American Heart Association, Step Two) for 12 weeks. Thirteen patients were excluded for non-compliance.

Thereafter, serum cholesterol of 43 RT patients (26 men and 17 women) remained elevated. These 43 RT patients were randomized between groups S and F after their informed consent, and medicated for 3 months with: simvastatin (10 mg/day; group S, n=25) or fish oil (6 g of fish oil containing 30% EPA [C20:5n-3] and 20% DHA [C22:6n-3] and 0.5 mg of vitamin E per day; group F; n=18).

Patient details at study baseline including age, sex, time of dialysis, graft follow-up, creatinine, body mass index, total prednisolone (PRD) dose, cyclosporine (CsA) dose, CsA concentration, 24-h urinary protein excretion, blood pressure, antihypertensive treatment, and serum lipid profile, are given methods with commercially available standards and antisera concentrations, 24-h urinary protein excretion, blood pressure, A1 and Apo B were measured by immunoturbidimetric method. LDL-C was calculated using the Friedewald formula (11). Serum Lp(a) was measured by an enzymatic immunoradiometric assay. Apo A1 and Apo B were measured by immunoturbidimetric methods with commercially available standards and antisera (Boehringer-Mannheim® GmbH, Mannheim, Germany). HDL-C was measured using the same reagents for the phosphotungstic acid precipitation method. HDL-C was calculated using the Friedewald formula (11). Serum Lp(a) was measured by an enzymatic immunoradiometric assay. Apo A1 and Apo B were measured by immunoturbidimetric methods with commercially available standards and antisera (Boehringer-Mannheim®). At baseline, there were no significant differences in lipids between groups S and F (Table 2).

The antihypertensive treatment generally consisted of enalapril (14/17 for group S and 11/13 for group F). Five patients of group S and six patients of group F received two antihypertensive drugs. A triple antihypertensive treatment was administered to two patients of both groups.

β-Blockers were part of the antihypertensive treatment in three patients of group S and four patients of group F. All these patients were on double or triple antihypertensive treatment (mean: 2.4±0.8 vs 1.4±0.5 antihypertensive drugs in the remaining patients; P<0.01), indicating that β-blockers were used as a second-line drug. Furthermore they had a different lipid profile compared to the remaining patients of the study (n=36), with greater baseline values of LDL-C (197±59 vs 168±26 mg/dl; P=0.04) and ApoB (105±25 vs 90±13 mg/dl; P=0.02) and lower values of HDL-C (51±14 vs 63±15 mg/dl; P=0.04) for similar body mass index (23.4±1.8 vs 25.6±3.8 kg/m²; P not significant).

Only one patient in group S (none of group F) received triple immunosuppressive maintenance therapy (CsA+PRD+Azathioprine). The remainder were maintained with double therapy (CsA+PRD). The CsA concentrations were measured monthly during the study and did not differ between the two groups.

Serum concentrations of TC, HDL-C, LDL-C, TG, Lp(a), Apo A1, and Apo B were determined in the early morning after a 12–14 h overnight fast. The serum was previously separated and stored at 4°C. Standard enzymatic methods were used to measure TC and TG (CHORD-PAP reagents; Boehringer-Mannheim® GmbH, Mannheim, Germany).

Statistical analysis was performed by Student’s paired t test. All data are reported as mean±SD, except for urinary protein excretion and Lp(a) that were expressed in terms of median and range. Data analysis was performed using the Mann–Whitney U test or the Student’s t-test for comparison of continuous variables with abnormal or normal population distributions, respectively. Differences were considered significant at P<0.05.

Results

All the patients were able to complete the 3-month study. None reported adverse effects with respect to the digestive, musculoskeletal, or respiratory systems, skin and skin appendages, special senses, or bleeding

Table 2. Plasma lipid concentrations after 3 months of simvastatin or fish oil therapy

<table>
<thead>
<tr>
<th></th>
<th>Group S (n=25)</th>
<th>Group F (n=18)</th>
<th>P</th>
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<tbody>
<tr>
<td>TC (mg%)</td>
<td>271±46</td>
<td>228±49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mg%)</td>
<td>180±78</td>
<td>134±45</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL-C (mg%)</td>
<td>177±40</td>
<td>144±43</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C (mg%)</td>
<td>58±14</td>
<td>56±16</td>
<td>ns</td>
</tr>
<tr>
<td>Lp(a) (mg%)</td>
<td>17 [9–161]</td>
<td>15 [9–164]</td>
<td>ns</td>
</tr>
<tr>
<td>Apo A1 (mg%)</td>
<td>135±24</td>
<td>149±30</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Apo B (mg%)</td>
<td>96±18</td>
<td>82±16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

C=cholesterol, TG=triglycerides. Values are means±SD except for Lp(a), where medians and ranges are shown. All values are expressed to the nearest ten.
episodes. In addition, no adverse hepatic effects were found as the serum transaminases remained stable. Furthermore, CPK and serum creatinine values remained stable. The baseline mean CsA concentration (group S: 186 ± 38 ng/ml, and group F: 189 ± 30 ng/ml; P not significant) was similar between the two groups and the mean body-weight remained stable throughout the study (62.7 kg for group S and 64.3 kg for group F). There were no variations in the haematological profile in both groups during the study. The values of TC, TG, LDL-C, HDL-C, Lp(a), Apo A1, and Apo B for the two groups, at the end of the study are showed in Table 2.

