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Favorable therapeutic efficacy of low-density lipoprotein apheresis for nephrotic syndrome with impaired renal function

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Abstract

Many reports have shown the therapeutic efficacy of LDL apheresis (LDL-A) in drug-resistant nephrotic syndrome (NS) for improvement of heavy proteinuria and severely impaired renal function. To obtain comprehensive results in a large number of cases, a post hoc analysis of the Prospective Observational survey on the Long-Term Effects of the LDL-Apheresis on the Drug Resistant Nephrotic Syndrome (POLARIS) study was performed by stratifying enrolled cases according to the pretreatment estimated glomerular filtration rate (eGFR) levels indicating normal (N) ($\geq$60 ml/min/1.73 m^2), moderately impaired (M) ($\geq$30 to <60 ml/min/1.73 m^2), and severely impaired (S) (<30 ml/min/1.73 m^2) renal function. Significant improvements of proteinuria and renal function were found in Group N and, most interestingly, in Group M. A tendency for improvement in proteinuria was found in Group S. Most cases in all groups had not entered end-stage renal disease at 2 years after LDL-A treatment. These results suggest that LDL-A has therapeutic efficacy even in cases in which renal function has declined to 30 ml/min/1.73 m^2.

KEYWORDS
eGFR, end-stage renal disease, LDL apheresis, nephrotic syndrome, renal dysfunction

1 | INTRODUCTION

Renal function in nephrotic syndrome (NS) is often impaired due to symptoms related to NS, such as low renal perfusion pressure, decreased filtration coefficient, acute tubular necrosis, and interstitial edema [1]. In most cases, such renal dysfunction resolves with improvement of NS. However, some cases with resistance to primary treatment, in particular drug therapy, have an increasing risk of progressive renal failure because management of drug therapy is difficult due to changes in drug clearance and pharmacokinetics caused by impaired renal function. Therefore, alternative therapy may be needed to prevent progression of renal damage in such cases.

LDL apheresis (LDL-A) is a blood purification therapy that removes LDL from the circulating blood flow and rapidly ameliorates dyslipidemia in various diseases, including NS [2]. Many reports have shown that LDL-A reduces the urinary protein level, even in refractory or drug-resistant NS. These include case reports and series but also multicenter surveillance [3], prospective interventional [4–6], and cohort [7,8] studies. LDL-A also has efficacy in patients with NS with severely damaged renal function [9,10]. This includes some cases with deterioration of renal function to a level requiring hemodialysis, in which recovery from NS and withdrawal from hemodialysis have occurred after introduction of LDL-A [11–13].

Based on these findings, LDL-A may be an effective alternative therapy for resistant NS with impaired renal function. However, most reports on this approach are single cases or case series with a small number of patients, and there has been no comprehensive study of LDL-A in

patients with renal dysfunction. Herein, we present the results of a post hoc analysis of cases from the POLARIS study [7,8], which was a prospective cohort study of the effect of LDL-A on drug-resistant NS cases with various diseases and stages of renal dysfunction. The cases were stratified into three groups based on pretreatment estimated glomerular filtration rate (eGFR) indicating normal renal function and moderate and severe renal impairment (≥60, 30–60, and <30 ml/min/1.73 m^2, respectively). Outcomes in these groups were examined to determine the extent to which renal impairment affects the efficacy and favorable prognosis of LDL-A.

2 | PATIENTS AND METHODS

2.1 | Study population

A post hoc analysis was conducted based on the results of the POLARIS study, which was a prospective, observational, multicenter, cohort study of the efficacy of LDL-A on nephrotic proteinuria immediately after LDL-A treatment and the outcome of NS at 2 years after completion of LDL-A treatment. The study protocol was registered and disclosed on the web site of the University Medical Network-Clinical Trial Registry (UMIN-CTR) in Japan (https://www.umin.ac.jp/; ID:UMIN000000871). The study investigators obtained internal review board (IRB) approval before starting the study. IRBs in the facilities of the principal investigators (Kitano Hospital; Approval Number: 06-25; Fukuoka University; Approval Number 6-110) provided approval for centers without an IRB.

A total of 64 episodes of LDL-A in 58 patients with NS resistant to full-dose steroids and/or saturated cyclosporin A treatment for at least 4 weeks were prospectively registered in the POLARIS study. Of the 64 episodes, 47 in which 24-h urinary data before and after LDL-A were obtained were included for evaluation of short-term efficacy. A total of 44 cases had 2-year outcome data and these were used for evaluation of long-term efficacy. The design and results of the POLARIS study have been published elsewhere [7,8].

