Table 1 Primary renal diseases of ESRD patients included in this survey

Renal diseases	Number of patients (%) Male/female/unknown				
	0–4 years	5–9 years	10–14 years	15–19 years	0–19 years
CAKUT	68 (43.0)	45 (45.0)	66 (40.2)	36 (30.5)	215 (39.8)
	39/29/0	33/12/0	46/19/1	29/7/0	164/67/1
Hereditary nephropathy	30 (19.0)	7 (7.0)	17 (10.4)	16 (13.6)	70 (12.9)
	12/18/0	3/4/0	13/3/1	11/5/0	39/30/1
FSGS	6 (3.8)	16 (16.0)	25 (15.2)	19 (16.1)	66 (12.2)
	3/3/0	11/5/0	14/11/0	14/5/0	42/24/0
Cystic kidney disease	17 (10.8)	10 (10.0)	19 (11.6)	6 (5.1)	52 (9.6)
	6/11/0	5/5/0	8/11/0	2/4/0	21/31/0
Glomerulonephritis	0 (0)	6 (6.0)	10 (6.1)	16 (13.6)	32 (5.9)
	0/0/0	1/5/0	6/4/0	2/4/0	19/13/0
HUS	4 (2.5)	1 (1.0)	2 (1.2)	2 (1.7)	9 (1.7)
	1/3/0	0/1/0	1/1/0	0/2/0	2/7/0
Ischemic renal failure	5 (3.2)	4 (4.0)	0 (0)	0 (0)	9 (1.7)
	1/4/0	1/3/0	0/0/0	0/0/0	2/7/0
Miscellaneous	20 (12.6)	7 (7.0)	12 (7.3)	8 (6.8)	47 (8.7)
	11/9/0	6/1/0	6/6/0	4/4/0	27/20/0
Unknown	0 (0)	4 (4.0)	6 (3.7)	8 (6.8)	18 (3.3)
	0/0/0	2/2/0	3/3/0	5/3/0	10/8/0
Missing	8 (5.1)	0 (0)	7 (4.3)	7 (5.8)	22 (4.2)
	4/4/0	0/0/0	5/2/0	4/3/0	13/9/0
Total	158 (100)	100 (100)	164 (100)	118 (100)	540 (100)
	77/81/0	62/38/0	102/60/2	81/37/0	322/216/2

Hereditary nephropathy includes Alport's syndrome, congenital nephrotic syndrome, and other specified types. Glomerulonephritis (GN) includes IgA nephropathy, membrano-proliferative GN, membranous nephropathy, crescentic GN, and other types of GN. Cystic kidney disease includes polycystic kidney disease, nephronophthisis, and other specified types

CAKUT congenital anomalies of the kidney and urinary tract, *FSGS* focal segmental glomerulosclerosis, *HUS* hemolytic uremic syndrome

The average incidence of ESRD over the 6-year period was 4.0 pmarp.

Primary renal disease in patients with ESRD

Primary renal diseases, categorized according to the European Renal Association and European Dialysis and Transplantation Association (ERA-EDTA) codes [5], with a minor modification, in the 540 pediatric ESRD patients evaluated in this survey are shown in Table 1. The most frequent primary renal disease was congenital anomalies of the kidney and urinary tract (CAKUT), including hypoplasia/dysplasia ± reflux nephropathy and obstructive uropathy, present in 39.8 % of these patients, followed by hereditary nephropathy (12.9 %), focal segmental glomerulosclerosis (FSGS; 12.2 %) and cystic kidney disease (9.6 %). Glomerulonephritis was observed in 5.9 % of these patients. CAKUT were the main causes of ESRD across all age groups and were more common in males than in females. Hereditary nephropathies including congenital nephrotic syndrome and Alport's syndrome were common in the youngest ESRD group and the adolescent ESRD group. FSGS and glomerulonephritis were less common in children aged less than 5 years as causes of ESRD. Cystic kidney disease caused 5–11 % of ESRD across all age group.

Initial treatment modalities of ESRD

Of the 540 patients newly diagnosed as having ESRD, six did not commence RRT because of their severe extra-renal comorbidities. In addition, RRT was not identified in four patients. Of the remaining 530 patients, 327 (61.7 %) were treated initially by peritoneal dialysis (PD), 85 (16.0 %) underwent hemodialysis, and 118 (22.3 %) underwent pre-emptive transplantation (Tx). The initial treatments by age group are shown in Fig. 1. Most children aged less than 5 years were treated initially by PD (89.0 %), with a small proportion undergoing pre-emptive Tx (2.6 %). In contrast, pre-emptive Tx was performed in 32.7, 29.2, and 30.2 % of children aged 5–9, 10–14, and 15–19 years, respectively. A comparison of initial treatment modalities in surveys of pediatric ESRD patients in 1998 [11] and 2006–2011 showed that the proportion of patients undergoing pre-emptive Tx markedly increased with time (Fig. 2).

