Table 2 Clinical findings and data at onset of relapse or non-relapse patients achieving CR

	Relapse	Non-relapse	*P* value
No. of patients	26	79	
Age (y.o)	44.5 ± 15.0	44.8 ± 16.4	NS
Female/Male	12/14	34/45	
Follow-up period (months)	151 ± 111	138 ± 79	NS
Initial treatment to remission (months)	33.4 ± 19.4	30.9 ± 20.4	NS
Systolic BP (mmHg)	119.5 ± 21.7	124.6 ± 21.6	NS
Diastolic BP (mmHg)	73.0 ± 4.8	73.9 ± 10.4	NS
Proteinuria (g/day)	6.4 ± 4.1	4.1 ± 2.3	0.02
Nephrotic syndrome (%)	75.0	64.5	NS
Serum creatinine (mg/dL)	0.90 ± 0.20	0.90 ± 0.31	NS
Serum total protein (g/dL)	4.65 ± 1.42	5.27 ± 1.03	NS
Serum albumin (g/dL)	2.60 ± 0.97	2.71 ± 0.80	NS
Serum cholesterol (mg/dL)	299 ± 55	314 ± 90	NS

NS Not significant

The relapse rate of the heterogeneous group (43 %) was higher than that of the homogeneous group (20 %). Therefore, a pattern of electron-dense deposition based on EM showing heterogeneous type may be a risk factor for relapse. On the other hand, there was no significant change in clinical findings and date at onset of according to the type of immune complex deposition (Table 3).

Patterns of immune complex deposition in re-biopsy specimens

During the follow-up period, nine relapsing patients underwent second renal biopsy. These re-biopsy specimens at relapse were examined to determine whether patterns of electron-dense deposits may change. Interestingly, the pattern of electron-dense deposits remained unchanged in most cases from onset to relapse (Fig. 3).

Correlation of relapse with immunosuppressive therapy

There were no significant associations between relapse rate and immunosuppressive therapy at onset (steroid alone, intravenous immunoglobulin, steroid with cyclophosphamide, or cyclosporine with or without steroid). Furthermore, 11 of 26 patients who showed relapse (42 %) achieved CR or ICR I, which was lower than the rate observed in patients with initial remission (74 %) (Table 4). The observation period of the relapses (86 months) was shorter than that of the initial remission (135 months).

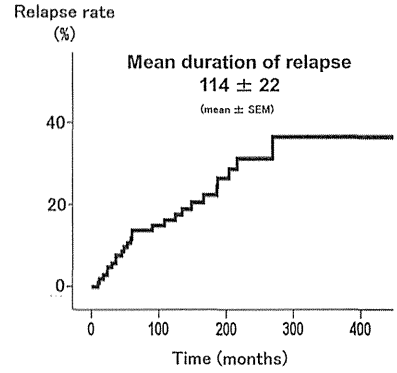

Fig. 2 Remission duration to relapse. The mean remission duration was 114 months, and the longest duration of remission was 456 months

Table 3 Clinical findings and data at onset of according to the type of immune complex deposition

	Homogeneous	Heterogeneous	*P* value
No. of patients	71	46	
Age (y.o)	49.6 ± 15.9	47.0 ± 13.7	NS
Female/Male	28/43	19/27	
Follow-up period (months)	125 ± 74	155 ± 92	NS
Systolic BP (mmHg)	121.4 ± 20.0	133.3 ± 12.6	NS
Diastolic BP (mmHg)	75.7 ± 9.2	78.1 ± 7.6	NS
Proteinuria (g/day)	4.9 ± 3.5	4.7 ± 2.3	NS
Nephrotic syndrome (%)	67.6	84.8	NS
Serum creatinine (mg/dL)	0.94 ± 0.43	0.98 + 0.43	NS
Serum total protein (g/dL)	4.86 ± 1.14	5.42 ± 1.09	NS
Serum albumin (g/dL)	2.41 ± 0.88	2.94 ± 0.76	NS
Serum cholesterol (mg/dL)	330 ± 101	259 ± 62	NS

NS Not significant

Discussion

In this study, the clinicopathological features of patients with relapse after remission were analyzed. There were no differences in initial clinical findings or data between the patients with and without relapse, with the exception of the higher degree of proteinuria at onset in patients with relapse. The relapse rate of the heterogeneous group was higher than that of the homogeneous group. In addition, patients with relapse achieved CR or ICR I. Finally, electron microscopic findings demonstrating heterogeneous type were associated with susceptibility to relapse.