2.2 | Stratification of subjects and outcome measures

To evaluate the influence of renal dysfunction on the efficacy of LDL-A, pretreatment eGFR was calculated using the novel equation revised by Matsuo et al. [14], which determines eGFR from three parameters: serum creatinine (SCr), age, and sex. Based on the pretreatment eGFR, episodes were stratified into three groups in patients with normal renal function (Group N, pretreatment eGFR ≥ 60 ml/min/1.73 m^2); moderately impaired renal function (Group M, pretreatment eGFR ≥ 30 to <60 ml/min/1.73 m^2); and severely impaired renal function (Group S, pretreatment eGFR < 30 ml/min/1.73 m^2). Urinary protein (UP), SCr, and eGFR before and after LDL-A treatment were collected for each episode and compared among the three groups for evaluation of short-term efficacy. Outcomes of NS 2 years after LDL-A treatment were compared between cases with pretreatment eGFR ≥ 30 and <30 ml/min/1.73 m^2 for evaluation of long-term efficacy.

2.3 | Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Analysis of differences in pretreatment levels of clinical parameters among the three groups was performed by one-way ANOVA with a Tukey post hoc test for parametric data or by Kruskal–Wallis test with a Steel-Dwass post hoc test for nonparametric data. A Fisher exact test was used for pairwise comparison of the effects of LDL-A on proteinuria and renal function. The value of $p < 0.05$ was considered significant.

3 | RESULTS

3.1 | Characteristics and stratification of subjects

Of the 47 episodes used for short-term evaluation (immediately after LDL-A) and the 44 cases used for long-term evaluation (2 years after LDL-A) in the original POLARLIS study, two episodes and one case were excluded due to a lack of data required to calculate eGFR. Thus, 45 episodes and 43 cases were examined for short- and long-term efficacy, respectively, in the present study. The 45 episodes were stratified into groups with normal (Group N, $n = 17$), moderately impaired (Group M, $n = 14$), and severely impaired (Group S, $n = 14$) renal function. The patient and episode characteristics in these groups are shown in Table 1 and the primary diseases in each group are shown in Table 2. The backgrounds and primary diseases of the patients were generally similar among the groups, but the proportions of cases with relapse, focal segmental glomerulosclerosis (FSGS), and cyclosporine A treatment tended to be lower in Group M, and use of anticoagulants tended to be higher in Group S.

TABLE 1 Episode characteristics in subjects for short-term analysis stratified into three groups based on eGFR before LDL-A

Episode characteristics	All cases	Group N	Group M	Group S
Total number	45	17	14	14
Renal biopsy (±)	40/5	15/2	12/2	13/1
First time/recurrent	26/19	9/8	10/4	7/7
Average number of LDL-A sessions		9.8 ± 2.5	9.5 ± 2.4	9.2 ± 2.9
Average amount of plasma per session (L)		3.4 ± 0.9	3.3 ± 0.6	3.6 ± 0.8
Concomitant drugs				
Cyclosporine A (±)	24/20[a]	11/6	5/8[a]	8/6
Steroid pulse therapy (±)	3/41[a]	0/17	2/11[a]	1/13
Diuretics (±)	25/17[b]	9/7[a]	7/7	9/3[c]
ARBs (±)	29/13[b]	13/3[a]	8/6	8/4[c]
Antiplatelet agents (±)	30/12[b]	10/6[a]	10/4	10/2[c]
Anticoagulants (±)	17/25[b]	7/9[a]	3/11	7/5[c]

Note: Group N: normal renal function with pretreatment eGFR ≥ 60 ml/min/1.73m^2. Group M: moderately impaired renal function with pretreatment eGFR ≥30–<60 ml/min/1.73m^2. Group S: severely impaired renal function with pretreatment eGFR <30 ml/min/1.73m^2.
Abbreviation: ARBs: angiotensin II receptor blockers; LDL-A, LDL apheresis.
[a]Data were not collected for one episode.
[b]Data were not collected for three episodes.
[c]Data were not collected for two episodes.