Survival and cause of death

Survival analysis of the 530 patients who commenced RRT is shown in Fig. 3. The 1- and 5-year survival rates were 96.9 and 91.5 %, respectively. Patients were

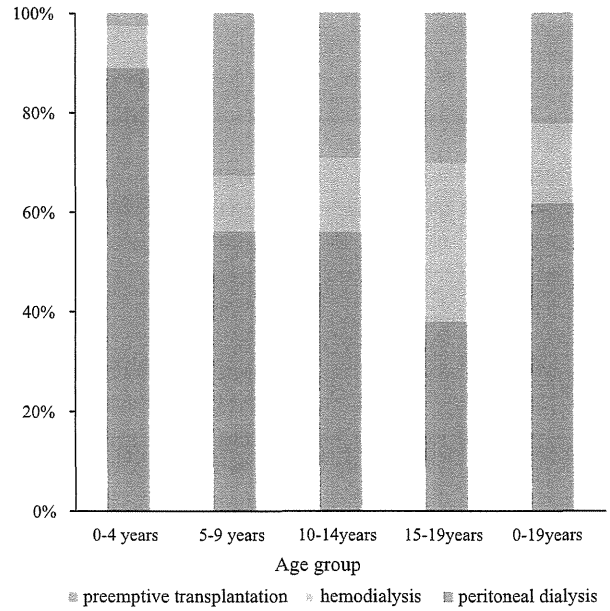

Fig. 1 Initial treatment modalities of end-stage renal disease by age group

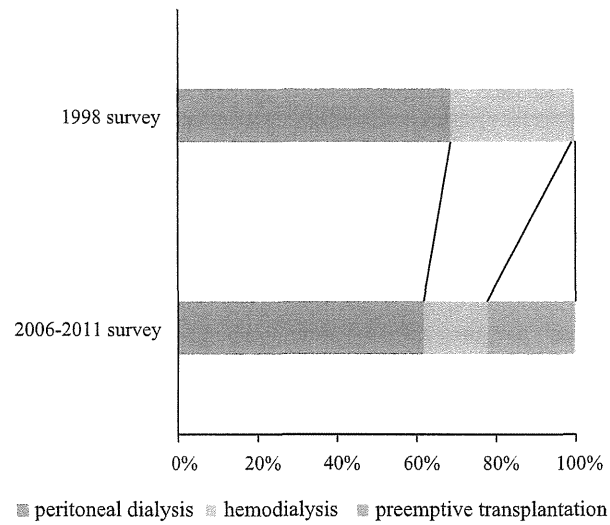

Fig. 2 Comparison of initial treatment modalities in Japanese patients with end-stage renal disease (ESRD) surveyed in 1998 [11] and in 2006–2011

followed up for a median 2.7 years (interquartile range 1.3–4.3 years). The mortality rate was 18.2 deaths per 1000 person-years of observation. During follow-up, 28 patients (5.4 %) died, all of whom were undergoing dialysis. Causes of death after the start of RRT, based on the United States Renal Data System [15] with a minor modification, are shown in Table 2. The main causes of death were infection (n = 11, 39.3 %) and cardiovascular causes (n = 5, 17.9 %).

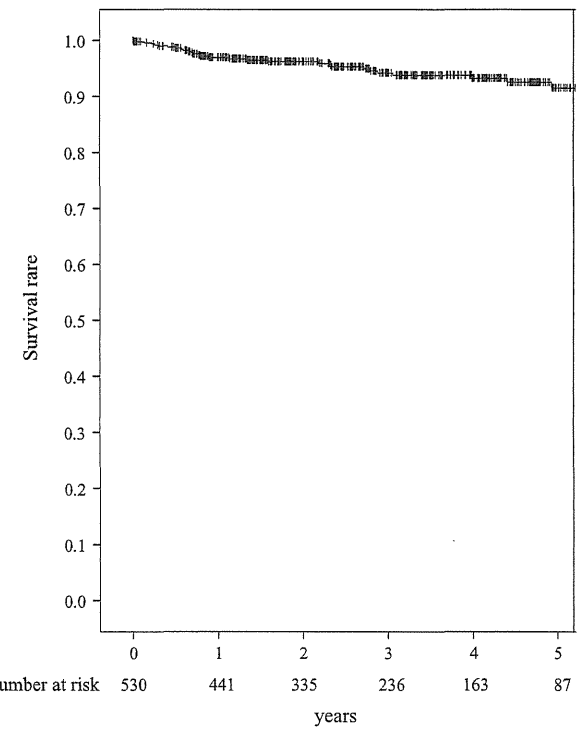

Fig. 3 Patient survival after the start of renal replacement therapy

Table 2 Causes of death after the start of renal replacement therapy

Renal diseases	Number of patients (%)
Infections	11 (39.3)
Cardiovascular	5 (17.9)
Cerebrovascular	0 (0)
Malignancy	0 (0)
Metabolic	0 (0)
Other	6 (21.4)
Unknown	4 (14.2)
Missing	2 (7.2)
Total	28 (100)

