Combined LDL-Apheresis and Statin Treatment in Homozygous and Heterozygous Familial Hyperlipoproteinaemia

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Combined LDL-Apheresis and Statin Treatment in Homozygous and Heterozygous Familial Hyperlipoproteinaemia

K. Derfler, A. Goldammer

Familial hypercholesterolaemia (FH) is due to an autosomal dominantly inherited deficiency of LDL-receptor expression on the cell surface, leading to excess concentrations of serum total- and LDL-cholesterol followed by severe premature atherosclerosis. In patients with heterozygous FH it has been demonstrated that despite statin therapy (80 mg of atorvastatin), LDL-apheresis could significantly stimulate the residual LDL-receptor expression via the reduction of available extracellular cholesterol resulting in delayed reappearance of hypercholesterolaemia in between treatments [J. Streicher et al. J Investig Med 1999; 47: 378–87]. The present results of a cross-over evaluation in FH patients maintained on LDL-apheresis received initially 40 mg of simvastatin, followed by a wash-out period of four weeks and thereafter atorvastatin at a dosage of 10 mg to 80 mg. LDL-cholesterol levels obtained before apheresis treatment were further lowered by 28% when patients were changed in medication from simvastatin (40 mg) to atorvastatin (80 mg; \(p < 0.05\)). When LDL-cholesterol concentrations were determined on 80 mg of atorvastatin and compared to the values at the end of the wash-out period a reduction of 39% (\(p < 0.005\)) in LDL-cholesterol levels before LDL-apheresis treatment was observed. Subsequent to therapeutic LDL-apheresis treatment the LDL-cholesterol levels increased in a first order kinetic to a range of LDL-cholesterol at day 7 (the day of the next treatment) almost equal to the pretreatment values observed at the beginning of the kinetic study. Statin-therapy however, was able to delay the occurrence of LDL-cholesterol significantly resulting in a continuous decrease in LDL-cholesterol pretreatment values (LDL-chol: without/with statin therapy: 257 ± 32 mg/dl; 156 ± 29 mg/dl, \(p < 0.005\)). No side effects had to be observed during simvastatin and atorvastatin therapy at escalating dosage. Fibrinogen concentrations remained almost unchanged for the entire study period the values obtained being within the normal range in general. From these results we conclude that statin treatment is recommended in patients maintained long-term on LDL-apheresis to improve the lipoprotein pattern in heterozygous FH. With these treatment options delayed progression or even regression of cardiovascular and vascular disease has been observed. J Clin Basic Cardiol 2001; 4: 139–144.

Key words: LDL-apheresis, familial hypercholesterolaemia, atorvastatin, fibrinogen

High concentrations of low-density lipoprotein (LDL) cholesterol have been recognised as the most important risk factor for coronary artery disease (CAD). Over the last decade, the development and use of inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, a rate-limiting key enzyme of cholesterol synthesis, have revolutionised the ability of physicians to decrease the rate of major cardiovascular events, bypass graft surgery, PTCA and stroke [1–12]. Clear evidence of the therapeutic benefits of lowering LDL-cholesterol dates from 1984, when the results of the Lipid Research Clinics Coronary Primary Prevention Trial, demonstrating a 19% reduction in CAD deaths and non-fatal myocardial infarction, were published [13]. A detailed analysis of results demonstrated that the extent of benefit depended upon the reduction in serum cholesterol that was achieved, which reflected drug compliance [13]. In secondary prevention reduction in cardiovascular events due to statin therapy has been proven by three intervention trials using simvastatin in the 4S study (Scandinavian Simvastatin Survival Study) and pravastatin for both the CARE (Cholesterol and Recurrent Events) evaluation and the LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease) study [14–16]. Following these investigations, statins were further evaluated for primary prevention in two trials involving pravastatin (West of Scotland Coronary Prevention Study [17] and lovastatin (Air Force/Texas Coronary Atherosclerosis Prevention Study; [18]).

Overall, a meta-analysis of randomised and controlled trials demonstrated statins as reducing the risk major complications of CAD by 31% and of total mortality by 21%, these benefits being equally evident in men and women and below and above the age of 65 [18]. The relation between plasma cholesterol (chol) and coronary events appears to be stronger if levels LDL-cholesterol are at elevated, rather than average, values [19, 20].

