A Combined Low-Density Lipoprotein Apheresis and Prednisone Therapy for Steroid-Resistant Primary Focal Segmental Glomerulosclerosis in Children

Motoshi Hattori, MD, Hiroko Chikamoto, MD, Yuko Akioka, MD, Hyogo Nakakura, MD, Daisuke Ogino, MD, Akira Matsunaga, MD, Akira Fukazawa, MD, Sanpei Miyakawa, MD, Miyuki Khono, MD, Hiroshi Kawaguchi, MD, and Katsumi Ito, MD

Background: Treatment of steroid-resistant (SR) primary focal segmental glomerulosclerosis (FSGS) remains a major challenge in nephrology. A prospective study was conducted to clarify the therapeutic role of low-density lipoprotein apheresis (LDL-A) in 11 nephrotic children with SR and cyclosporine A (CsA)-resistant primary FSGS.

Methods: Based on entry criteria, all 11 eligible patients had biopsy-proven primary FSGS presenting with nephrotic syndrome (NS) and were resistant to steroid and conventional-dose CsA therapy. LDL-A was performed twice a week for 3 weeks (first course), then weekly for 6 weeks (second course). Beginning from the second LDL-A course, a dosage of 1 mg/kg/d of prednisone was administered for 6 weeks, then tapered. Results: Seven patients experienced remission of NS, 5 of whom achieved complete remission within 4 weeks after initiating prednisone therapy with LDL-A. These 5 patients maintained normal renal function during follow-up (median, 4.4 years). Of 2 patients with partial remission, 1 patient maintained stable renal function during follow-up (4.5 years), whereas the other patient showed a gradual decline in renal function and progressed to end-stage renal failure (ESRF) 7.8 years after LDL-A therapy. Four patients who were considered to experience treatment failure had persistent NS and progressed to ESRF in 1.3 years (median) after LDL-A therapy. Complete remission (n = 5) was associated with significantly more highly selective proteinuria compared with treatment failure (n = 4). Conclusion: This study suggests that combined LDL-A and prednisone therapy can be a valuable addition to therapeutic options for treating patients with SR-FSGS. The role of LDL-A in treating these patients deserves to be assessed further in larger randomized controlled trials. Am J Kidney Dis 42:1121-1130.

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INDEX WORDS: Steroid-resistant primary focal segmental glomerulosclerosis (SR-FSGS); low-density lipoprotein apheresis (LDL-A); children.

Primary focal segmental glomerulosclerosis (FSGS) is a clinicopathologic entity defined by the presence of proteinuria, commonly nephrotic in range, and segmental glomerular scars involving some, but not all, glomeruli. Patients with primary FSGS are resistant to standard oral prednisone protocols (prednisone, 2 mg/kg/d, for 4 to 8 weeks) in approximately 80% of cases, and the majority of nephrotic patients with steroid-resistant (SR) primary FSGS progress to end-stage renal disease. This poor prognosis has led to the use of multiple treatment regimens. Prolonged oral prednisone therapy, cytotoxic drugs, cyclosporine A (CsA), and intravenous methylprednisolone pulse therapy have been used alone and/or in a variety of combinations. Although variable success has been reported with these treatment regimens, treatment of SR primary FSGS (SR-FSGS) is still one of the major challenges in the field of nephrology.

Recently, low-density lipoprotein apheresis (LDL-A) using a dextran sulfate cellulose column has been proposed as a possible therapeutic intervention for patients with SR-FSGS. Although encouraging results have been shown in some patients with primary FSGS, no clear-cut conclusions have been drawn concerning the therapeutic benefits of LDL-A in the treatment of patients with SR-FSGS.

In the present study, we evaluated the clinical courses of 11 nephrotic children with SR-FSGS who were prospectively treated with a fixed

From the Department of Pediatric Nephrology, Tokyo Women’s Medical University, School of Medicine, Tokyo, Japan.