Discussion

The JSPN has updated the epidemiological and demographic information on the incidence, primary renal disease, initial treatment modalities, and survival in Japanese pediatric ESRD patients, aged less than 20 years, over the period 2006–2011. However, some important information, including the prevalence and probability of undergoing Tx, could not be updated in this survey.

There are marked variations in the incidence of pediatric ESRD across countries [13]. A previous survey by the JSPN, performed in 1998, reported that the incidence of ESRD in Japanese children aged less than 20 years was 4.0

pmarp [11], much lower than in other high-income countries, including 9.5 pmarp in 11 Western European countries and in Australia and 15.5 pmarp in the USA [13], despite Japan having one of the highest incidence rates of ESRD in adults [13, 16]. The current survey showed that the average incidence of ESRD in 2006–2011 was 4.0 pmarp, confirming the lower incidence of ESRD in Japanese children. Because the reasons for this lower incidence remain unclear [16], further research is needed to determine the specific factors responsible for the lower rate of ESRD in Japanese children.

Causes of ESRD also vary across races and countries. FSGS is more common in blacks than in whites, genetic diseases are more prevalent in the Middle East than in Europe, and infection-related renal diseases are more frequent in less-developed countries [12, 13]. In the USA, Europe, and Australia and New Zealand, CAKUT are the main cause, accounting for around 40 % of pediatric ESRD patients [13]. The current Japanese survey showed that CAKUT were also the most common cause of renal disease, accounting for 39.8 % of all pediatric Japanese ESRD patients. In contrast, it has been indicated that the proportion of pediatric ESRD caused by glomerulonephritis, including FSGS, was higher in Japan than in Europe or the USA [12, 13]. The 1998 Japanese survey reported that the proportions of pediatric ESRD patients with FSGS and glomerulonephritis were 21.0 and 13.3 %, respectively [11], whereas the current survey showed that these proportions were much lower, 12.2 and 5.9 %, respectively. The Australia and New Zealand Dialysis and Transplant Registry also showed a decline over time in glomerulonephritis as a cause of ESRD [10]. Additional surveys are needed to confirm this trend in the etiology of ESRD in Japanese children.

The initiation of RRT is highly dependent upon the economy and availability of healthcare resources [12, 17]. In countries where RRT is readily available, the most favored renal replacement modality in children is Tx because dialysis is associated with cardiovascular damage, access complications, infection, retarded linear growth and cognitive development in children [12]. Pre-emptive Tx is an especially attractive option for children with ESRD because pre-emptive Tx potentially avoids exposure to negative outcomes associated with dialysis [18]. While the previous Japanese survey in 1998 reported that only one patient (0.9 %) underwent pre-emptive Tx [11], this survey notably found that 22.3 % of patients were initially treated by pre-emptive Tx. In the USA, Europe, and Australia and New Zealand, around 15–20 % of children newly diagnosed with ESRD undergo pre-emptive Tx [13]. Thus, the use of pre-emptive Tx as an initial treatment modality for Japanese children with ESRD is comparable to that of USA, Europe, and Australia and New Zealand. The evolved immunosuppression protocols using calcineurin inhibitors, mycophenolate mofetil and basiliximab reduced acute rejection episodes and improved the patient and graft survival [19]. The improved treatment following Tx and the increased awareness of effectiveness of pre-emptive Tx seem to be responsible for the marked increase in pediatric pre-emptive Tx in Japan.

The 5-year survival rate of Japanese children with ESRD who received RRT was 91.5 %, which was similar to that reported from Europe (the 4-year survival rate was 92.9 % in European RRT children) [8]. The mortality rate of 18.2 deaths per 1000 person-years of observation was similar to that observed in the 1998 survey [11] and in pediatric ESRD patients in Australia and New Zealand [9]. The two main causes of death in Japanese ESRD patients receiving RRT were infections and cardiovascular disease, similar to findings in Western countries [12, 13]. Superior survival has been reported in patients with a functioning graft than in patients on dialysis, with the poorest survival rates observed in infants with ESRD [13]. Further studies are required to determine risk factors for mortality in Japanese pediatric ESRD patients.