Despite the efficiency of the different statins, an extended group of patients concerned by homozygous and heterozygous familial hyperlipoproteinaemia (FH) does not achieve target LDL-cholesterol (LDL-chol) levels when treated with these substances even at the highest recommended dosage [21–32]. Thus, beside the search for new lipoprotein lowering agents extracorporeal treatment modalities have gained wider clinical acceptance during recent years to offer a possibility to reach LDL-cholesterol levels close to or even below the recommended target values [21, 23, 24, 28, 29, 31, 33–43].

LDL-apheresis, a procedure for removing apolipoprotein (Apo) B-containing lipoproteins from the plasma or from the whole blood, has been developed to treat patients with homozygous and severe heterozygous FH. It is effective in all patients with failure or incomplete response to standard therapy because of very high baseline lipoprotein levels. Methods for performing selective removal of Apo B-containing lipoproteins (ie mainly LDL-cholesterol, Lp(a), VLDL-cholesterol and VLDL-triglycerides) columns containing immobilised antibodies to human Apo-B [32, 44–47], columns containing dextran sulfate cellulose [24, 44, 48–49] and the heparin-induced extracorporeal LDL precipitation (HELP) differing to the other systems by a limited plasma volume that can be processed due to an unspecified loss in fibrinogen which, however, might offer a different treatment option [26, 27]. A whole blood compatible column containing a modified polycrylate gel has recently been demonstrated to be a further safe, easily to be processed and highly effective LDL-
apheresis procedure, offering a significantly shorter duration of treatment to the patients [31, 35, 44, 50–52]. During a single LDL-apheresis treatment Apo-B containing lipoprotein removal is approximately 70%. However, resynthesis of the lipoproteins removed requires additional drug treatment to delay the occurrence of hyperlipidemic state [23, 24, 27, 29, 31, 34, 35, 39, 44, 47, 49–51, 53–55].

Patients and Methods

Fourteen patients were included to this long-term evaluation. Four were classified to have homozygous FH (age 38.8 ± 21 years; body mass index [BMI] 22.8 ± 2.1) and 10 suffered from heterozygous FH (age 47 ± 9 years; BMI 25.4 ± 2.6). CAD was assured by repeated coronary angiography in three of the homozygous (Table 1) and in all heterozygous (Table 2) patients.

LDL-apheresis

All patients were treated intermittently by each of the extracorporeal procedures used for LDL-apheresis as recently published [44]. The efficiency in removing Apo-B containing lipoproteins was comparable for all the systems. Treatments were carried out in general at weekly intervals.

All LDL-apheresis treatments were performed using a peripheral venous vascular access. For initial plasma separation with the Autopheresis-C therapeutic plasma system (TPS; Baxter, Deerfield, IL) blood was drawn from an antecubital vein via a 17 gauge needle at a flow rate of 50 to 80 ml/min. Heparin (input rate 1000 U/h; not exceeding 5000 U) and citrate (ACD-A, anticoagulant citrate dextrose, formula A, Baxter, Munich, Germany) were added for anticoagulation. The ratio of citrate to whole blood flow was kept at 1:20 (5%).

The blood volume to be treated was individually calculated for each patient by the formula by Nadler et al. and the 1.6-fold blood volume was processed during each treatment session [56].

Laboratory methods

Pre- and post-treatment measurements were performed from blood samples taken immediately before LDL-apheresis was started. Posttreatment measurements were performed from blood samples taken immediately after the procedure. For the evaluation of treatment and triglycerides were measured enzymatically using a commercial kit (Roche, Germany). Lipoprotein lipids were measured according to the lipid research clinics methods with slight modifications as recently described [31, 44, 47, 50]. Very low density lipoproteins (VLDL) were removed by ultracentrifugation (d < 1.006 g/ml), LDL-cholesterol was separated from the infranatant (d < 1.032 g/ml) by heparin and polyanion precipitation using manganese chloride, and HDL-cholesterol was determined from the supernatant. Lp(a) was determined quantitatively using an enzyme immunoassay (Innotest Lp(a); Innogenetics, Belgium). Additional biochemical analyses were performed in the central laboratory of the hospital by standard methods. Plasma fibrinogen concentration was determined according to Claus by using thrombin and control plasma from the Behringwerke, Marburg, FRG [57].

Statistical Analysis

Values are presented as means ± 1 standard deviation (SD). Differences between pre- and post-apheresis levels and various dosages of atorvastatin were compared by one-way ANOVA and Tukey multiple range comparison test. Reincrease in lipoproteins in between of two LDL-apheresis sessions and the lipoprotein concentrations according to various treatment modalities were tested for significance by one-way ANOVA. In general p-values < 0.05 were considered as significant.