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Address reprint requests to Motoshi Hattori, MD, Department of Pediatric Nephrology, Tokyo Women’s Medical University, School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: hattori@kc.twmu.ac.jp

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protocol of LDL-A therapy to clarify the therapeutic role of LDL-A for pediatric nephrotic patients with SR-FSGS.

PATIENTS AND METHODS

Patients

The study was approved by the Ethical Committee of the Tokyo Women’s Medical University, School of Medicine (Tokyo, Japan). Patients were included in this study if they: (1) had biopsy-proven primary FSGS; (2) had SR disease, defined as failure to achieve a complete or partial remission of proteinuria after 8 weeks of prednisone therapy at a dose of 2 mg/kg/d; (3) were treated unsuccessfully with conventional-dose CsA therapy (5 to 6 mg/kg/d as starting dose and maintained at a 12-hour trough level [whole-blood levels measured by monoclonal assay] between 100 and 150 ng/mL for 12 to 16 weeks) combined with alternate-day prednisone (0.5 to 1.0 mg/kg/48 h); and (4) showed persistent nephrotic-range proteinuria. Eleven nephrotic children with both SR and CsA-resistant primary FSGS were treated prospectively with a fixed protocol of LDL-A therapy between October 1991 and December 1998. LDL-A therapy was initiated after written informed consent was obtained from all patients (or parents) enrolled in this study.

Treatment Protocol

LDL-A was performed using a polysulfone hollow-fiber filter (Sulflux; Kaneka Corp, Osaka, Japan) as the plasma separator and a dextran sulfate cellulose column (Liposorber LA-15; Kaneka Corp) as the LDL adsorber, as reported previously. A volume of 60 mL/kg of body weight of plasma was treated at each session. Blood access was obtained mainly through a double-lumen central vascular access and, occasionally, by puncture of antecubital veins and/or a radial artery. The LDL-A regimen consisted of twice-weekly treatment for 3 weeks (first course), then weekly treatment for 6 weeks (second course). Beginning at the second course of LDL-A, prednisone, 1 mg/kg/d, was administered for 6 weeks, followed by a tapering schedule during subsequent months. Short-term effects of LDL-A as monotherapy and combination therapy with prednisone were evaluated at 3 and 9 weeks after initiating LDL-A.

Definitions and Criteria for Treatment Response

Nephrotic syndrome (NS) is defined as the presence of proteinuria (protein ≥ 40 mg/m²/h) and a serum albumin level less than 2.5 g/dL (<25 g/L), with or without edema.
poalbuminemia. 17 Treatment failure is de
achieve complete or partial remission.

Hypertension is de
fixed in 10% buffered formalin, embedded in paraf
fixed in 10% buffered formalin, embedded in paraf

Pathological Examination
Renal biopsies were performed before LDL-A therapy in all patients. Renal biopsy specimens for light microscopy were fixed in 10% buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin, Masson trichrome, periodic acid–Schiff, and periodic acid–silver methenamine using conventional methods.14 Immunofluorescence and electron microscopy also were performed to rule out other types of renal disease associated with segmental sclerotic lesions. In addition to establishing the diagnosis of primary FSGS, the number of glomeruli with either segmental or global sclerosis was assessed. Also, the degree of tubular atrophy and interstitial fibrosis was graded semiquantitatively on a scale of 0 to 3 (absent, mild, moderate, and severe, respectively), as previously reported.15

Biochemistry
Total cholesterol (TCh) and triglyceride concentrations were analyzed by means of enzymatic methods, and high-density lipoprotein cholesterol was measured using the polyethylene glycol 6000 precipitation method in blood samples collected after a 12-hour fast. Urinary protein was measured by means of the pyrogallol red method and evaluated by 24-hour quantitative measurement.15 Glomerular filtration rate (GFR) was determined by using the creatinine clearance value when available, and otherwise calculated from the following formula:

\[
\text{GFR} = \frac{\text{body length (cm)/serum creatinine (mg/dL)}}{0.55}
\]

The selectivity index (SI) was calculated according to the Cameron and Blandford16 method, using the following formula:

\[
\text{SI} = \frac{\text{uIgG/sIgG}}{(sTf/uTf)}
\]

where Tf is transferrin, u is urinary, IgG is immunoglobulin G, and s is serum.

