Efficacy of LDL apheresis for initial induction therapy of nephrotic membranous nephropathy

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BACKGROUND

Low-density lipoprotein apheresis (LDL-A) is a blood purification therapy that selectively removes lipoproteins such as LDL. In nephrotic syndrome (NS) such as focal segmental glomerular sclerosis (FSGS), hyperlipidemia is one of common complications, which evokes inflammation, leading to glomerular and tubulointerstitial damage. **LDL-A has been supposed to be beneficial for steroid-resistant and longstanding FSGS.** Some cases of **membranous nephropathy (MN) also cause NS**, which are difficult to achieve natural remission. LDL-A may contribute to inhibition of development of renal dysfunction by attaining early remission. However there are few reports assessing efficacy of LDL-A on conventional treatment for initial induction therapy of nephrotic MN.

OBJECTIVE

We retrospectively evaluated efficacy of addition of LDL-A therapy to conventional treatment at initiation of therapy.

METHODS

STUDY POPULATION

During the period **from March 2000 to May 2015**, patients who were diagnosed as initial **biopsy-proven nephrotic MN** and immediately started steroid therapy in that in-hospital period.

Exclusion criteria **:** Patients who were proven to secondary MN with systemic screening and immunofluorescence staining of renal biopsy specimen, cases without urinary protein data, patients who had received steroid therapy prior to admission due to other diseases such as rheumatism, patients who received only LDL-A without steroid therapy due to malignant tumor.

STUDY DESIGN

- **Retrospective, observational, single-centered.** Investigators obtained an IRB approval (Japanese Red Cross Nagoya Daini Hospital #1158) before participating in this study.
- **Comparison**: additional LDL-A on conventional treatment group (LDL-A) versus conventional treatment group (non LDL-A).
- **LDL-A modality**: dextran sulfate cellulose column absorption technique (Liposorber LA-15, Kaneka, Japan) and polyethylene membrane plasmaseparator system (Sulflux FP-08, Kaneka, Japan). Plasma processing amount was 4 liters in all cases.

DEFINITION

NS : meets criteria established by a research group of Ministry of Health, Labor and Welfare of Japan in 2010.
Urinary protein (UP) ≧3.5g/day or gCr, and hypoalbuminemia: serum albumin ≦3.0g/dl
Complete remission (CR) : UP<0.3g/day
Partial remission type 1 (PR1) : UP≧0.3g/day and <1.0g/day
Partial remission type 2 (PR2) : UP≧1.0g/day and <3.5g/day
Relapse : After CR, episodes of UP≧1g/day or 3 continuous episodes of UP paper test≧ (2+)

CLINICAL PARAMETERS

- **Baseline, on the first day of steroid therapy:** age・sex・past history (PH) of malignant tumor・ BMI・ selectivity index・blood pressure・laboratory data (TP, Alb, IgG, Tchol, TG, LDL, Cr, BUN, CRP)・urine data (UP)・ BW・dosage of predonisolone (PSL) and cyclosporine (CsA)
- **Treatment:** statin・ARB・anticoagulation・dipyridamole・albumin transfusion・type of immunosuppressant (cyclosporine (CsA), tacrolimus, and mizoribine)
- **Effectiveness:**

1)**CR/PR1/PR2**, and days to those episodes
2)**After 4 or 8 week of steroid treatment**: blood pressure・laboratory data (TP, Alb, IgG, Tchol, TG, LDL, Cr, BUN)・urine data (UP)・BW・dosage of predonisolone (PSL) and cyclosporine (CsA)・change of those from first treatment day

- **Adverse events**: infectious complications in hospital・bleeding related to blood access・allergic reaction to LDL-A
- **Pathological features:** presence of FSGS lesion

OUTCOME

1)the difference of UP and Alb between those at 0, 4 and 8 weeks after treatment. 2)time to CR/PR1/PR2.

STASTICAL ANALYSIS

Mann-Whitney analysis for continuous variables and Fisher's exact test for categorical variables were used to compare data between groups. Difference of days to CR/PR1/PR2 between was analyzed with Logrank test.