Results

Lipoprotein levels were evaluated in ten patients with heterozygous and four patients with homozygous FH during long-term LDL-apheresis and concomitant simvastatin (40 mg) or atorvastatin (at escalating dosage: from 10 mg to 80 mg) therapy. Efficacy of different dosage of atorvastatin was evaluated after a treatment period of four weeks followed by a further increase the atorvastatin dosage. The detailed data are presented in Table 3 for the homozygous and in Table 4 for the

Table 1. CAD in patients with homozygous FH on long-term LDL-apheresis

<table>
<thead>
<tr>
<th>n</th>
<th>MI</th>
<th>Bypass graft</th>
<th>PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CAD</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 VD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 VD</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>3 VD</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; VD = vessel disease

Table 2. CAD in patients with heterozygous FH on long-term LDL-apheresis

<table>
<thead>
<tr>
<th>n</th>
<th>MI</th>
<th>Bypass graft</th>
<th>PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CAD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 VD</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2 VD</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3 VD</td>
<td>6</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; VD = vessel disease
heterozygous patients. Total- and LDL-chol levels significantly decreased when atorvastatin was given at escalating dosages. Triglyceride values were lowest when 60 mg and 80 mg of atorvastatin were given in heterozygous and homozygous patients (Figure 1). Figure 2 presents the development of LDL-cholesterol in LDL-apheresis patients with homozygous and patients with heterozygous FH. The recovery of LDL-cholesterol was evaluated combined for all 14 patients.

**Recovery of Lipoproteins Between Two LDL-Apheresis Treatments Scheduled at Weekly Intervals in Patients with Homozygous and Heterozygous FH**

At the end of the “wash-out” period (4 weeks without simvastatin) Mean LDL-chol levels were lowered by 79 ± 7 % by one single LDL-apheresis treatment (from 256.8 ± 32 mg/dl to 53.8 ± 18.1 mg/dl; p < 0.001). During the initial 24 hours after treatment a 46.4 % (46.6 mg/dl) increase in LDL-chol was observed, the level of LDL-chol reaching 100.4 ± 16.6 mg/dl (Figure 3). For the following days (2 to 7) the increase in LDL-

**Table 3.** Lipoprotein values and fibrinogen levels in patients with homozygous FH on long-term LDL-apheresis at weekly intervals. A: patients on 40 mg of simvastatin and immediately before the initiation of the “wash-out” period.

<table>
<thead>
<tr>
<th>mg/dl</th>
<th>A 10 mg Atorva</th>
<th>20 mg Atorva</th>
<th>40 mg Atorva</th>
<th>60 mg Atorva</th>
<th>80 mg Atorva</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Chol</td>
<td>287 ± 52</td>
<td>307 ± 86</td>
<td>276 ± 68</td>
<td>281 ± 44</td>
<td>259 ± 49*</td>
</tr>
<tr>
<td>LDL-Chol</td>
<td>208 ± 17</td>
<td>241 ± 72</td>
<td>214 ± 81</td>
<td>226 ± 34</td>
<td>204 ± 38*</td>
</tr>
<tr>
<td>TG</td>
<td>144 ± 123</td>
<td>126 ± 84</td>
<td>194 ± 189</td>
<td>135 ± 100</td>
<td>126 ± 87</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>214 ± 27</td>
<td>233 ± 28</td>
<td>n.e.</td>
<td>219 ± 19</td>
<td>210 ± 8</td>
</tr>
</tbody>
</table>

Values are means ± 1 SD; n.e. = not evaluated; T-Chol = total cholesterol; TG = triglycerides; Atorva = atorvastatin. * p < 0.05 when compared to A and Atorva 10 mg.

**Table 4.** Lipoprotein values and fibrinogen levels in patients with heterozygous FH on long-term LDL-apheresis at weekly intervals. A: patients on 40 mg of simvastatin and immediately before the initiation of the “wash-out” period.