TABLE 2 Primary diseases in each group

Disease	Group N ($n = 17$)	Group M ($n = 14$)	Group S ($n = 14$)
Focal segmental glomerulosclerosis	11	6[a]	11[b]
Membranous nephropathy	1	0	3
Henoch-Schönlein purpura nephritis	1	0	0
Minimal change nephrotic syndrome	0	1	1
Renal amyloidosis	1	1	0
Others	1[c]	4[d]	0
Uncertain	1	2	0

Note: Group N: normal renal function with pretreatment eGFR ≥ 60 ml/min/1.73 m^2. Group M: moderately impaired renal function with pretreatment eGFR ≥ 30–<60 ml/min/1.73 m^2. Group S: severely impaired renal function with pretreatment eGFR < 30 ml/min/1.73 m^2.
[a]Including one patient complicated with membranous nephropathy.
[b]Including two patients complicated with other renal diseases: membranous nephropathy and diabetic nephropathy, respectively.
[c]Lupus nephropathy.
[d]Membranoproliferative glomerulonephritis; crescentic glomerulonephritis; IgA nephropathy; hepatitis B virus-associated nephropathy.

3.2 | Pretreatment clinical parameters

Pretreatment clinical parameters in Groups N, M, and S are shown in Table 3. Since the groups were stratified based on pretreatment eGFR, there were significant differences in pretreatment eGFR, SCr, and creatinine clearance. The pretreatment UP level also differed significantly among the groups, but no other parameters had significant differences, including serum proteins and lipoproteins.

3.3 | Changes in clinical parameters from before to after LDL-A

Changes in UP, SCr, and eGFR in Groups N, M, and S from before to after LDL-A are shown in Figures 1–3, respectively. Significant improvements in UP after LDL-A were seen in Group N ($p = 0.00026$; Figure 1(a)) and, more interestingly, in Group M ($p = 8.74 \times 10^{-5}$; Figure 1(b)). In Group S, 9 of 14 episodes had decreases in UP after LDL-A, but a few episodes had no response

TABLE 3 Clinical parameters of subjects in short-term analysis stratified into three groups based on eGFR before LDL-A

Clinical parameter	Unit	Group N ($n = 17$)	Group M ($n = 14$)	Group S ($n = 14$)	p-value
Serum total protein	g/dl	4.51 ± 0.71	4.21 ± 0.62	4.52 ± 0.65	n. s.[a]
Serum albumin	g/dl	2.28 ± 0.62	2.05 ± 0.58	2.10 ± 0.67	n. s.[b]
Serum creatinine	mg/dl	0.75 ± 0.16[#]	1.36 ± 0.32[#]	3.70 ± 1.73	$p < 0.001$[b]
eGFR	ml/min/1.73 m^2	81.87 ± 17.69[#,$]	41.44 ± 7.58[#]	15.64 ± 7.54	$p < 0.001$[a]
Urinary protein	g/day	6.00 ± 2.62	5.03 ± 2.42	8.00 ± 3.13	$p < 0.05$[b]
Triglyceride	mg/dl	321.00 ± 189.93	196.64 ± 110.61	259.21 ± 137.45	n. s.[a]
Total cholesterol	mg/dl	334.50 ± 95.08	317.33 ± 103.79	326.36 ± 138.24	n. s.[b]
LDL-cholesterol	mg/dl	192.70 ± 106.72	203.92 ± 87.55	213.82 ± 112.77	n. s.[b]
HDL-cholesterol	mg/dl	81.29 ± 24.29	68.26 ± 26.05	62.99 ± 16.82	n. s.[a]
Fibrinogen	mg/dl	410.73 ± 96.97	327.31 ± 119.86	442.48 ± 186.31	n. s.[a]
TAT	ng/ml	8.58 ± 8.24	26.32 ± 45.70	8.43 ± 7.41	n. s.[a]

Note: Group N: normal renal function with pretreatment eGFR ≥ 60 ml/min/1.73 m^2. Group M: moderately impaired renal function with pretreatment eGFR ≥ 30 to <60 ml/min/1.73 m^2. Group S: severely impaired renal function with pretreatment eGFR < 30 ml/min/1.73 m^2.
Abbreviations: eGFR: estimated glomerular filtration rate; TAT, thrombin-antithrombin III complex.
[#]$p < 0.001$ vs. Group S.
[$]$p < 0.001$ vs. Group M.
[a]Kruskal–Wallis.
[b]One-way ANOVA.

