

Original Paper

A Prospective Observational Survey on the Long-Term Effect of LDL Apheresis on Drug-Resistant Nephrotic Syndrome

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Key Words

LDL apheresis · Drug-resistant nephrotic syndrome · Long-term outcome · Nephrotic syndrome · POLARIS study · Prospective study · Urinary protein

Abstract

Background/Aims: LDL apheresis (LDL-A) is used for drug-resistant nephrotic syndrome (NS) as an alternative therapy to induce remission by improvement of hyperlipidemia. Several clinical studies have suggested the efficacy of LDL-A for refractory NS, but the level of evidence remains insufficient. A multicenter prospective study, POLARIS (Prospective Observational Survey on the Long-Term Effects of LDL Apheresis on Drug-Resistant Nephrotic Syndrome),

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was conducted to evaluate its clinical efficacy with high-level evidence. **Methods:** Patients with NS who showed resistance to primary medication for at least 4 weeks were prospectively recruited to the study and treated with LDL-A. The long-term outcome was evaluated based on the rate of remission of NS 2 years after treatment. Factors affecting the outcome were also examined. **Results:** A total of 58 refractory NS patients from 40 facilities were recruited and enrolled as subjects of the POLARIS study. Of the 44 subjects followed for 2 years, 21 (47.7%) showed remission of NS based on a urinary protein (UP) level <1.0 g/day. The UP level immediately after LDL-A and the rates of improvement of UP, serum albumin, serum creatinine, eGFR, and total and LDL cholesterol after the treatment session significantly affected the outcome. **Conclusions:** Almost half of the cases of drug-resistant NS showed remission 2 years after LDL-A. Improvement of nephrotic parameters at termination of the LDL-A treatment was a predictor of a favorable outcome.

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Introduction

In nephrotic syndrome (NS), plasma proteins are lost in urine, and compensating protein synthesis including lipoprotein evokes a hypercholesterolemic condition. Persistent hypercholesterolemia may promote progressive renal injury [1]; thus, hypercholesterolemia is not only a complication, but also an exacerbating factor. Therefore, rapid normalization of hypercholesterolemia is important for prevention of progression of renal injury in NS.

LDL apheresis (LDL-A) is a blood purification therapy that removes LDL from the circulating blood flow and rapidly reduces the plasma cholesterol level. LDL-A was originally developed for treatment of serious hyperlipidemia, such as familial hypercholesterolemia that is unresponsive to ordinary lipid-lowering drugs [2]. Subsequently, LDL-A began to be used to improve dyslipidemia in NS (initially to prevent renal injury) and was found to improve nephrotic symptoms, including the level of urinary protein (UP) and hyperproteinemia [3], in addition to ameliorating dyslipidemia.

Several studies in patients with NS have shown relatively favorable therapeutic effects even for refractory types of NS such as focal segmental glomerulosclerosis (FSGS), and not only in adults [4–7], but also in pediatric patients [8, 9]. However, the evidence levels of these studies have been relatively low, because most were retrospective analyses or had a small number of subjects. To establish more convincing evidence for the efficacy of LDL-A, we performed a prospective cohort study, POLARIS (Prospective Observational Survey on the Long-Term Effects of LDL Apheresis on Drug-Resistant Nephrotic Syndrome), in which patients with NS that were unresponsive to primary medication were prospectively recruited and followed up for 2 years after LDL-A treatment. We have preliminarily analyzed the effect of LDL-A on recovery from NS immediately after treatment and revealed a rapid normalization of proteinuria in approximately half of the subjects [10]. In the current report, we evaluated the 2-year outcome of the same cohort and examined factors that affect clinical efficacy as the final results of the POLARIS study.

Subjects and Methods

Study Design and Subjects

The POLARIS study is a prospective, observational, multicenter cohort study based on a central registration system. The study protocol was approved by the Institutional Review

Boards at Fukuoka University Hospital, Fukuoka, and the Tazuke Kofukai Medical Research Institute, with which the core investigators (T. Saito and E. Muso) are affiliated. The study is also registered in the University Medical Information Network, Japan (ID: UMIN000000871).