Statistical Analysis
Data are presented as mean ± SD, unless otherwise indicated. Statistical analysis was performed using nonparametric Wilcoxon’s signed-rank test, nonparametric Mann-Whitney U test, and Fisher’s exact probability test, as appropriate. Differences are considered significant at \( P < 0.05 \). Statistical calculations were computed using Statview 5.0 (Abacus Concepts, Berkeley, CA).

RESULTS

Clinical Features
Clinical and laboratory data for the 11 patients treated with a combined LDL-A and prednisone therapy are listed in Table 1. There were 6 boys and 5 girls, and mean age at disease onset was 10.9 ± 2.7 years (median, 12.0 years; range, 7.0 to 14.4 years). All patients presented with NS.

Table 1. Clinical and Laboratory Data for Patients With SR-FSGS Treated With Combined LDL-A and Prednisone Therapy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age at Onset (y)</th>
<th>LDL-A therapy (y)</th>
<th>Steroid Resistance</th>
<th>Prior Treatment</th>
<th>Lipid-Lowering Drugs</th>
<th>Proteinuria* (g/m²/d)</th>
<th>Serum Albumin* (g/dL)</th>
<th>Serum-TCh* (mg/dL)</th>
<th>GFR* (mL/min/1.73 m²)</th>
<th>Response to LDL-A Therapy†</th>
<th>Follow-Up (y)</th>
<th>Outcome at Last Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>7.0</td>
<td>0.8</td>
<td>Primary CsA/MP</td>
<td>P/S</td>
<td>6.8</td>
<td>2.3</td>
<td>508</td>
<td>124.7</td>
<td>CR</td>
<td>11.1</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>7.2</td>
<td>1.4</td>
<td>Secondary CsA/CPM/MP</td>
<td>P/S</td>
<td>12.4</td>
<td>1.4</td>
<td>539</td>
<td>46.2</td>
<td>F</td>
<td>0.6</td>
<td>F</td>
<td>ESRF</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>8.5</td>
<td>3.0</td>
<td>Secondary CsA/MP</td>
<td>P/S</td>
<td>10.2</td>
<td>2.1</td>
<td>573</td>
<td>104.6</td>
<td>F</td>
<td>1.5</td>
<td>1.5</td>
<td>ESRF</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>8.9</td>
<td>3.4</td>
<td>Secondary CsA/CPM/MP</td>
<td>P/S</td>
<td>7.0</td>
<td>2.0</td>
<td>644</td>
<td>128.5</td>
<td>CR</td>
<td>4.1</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>10.4</td>
<td>0.7</td>
<td>Primary CsA/MP</td>
<td>P/S</td>
<td>10.8</td>
<td>1.9</td>
<td>398</td>
<td>126.9</td>
<td>CR</td>
<td>4.0</td>
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<td>CR</td>
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<td>6</td>
<td>F</td>
<td>12.0</td>
<td>3.8</td>
<td>Secondary CsA/CPM/MP</td>
<td>P/S</td>
<td>8.0</td>
<td>2.0</td>
<td>594</td>
<td>118.8</td>
<td>CR</td>
<td>4.4</td>
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<td>7</td>
<td>F</td>
<td>12.2</td>
<td>2.9</td>
<td>Secondary CsA/CPM/MP</td>
<td>P</td>
<td>11.2</td>
<td>1.5</td>
<td>452</td>
<td>122.4</td>
<td>CR</td>
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<td>8</td>
<td>F</td>
<td>12.4</td>
<td>1.1</td>
<td>Primary CsA/MP</td>
<td>P/S</td>
<td>7.4</td>
<td>2.3</td>
<td>458</td>
<td>108.5</td>
<td>F</td>
<td>1.6</td>
<td>1.6</td>
<td>ESRF</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>12.5</td>
<td>1.9</td>
<td>Primary CsA/CPM/MP</td>
<td>P/S</td>
<td>9.8</td>
<td>2.1</td>
<td>362</td>
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<td>F</td>
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<tr>
<td>10</td>
<td>F</td>
<td>14.3</td>
<td>1.0</td>
<td>Secondary CsA/MP</td>
<td>P</td>
<td>8.3</td>
<td>1.9</td>
<td>576</td>
<td>114.6</td>
<td>PR</td>
<td>4.5</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>14.4</td>
<td>2.1</td>
<td>Primary CsA/CPM/MP</td>
<td>P/S</td>
<td>14.7</td>
<td>1.5</td>
<td>478</td>
<td>66.2</td>
<td>PR</td>
<td>7.8</td>
<td>7.8</td>
<td>ESRF</td>
</tr>
</tbody>
</table>