<table>
<thead>
<tr>
<th>mg/dl</th>
<th>A 10 mg Atorva</th>
<th>20 mg Atorva</th>
<th>40 mg Atorva</th>
<th>60 mg Atorva</th>
<th>80 mg Atorva</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-Chol</td>
<td>296 ± 40</td>
<td>272 ± 55</td>
<td>232 ± 49</td>
<td>224 ± 34</td>
<td>197 ± 27*</td>
</tr>
<tr>
<td>LDL-Chol</td>
<td>213 ± 45</td>
<td>192 ± 56</td>
<td>173 ± 43</td>
<td>169 ± 34</td>
<td>151 ± 24*</td>
</tr>
<tr>
<td>TG</td>
<td>158 ± 80</td>
<td>206 ± 74</td>
<td>180 ± 75</td>
<td>142 ± 44</td>
<td>122 ± 41</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>273 ± 43</td>
<td>279 ± 54</td>
<td>n.e.</td>
<td>280 ± 33</td>
<td>280 ± 36</td>
</tr>
</tbody>
</table>

Values are means ± 1 SD; n.e. = not evaluated; T-Chol = total cholesterol; TG = triglycerides; Atorva = atorvastatin. * p < 0.05 when compared to A and Atorva 10 mg.
cholesterol ranged from 32.0 mg/dl per day to 13.1 mg/dl per day. Before the next LDL-apheresis the LDL-cholesterol level had reached 239.9 ± 35.0 mg/dl.

When 4 weeks on 80 mg of atorvastatin
When the FH patients on LDL-apheresis treatment were on 80 mg for atorvastatin for a period of 4 weeks the recovery of LDL-cholesterol was estimated again. During the recent apheresis procedure LDL-cholesterol was lowered by 82 ± 11 % (from 155.7 ± 29.1 mg/dl to 28.8 ± 14.2 mg/dl; p < 0.001). Within the first 24 hours after treatment an increase in LDL-cholesterol by 57 % (38.2 mg/dl) occurred. From day 2 to day 7 the increase in LDL-cholesterol ranged from 21.4 mg/dl per day to 10.1 mg/dl per day. The treatment of atorvastatin at an escalating dose resulted in a decrease in LDL-cholesterol pretreatment levels from 257 mg/dl to 157 mg/dl (e minus 100 mg/dl; –39 %; p < 0.001). Comparing the LDL-cholesterol pretreatment levels when patients were on 40 mg of simvastatin to that when on 80 mg of atorvastatin a further LDL-cholesterol reduction of 26 % was obtained.

Fibrinogen concentrations
Fibrinogen values were evaluated when patients received simvastatin (40 mg) and when patients were on increasing doses of atorvastatin (Figure 4). Slight differences in fibrinogen concentrations were observed (p = n.s.)

Side effects
In none of the patients side effects had to be observed either when patients were on 40 mg of simvastatin or on atorvastatin at escalating dosage up to 80 mg per day.

Discussion
The use of different LDL-apheresis procedures to treat patients with homozygous and serious heterozygous FH has gained wider clinical acceptance during the last decade [22–24, 27, 29, 31, 32, 34, 35, 43, 44, 49–51, 54, 55, 60]. Beside extensive reduction in Apo-B containing lipoproteins during one single apheresis treatment, delayed recovery in these lipoproteins has been reported when LDL-apheresis procedures were combined with statin therapy [22–24, 27, 29, 31, 32, 34, 35, 43, 44, 49–51, 54, 55, 58–62]. Beside the use of different LDL-apheresis procedures to treat patients with homozygous and serious heterozygous FH has been accepted for publication [58]. The difference in fibrinogen concentrations reported by Wierzbicki et al. were within the recommended normal range [71].

In conclusion, our results demonstrate statin treatment to be beneficial in patients with failure or insufficient response to LDL-cholesterol lowering drug treatment and for this reason being on long-term LDL-apheresis therapy. Atorvastatin has demonstrated a comparable lipoprotein capacity at a dosage of 10 mg when compared to the treatment of 40 mg of simvastatin. However, the dose escalation resulted in further reduction in LDL-cholesterol by 26 % and a delayed recovery in Apo-B containing lipoproteins. Fibrinogen concentrations remained stable within the normal range both when LDL-}

**Figure 4.** Fibrinogen concentrations obtained in patients treated long-term with LDL-apheresis and addition of different statin therapy. A: simvastatin (40 mg), B: atorvastatin 10 to 80 mg.
apheresis patients were on 40 mg of simvastatin or on 10 mg to 80 mg of atorvastatin. Thus, this drug offers further beneficial lipoprotein lowering capacity even in patients with homozygous and heterozygous FH treated by long-term LDL-apheresis.

References


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