Finally, epidemiological and demographic information on pediatric ESRD patients around the world is important to better understand this disease and to improve patient care. Because single country data may be underpowered to draw meaningful insights, international collaborations are required to improve the outcomes of children with ESRD [20, 21].

In conclusion, this survey of epidemiological and demographic information on Japanese children aged less than 20 years with ESRD over the period 2006–2011 confirmed that the incidence of ESRD is lower in Japan than in other high-income countries. Notably, there has been a marked increase in the use of pre-emptive Tx as the initial treatment modality for these patients.

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Conflict of interest The authors have declared that no conflict of interest exists.

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ORIGINAL ARTICLE

Immediate therapeutic efficacy of low-density lipoprotein apheresis for drug-resistant nephrotic syndrome: evidence from the short-term results from the POLARIS Study

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Abstract
Background Hyperlipidemia is not merely a complication but a major exacerbating factor in longstanding nephrotic syndrome (NS). Low-density lipoprotein apheresis (LDL-A) has been reported to ameliorate dyslipidemia and induce rapid remission of NS. Several clinical studies have suggested the therapeutic efficacy of LDL-A, but the level of clinical evidence is insufficient. Therefore, a multicenter prospective study, POLARIS (Prospective Observational Survey on the Long-Term Effects of LDL Apheresis on Drug-Resistant Nephrotic Syndrome), was initiated in Japan.
Method Patients with drug-resistant NS were prospectively recruited into the study and treated with LDL-A in facilities that were registered in advance. In the POLARIS study design, the clinical data are to be followed up for 2 years. In the current study, we aimed at evaluating the short-term efficacy based on the treatment outcome of LDL-A immediately after completion of treatment.
Results Along with rapid improvement of hyperlipidemia, LDL-A significantly improved proteinuria and hypoproteinemia after treatment. More than half of the patients showed remission of NS based on the urinary protein level at the completion of LDL-A. The duration of NS before the start of treatment was significantly shorter in patients who responded to LDL-A.
Conclusions An analysis of patients registered in the POLARIS study indicated that LDL-A has short-term efficacy for drug-resistant NS. Rapid relief of dyslipidemia by LDL-A may provide early remission in about half of the NS patients who are resistant to conventional medication. Completion of the POLARIS study may reveal additional long-term effects of LDL-A in these patients.

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Keywords Short-term results · Drug-resistant nephrotic syndrome · LDL apheresis · Lipid nephrotoxicity

Introduction

Hyperlipidemia is a common complication of nephrotic syndrome (NS), with patients often having elevated serum levels of the so-called "malignant" lipoprotein species such as low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL), which contribute to vascular atherogenicity and subsequent organ injury. In NS, persistent elevation of these lipids in serum may exacerbate glomerular and tubulointerstitial damage, and in some cases, the clinical condition may deteriorate to end-stage renal failure (ESRD) [1]. To prevent progression of renal impairment, prompt lipid-lowering therapy for prolonged hyperlipidemia is required in patients with NS resistant to primary medication. HMG-CoA reductase inhibitors appear to be most effective among various lipid-lowering therapies and sometime provide remission of clinical symptoms of NS [2]; however, the effect is gradual and requires a long administration period [3].

LDL-A is a blood purification therapy that selectively removes apoprotein B-containing lipoproteins such as LDL from circulating blood and rapidly reduces the plasma cholesterol level. LDL-A was originally developed for prevention of progression of coronary atherosclerosis in patients with serious hyperlipidemia such as familial hypercholesterolemia [4]. In the late 1980's, LDL-A began to be used to improve dyslipidemia in NS, initially to prevent organ damage. However, LDL-A was found to improve both the dyslipidemic condition and clinical symptoms including proteinuria and hypoproteinemia [5].

Based on the early clinical outcomes, LDL-A became used as an adjunctive treatment in addition to medication. Several studies of LDL-A in patients with drug-resistant NS were performed and showed relatively favorable therapeutic effects [6, 7]. Muso et al. [8] found that patients with steroid-resistant NS showed marked reduction of the urinary protein (UP) level and elevation of serum albumin in more than 60 % of cases treated with LDL-A. To clarify whether these beneficial effects were attributable to LDL-A, the K-FLAT (Kansai FGS LDL Apheresis Treatment) study was conducted as a multicenter controlled trial using a fixed protocol of comparison of combination therapy of steroids and LDL-A with steroid therapy alone. This study showed that combination therapy had more beneficial effects than steroid monotherapy, with more rapid relief from NS and a significantly higher remission rate after two years of therapy [9, 10].