NOTE. To convert serum albumin in g/dL to g/L, multiply by 10; serum total cholesterol in mg/dL to mmol/L, multiply by 0.02586.

Abbreviations: MP, methylprednisolone; CPM, cyclophosphamide; P, probucol; S, statins; CR, complete remission; F, treatment failure; PR, partial remission.

*Data were obtained at the time of the initiation of LDL-A therapy.
†Assessed at the end of the second course of LDL-A.
‡The follow-up period is defined as time from the initiation of LDL-A therapy to the time of developing ESRF or the latest observation.
Mean interval between disease onset and initiation of LDL-A therapy was 2.0 ± 1.1 years (median, 1.9 years; range, 0.7 to 3.8 years). Based on entry criteria, all 11 eligible patients had biopsy-proven primary FSGS and SR disease and were treated unsuccessfully with conventional-dose CsA in combination with alternate-day prednisone. Five patients had SR disease after the first course of prednisone therapy (primary steroid resistance), whereas in the remaining 6 patients, the disease became SR during treatment for relapse (secondary steroid resistance). Nine of these 11 patients were administered pulse methylprednisolone (30 mg/kg/dose to a maximum of 1 g) for 3 consecutive days after standard oral prednisone therapy, but without response. Also, 8 patients were administered a course of cyclophosphamide (2.5 to 3 mg/kg/d for 8 weeks) without a favorable response. All except 1 patient (no. 7) were administered both probucol and statins.

At the beginning of LDL-A therapy, nephrotic-range proteinuria, hypoalbuminemia, and significant hypercholesterolemia were present in all patients. Mean urinary protein excretion was 9.7 ± 2.5 g/m²/d (range, 6.8 to 14.7 g/m²/d), mean serum albumin concentration was 1.9 ± 0.3 g/dL (19 ± 3 g/L; range, 1.4 to 2.3 g/dL [14 to 23 g/L]), and mean serum TCh value was 507 ± 87 mg/dL (13.1 ± 2.2 mmol/L; range, 362 to 644 mg/dL [9.4 to 16.7 mmol/L]). Three patients had a decreased GFR (46.2, 62.0, and 66.2 mL/min/1.73 m²) at the beginning of LDL-A therapy. Hypertension was noted in 2 patients (nos. 2 and 11).

### Histological Findings

Histological data for the 11 patients are listed in Table 2. All patients underwent a percutaneous renal biopsy 3.5 ± 1.8 weeks (median, 3 weeks; range, 2 to 6 weeks) before the initiation of LDL-A therapy, and the total number of glomeruli, which were enumerated in serial sections, varied from 11 to 31 per sample (20 ± 7 glomeruli/sample). Mean percentages of glomeruli with segmental sclerosis and global sclerosis were 20.8% ± 6.2% (median, 21.4%; range, 12.9% to 30.8%) and 9.4% ± 5.9% (median, 10.7%; range, 0% to 18.2%), respectively. Mean tubular atrophy and interstitial fibrosis score was 1.5 ± 0.9 (median, 1; range, 0 to 3).