RESULTS

Characteristics of patients

	LDL-A (11)	Non LDL-A (27)	*p*
age, yr	67 (52.5 - 74.50)	66 (59 - 73)	1.000
male (%)	54.50	74.10	0.272
PH of tumor (%)	0.00	11.10	0.542
BMI, kg/m^2	24.13 (22.77 - 27.89)	24.24 (22.68 - 25.75)	0.910
selectivity index	0.28 (0.19 - 0.30)	0.21 (0.14 - 0.27)	0.417
CRP, mg/dl	0.26 (0.20 - 0.61)	0.20 (0.20 - 0.47)	0.459

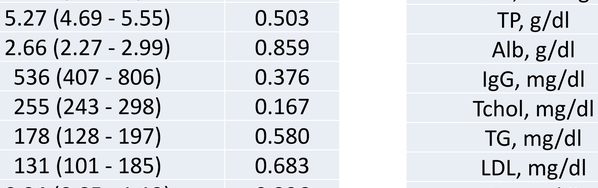
Treatment

	LDL-A (11)	Non LDL-A (27)	*p*
mPSL pulse (%)	9.1	0	0.290
statin (%)	63.6	70.4	0.710
ARB (%)	54.5	59.3	1.000
anticoagulation (%)	64	7	0.001
dipyridamol (%)	0	4	1.000
albumin transfusion (%)	0	0	-
cyclosporine (%)	100	77.8	0.154
tacrolimus (%)	0	0	-
mizoribine (%)	0	0	-

Pathological features

	LDL-A (11)	Non LDL-A (27)	*p*
FSGS lesion* (%)	63.6	11.1	0.002

*Examples of FSGS lesion with MN



Clinical parameters

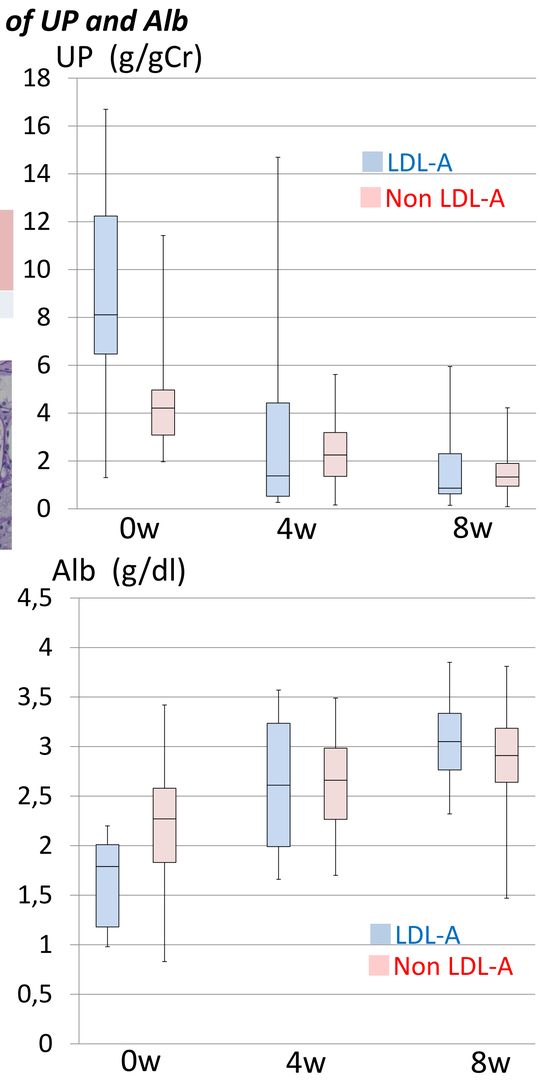
Baseline

	LDL-A (11)	Non LDL-A (27)	*p*
sBP, mmHg	148 (132 - 154)	133 (120 - 149)	0.257
dBP, mmHg	85 (79 - 97)	80 (70 - 86)	0.148
TP, g/dl	4.61 (4.35 - 4.80)	5.13 (4.60 - 5.85)	0.016
Alb, g/dl	1.79 (1.18 - 2.01)	2.27 (1.83 - 2.58)	0.004
IgG, mg/dl	635 (611 - 706)	679 (497 - 1080)	0.748
Tchol, mg/dl	409 (323 - 471)	317 (239 - 369)	0.030
TG, mg/dl	198 (174 - 293)	218 (130 - 304)	0.830
LDL, mg/dl	267 (199 - 322)	192 (142 - 219)	0.028
Cr, mg/dl	1.22 (0.93 - 1.59)	0.83 (0.74 - 0.96)	0.011
BUN, mg/dl	13.00 (11.65 - 25.85)	14.20 (11.70 - 15.70)	0.687
UP, g/gCr	8.11 (6.47 - 12.2)	4.21 (3.08 - 4.97)	0.001
PSL, mg/kg	0.56 (0.48 - 0.63)	0.59 (0.51 - 0.69)	0.607
CsA, mg/day	75.00 (67.50 - 75.00)	75.00 (42.50 - 75.00)	0.387