Following these results, the Japanese Society of Kidney and Lipids Research performed a nationwide survey to examine the therapeutic effects of LDL-A for NS in actual clinical practice, and showed that LDL-A was a highly effective mid- and long-term treatment [11]. However, these results had the limitation that the data were obtained from a retrospective questionnaire survey based on the case reports. To establish more clear-cut evidence for the efficacy of LDL-A, we

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conducted a prospective trial named the POLARIS (Prospective Observational Survey on the Long-Term Effect of LDL Apheresis on Drug-Resistant Nephrotic Syndrome) study. The goal of the POLARIS study is to investigate the short-, mid- and long-term outcomes for 2 years after treatment, and the patients are currently being followed up. In this report, we examined outcomes immediately after LDL-A treatment in patients in the POLARIS study to evaluate the short-term therapeutic efficacy of LDL-A and to identify the factors that influence this efficacy.

Methods

Study design and patient population

The POLARIS study is a prospective, observational, multicenter, cohort study based on a central registration system. The study protocol was registered and disclosed on the web site (http://www.umin.ac.jp/) of the University Medical Information Network (UMIN), Japan (ID: UMIN000000871). In principle, investigators obtained an internal review board (IRB) approval before participating in the study. Otherwise, the IRB approvals in the facilities where the principal investigators belong (Kitano Hospital: 06-12-011 for E. M. and Fukuoka University: 6-110 for T. S.) acted for them in the case that an IRB was not organized.

Since the POLARIS study is an observational study and intended to reveal actual efficacy of LDL-A in combination with standard therapy in ordinary clinical practice, the protocol does not intervene with each patient's treatment course. Therefore, actual treatment regimen of each episode was left to the discretion of the individual attending doctors. During 2 years of registration period, a total of 64 episodes of LDL-A treatment in 58 patients with NS who were resistant to primary medication, which is generally full-dose steroids or saturated cyclosporine A treatment for at least 4 weeks, and considered by their attending doctor to be a candidate for LDL-A treatment were prospectively registered in the POLARIS study before the treatment started. Each patient was informed of the outline of the study and the risks and benefits of LDL-A before enrollment, and then registered in the study with written informed consent. Although the type of LDL-A modality was not specified in the protocol, dextran sulfate cellulose column adsorption technique (Liposorber LA-15, Kaneka Corporation, Osaka, Japan) was used in all cases.

In the current study, the short-term efficacy of LDL-A in addition to prior medication was evaluated in patients with NS in whom the proteinuria level was not reduced to <1.0 g/day after the initial treatment for at least 4 weeks, although the original study design stipulates that the clinical outcome of the patients will be followed for 2 years after the treatment. Of the 64 episodes originally registered in the POLARIS study, 17 episodes were excluded from analysis in the current study for the following reasons: lack of UP data in 7 episodes, UP data estimated from the UP/urinary creatinine ratio of casual urine in 7 episodes, UP level already reduced to <1.0 g/day at the initiation of LDL-A in 7 episodes, and treatment with LDL-A less than 4 weeks after primary medication in 2 episodes. Therefore, short-term clinical data for 47 episodes in 44 patients were analyzed in this study. Clinical data for these patients were collected at initiation and after completion of LDL-A. The UP data analyzed in the study were evaluated in 24-h urine.

Laboratory findings

Clinical parameters were evaluated based on the data collected by attending doctors at the initiation and completion of LDL-A in the respective facilities. Practical measurement of parameters was entrusted to the doctors at each facility.

Statistical analysis

Comparison of clinical parameters between before and after LDL-A,and between effective and non-effective episodes were analyzed by the paired t test and Student's t test, respectively. Evaluation of factors that affect treatment outcome was analyzed by Chi-square test or Fischer's exact test. $p < 0.05$ was taken as significant. Data were expressed as mean ± SD.

The definition of clinical efficacy

The short-term clinical efficacy was evaluated on a three-category scale based on the UP level before initiation of LDL-A and within four weeks after completion of LDL-A, as follows: very effective, the UP level before LDL-A was ≥3.5 g/day and was reduced to <1.0 g/day after LDL-A; effective, the UP level before LDL-A was ≥3.5 g/day and was reduced to <3.5 g/day (but ≥1.0 g/day) after LDL-A, or the UP level before LDL-A was <3.5 g/day (but ≥1.0 g/day) and was reduced to <1.0 g/day after LDL-A; non-effective, cases other than those in which LDL-A was judged to be very effective or effective.