### Responses to LDL-A Therapy

Short-term effects of LDL-A as monotherapy and combination therapy with prednisone on hyperlipidemia, proteinuria, and renal function were assessed at 3 (immediately after completion of the first course of 6 LDL-A sessions) and 9 weeks (immediately after completion of the second course of 6 LDL-A sessions in combination with prednisone at a dose of 1 mg/kg/d for 6 weeks), respectively.

Changes in serum TCh and urinary protein levels are shown in Figs 2 and 3, respectively. A

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**Table 2. Histological Data for Patients With SR-FSGS Treated With Combined LDL-A and Prednisone Therapy**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Renal Biopsy to LDL-A (wk)</th>
<th>Total No. of Glomeruli</th>
<th>Glomeruli With Segmental Sclerosis (%)</th>
<th>Glomeruli With Global Sclerosis (%)</th>
<th>Tubulointerstitial Score (0-3)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>21</td>
<td>14.3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>2</td>
<td>2</td>
<td>15</td>
<td>26.7</td>
<td>13.3</td>
<td>3</td>
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<td>3</td>
<td>2</td>
<td>28</td>
<td>14.3</td>
<td>10.7</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>31</td>
<td>12.9</td>
<td>9.7</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>27</td>
<td>25.9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>18</td>
<td>16.7</td>
<td>11.1</td>
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<td>7</td>
<td>6</td>
<td>14</td>
<td>21.4</td>
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<td>6</td>
<td>26</td>
<td>30.8</td>
<td>11.5</td>
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<td>27.3</td>
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<td>18</td>
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<td>1</td>
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<td>3</td>
<td>12</td>
<td>16.7</td>
<td>16.7</td>
<td>2</td>
</tr>
</tbody>
</table>

*Degree of tubular atrophy and interstitial fibrosis was graded semiquantitatively on a scale of 0 to 3 (0, absent; 1, mild; 2, moderate; 3, severe).
A significant decrease in serum TCh levels was observed in all patients after initiating LDL-A therapy (507 ± 87 mg/dL [13.1 ± 2.2 mmol/L] to 207 ± 25 mg/dL [5.4 ± 0.6 mmol/L] at week 3 and 250 ± 75 mg/dL [6.5 ± 1.9 mmol/L] at week 9; P < 0.01; Fig 2). Serum triglyceride levels also decreased significantly, whereas serum high-density lipoprotein cholesterol levels remained unchanged after LDL-A therapy (data not shown). These results were consistent with those of previous reports.5-7

Responses to LDL-A therapy are listed in Table 1. LDL-A as monotherapy failed to reduce proteinuria at the end of the first course (9.7 ±
2.5 to 9.1 g/m²/d of protein). However, overall, 7 patients showed a response to our treatment regimen, with clinical remission of nephrotic-range proteinuria at the end of the second course. Of special note, 5 of these patients achieved complete remission within 4 weeks (mean, 3.2 ± 0.8 weeks; range, 2 to 4 weeks) after introducing prednisone concomitantly with LDL-A, whereas there was no improvement in proteinuria in the remaining 4 patients (Fig 3). Based on criteria for treatment response, these 4 patients were considered to have treatment failure.

**Outcome**

Patients were followed up for a mean of 4.7 ± 3.7 years (median, 4.1 years; range, 0.6 to 11.1 years) after LDL-A therapy, and the clinical outcome of each patient at the latest observation is listed in Table 1.

During follow-up of 5 patients who achieved complete remission with combined LDL-A and prednisone therapy, 3 of these patients experienced a relapse at various intervals after stopping prednisone treatment, but subsequently achieved complete remission with reinitiation of standard prednisone therapy. As shown in Fig 4, these 5 patients maintained normal renal function during the follow-up period (median, 4.4 years; range, 4.0 to 11.1 years).