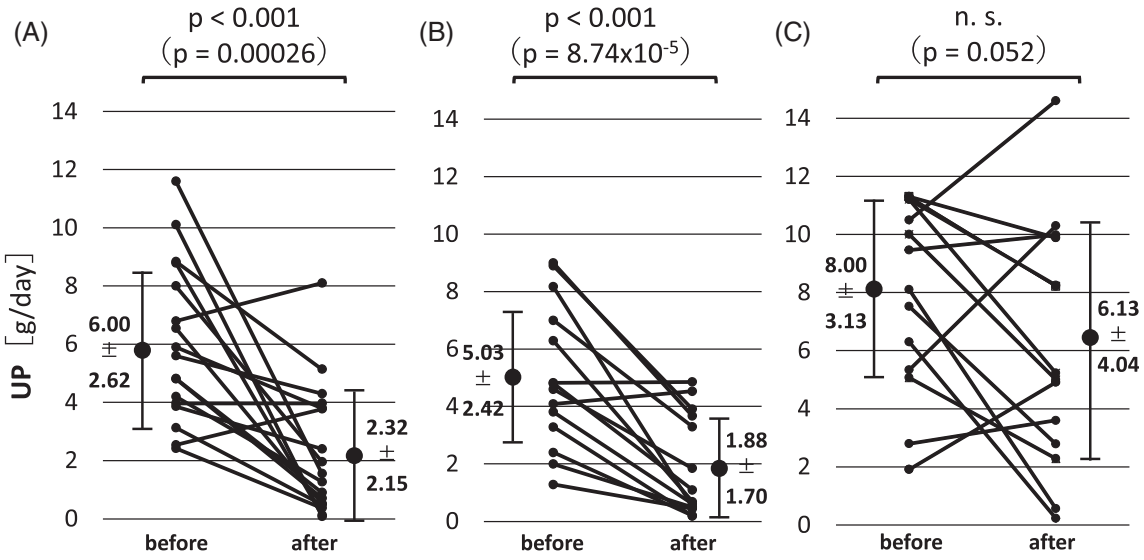

FIGURE 1 Changes in urinary protein (UP) levels before and after LDL apheresis (LDL-A) in Groups N (a), M (b), and S (c). Changes of UP before and after LDL-A for each episode are shown as solid lines. The mean ± SD UP levels before and after LDL-A are also shown

and nephrotic UP remained, which prevented a significant change in this group ($p = 0.052$, n.s.; Figure 1(c)). Regarding clinical parameters of renal function, the average SCr and eGFR in group N remained within normal ranges and with no significant change after LDL-A for SCr ($p = 0.258$, n.s.; Figure 2(a)) or eGFR ($p = 0.258$, n.s.; Figure 3(a)). In Group M, amelioration of impaired renal function was apparent with a significant decrease of SCr ($p = 0.020$, Figure 2(b)) and an increase of eGFR ($p = 0.007$; Figure 3(b)). In contrast, renal function in group S did not significantly improve from pre-LDL-A averages of 3.70 ± 1.73 ng/ml for SCr ($p = 0.214$, n.s.; Figure 2(c)) and 15.6 ± 7.5 ml/min/1.73 m^2 for eGFR ($p = 0.056$, n.s.; Figure 3(c)).

However, in more precise analysis in 14 cases of Group S, nine showed the decrease of UP from 9.11 ± 2.28 to 4.71 ± 3.31 g/day and five did increase of UP from 6.00 ± 3.45 to 8.67 ± 3.98 g/day after LDL-A.