Patients with NS resistant to primary medication for at least 4 weeks after drug treatment had first been administered were prospectively registered as subjects in the POLARIS study from January 1, 2007, to December 31, 2008. Each subject was informed about the outline of the study as well as the risks and benefits of LDL-A before enrollment and then provided written informed consent before registration in the study. The overall study was conducted in accordance with the Declaration of Helsinki.

This study was planned to be conducted as an observational study intended to reveal the actual efficacy of LDL-A in combination with standard therapy in ordinary clinical practice. Therefore, the study protocol does not specify each patient's treatment regimen, leaving this to the attending physician's discretion. The laboratory data were measured at each treatment site.

Evaluation of Outcome

The 2-year outcome after LDL-A was evaluated by the attending doctor of each subject using a 4-category scale that has been shown to be effective in Japan [11]: complete remission = UP undetectable; incomplete remission I = UP <1.0 g/day; incomplete remission II = UP ≥ 1.0 to <3.5 g/day, and no effect = UP ≥ 3.5 g/day. In this study, complete remission or incomplete remission I was defined as a favorable outcome, and the other categories as a poor outcome. The rate of subjects with a favorable outcome was evaluated 2 years after the LDL-A treatment.

Results

Subject Background and Clinical Characteristics

As shown in figure 1, 58 patients with NS were initially registered, but 5 were excluded due to unavailability of background data (n = 3) and violation of inclusion criteria (n = 2). During the 2 years of follow-up, 3 died of diseases unrelated to NS and 6 were lost to follow-up, resulting in 44 subjects analyzed in the current study. Although the type of LDL-A modality was not specified in the protocol, the dextran sulfate adsorption system (Liposorber®; Kaneka Corporation, Osaka, Japan) was used in all cases. The average number of LDL-A sessions in each LDL-A treatment series was 9.6 ± 2.7. The average volume of treated plasma in each session was 3.5 ± 0.8 liters. Other characteristics of the patients and the LDL-A treatment are also described in table 1. As for primary diseases of the subjects, FSGS was found in the majority of cases, presenting in 28 subjects (63.6%), which presumably reflects the actual situation of clinical practice. The other primary diseases were: membranous nephropathy (n = 4); minimal change NS (MCNS), renal amyloidosis, and undescribed cases (n = 2 each), and lupus nephritis, membranoproliferative glomerulonephritis, Henoch-Schönlein purpura nephritis, crescentic glomerulonephritis, diabetic nephropathy, and hepatitis B virus-associated nephropathy (n = 1 each).

Outcomes at the 2-Year Follow-Up

During the follow-up period, 3 subjects died of diseases unrelated to NS (cerebral infarction, lung cancer, and methicillin-resistant *Staphylococcus aureus* pneumonia) and 6 were lost to follow-up, leaving 44 subjects eligible for analysis at the 2-year follow-up (fig. 1). A favorable outcome was found in 47.7% (21/44; 11 subjects in complete remission and 10 in incomplete remission I), whereas 23 subjects had an unfavorable outcome (11 in incomplete remission II and 12 with no effect) (fig. 2).

Fig. 1. Flowchart of enrollment and follow-up of patients registered in the study. A total of 58 patients were enrolled in the POLARIS study. However, 5 of them were excluded because LDL-A treatment was started within 4 weeks of drug treatment in 2 patients and the primary data including clinical parameters before and immediately after treatment were not collected in 3 patients. Thus, 53 patients were followed up for 2 years as the subjects of the study. During the follow-up period, 3 died of diseases unrelated to NS (cerebral infarction, lung cancer, and methicillin-resistant *S. aureus* pneumonia) and 6 were lost to follow-up, leaving 44 subjects for evaluation of 2-year outcomes.