This study indicated that 23 % of IMN relapsed within the period examined. There is little evidence regarding the rate of relapse of IMN after remission. In Europe and the

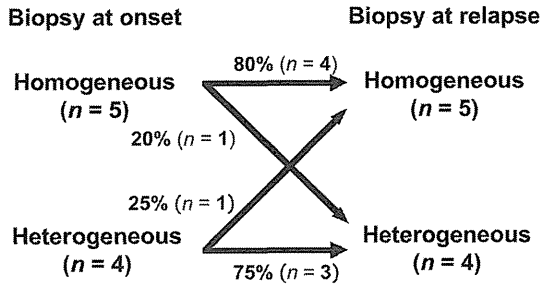

Fig. 3 Pathological findings after relapse. Type of electron-dense deposits did not change in most cases from onset to relapse

Table 4 Remission rate in patients with relapse

	Initial treatment	After relapse
No. of patients	146	26
Follow-up period (months) (mean ± SEM)	135 ± 7	86 ± 16
Remission (CR + ICR I)	74 %	42 %
ICR II	14 %	15 %
Nephrotic syndrome	4 %	31 %
End-stage renal disease	8 %	12 %

USA, 30–50 % of IMN patients relapse after remission [15–18]. However, the clinical manifestations of relapsing IMN in Japan remain unclear. Eriguchi et al. [19] reported relapse in 30 of 90 Japanese patients (33 %) with IMN who had achieved remission. Yuan et al. [20] reported relapse in 5 of 32 Chinese patients (19.2 %) with nephrotic IMN who were treated with i.v. pulse cyclophosphamide together with steroid and achieved remission. Based on these results together with those of the present study, the relapse rate in Japan may be lower than those in Europe and the USA. However, given the lack of evidence, further studies are required to compare the relapse rates among various races and their effects on long-term prognosis.

Our clinicopathological study revealed that the heterogeneous pattern on electron microscopy was a distinct risk factor for relapse. We reported previously that synchronous heterogeneous type dense deposition in IMN patients was an independent poor prognostic factor compared with the homogeneous type [12]. These findings suggest that electron microscopic examination of the immune complex deposition pattern may be a useful tool for estimating disease activity and clinical outcome. Ehrenreich et al. [10] first described the evolution of glomerular capillary lesions in terms of four stages: initial subepithelial dense deposits (stage I); a subsequent basement membrane spike response (stage II); eventual incorporation of the deposits within the glomerular basement membrane (stage III); and finally formation of a markedly thickened basement membrane (stage IV). Patients with single generation of deposits showed restoration of a normal glomerular basement membrane with intramembranous lucencies, e.g., IV, in complete remission. Alternatively, the present study indicated that the heterogeneous pattern of electron microscopic findings is a risk factor for relapse. Detailed molecular mechanism involved in this process remains investigated so far. The mechanism may be speculated that the patients of heterogenous type had some underlining factors for repeated depositions to glomerulus basement membrane, which may keep damage glomeruli subclinically even after patients achieved remission in clinical settings. In this condition, some certain triggering stimuli might re-activate glomerular damage. These underlying molecular mechanisms will be examined in the future.

Analyses of the present data indicated that there were no significant differences between the patients with and without relapse in terms of age, time to remission, initial creatinine level, or serum albumin level. However, proteinuria was more evident in the patients with relapse. Bohdan et al. [21] reported relapses in 16 of 55 IMN patients with CR, in whom the severity of proteinuria was greater than in the no-relapse group. These data may support our suggestion that a lower level of proteinuria at onset of IMN is a factor involved in maintenance of remission. Further, the contents of immunosuppressive therapy may be related to relapse. Surprisingly, our data revealed no significant associations between relapse rate and immunosuppressive therapy at onset (steroid alone, intravenous immunoglobulin, steroid with cyclophosphamide, or cyclosporine with or without steroid). Further studies are required to determine the clinical characteristics involved in relapse.

Importantly, 11 of 26 patients with relapse (42 %) achieved CR or ICR I, which was lower than the rate observed among patients with initial remission (74 %). This was partly because the observation period of the relapse (86 months) was shorter than that of the initial remission (135 months). In support of our suggestion, some papers have reported the rate of second remission. Manos et al. reported relapse in 8 of 15 IMN patients who had achieved remission. Of these eight patients, three (38 %) went into second remission [15]. Ponticelli et al. [17] reported the relapses of non-nephrotic in 22 of 74 patients of IMN who had achieved CR. Twelve of the 22 patients (55 %) went into second remission. Taken together with the results of the present study, re-remission after relapse is anticipated, although studies of re-remission rate are required.