One (no. 10) of 2 patients who achieved partial remission of proteinuria with combined LDL-A and prednisone therapy maintained the status of partial remission with stable renal function during the follow-up period (4.5 years), whereas the other patient (no. 11) showed a transient increase in GFR, but subsequently a gradual decline in renal function and progression to ESRF 7.8 years after LDL-A therapy (Fig 4).

Based on criteria for treatment response, 4 patients were considered to experience treatment failure. After completion of LDL-A therapy, these 4 patients showed persistent nephrotic-range pro-
teinuria and an increase in hyperlipidemia to pretreatment levels. Changes in renal function in these patients are shown in Fig 4. A transient increase in GFR was observed on introducing LDL-A therapy, but renal function declined rapidly thereafter and progressed to ESRF a median of 1.3 years (range, 0.6 to 1.6 years) after LDL-A therapy.

Predicting Factors for Treatment Response

To elucidate factors predicting treatment response, patients were categorized into a group that achieved complete remission (n = 5) and another group considered to experience treatment failure (n = 4), and some clinical and pathological features at the time of initiation of LDL-A were compared (Table 3). Patients with disease that responded to combined LDL-A and prednisone therapy had significantly more highly selective proteinuria and less chronic tubulointerstitial lesions (interstitial fibrosis and tubular atrophy) compared with those with disease that did not respond to our treatment regimen. There were no differences between the 2 groups in age at onset, time from onset to beginning of LDL-A therapy, frequency of primary steroid resistance, urinary protein and serum TCh levels, percentage of patients with reduced renal function, and extent of glomerular involvement on biopsy.

Complications of LDL-A Therapy

Although a complication related to vascular access (catheter infection) was seen in 1 patient, there were no other remarkable complications during or after LDL-A therapy.

DISCUSSION

Treatment of SR-FSGS is still one of the major challenges in the field of nephrology. Azathioprine and chlorambucil are not effective in many cases of SR-FSGS.22 The International Study of Kidney Disease in Children reported no benefit of cyclophosphamide in children with SR-FSGS.23 Use of CsA in SR-FSGS has produced somewhat more favorable results than cytotoxic drugs.24 Although combined CsA and alternate-day prednisone therapy can be effective in inducing remission in patients with SR-FSGS,10,11 the prognosis of patients with disease that does not respond to CsA is negative.25 Niaudet11 reported that of 12 children with SR-FSGS for which combined CsA and alternate-day prednisone therapy failed, 6 patients showed persistent NS and 5 patients progressed to ESRF. A similar poor prognosis in children with both SR and CsA-resistant primary FSGS was reported by Hino et al.12 All patients enrolled in this study had biopsy-proven primary FSGS and SR disease and were treated unsuccessfully with conventional-dose CsA therapy in combination with alternate-day prednisone.11,12 Thus, the prognosis of our patients at entry was considered grave, and this was our rationale for setting the inclusion criteria in the present study.

The present study shows that 5 of 11 patients with both SR and CsA-resistant primary FSGS entered complete remission on introducing combined LDL-A and prednisone therapy and maintained normal renal function during the follow-up period (median, 4.4 years; range, 4.0 to

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Table 3. Comparison of Some Clinical and Morphological Parameters Between 2 Patient Categories Grouped According to Treatment Response