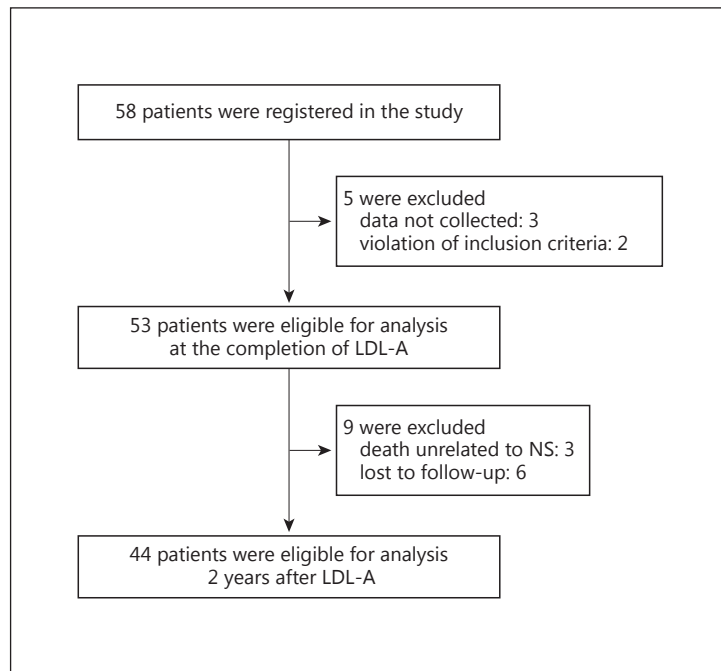


Table 1. Subject background and treatment characteristics

Characteristics	Value
Subjects	53
Age (range), years	55.8±18.1 (18–87)
Male/female	33/20
First time/recurrent	31/21 ^a
Renal biopsy (+/-)	44/8 ^a
Concomitant administration of cyclosporine A (+/-)	24/27 ^b
Concomitant administration of steroid pulse therapy (+/-)	4/47 ^b
Number of LDL-A sessions	9.6±2.7
Treated amount of plasma, l	3.5±0.8

Values are presented as means ± SD or n.

^a Data not collected for 1 subject. ^b Data not collected for 2 subjects.

Factors Affecting Outcome

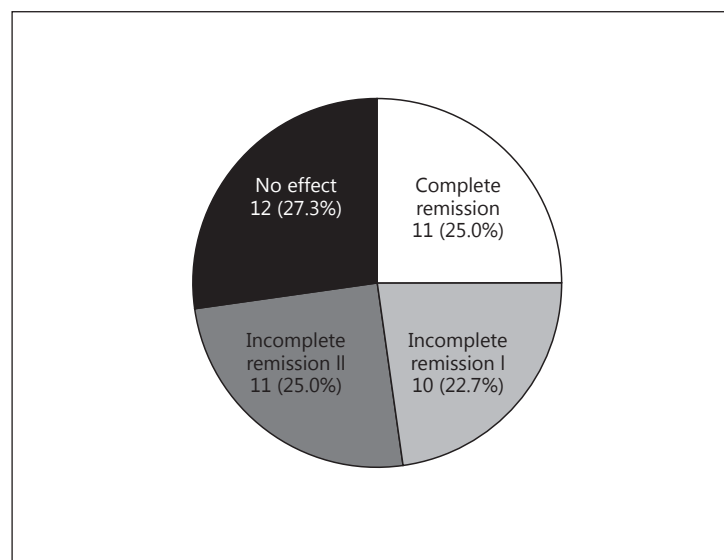
The subjects' background factors, including age, sex, BMI, primary or recurrent cases, concomitant calcineurin inhibitor administration, concomitant steroid pulse therapy, and the number of LDL-A sessions, were not significantly correlated with outcome. Most serum and urine parameters before and after treatment also showed no significant correlation. However, the UP level immediately (within up to 4 weeks) after LDL-A was strongly associated with 2-year outcome ($p < 0.0001$) (table 2). Of the 20 subjects relieved from nephrotic-range proteinuria with a UP level of <3.5 g/day immediately after LDL-A, 16 (80.0%) had favorable outcomes, whereas only 4 of the 22 subjects (18.2%) without posttreatment relief from NS achieved favorable outcomes ($p < 0.001$, χ^2 test).