In conclusion, the findings of the present study suggest that IMN patients with relapse achieved CR or ICR I and that electron microscopic findings demonstrating

heterogeneous type indicated susceptibility to relapse. Thus, our results suggest the value of a prompt diagnosis based on electron microscopic findings in patterns with IMN.

Acknowledgments This study was supported in part by a Grant-in-Aid for Progressive Renal Diseases Research, Research on Rare and Intractable Disease, from the Ministry of Health, Labour and Welfare of Japan.

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

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Clin Exp Nephrol
DOI 10.1007/s10157-014-0996-8

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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Received: 20 June 2013 / Accepted: 28 May 2014

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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Published online: 17 June 2014

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 $\pm$ 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

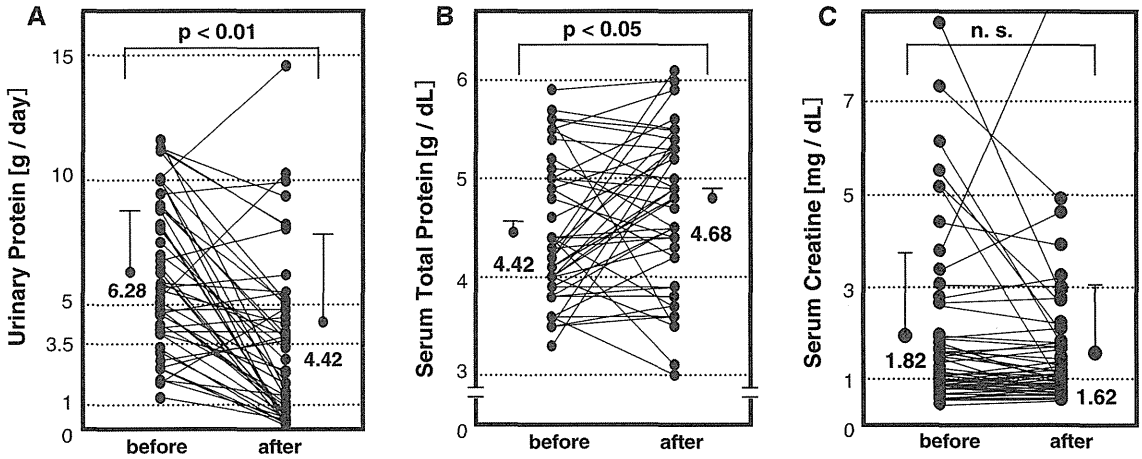

Fig. 1 Changes in UP (**a**), SP (**b**), and SCr (**c**) levels from before to after LDL-A in individual episodes. The UP and SCr levels decreased in 37 (69.6 %) and 27 (55.4 %) of the 47 episodes, respectively, and the SP level increased in 30 (60.0 %) of 46 episodes (data were not collected in one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

Table 6 Patient and episode characteristics of effective and non-effective episodes

Patient and episode characteristics	Effective	*n*	Non-effective	*n*	*p*-value
Age (years)	55.57 ± 19.09	23	55.20 ± 15.36	20	n.s.[a]
BMI	24.01 ± 5.55	24	22.76 ± 4.15	16	n.s.[a]
Average number of LDL-A sessions	9.52 ± 2.55	25	9.77 ± 12.72	22	n.s.[a]
Average frequency of LDL-A sessions (per week)	1.92 ± 0.49	25	1.83 ± 0.47	20	n.s.[a]
Average amount of plasma per session (L)	3.37 ± 0.57	23	3.67 ± 0.98	20	n.s.[a]
Duration of NS before the treatment <8 weeks	11 (48.8 %)	24	2 (5.3 %)	19	<0.05[b]
Male	14 (56.0 %)	25	14 (63.6 %)	22	n.s.[b]
Fatigue	17 (73.9 %)	23	13 (72.2 %)	18	n.s.[c]
Edema	23 (92.0 %)	25	16 (76.2 %)	21	n.s.[c]
First time	14 (56.0 %)	25	13 (61.9 %)	21	n.s.[b]
Renal biopsy	21 (84.0 %)	25	19 (86.4 %)	22	n.s.[c]
Cyclosporine A administration	12 (50.0 %)	24	12 (54.5 %)	22	n.s.[b]
Steroid pulse therapy	1 (4.2 %)	24	3 (13.6 %)	22	n.s.[c]