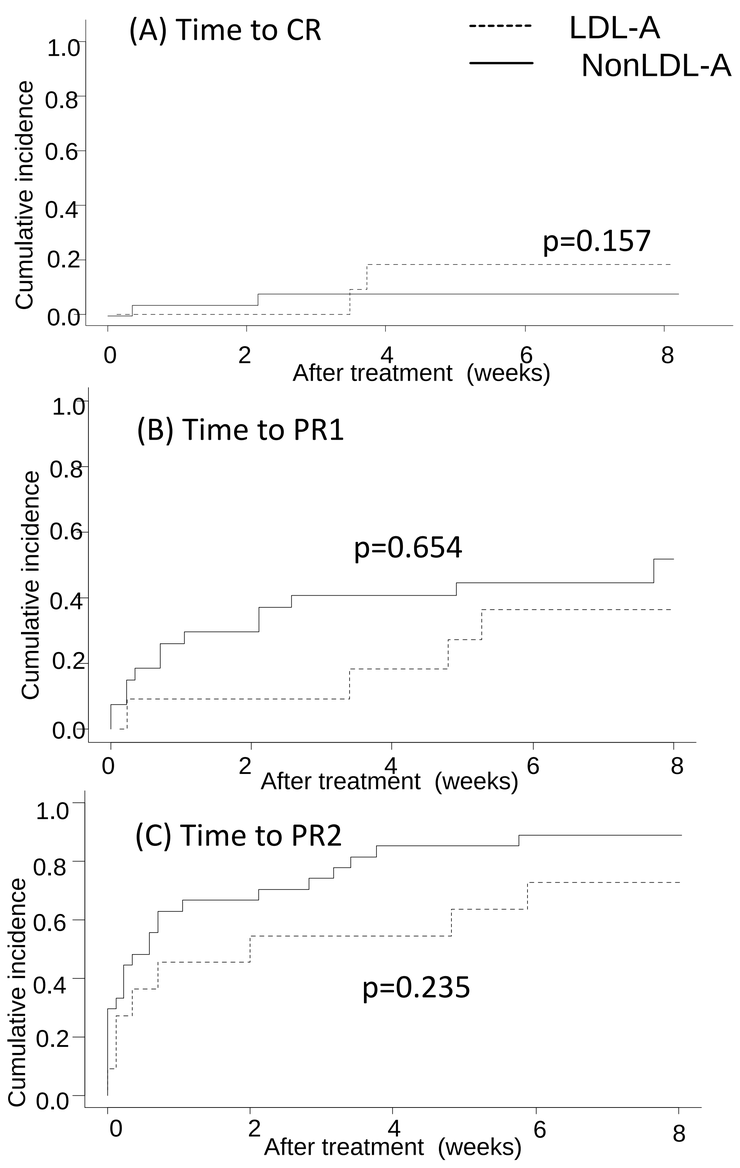
After 4 weeks

	LDL-A (11)	Non LDL-A (27)	*p*
sBP, mmHg	123 (113 - 127)	126 (115 - 132)	0.362
dBP, mmHg	70 (64 - 78)	78 (62 - 83)	0.278
TP, g/dl	4.76 (4.50 - 5.57)	5.27 (4.69 - 5.55)	0.503
Alb, g/dl	2.61 (1.99 - 3.24)	2.66 (2.27 - 2.99)	0.859
IgG, mg/dl	487 (371 - 586)	536 (407 - 806)	0.376
Tchol, mg/dl	292 (256 - 353)	255 (243 - 298)	0.167
TG, mg/dl	181 (115 - 253)	178 (128 - 197)	0.580
LDL, mg/dl	126 (105 - 165)	131 (101 - 185)	0.683
Cr, mg/dl	1.07 (0.92 - 1.23)	0.94 (0.85 - 1.13)	0.326
BUN, mg/dl	23.30 (18.10 - 28.40)	18.00 (15.50 - 23.25)	0.161
UP, g/gCr	1.38 (0.52 - 4.43)	2.25 (1.35 - 3.19)	0.775
PSL, mg/kg	0.49 (0.34 - 0.60)	0.53 (0.46 - 0.66)	0.209
CsA, mg/day	75.00 (60.00 - 80.00)	60.00 (37.50 - 75.00)	0.148
UP reduction rate, %	71.2 (54.2 - 90.5)	54.3 (9.28 - 70.4)	0.036
Alb increase rate, %	60.18 (48.36 - 71.46)	16.18 (6.17 - 44.74)	0.002
BW reduction rate, %	7.69 (4.71 - 11.01)	3.71 (2.40 - 7.16)	0.082
LDL reduction rate, %	54.79 (37.38 - 61.38)	18.87 (7.65 - 47.00)	0.016
Cr reduction rate, %	-4.44 (-13.51 - 25.02)	-13.25 (-24.11 - -2.09)	0.108