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age at Onset (y)</th>
<th>Onset to LDL-A (y)</th>
<th>Resistance (%)</th>
<th>Proteinuria* (g/m²/dl)</th>
<th>SI*</th>
<th>Serum TCh* (mg/dL)</th>
<th>Patients With Reduced Renal Function (%)</th>
<th>Glomerular Lesions† (0-3)</th>
<th>Tubulointerstitial Lesions† (0-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (n = 5)</td>
<td>10.1 ± 2.2</td>
<td>2.3 ± 1.5</td>
<td>40</td>
<td>8.8 ± 2.1</td>
<td>0.05 ± 0.02</td>
<td>519 ± 101</td>
<td>0</td>
<td>23.8 ± 5.8</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>Failure (n = 4)</td>
<td>10.2 ± 2.7</td>
<td>1.9 ± 0.8</td>
<td>50</td>
<td>10.0 ± 2.0</td>
<td>0.25 ± 0.04</td>
<td>483 ± 94</td>
<td>50</td>
<td>38.2 ± 9.1</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>P§</td>
<td>0.624</td>
<td>0.807</td>
<td>&gt;0.999</td>
<td>0.462</td>
<td>0.012</td>
<td>0.624</td>
<td>0.167</td>
<td>0.086</td>
<td>0.010</td>
</tr>
</tbody>
</table>

NOTE. Data expressed as mean ± SD. To convert serum total cholesterol in mg/dL to mmol/L, multiply by 0.02586.

Abbreviations: CR, patients who achieved complete remission; Failure, patients considered to have had treatment failure; LDL-A, low-density lipoprotein apheresis; SI, selectivity index; TCh, total cholesterol.

†Values were obtained from each patient at the time of initiation of LDL-A therapy.
‡Degree of tubular atrophy and interstitial fibrosis was graded semiquantitatively on a scale of 0 to 3.
§Comparison between groups was performed by means of Mann-Whitney U-test for continuous variables and Fisher's exact test for categorical variables.
11.1 years). The prompt response supports the hypothesis that combined LDL-A and prednisone therapy is responsible for the clinical remission in our patients, and this observed response is of clinical interest. A similar favorable response was observed in adult patients with FSGS in a prospective study (14 patients; mean age, 37.3 ± 16.8 years; concomitant medication, 0.8 mg/kg of prednisone; urinary protein excretion decreased 1 to 4 weeks after the start of LDL-A, and a decrease in urinary protein < 3.5 g/d was observed in 8 of 14 patients).\(^7\)

However, before proceeding to analyze our data, several general considerations that may influence data interpretation deserve mention.\(^26\) Our study contained only a small number of patients and was not a randomized, controlled trial. In addition, we compared our results with those of previous reports, although we realize the risk that differences in general care over time may be misconstrued as benefits of LDL-A. One cannot rule out spontaneous remission, although this is rare and occurs in less than 5% of nephrotic patients with primary FSGS.\(^24\) Moreover, we are aware that some patients included in this study might have responded to more prolonged prednisone treatment,\(^28\) or the Tune-Mendoza protocol of combined high-dose pulse steroids and cytotoxic drugs.\(^3,9\) Without controls, the present results may not allow definite conclusions regarding the therapeutic benefits of LDL-A therapy for pediatric patients with SR-FSGS. However, the good clinical response to combined LDL-A and prednisone therapy observed in our patients suggests that this treatment regimen can be a valuable addition to therapeutic options for treating SR-FSGS. Moreover, our treatment protocol may offer an opportunity to reduce or even avoid the potential adverse effects of steroids and cytotoxic drugs because many therapeutic protocols reported to be effective seem to be potentially harmful.\(^1\) Thus, although there is a need for more studies on the effectiveness of LDL-A in patients with SR-FSGS, combined LDL-A and prednisone therapy should be considered as a possible rescue therapy arm in future study protocols.

As long as the exact pathophysiological characteristics of FSGS remain known,\(^29-31\) the mechanisms by which LDL-A benefits patients with SR-FSGS will be largely obscure. It has been proposed that hyperlipidemia contributes to the progression of renal disease, but the exact mechanism also is incompletely understood.\(^33\) However, because a reduction in lipid levels may have hemodynamic effects that could be relevant to the mechanism of GFR improvement,\(^33\) the prompt and transient increase in GFR observed after initiating LDL-A may be attributed to the LDL-A therapy. In this series, concomitant medications included statins and/or probucol, both known to have beneficial effects other than specific lipid-lowering actions.\(^32,34,35\) Effects of these drugs can be excluded because they were maintained without changes in dosage and administration methods during the period of LDL-A therapy.