[a] Student's t test
[b] Chi-square test
[c] Fisher's exact test

respectively), and also UP at pre-treatment also showed lower trend in effective episodes ($p = 0.075$) (Tables 5, 6). Not to be argued, UP and SP are distinctive indicators for severity of NS. It is suggested that patient's clinical condition has an influence on efficacy of LDL-A treatment. Hattori et al. reported that a higher selectivity index and lower degree of tubular damage were observed in pediatric patients with steroid-resistant NS who responded to LDL-A treatment compared to those who did not respond. We evaluated the duration after onset of NS dichotomized by within or more than 8 weeks. As shown in Table 7, of 13 episodes in which LDL-A was applied within 8 weeks after the onset, 11 (84.6 %) were effectively treated and recovered from nephrotic condition, whereas efficacy of the other episodes was poor (13/30, 43.3 %). Taken together, it could be considered that the less serious glomerular dysfunction and/or renal tissue damage of patients, the more likely for them to achieve effective treatment. Therefore, we suggest that LDL-A should be used immediately when a patient with NS appears not to respond to primary medication to prevent progression of renal injury.

The results of the study showed the short-term clinical efficacy of LDL-A for the treatment of drug-resistant NS in the population of patients in the POLARIS study. However, several limitations in this study need to be addressed. Most importantly, this study was conducted in an observational manner and did not intervene with concomitant therapies including medications. Therefore, the contribution of the concomitant therapies was not elucidated. In addition, the study was a single-arm study without a control group and accordingly it was difficult to directly demonstrate the efficacy of the treatment. Furthermore, the sample size was rather small to make a convincing evaluation. Although the above-mentioned limitations should be taken into consideration, this study was performed prospectively in a nationwide multicenter cohort with many more NS episodes than in previous studies and demonstrated comparable efficacy to that in the previous studies. It will be intriguing to see whether the improved clinical conditions produced by LDL-A will continue for a longer period. The final results of the POLARIS study may reveal the long-term clinical efficacy of LDL-A as an alternative therapy for drug-resistant NS.

Table 7 Comparison of the therapeutic efficacy of LDL-A between patients who received treatment at less than ($n = 13$) and more than ($n = 30$) 8 weeks after onset of NS

Efficacy	Period before treatment	
	<8 weeks	≥8 weeks
Effective (*n*)	11	13
Non-effective (*n*)	2	17
Rate	84.6 %	43.3 %

The data for 4 episodes were not collected

Acknowledgments This study was supported by The Kidney Foundation, Japan and in part by a grant in relation to Progressive Renal Disease from the Ministry of Health, Labor and Welfare Research Project for Specially Selected Disease. The authors express their appreciation to all the investigators who reported clinical data in this study, including Atsushi Oyama (Nishi-Kobe Medical Center), Noriaki Henmi (Fukaya Red Cross Hospital), Noriko Mori (Shizuoka General Hospital), Osamu Nishi, (Nishi Clinic), Yasukiyo Mori (Kyoto Prefectural University of Medicine), Megumu Fukunaga (Toyonaka Municipal Hospital), Masahiko Miyamoto (Osaka Red Cross Hospital), Kenji Arizono (Kumamoto Chuo Hospital), Takako Suzuki (Moriyama Rehabilitation Hospital), Kazuhiko Hora (Hokushin General Hospital), Hiroshi Makino (Okayama University), Hideyasu Kiyomoto (Kagawa University), Yutaka Ando (Osaka Minami Medical Center), Yoshiharu Tsubakihara (Osaka General Medical Center), Kosuke Ota (Okayama Medical Center), Masamichi Fukuda (Iwakuni Medical Center Hospital), Yukiko Abe (Shin-Oura Hospital), Mitsuhiro Yoneda (Fuke Chiba Hospital), Hiroshi Ohtani (Akita Kumiai General Hospital), Tokuichiro Sugimoto (Mitsui Memorial Hospital), Shizunori Ichida (Japanese Red Cross Nagoya Daiichi Hospital), Kentaro Wada (Nippon Kokan Fukuyama

Hospital), Rhosuke Yoshihara (Konan Kakogawa Hospital), Shoichi Fujimoto (University of Miyazaki), Morihiro Kondo (Rakuwa-kai Otowa Hospital), Takeshi Nakanishi (Hyogo College of Medicine), Kazuhiko Tsuruya (Kyusyu University), Fumiki Tanigawa (Shimonoseki Kosei Hospital), Masami Hashimoto (Onomichi General Hospital), Akiko Nakamura (Saga Prefectural Hospital Koseikan), Soshi Yorifuji (Osaka Saiseikai Nakatsu Hospital), Tamaki Sasaki (Kawasaki Medical School).

Conflict of interest None of the authors report a conflict of interest with this study.

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Clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis: a retrospective multicenter study

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Abstract

Introduction: Immunoglobulin G4 (IgG4)–related aortitis/periaortitis and periarteritis are vascular manifestations of IgG4-related disease. In this disease, the affected aneurysmal lesion has been suspected to be at risk of rupture. In this study, we aimed to clarify the clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis.