After 3 months of low-dose simvastatin there were significant reductions in the TC (15.9%), TG (15.6%), LDL-C (18.6%) and Apo B (15.6%) concentrations. The Apo A1 concentration increased by 10.4%. There were no significant changes in HDL-C and Lp(a) concentrations.

The group receiving fish oil registered significant reductions in TC (9.8%), TG (14.1%), and HDL-C (16.9%) concentrations. The LDL-C, Lp(a), Apo A1, and Apo B concentrations remained stable.

The TC/HDL-C ratio decreased significantly in group S (5.0 ± 2.0 to 4.3 ± 1.4; P = 0.02) and slightly increased in group F (4.4 ± 1.0 to 4.6 ± 0.9; P = 0.38).

At the end of the study, the lipids values were not significantly different between the two groups. Nevertheless the Apo B mean value tended to be lower in group S (group S: 82 ± 16/group F: 92 ± 16; P = 0.07).

Discussion

The post-RT lipid profile, especially if the patients receive CsA maintenance treatment, has been a subject of debate [12]. Several studies have showed a pattern of elevated concentrations of TC, LDL-C and VLDL-C1 [13]. HDL-C is usually normal or high, but there are occasional reports of low values [14,15]. The prevalence of hyperlipidaemia post-RT ranges from 16% to 72% in the literature [13,16]. In our renal transplant department, the prevalence of hypercholesterolaemia in the first and fifth year post-RT is 70% and 81%, respectively.

Lovastatin, simvastatin, and fluvasatin therapy are associated with serious side effects, such as rhabdomyolysis and acute renal failure, in heart or kidney transplant patients treated with CsA [17–19]. However, low-dose HMG-CoA reductase inhibitor can be used in CsA-treated patients without significant risk of rhabdomyolysis [20]. Reduced dose of HMG-CoA reductase inhibitors in CsA-treated patients is indicated because there is a suggested decreased hepatic metabolism of these inhibitors associated with CsA [21,22]. Drugs known to increase the risk of myopathy in this setting (eg, itraconazole, nicotinic acid, erythromycin and gemfibrozil) must be avoided [18,23].

Simvastatin, at low dose (10 mg/day), has been successfully used for post-RT hyperlipidaemia control, even for RT recipients treated with CsA [6,24]. Martinez-Hernandez et al. used a lower dose of simvastatin than used in this study (5 mg/day vs 10 mg/day) in a randomized single-blind placebo crossover study [25] found that reductions in TC, LDL-C, and Apo B after 8 weeks of simvastatin therapy were significantly greater than with placebo. In our study it was remarkable that simvastatin significantly reduced the concentrations of TC, TG, LDL-C, and Apo B. It also reduced the ratio TC/HDL-C.

Dietary supplementation with fish oil is known to exert beneficial effects on serum lipid concentrations [7] and on mortality from cardiovascular disease [8]. Advantageous effects on renal reserve filtration capacity in CsA-treated RT recipients has been demonstrated [26].

In our study, fish oil was associated with a reduction of TC, HDL-C, and TG. The reduction of HDL-C with consumption of fish oil is not detrimental, since it is related to an increase in HDL receptors and accelerated turnover of HDL-C [27]. However, in nonhuman primates the prevention of atherosclerosis by fish oil was associated with reductions in concentrations of HDL-C [28].

Serum concentrations of Lp(a) in humans are anywhere between 0 and >100 mg/dl. Its is similar in composition with LDL-C, but with a higher protein content and its physiological function is uncertain. Our observations agree with other studies, which reported reductions or no effect of HMG-CoA-reductase inhibitors on Lp(a) concentration [29,30].

We conclude that low-dose simvastatin and fish oil (6 g/day) are effective in correcting hyperlipidaemia in RT recipients, even in lipid lowering diet resistant RT recipients. The lipid variations were strictly related with simvastatin or fish oil, as other variables which could interfere, such as β-blockers, were maintained constant during the study. Our patients tolerated the treatment, without side effects, such as myopathy related to simvastatin or haemorrhagic episodes related to fish oil. The post-RT hyperlipidaemia treatment remains a subject of debate and future randomized controlled trials, with longer follow-up, are necessary to assess the value of lipid-lowering therapy in cardiovascular risk of these patients.

These results were presented at the XXXIIIrd Congress of the EDTA Congress (Amsterdam; Netherlands), June 1996.

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