Correlations between 2-year outcome and change of serum and urine parameters before and immediately after LDL-A treatment were also examined. This analysis revealed that the

Table 2. Mean values of serum and urine parameters immediately after LDL-A treatment in subjects with favorable and poor outcomes

Clinical parameter	Favorable outcome	n	Poor outcome	n	p value
Serum total protein, g/dl	4.9±0.7	21	4.6±0.8	23	0.230
Serum albumin, g/dl	2.9±0.8	21	2.5±0.7	23	0.061
Serum creatinine, mg/dl	1.2±0.7	21	2.0±2.0	23	0.092
eGFR, ml/min/m ²	61.0±27.2	21	46.6±28.2	22	0.095
UP, g/day	1.7±1.8	20	6.2±3.5	22	<0.0001
Triglycerides, mg/dl	240.2±156.3	19	241.6±214.0	19	0.981
Total cholesterol, mg/dl	194.3±65.6	20	253.1±157.0	22	0.128
LDL cholesterol, mg/dl	83.1±60.4	18	115.1±58.9	21	0.103
HDL cholesterol, mg/dl	66.5±18.3	18	78.1±28.7	17	0.162
Fibrinogen, mg/dl	271.1±77.2	15	354.8±130.7	10	0.055
Thrombin-antithrombin III complex, ng/ml	14.7±38.6	14	3.3±3.1	6	0.488

Fig. 2. Remission rate at 2 years after LDL-A treatment. The outcomes 2 years after LDL-A treatment for 44 subjects were evaluated with a 4-category scale as described in the Subjects and Methods section. Complete remission or incomplete remission I was defined as a favorable outcome, and incomplete remission II or no effect as a poor outcome. The rate of favorable outcomes was 47.7% (21/44).



rates of improvement of serum albumin, eGFR, UP, and total and LDL cholesterol were significantly higher in subjects with a favorable outcome (table 3). Regarding primary diseases, the 2 subjects with MCNS had a favorable outcome, and the 2 subjects with renal amyloidosis had a poor outcome, but other primary diseases showed no correlation with outcome. In addition, the subjects with non-FSGS in this study on the whole showed slightly better outcomes than those with FSGS (table 4).

Discussion

The POLARIS study was conducted as a prospective evaluation of the response to and outcome of LDL-A treatment in patients with NS who had a poor response to primary medication in an actual clinical setting. We had reported that LDL-A had a short-term clinical

Table 3. Percent change of serum and urine parameters before and immediately after LDL-A treatment in subjects with favorable and poor outcomes

Clinical parameter	Favorable outcome	n	Poor outcome	n	p value
Serum total protein	9.9±21.0	19	8.7±12.9	22	0.816
Serum albumin	39.5±34.4	21	16.2±20.5	23	0.009
Serum creatinine	-17.8±26.1	21	3.8±39.1	23	0.038
eGFR	46.4±78.9	21	8.4±34.7	22	0.046
UP	-62.2±57.1	20	-11.7±44.4	22	0.003
Triglycerides	-0.9±50.2	19	1.5±65.5	19	0.901
Total cholesterol	-42.0±19.7	20	-15.9±46.5	22	0.026
LDL cholesterol	-59.6±27.4	18	-31.4±41.0	20	0.019
HDL cholesterol	0.44±25.51	18	15.89±24.89	15	0.090
Fibrinogen	-18.97±26.78	15	-6.32±31.02	10	0.288
Thrombin-antithrombin III complex	-19.04±64.79	13	-42.95±39.08	5	0.456

Table 4. Frequency of primary diseases in subjects with favorable and poor 2-year outcomes

Disease	Favorable outcome		Poor outcome	
FSGS	12 ^a	42.9%	16 ^b	57.1%
Non-FSGS	7	50.0%	7	50.0%
MN	1		3	
MCNS	2		0	
RA	0		2	
Others	4 ^c		2 ^d	
Not described	2		0	
Total	21	47.7%	23	52.3%

MN = Membranous nephropathy; RA = renal amyloidosis.

^a Including 1 subject complicated with another renal disease (MN).

^b Including 2 subjects complicated with other renal diseases (MN: 1; diabetic nephropathy: 1). ^c Lupus nephritis: 1; crescentic glomerulonephritis: 1; diabetic nephropathy: 1; hepatitis B virus-associated nephropathy: 1. ^d Membranoproliferative glomerulonephritis: 1; Henoch-Schönlein purpura nephritis: 1.

efficacy, with relief from NS as early as 4 weeks after treatment in approximately half of the treated cases [10]. In this study, we examined the long-term outcome and found that nearly half of the subjects (21/44; 47.7%) had relief from NS 2 years after treatment. These results suggest that the therapeutic efficacy of LDL-A immediately after treatment was largely maintained for 2 years.