Methods: We retrospectively evaluated clinical features, including laboratory data, imaging findings and the course after corticosteroid therapy, in 40 patients diagnosed with IgG4-related aortitis/periaortitis and periarteritis on the basis of periaortic/periarterial radiological findings, satisfaction of the comprehensive diagnostic criteria or each organ-specific diagnostic criteria, and exclusion of other diseases.

Results: The patients were mainly elderly, with an average age of 66.4 years and with a marked male predominance and extensive other organ involvement. Subjective symptoms were scanty, and only a small proportion had elevated serum C-reactive protein levels. The affected aorta/artery were the abdominal aortas or the iliac arteries in most cases. Thirty-six patients were treated with prednisolone, and the periaortic/periarterial lesions improved in most of them during the follow-up period. Two (50.0%) of four patients with luminal dilatation of the affected lesions before corticosteroid therapy had exacerbations of luminal dilatation after therapy, whereas none of the twenty-six patients without it had a new appearance of luminal dilatation after therapy.

Conclusions: The results of this retrospective multicenter study highlight three important points: (1) the possibility of latent existence and progression of periaortic/periarterial lesions, (2) the efficacy of corticosteroid therapy in preventing new aneurysm formation in patients without luminal dilatation of periaortic/periarterial lesions and (3) the possibility that a small proportion of patients may actually develop luminal dilatation of periaortic/periarterial lesions in IgG4-related aortitis/periaortitis and periarteritis. A larger-scale prospective study is required to confirm the efficacy and safety of corticosteroid therapy in patients with versus those without luminal dilatation and to devise a more useful and safe treatment strategy, including administration of other immunosuppressants.

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Introduction

Immunoglobulin G4 (IgG4)–related disease (IgG4-RD) is a recently recognized systemic inflammatory disease with multiorgan involvement [1-3]. IgG4-RD is characterized by tumefactive lesions, a dense lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells, storiform fibrosis and elevated serum IgG4 levels. Writing from a pathological viewpoint, Stone *et al.* [4] and Kasashima *et al.* [5,6] described some patients with chronic aortitis/periaortitis or inflammatory aortic aneurysm as also having an IgG4-related condition. Microscopically, these lesions have a predilection for the adventitia and periaortic/periarterial tissue, although they also affect the media, indicating the disease have not just a periaortitis component but also an aortitis one [4-9]. In addition, Inoue *et al.* reported characteristic computed tomography (CT) findings of 17 Japanese patients with IgG4-related periaortitis and/or periarteritis. Macroscopically, this disease represents periaortic or periarterial, circumferential or partial, thickened or masslike lesions with or without aneurysmal change [10]. Presumably, IgG4-related periaortitis and periarteritis may have some overlap with IgG4-related retroperitoneal fibrosis. Inoue *et al.* proposed that this discrimination is dependent on the predominant location of the lesions. They deemed *periaortitis* appropriate to refer to lesions with predominant periaortic and concentric involvement, whereas periureteral or plaquelike lesions should be referred to as *retroperitoneal fibrosis* [10]. In this context, the concept of IgG4-related aortitis/periaortitis and periarteritis (PAo/PA) has been proposed [9]. However, the clinical characteristics and course after corticosteroid therapy in patients with IgG4-related PAo/PA have not been well-clarified. Moreover, although corticosteroid therapy has been suspected to increase the risk of aneurysm formation or rupture [5,8,10], the precise incidence of these complications and their timing in the clinical course have not been elucidated.

This state of affairs prompted us to undertake the present study to clarify the clinical characteristics and course after corticosteroid therapy in patients with IgG4-related PAo/PA.