It is of interest that LDL-A as monotherapy failed to reduce proteinuria at the end of the first course; however, 5 patients achieved complete remission within 4 weeks, just after introducing prednisone in combination with LDL-A. Although removal of some circulating factors responsible for proteinuria by dextran sulfate adsorption is one of several hypotheses proposed to explain the benefits of LDL-A,\(^36\) induction of complete remission only after concomitant administration of prednisone with LDL-A may suggest that LDL-A might have influenced the sensitivity to steroids. Because in vitro study showed that very low-density lipoproteins (VLDLs) induced a dose-dependent reduction in number of specific binding sites for dexamethasone in cultured smooth muscle cells,\(^37\) the improvement in hyperlipidemia, including both high LDL and VLDL levels, by LDL-A might upregulate the steroid binding of systemic cells in patients with primary FSGS and could result in clinical remission of proteinuria. A similar possibility was postulated in another LDL-A study.\(^38\) However, because previous study suggested that factors other than glucocorticoid receptors that mediate the cellular effects of glucocorticoid may be involved in the variable responses of patients with idiopathic NS to glucocorticoid,\(^39\) additional studies are needed to clarify the molecular mechanisms underlying this variable steroid responsiveness in patients with NS.

Patients with disease that responded to our treatment regimen had significantly fewer chronic
tubulointerstitial lesions and more highly selective proteinuria compared with patients with disease that did not respond to this therapy. The histological feature most consistently predictive of a poor prognosis is the presence of advanced interstitial fibrosis. Therefore, given results of the present study, our treatment regimen will be useful, particularly if applied early in the course of disease. Assessment of selectivity of proteinuria was simplified in 1966 by Cameron and Blandford, who introduced SI determination. Although its value in predicting response to steroid therapy in NS has been proposed, SI seems to find little place in clinical practice. However, recent studies highlighted the clinical significance of selectivity of proteinuria. SI alone or in combination with fractional excretion of α₂-microglobulin has a predictive value for renal outcome and response to therapy in patients with NS. Results of the present study also support the clinical value of SI and show that SI seems to be useful for predicting response to combined LDL-A and prednisone therapy in patients with SR-FSGS.

Finally, studies have indicated that patients with a diagnosis of primary FSGS do not constitute a homogeneous population. The clinical course of patients with primary FSGS is highly variable; ranging from complete or partial remission to persistent nonnephrotic or nephrotic proteinuria with no or moderate loss of renal function to progression to ESRF. Recurrence of the disease in only 20% to 50% of allograft recipients who may share the presence of circulating glomerular permeability factors lends additional support to the assertion that primary FSGS is clinically and biologically diverse. Moreover, sporadic forms of FSGS secondary to mutations in podocin have been recognized. Results of the present study showing the usefulness of combined LDL-A and prednisone therapy in a portion of patients with SR-FSGS support the concept that primary FSGS is a heterogeneous condition that can result from a number of pathogenetic mechanisms with different prognostic and therapeutic implications. Hopefully, our experience might provide some information leading to a more accurate mechanism-based clinicopathologic and biological classification of primary FSGS and the design of improved therapeutic strategies.

In conclusion, because all patients enrolled in this study had severe forms of primary FSGS with a grave prognosis at entry, our preliminary experience suggests that combined LDL-A and prednisone therapy can be a valuable addition to therapeutic options for treating patients with SR-FSGS. Of all clinical and histological characteristics of primary FSGS evaluated, only remission of proteinuria predicts a favorable outcome in nephrotic patients with primary FSGS. Therefore, to establish a more effective management approach to patients with SR-FSGS, the therapeutic role of LDL-A in treating these patients deserves to be assessed further in larger randomized, controlled trials.

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