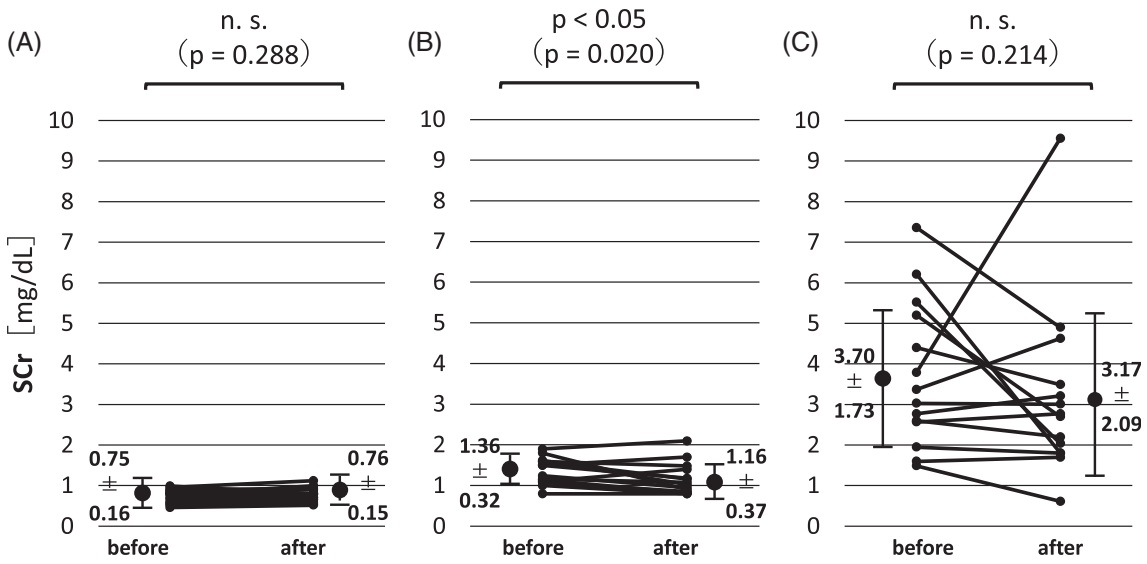

FIGURE 2 Changes in serum creatinine (SCr) levels before and after LDL apheresis (LDL-A) in Groups N (a), M (b), and S (c). Changes of SCr before and after LDL-A for each episode are shown as solid lines. The mean ± SD SCr levels before and after LDL-A are also shown

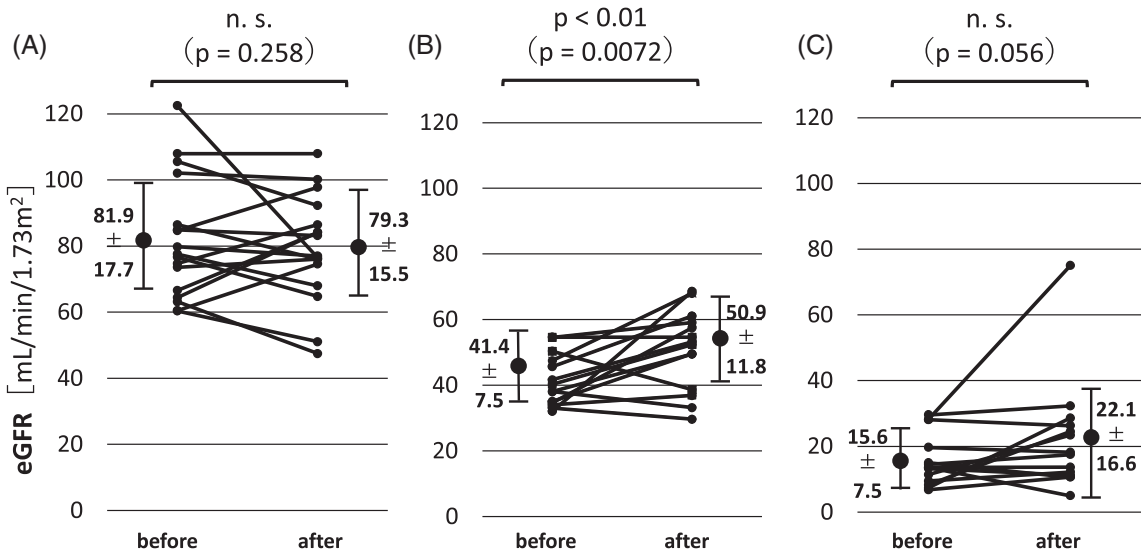

FIGURE 3 Changes in estimated glomerular filtration rate (eGFR) before and after LDL apheresis (LDL-A) in Groups N (a), M (b), and S (c). Changes of eGFR before and after LDL-A for each episode are shown as solid lines. The average ± SD eGFR before and after LDL-A are also shown

Although as shown above, average UP before LDL-A was rather higher in the former than the latter group, there was no significant difference of other pre-LDL-A clinical parameters between these two groups (data not shown). It should be noted that even in the cases with severely damaged renal function, after LDL-A, the former group showed marked improvement of average levels of eGFR from 16.35 ± 7.44 to 25.80 ± 18.69 ml/min/1.73 m^2; on the other hand, in the latter group, the improvement was faint from 14.36 ± 7.53 to 15.42 ± 8.42 ml/min/1.73 m^2.