Methods

Patients

From among 333 patients with IgG4-RD at Kanazawa University Hospital, Sapporo Medical University Hospital, Nagaoka Red Cross Hospital, Toranomon Hospital, Toyama University Hospital and Kanazawa Medical University Hospital between 1 January 1995 and 30 September 2013, we identified 40 with IgG4-related PAo/PA (Table 1). The diagnosis of this disease was made on the basis of the presence of consistent periaortic/periarterial radiological findings, the fulfillment of the published comprehensive diagnostic criteria (CDC) [11] or each organ-specific diagnostic criteria [12-14] and exclusion of other diseases. The diagnosis of extravascular lesions was made on the basis of physical examination, imaging findings and/or histopathological examination, in addition to exclusion of other conditions. According to the CDC, 25 patients (patients 2 through 5, 7, 8, 10, 11, 13 through 17, 19, 21 through 23, 26 through 28, 32, 34 through 36 and 38 in Table 1) were diagnosed with definite IgG4-RD, three (patients 1, 9 and 37) with probable IgG4-RD and 12 (patients 6, 12, 18, 20, 24, 25, 29 through 31, 33, 39 and 40) with possible IgG4-RD. Three (patients 6, 18 and 29) of these twelve patients fulfilled the revised diagnostic criteria for autoimmune pancreatitis (AIP) [13]. Well-experienced physicians of this disease diagnosed the remaining nine patients with IgG4-RD on the basis of a consistent clinical picture with elevated serum IgG4 concentrations and exclusion of other diseases. Twenty-nine (80.6%) of thirty-six patients who had extravascular IgG4-related organ involvement underwent biopsy of affected organs and showed histologically typical light microscopic findings [15] and copious IgG4-positive plasma cell infiltration. Histological evaluation of periaortic/periarterial lesions was performed in only one patient (patient 37) by means of incisional biopsy of the periaortic mass lesions, which did not show any vascular structures but histological findings compatible with IgG4-related retroperitoneal fibrosis. We retrospectively evaluated baseline clinical features, including subjective symptoms, laboratory data and imaging findings, in these 40 patients. Because follow-up data were absent or inadequate for seven patients (patients 1, 2, 21, 33, 37, 39 and 40), we limited the analysis of the clinical course to the remaining thirty-three patients (Figure 1). Two patients (patients 8 and 17) had been included in earlier studies ([16] and [17], respectively).

This study was approved by the Medical Ethics Committee of Kanazawa University, the institutional review board of Sapporo Medical University Hospital, the Ethics Committee of Nagaoka Red Cross Hospital, the institutional review board of Toranomon Hospital, the review board of the University of Toyama and the Research Ethics Committee of Kanazawa Medical University. Informed consent for publication of all data and samples was obtained from each patient. The research was conducted in compliance with the Declaration of Helsinki.

Imaging evaluation

All patients underwent whole-body CT examinations at the time of the initial diagnosis, and follow-up CT data were available for 33 patients, 31 of whom received corticosteroid therapy. All imaging data were reviewed by a single radiologist with extensive experience in IgG4-RD at Kanazawa University Hospital. Periaortic/periarterial lesions were described as circumferential or partial thickened wall

Table 1 Baseline characteristics of 40 patients with IgG4-related aortitis/periaortitis and periarteritis

Patient	Follow-up (mo)	IgG (mg/dl)	IgG4 (mg/dl)	IgE (IU/ml)	CRP (mg/dl)	Location of vascular lesion	Luminal dilatation before Tx	Extravascular lesions	Symptoms	Risk factor of arteriosclerosis	Initial PSL Tx (mg/day)
1	204	1,894	128	543	6.2	AA	(–)	La, Sa	abdo P, fever	(–)	30
2	120	2,840	693	468	0.1	AA	(–)	Sa	(–)	DM, Sm	30
3	96	5,970	3,100	259	1.56	AA	(–)	La, Sa, Hy, Pa	malaise	DM, HT	40
4	78	2,140	557	266	<0.10	AA, IA	(+)	La, Sa	(–)	DL, Sm	50
5	70	1,500	173	151	0.3	IA, SMA	(–)	Pa, RF	abdo P	DM, HT, DL, Sm	20
6	63	2,970	1,330	419	<0.10	AA	(–)	La, Sa, Pa, Ki, RF	malaise	DM, HT, DL, Sm	40
7	63	2,130	715	253	<0.10	IA	(–)	La, Sa	(–)	DM, DL, Sm	40
8	63	2,731	269	975	0.6	AA	(–)	Sa, RF	(–)	DM, HT, DL, Sm	30
9	57	1,790[b]	105[b]	212[b]	1.5[b]	AA, IA	(+)	Hy, Lu, Pa, Ly	(–)	DL	40
10	54	2,570	1,420	345	0.3	AA, IA	(+)	Pa	(–)	DM, HT	20
11	48	2,950	1,540	7.9	<0.1	AA	(–)	Sa, Bi, Pa, Pr	(–)	DM	30
12	43	1,487	196	447	0.6	AA, IA	(–)	RF	abdo P	DM, HT, DL, Sm	0
13	37	2,563	1,330	283	0.09	AA	(–)	Sa, Ki	pollakiuria	DL, Sm	45
14	35	2,319	734	542	1.19	TA, AA	(–)	Sa, Pa, Ki	(–)	DM, DL	40
15	34	1,458	158	452	0.22	AA	(–)	Sa, Ly	(–)	DM, HT, DL, Sm	30
16	27	2,081	870	1,285	0.0	AA, IA	(–)	Sa, RF, Pr	(–)	DM, HT	20
17	27	1,756	408	513	0.2	AA, IA	(–)	Sa, Pa, Ki	(–)	DM, HT, DL, Sm	20
18	27	1,762	144	24	0.32	AA, IA	(+)	Pa	(–)	DL, Sm	20
19	25	2,024	292	1,400	0.14	AA	(–)	Pa, RF	(–)	DM, HT, Sm	40
20	24	2,262	299	443	<0.05	AA	(–)	(–)	(–)	HT	0
21	24	2,184	236	365	0.3	AA	(+)	La, Sa	fever	DM, HT, DL	30
22	22	3,484	1,896	247	0.0	AA	(–)	La, Sa, Pa, Ki, Ly	(–)	Sm	35
23	15	4,171	2,120	<20	0.32	AA, IA	(–)	La, Sa, Ki	(–)	DM, HT, Sm	40
24	13	1,837	261	687	0.06	IA	(–)	RF	(–)	HT, DL	30
25	13	1,454	196	350	0.13	AA, IA	(–)	(–)	abdo P	Sm	15
26	10	2,213	455	NA	0.56	AA, IA	(–)	Sa, Ki	arthralgia	HT, DL, Sm	40
27	10	3,120	1,020	1,760	1.5	AA, IA, IMA	(–)	La, Sa	hoarseness, fever	Sm	30
28	9	2,936	1,070	17	0.0	TA, AA, IA	(–)	La, Sa, Pa, Ki	thirst	DM, DL, Sm	40
29	9	10,121	2,500	<20	0.37	IA	(+)	Pa, Ki, Ly	malaise	DM	50
30	9	1,200	147	NA	2.94	AA, IA	(–)	(–)	fever, malaise	DM, HT	30