Results

Characteristics of patients and episodes

The characteristics of the 47 episodes and 44 patients are shown in Table 1. The average number of LDL-A sessions was 9.6 times for each treatment and the average amount of

Table 1 Patient and episode characteristics

Patient characteristics	
Total number	44
Age (mean ± SD) (years)	55.4 ± 17.3
Age (range) (years)	18–84
Gender (male/female)	27/17
Episode characteristics	
Total number	47
Renal biopsy (±)	41/6
First time/recurrent	27/19 *
Average number of LDL-A sessions	9.6
Average amount of plasma per session [L]	3.5 L
Concomitant drugs	
Cyclosporine A administration (±)	24/22[a]
Steroid pulse therapy (±)	4/42[a]
Diuretics administration (±)	26/21
ARB[b] administration (±)	29/18
Anti-platelet agents (±)	31/16
Ant-coagulant (±)	17/30

[a] Data were not collected for one episode

[b] Angiotensin II receptor blocker

Table 2 Classification of primary diseases

Disease	Episodes	Patients
Focal segmental glomerulosclerosis[a]	26	23[a]
Membranous nephropathy	4	4
Henoch-Schönlein purpura nephritis	3	3
Minimal change nephrotic syndrome	2	2
Renal amyloidosis	2	2
Others[b]	5	5
Uncertain	5	5

[a] Including three patients complicated with other renal diseases (membranous nephropathy 2, diabetic nephropathy 1)

[b] Membranoproliferative glomerulonephritis; crescentic glomerulonephritis; IgA nephropathy; lupus nephropathy; hepatitis B virus-associated nephropathy

3.5 L of plasma was treated in each session. The primary diseases of the patients are shown in Table 2. Focal segmental glomerulosclerosis (FSGS) was the most frequent primary disease, presenting in 23 patients (52.3 %). The other patients had a variety of primary diseases.

Effects of LDL-A on serum and urine parameters

The clinical parameters before and after the course of LDL-A treatment are shown in Table 3. The serum total protein (SP) and serum albumin (SA) levels increased significantly after LDL-A and the reduction of the UP level was also significant. The LDL cholesterol (LDL-c) level decreased by more than 50 % and total cholesterol (TC) was also reduced significantly after LDL-A. Significant decreases of fibrinogen (Fb) and thrombin–antithrombin III complex (TAT) were also observed.

The changes in UP, SP, and SCr levels in individual episodes from before to after LDL-A are shown in Fig. 1. The UP and the SCr levels decreased in 76.6 % (36/47) and 56.5 % (26/46) of the episodes, and the SP level increased in 53.2 % (25/47) of the episodes.

We also evaluated the change in UP level before and after LDL-A in each primary disease of NS (Table 4). Since types of primary diseases were wide-ranging and the number of episodes with those other than FSGS (non-FSGS) was small (1–4 at most), it is considered to be difficult to review the trend of UP reduction in each type of diseases. However, as a whole, even episodes with non-FSGS showed almost equivalent level of UP to those with FSGS both in before and after LDL-A.

Evaluation of the clinical efficacy of LDL-A

The short-term clinical efficacy of LDL-A was evaluated using the UP level derived from 24-h urine at completion of the treatment. LDL-A was evaluated as very effective in 10/47 episodes (21.3 %) and effective in 15 (31.9 %). Therefore, 25 (53.1 %) episodes were treated effectively. LDL-A was judged to be non-effective in the other 22 (46.8 %) episodes, including some in which the UP level increased after LDL-A.

The percentage of episodes in which LDL-A was clinically effective (i.e., the total of very effective and effective) was 53.8 % (14/26) in cases with FSGS as the primary disease. A similar rate of 50 % (8/16) was found for episodes derived from primary diseases other than FSGS.

Factors that affect clinical efficacy

The factors examined in this study including the patient and the episode characteristics, and the level of clinical parameters, were compared between effective and non-effective treatments (Tables 5 and 6). Almost all the factors were not likely to be associated with clinical efficacy. However, the level of SP at pre-treatment was significantly higher ($p = 0.049$, Student's t test) and also that of UP showed higher trend ($p = 0.075$, Student's t test) in effective treatments than in non-effective. In addition, the rate of episodes in which LDL-A treatment started within 8 weeks after the onset of NS was significantly higher than those in which it took 8 weeks or longer (48.8 vs. 5.3 %, $p = 0.012$, Chi-square test) implying that the earlier the treatment is applied, the more likely effective treatment is obtained.