3.4 | Effects of improved proteinuria and renal function on 2-year outcomes

Since LDL-A was able to improve proteinuria and renal function in cases with eGFR as low as 30 ml/min/1.73 m^2, we then investigated whether these therapeutic effects could affect long-term outcomes at 2 years after LDL-A by examining 43 cases with eGFR ≥ 30 (n = 29) and <30 (n = 14) ml/min/1.73 m^2. The non-NS and non-end-stage renal disease (ESRD) rates were compared in these two groups (Table 4). Cases with eGFR ≥ 30 ml/min/1.73 m^2

TABLE 4 Effects of improved proteinuria and renal function on 2-year outcomes

eGFR (ml/min/1.73 m^2)	*n*	Non-NS	NS	% non-NS (%)	*p* value	Non-ESRD	ESRD	% non-ESRD (%)	*p* value
≥30	29	26	3	89.7	$p < 0.05$	28	1	96.6	$p < 0.05$
<30	14	7	7	50.0	$p = 0.022$	9	5	64.3	$p = 0.010$

Abbreviations: ESRD, end-stage renal disease; NS, nephrotic syndrome.

had significantly higher non-NS (89.3% [26/29] vs. 50.0% [7/14], $p = 0.022$) and non-ESRD (96.6% [28/29] vs. 64.3% [9/14], $p = 0.010$) rates.

In 14 cases with eGFR < 30, the improved rate of UP by LDL-A was higher in nine non-ESRD than in five ESRD cases (from 7.96 ± 2.87 to 4.86 ± 3.29 g/day, improved: rate 23% vs. from 8.31 ± 2.59 to 8.48 ± 4.28 g/day, improved rate: minus 6%, respectively), although the statistical significance was not obtained due to low number of samples.

4 | DISCUSSION

In this post hoc analysis of the POLARIS study, we found that LDL-A exerts a lowering effect on UP, even in patients with impaired renal function if eGFR is ≥30 ml/min/1.73 m^2. In such patients, we also showed that LDL-A ameliorates renal function itself and contributes to avoidance of ESRD.

It is well established that LDL-A has beneficial effects on drug-resistant NS and is utilized as a therapeutic option for patients resistant to primary medication [2]. LDL-A is also effective in nephrotic cases with both drug resistance and impaired renal function. Shah et al. [9] presented a case series of seven pediatric patients treated by LDL-A for recurrent FSGS post-transplantation. All the patients achieved partial or complete remission after LDL-A treatment. The eGFR at LDL-A initiation was in the normal range in two patients, but the other five had eGFR <60 ml/min/1.73 m^2. Several reports have also shown the beneficial effects of LDL-A in patients with severe renal dysfunction with eGFR as low as 14.5 ml/min/1.73 m^2 [10] and in those with renal function so severely deteriorated that acute renal replacement therapy was required [11–13]. Given these reports, we examined the extent to which renal dysfunction reduces the therapeutic efficacy and favorable prognosis of LDL-A in cases in the POLARIS study, using a sample size that permitted statistical analysis.

Significant reductions of UP immediately after LDL-A occurred to similar extents in patients with normal and moderately impaired renal function. In patients with severely impaired renal function, the pretreatment UP level was higher than in the other two groups, and a marked reduction of UP occurred in 9 of 14 cases (66%). These results indicate that LDL-A will almost certainly decrease UP in patients with a pretreatment eGFR of ≥30 ml/min/1.73 m^2 and in about half of cases with eGFR <30 ml/min/1.73 m^2. This change could protect or postpone entry into ESRD, as previously found.

In addition to a UP lowering effect, this study also showed that LDL-A can improve renal function. In patients with normal renal function, pretreatment SCr and eGFR were already in the normal range, and thus, there was no significant improvement of renal function parameters. This could indicate a low risk of apheresis and shows that the significant improvement of UP contributed to maintenance of renal function after LDL-A in these patients. More importantly, the beneficial effect of LDL-A on amelioration of nephrotic UP and significant improvement of renal dysfunction with reduction of SCr and increase of eGFR were also seen in patients with moderately impaired renal function. There was no significant improvement in cases with severe renal function impairment. In this group, as shown in Section 3, those with improved UP after LDL-A showed marked improvement of average levels of eGFR. These findings suggest that LDL-A is likely to improve renal function in patients with NS with a pretreatment eGFR of ≥30 ml/min/1.73 m^2. Even in cases close to ESRD, as the immediate improvement of UP after LDL-A could possibly contribute to postpone or avoidance of ESRD in long-term outcome, LDL-A could be recommended to be tried due to the substantial chance of a marked recovery coupled with the low risk of the procedure.