Table 1 Baseline characteristics of 40 patients with IgG4-related aortitis/periaortitis and periarteritis *(Continued)*

31	8	1,475	210	111	0.3	IA	(–)	Sa	(–)	(–)	40
32	4	2,938	1,520	48	0.1	AA	(–)	La, Sa, Ki, RF	(–)	Sm	30
33	4	1,463	672	216	0.13	AA	(–)	Sa, Pl, Ca	(–)	Sm	0
34	3	2,439	782	703	0.2	AA, IA	(–)	La, Ki, RF	(–)	DM, DL, Sm	20
35	3	2,244	503	311	0.0	AA, IA	(–)	Ki	edema	(–)	30
36	2	1,950	711	737	0.0	AA	(–)	La, Sa, Lu, Ki	(–)	Sm	35
37	2	1,328	106	19	0.28	AA, IA	(+)	RF	(–)	DL	0
38	1	4,420	2,680	174	0.1	IA	(–)	La, Sa, Bi, Pa, Ki, Ne	diarrhea	Sm	50
39	1	2,276	835	<20	0.91	IA	(–)	Sa	(–)	HT	15
40	1	1,600	206	212	0.38	AA	(–)	(–)	abdo P, malaise	Sm	30

AA, Abdominal aorta; *abdo,* Abdominal; *Bi,* Bile tract; *Ca,* Pericarditis; *CRP,* C-reactive protein; *DL,* Dyslipidemia; *DM,* Diabetes mellitus; *F,* Female; *HT,* Hypertension; *Hy,* Hypophysitis; *IA,* Iliac artery; *IgE,* Serum immunoglobulin E at diagnosis; *IgG,* Serum immunoglobulin G at diagnosis; *IgG4,* Serum immunoglobulin G4 at diagnosis; *IMA,* Inferior mesenteric artery; *Ki,* IgG4-related kidney disease; *La,* Lacrimal gland, *Lu,* Lung; *Ly,* Lymph node; *M,* Male; *Mo,* month; *NA,* Not available; *Ne,* Nerve; *P,* Pain; *Pa,* Pancreas; *Pl,* Pleuritis; *Pr, P*rostate; *PSL,* Prednisolone; *RF,* Retroperitoneal fibrosis; *Sa,* Salivary gland; *Sm,* Past or current smoking; *SMA,* Superior mesenteric artery; TA, Thoracic aorta; *Tx,* Treatment. [b]Value under corticosteroid therapy.