Table 3 Clinical parameters before and after LDL-A treatment

Clinical parameter	Unit	*n*	Before	After	*p* value
Serum total protein (SP)	(g/dL)	46	4.42 ± 0.69	4.68 ± 0.81	<0.05
Serum albumin (SA)	(g/dL)	47	2.15 ± 0.63	2.63 ± 0.79	<0.01
Serum creatinine (SCr)	(mg/dL)	47	1.82 ± 1.60	1.62 ± 1.57	n.s.
Creatinine clearance (CCr)	(mL/min)	23	58.59 ± 41.35	65.11 ± 41.39	<0.05
Urinary protein (UP)	(g/day)	47	6.28 ± 2.96	3.46 ± 3.34	<0.01
Triglyceride (TG)	(mg/dL)	40	262.74 ± 155.17	241.30 ± 182.14	n.s.
Total cholesterol (TC)	(mg/dL)	40	331.10 ± 113.25	210.38 ± 77.42	<0.01
LDL cholesterol (LDL-c)	(mg/dL)	38	205.86 ± 100.84	92.37 ± 56.64	<0.01
HDL-cholesterol (HDL-c)	(mg/dL)	34	69.49 ± 22.58	73.64 ± 23.40	n.s.
Fibrinogen (Fb)	(mg/dL)	28	374.46 ± 130.04	297.92 ± 108.87	<0.01
Thrombin-antithrombin III complex (TAT)	(ng/mL)	18	16.39 ± 33.60	12.21 ± 34.10	<0.05

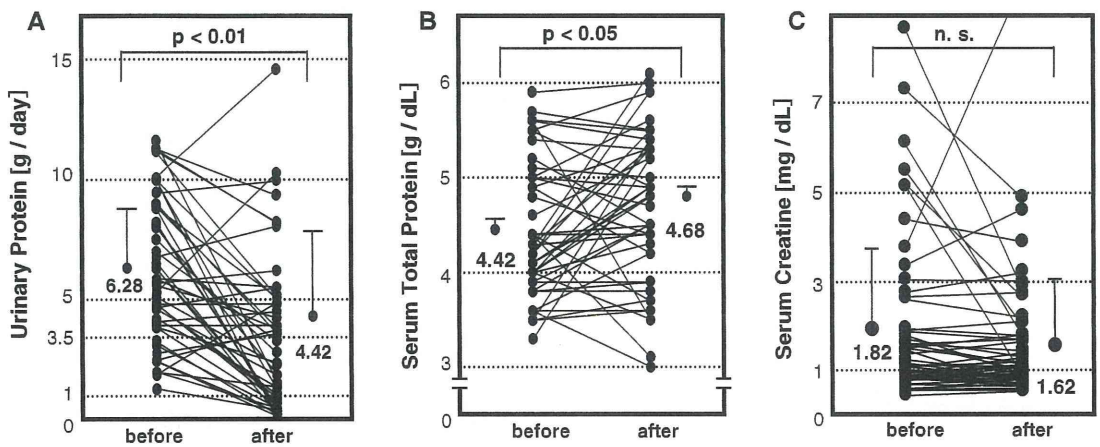

Fig. 1 Changes in UP (**a**), SP (**b**), and SCr (**c**) levels from before to after LDL-A in individual episodes. The UP and SCr levels decreased in 37 (69.6 %) and 27 (55.4 %) of the 47 episodes, respectively, and the SP level increased in 30 (60.0 %) of 46 episodes (data were not collected in one episode)

Discussion

The POLARIS study was designed as a prospective cohort study to evaluate clinical efficacy of LDL-A. In the actual clinical practice, LDL-A treatment is usually applied as an adjunctive therapy in the case that patients did not respond to standard medication and often had no option left and we considered that it was difficult not only to intervene with each patient's treatment prescription but also to conduct a controlled study with non-treatment group in which the patients could reach serious stage. Therefore, the study was conducted as an observational, cohort study. In this report, we examined the short-term efficacy at a point immediately after treatment among the patients registered in the POLARIS study. Clinical efficacy was evaluated based on the recovery of a patient from the nephrotic state. Analysis of short-term clinical data showed efficacy of LDL-A in more than half of the episodes (25/47, 53.1 %) with relief from the nephrotic state as early as four weeks after treatment.

Muso et al. found that LDL-A for steroid-resistant NS decreased the UP level in 6 (66.7 %) of 11 episodes at 2 weeks after treatment [8]. Muso and colleagues then confirmed the clinical efficacy of LDL-A in the K-FLAT study, in which LDL-A in combination with steroids reduced the UP level to <3.5 g/day in 13 (76.4 %) of 17 episodes within one or 2 weeks after treatment, whereas only 5 (50 %) of 10 episodes achieved the same UP level with steroid treatment alone [9, 10]. Hattori et al. used LDL-A in pediatric patients with steroid-resistant NS and demonstrated rapid relief from NS (a decrease in UP to <40 mg/m^2/h) in 7 (63.7 %) of 11 patients, even before the completion of LDL-A treatment [6]. The results of the current prospective study indicate that more than half of the drug-resistant NS cases are likely to be remitted by LDL-A. This response rate is slightly lower than those in previous

reports, but the level of evidence in the current study is higher.