We had previously conducted a retrospective survey to examine the long-term outcome of patients with NS treated with LDL-A and found a favorable outcome rate of 62.1% (18/29) [7], which is considerably higher than that in the current prospective study. This discrepancy may be due to selection bias, because the subjects in the retrospective study were selected from cases reported in journals or at conferences. Cases selected for presentation tend to be biased toward favorable results. The current study is important in that it determines the outcome prospectively after LDL-A in patients with NS who were unresponsive to ordinary medication.

Several reports have evaluated the efficacy of LDL-A for non-FSGS diseases, such as MCNS [12], membranous nephropathy [13, 14], lupus nephritis [15–17], and diabetic nephropathy [18–21], but most are case reports/series with a limited number of subjects. Although the number of subjects with each disease apart from FSGS is small, we examined a total of 16 subjects with non-FSGS registered in the POLARIS cohort and found that LDL-A treatment reduced the UP level in those patients at a comparable rate to that in FSGS cases immediately after treatment [10]. In the current study, we were able to examine a total of 14 non-FSGS subjects and showed that the rate of favorable outcomes was 50.0%, which is comparable to – or even better than – the rate in FSGS subjects, reflecting the immediate proteinuria-reducing effect (table 4). This suggests that therapeutic mechanisms of LDL-A may be involved in some factors common to NS.

On the basis of reviewing previous reports, several mechanisms could be proposed to explain the therapeutic effects of LDL-A: improvements in glomerular injuries, which are likely to be caused by activated macrophages through amelioration of dyslipidemia [22, 23]; direct adsorption and removal of circulating noxious factors (e.g., coagulation factors including fibrinogen and von Willebrand factor [24, 25]), and recovery of the drug potency of lipophilic drugs, such as cyclosporine, the availability of which is impaired in the hyperlipidemic condition [26, 27].

In this study, factors that could affect the outcome of the subjects were examined. No baseline clinical parameters and conditions (i.e., serum and urine parameters before treatment and subject background) examined in this study showed a significant correlation with 2-year outcome, and most serum and urine parameters after treatment were not correlated with outcome. However, the UP levels after treatment differed significantly between subjects with favorable and those with poor outcomes, with mean values of 1.68 ± 1.76 and 6.18 ± 3.14 g/day (table 2), respectively; furthermore, 80% of the subjects who achieved posttreatment relief from NS (UP <3.5 g/day) had a favorable outcome. Several studies have also shown that proteinuria in the nephrotic range is associated with a poor prognosis and onset of end-stage renal disease over several years, while recovery from nephrotic proteinuria portends a favorable outcome for several types of NS, including FSGS [28, 29], membranous nephropathy [30, 31], and IgA nephropathy [32, 33]. Improvement of parameters representing disease conditions of NS, including serum albumin, eGFR, UP, and total and LDL cholesterol, was also significantly associated with favorable outcome (table 4), which suggests that an early rapid alleviation of pathological conditions of NS by LDL-A contributes to a favorable outcome.

Summing up the results obtained in the POLARIS study, it is conceivable that, regardless of the type of primary disease, LDL-A rapidly ameliorated proteinuria in nearly half of the patients with NS who failed to respond to primary medication and that most of these patients then had a favorable 2-year outcome. Although this study was conducted as a single-arm trial with no controls, the efficacy of LDL-A is considered to be fairly convincing, since it is well known that drug-resistant patients with NS generally have a poor prognosis.

We recognize that there are several limitations to this study. Most importantly, the study was performed as a single-arm observational study with no control group, and the sample size of 44 was relatively small for a definitive evaluation of treatment efficacy and outcome. However, the study produced quantitative results that reflect the clinical efficacy of LDL-A in actual clinical practice. We consider that LDL-A treatment exerts a rapid amelioration of nephrotic conditions (especially proteinuria) and ensures a favorable outcome in nearly half of drug-resistant patients with NS regardless of the primary disease. Further investigation with a larger number of subjects and preferably controls is needed to confirm the findings of the current study.

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