The mechanism of the beneficial effects of LDL-A may be based on improvement of NS. However, rapid amelioration of renal function prior to remission of NS has been reported in some cases [12,13], and thus, a mechanism other than amelioration of NS may also contribute. Dextran sulfate, which is used in the LDL absorption column [15], is a polysaccharide rich in negative charge that activates the kinin-kallikrein system to produce bradykinin [16]. Bradykinin has been shown to be a potent vasodilator that stimulates diuresis, excretion of electrolytes, and renal blood flow in animal studies. These beneficial effects were later proved to be mediated through induction of prostaglandins and nitric oxide (NO) by bradykinin [17]. Indeed, LDL-A using a dextran

sulfate cellulose adsorption column has been reported to stimulate production of prostaglandin E2 (PGE2) [18], I2 (PGI2) [19], and NO [20,21], along with production of bradykinin. It is also likely that in NS-derived renal dysfunction, LDL-A improves renal function through amelioration of renal perfusion by stimulating prostaglandins and NO resulting from induction of bradykinin.

LDL-A may also eliminate factors that have a negative influence on renal function, such as thromboxane A2 (TXA2) and endothelin (ET), both of which are vasoconstrictors that mediate a decrease of renal blood flow [22]. TXAs also stimulate platelet aggregation, and we have shown that the serum level of TXA2 was significantly reduced after LDL-A in a multicenter prospective study in refractory NS in FSGS cases [4]. A significant decrease of serum ET-1 after LDL-A has been shown in hemodialysis for patients with diabetes and arteriosclerosis obliterans (ASO) [23], and a similar reduction is likely in NS. Therefore, LDL-A may exert beneficial effects on impaired renal function through normalization of dyslipidemia and improvement of proteinuria, and through vasodilating effects mediated by dextran sulfate.

As described above, LDL-A ameliorated renal dysfunction and proteinuria immediately after treatment, even in cases with impaired renal function with eGFR as low as 30 ml/min/1.73 m^2. Thus, long-term outcomes were evaluated for cases with eGFR $\geq$ 30 and <30 ml/min/1.73 m^2. Favorable long-term outcomes were achieved in cases with eGFR $\geq$ 30 ml/min/1.73 m^2: only 3 of the 29 cases did not recover from NS (non-NS rate 89.7%) and 1 did not avoid maintenance hemodialysis (non-ESRD rate 96.6%). eGFR $<$ 60 lmin/1.73m^2 is a risk factor for ESRD in CKD [24,25] and the risk for ESRD is increased in NS with impaired renal function because prolonged renal dysfunction accelerates progressive renal disease. Our post hoc analysis showed that LDL-A could lead to avoidance of ESRD in significantly high rate in cases with eGFR $\geq$ 30 ml/min/1.73 m^2. This suggests that LDL-A could be effective even in cases with impaired renal function and contributes to favorable long-term outcomes, especially in avoidance of ESRD, as well as short-term improvement of proteinuria and renal function.

There are several limitations of this study. As a post hoc analysis of the POLARIS trial, the data were not originally collected for analysis of the influence of renal dysfunction on LDL-A. Thus, several cases had to be excluded from the original POLARIS cohort due to the lack of eGFR data. There was also some variation in the patient background, including primary diseases and concomitant drugs especially during 2 years of follow-up period among the stratified groups, which might have affected the therapeutic efficacy of LDL-A.

5 | CONCLUSIONS

This post hoc analysis of POLARIS showed that LDL apheresis had favorable therapeutic efficacy and outcomes in patients with drug-resistant nephrotic syndrome with impaired renal function up to at least an eGFR of 30 ml/min/1.73 m^2. LDL apheresis may also cause a marked improvement of renal dysfunction, even in cases close to end-stage renal disease. These results indicate that further studies of the efficacy of LDL apheresis in nephrotic syndrome with impaired renal function are warranted.

CONFLICT OF INTEREST

Eri Muso received lecture fees from Kaneka Medix Corporation. None of the other authors have a conflict of interest to declare.

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