A number of studies which reported therapeutic efficacy of LDL-A have been accumulated so far and those studies intended mostly for patients with FSGS. Although there have been several reports which showed therapeutic efficacy of LDL-A in patients with non-FSGS, most of them were case reports or case series with limited numbers of patients [12, 13]. However, in the POLARIS study, nearly half of the patients and the episodes registered in the study were non-FSGS and interestingly no significant difference of therapeutic effect was observed between FSGS and non-FSGS.

Table 4 Change of urinary protein before and after LDL-A treatment for each primary disease

Primary diseases	n[a]	Before	After
Focal segmental glomerulosclerosis	26	6.47 ± 2.98	3.26 ± 3.13
Membranous nephropathy	4	8.97 ± 2.29	6.95 ± 6.48
Henoch-Schönlein purpura nephritis	3	6.67 ± 4.50	3.15 ± 1.43
Minimal change nephrotic syndrome	2	1.96 ± 0.06	2.70 ± 3.13
Renal amyloidosis	2	5.45 ± 1.92	6.32 ± 2.52
IgA nephropathy	1	1.29	0.44
Membranoproliferative glomerulonephritis	1	4.60	1.85
Crescentic glomerulonephritis	1	3.81	0.61
Lupus nephropathy	1	8.79	0.13
Hepatitis B virus-associated nephropathy	1	8.90	3.91
non-FSGS	16	6.13 ± 3.41	3.89 ± 4.01

[a] Episodes with not specified primary disease were excluded

From reviewing previous reports, several possible mechanisms have been proposed for the beneficial therapeutic effect of LDL-A. Firstly, direct lowering of serum lipids including LDL, oxidized LDL, and VLDL was reported to contribute to regression of glomerular injury [14, 15]. Secondly, LDL-A is known to remove pathogenic factors other than noxious lipids. LDL-A can improve hypercoagulability by reduction of coagulation factors including von Willebrand's factor and fibrinogen [16, 17], and can also improve renal hemodynamics by reducing vasoconstrictive eicosanoids such as thromboxane A2 and increasing prostaglandin I2 [9]. Thirdly, it is conceivable that LDL-A should help with improvement of therapeutic effect of antiproteinuric drugs including steroids and/or calcineurin inhibitors because bioavailability of those drugs is known to be impaired under hyperlipidemic condition [18–20]. Enrollment in the current study required a patient to be resistant to medication; and therefore, steroids and/or CsA were administered in almost all episodes concomitantly with LDL-A. In contrast, Stenvinkel et al. [21] showed that LDL-A was effective for improving the condition of NS patients with hypercholesterolemia without any additional medication. However, a clear effect of LDL-A was not observed until 6 weeks after treatment, whereas the clinical effect in our study emerged immediately after or even during LDL-A treatment. Therefore, it is likely that improvement due to the effects of concomitant steroids or CsA contributed to the short-term clinical efficacy of LDL-A.

In addition to above-mentioned mechanisms for exerting the therapeutic effect, factors that affect the clinical efficacy of LDL-A were examined based on the results obtained in this study. The level of serum total protein at pre-treatment and duration of NS before the treatment were significantly affected by the efficacy ($p = 0.049$, 0.012,

Table 5 Serum and urine parameters at pre-treatment in effective and non-effective episodes

Clinical parameter	Unit	Effective	n	Non-effective	n	p-value
Serum total protein (SP)	(g/dL)	4.60 ± 0.67	25	4.20 ± 0.66	21	0.049
Serum albumin (SA)	(g/dL)	2.27 ± 0.57	25	2.03 ± 0.68	22	0.200
Serum creatinine (SCr)	(mg/dL)	1.48 ± 1.27	25	2.22 ± 1.86	22	0.117
Creatinine clearance (CCr)	(mL/min)	65.34 ± 45.13	13	71.71 ± 44.51	10	0.385
estimated glomerular filtration rate (eGFR)	(mL/min/m^2)	52.33 ± 26.12	25	44.14 ± 35.94	22	0.381
Urinary protein (UP)	(g/day)	5.56 ± 2.64	25	7.10 ± 3.15	22	0.075
Triglyceride (TG)	(mg/dL)	260.55 ± 175.58	22	265.59 ± 129.87	18	0.920
Total cholesterol (TC)	(mg/dL)	342.20 ± 99.71	20	324.00 ± 127.31	20	0.618
LDL cholesterol (LDL-c)	(mg/dL)	207.90 ± 94.14	20	203.46 ± 111.09	18	0.432
HDL-cholesterol (HDL-c)	(mg/dL)	72.08 ± 18.80	20	65.76 ± 27.44	14	0.895
Fibrinogen (Fb)	(mg/dL)	347.06 ± 109.53	16	413.34 ± 149.69	12	0.187
Thrombin-antithrombin III complex (TAT)	(ng/mL)	20.39 ± 40.84	12	8.38 ± 7.31	6	0.491