The difference of time-dependent change of UP and Alb



Comparison of time required for remission



After 8 weeks

	LDL-A (11)	Non LDL-A (27)	*p*
sBP, mmHg	118 (106 - 136)	126 (113 - 139)	0.440
dBP, mmHg	68 (63 - 74)	71 (67 - 75)	0.536
TP, g/dl	5.32 (5.05 - 5.56)	5.30 (4.98 - 5.49)	0.850
Alb, g/dl	3.05 (2.77 - 3.34)	2.91 (2.64 - 3.19)	0.449
IgG, mg/dl	470 (352 - 536)	534 (335 - 655)	0.533
Tchol, mg/dl	326 (229 - 373)	261 (227 - 288)	0.170
TG, mg/dl	199 (164 - 227)	173 (150 - 234)	0.639
LDL, mg/dl	127 (100 - 172)	109 (98 - 135)	0.468
Cr, mg/dl	1.10 (0.89 - 1.31)	0.90 (0.80 - 1.16)	0.281
BUN, mg/dl	20.70 (17.95 - 27.15)	18.00 (15.60 - 24.53)	0.273
UP, g/gCr	0.86 (0.63 - 2.30)	1.33 (0.95 - 1.90)	0.634
PSL, mg/kg	0.35 (0.25 - 0.42)	0.43 (0.38 - 0.48)	0.027
CsA, mg/day	75.00 (67.50 - 80.00)	60.00 (0.00 - 75.00)	0.052
UP reduction rate, %	83.2 (74.8 - 88.4)	63.4 (42.7 - 80.5)	0.030
Alb increase rate, %	84.36 (68.19 - 127.22)	29.46 (15.70 - 54.29)	<0.001
BW reduction rate, %	8.81 (4.21 - 12.11)	4.48 (1.40 - 6.90)	0.106
LDL reduction rate, %	51.15 (39.96 - 62.54)	40.36 (19.56 - 51.90)	0.204
Cr reduction rate, %	-1.64 (-28.31 - 27.39)	-2.94 (-21.63 - 5.28)	0.465

Adverse events

Infectious complications in hospital

LDL-A		Non LDL-A
fever with unknown cause	1	none
Bacteremia (intestinal bacteria)	1	

- The above-mentioned infectious complications had existed when hospitalized.
- There were no bleeding related to blood access and allergic reaction to LDL-A.

DISCUSSION

- Several studies suggested efficacy of LDL-A for remission of drug-resistant NS, which caused by FSGS, MN, IgAN, and so on, but their timings of initiation of LDL-A and their primary diseases were not unified (Muso E. Nephron 2001,89:408 (K-FLAT) , Muso E. Clin Exp Nephrol 2015,19:379 (POLARIS)).
- **Here we investigated cases of idiopathic MN with NS**. MN is most popular cause among elderly NS. In general Japanese patients with MN have comparably good prognosis of kidney function (Shiiki H.Kidney int 2004;65:1400), and moreover long-term observation shows that about 30% of NS with MN cases get natural remission (Bazzi C. Kidney Int 2000;58:1732). On the other hand 37.8% of NS with MN extend to drug-resistant, and improvement of proteinuria affects renal prognosis (Troyanov S. Kidney int 2004; 66: 1199). Furthermore long-term treatment requires large amount of immunosuppressive agents, which can lead to carcinogenesis and susceptibility of infection. Therefore more rapid remission is desirable and it has been expected to assess efficacy of early commencement of LDL-A in addition to steroid therapy.
- Hence we studied effect of LDL-A **as initial induction therapy** for nephrotic MN to achieve earlier remission. Proteinuria, hypoalbuminemia, dyslipidemia and renal insufficiency of LDL-A group was significantly severer than that of Non LDL-A group, however after 4 or 8 weeks, it seems to catch up with the other, in fact, the extent of improvement was significantly better. There was no adverse event caused by LDL-A, so that LDL-A would be relatively safe therapy for nephrotic MN.
- Presence of FSGS lesion on renal pathology probably contributes the severity of nephrotic MN (Qiu-hua Gu, Medicine 2016,95:21). Actually, patients of LDL-A group more often had this than the other. LDL-A seems to be effective regardless of FSGS lesion. So **MN with FSGS lesion also would be suitable for LDL-A** on conventional treatment for initial induction therapy.
- **Limitation:** This retrospective, observational study could not establish the criteria of conducting LDL-A, that is, the severity of groups on admission was different. Therefore we might only saw natural course of UP of nephrotic MN remission. In addition, this study was conducted in single center, which limited sample size to small. Numbers and timings of LDL-A may affect the efficacy.

CONCLUSION

LDL-A had short-term effect for nephrotic MN as initial induction therapy. Detailed and prospective study with more cases could be required.

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