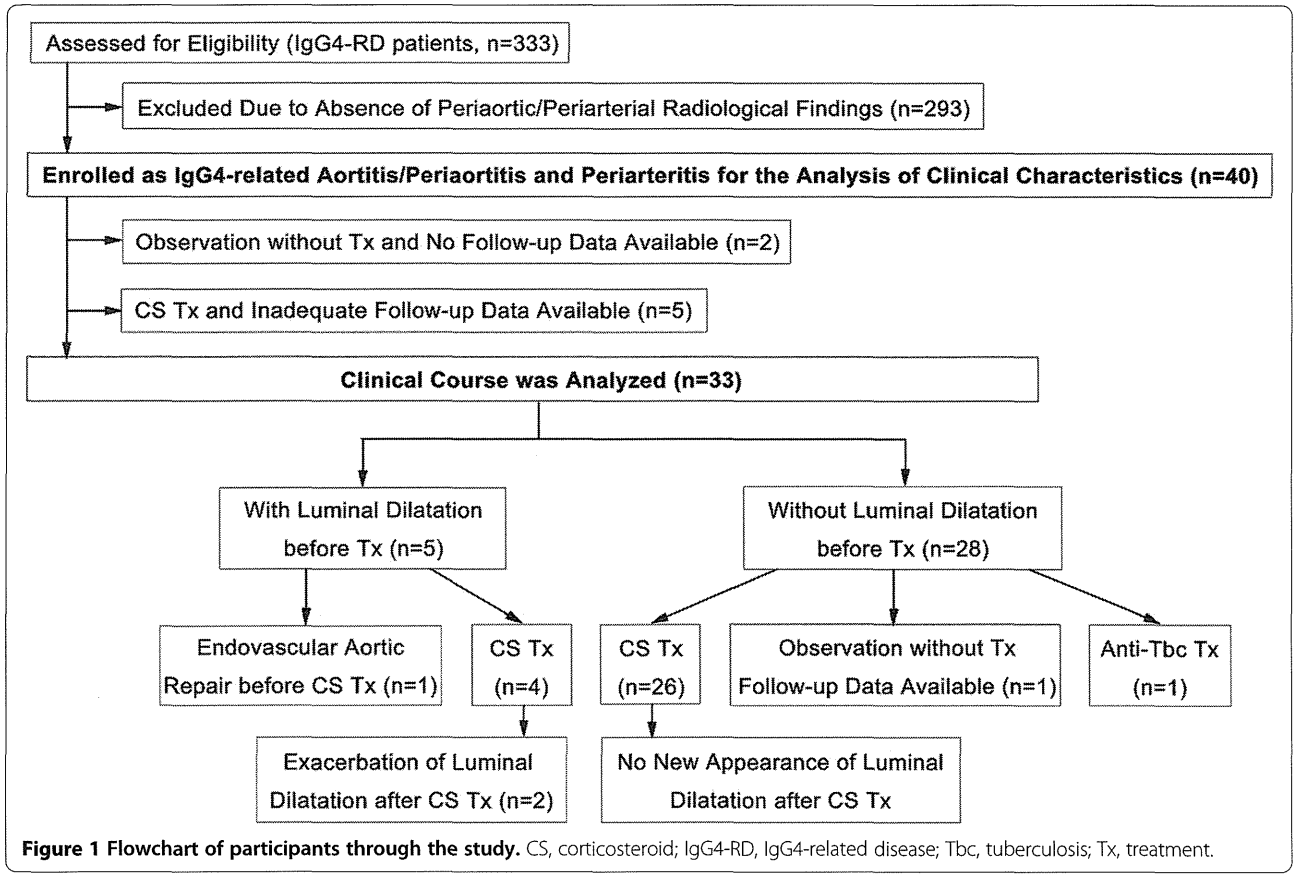

Figure 1 Flowchart of participants through the study. CS, corticosteroid; IgG4-RD, IgG4-related disease; Tbc, tuberculosis; Tx, treatment.

of the affected aortas/arteries with homogeneous enhancement visualized by contrast-enhanced CT. At the time of diagnosis, we also evaluated the findings of 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) for 20 patients and of gallium scintigraphy for 12 patients.

At the time of initial diagnostic CT imaging, after noting the affected site of aortas/arteries and extravascular lesions, we measured the maximum vascular wall thickness and diameter of the lumen in both affected and adjacent sites in each lesion. These two values were then longitudinally evaluated in the 33 patients whose follow-up imaging and clinical course information were available.

Improvement and relapse of periaortic/periarterial lesions during the clinical course were defined as decrease and reincrease of vascular wall thickness, respectively, at the same site as the maximum vascular wall thickness measured at the time of initial diagnosis. Luminal dilatation of periaortic/periarterial lesions was defined as being present when the luminal diameter of the affected site was more than 3 mm larger than that of adjacent normal sites. Exacerbation of luminal dilatation was defined as being present when more than 5-mm expansion of the luminal diameter was observed at the same site as the luminal dilatation detected at the time of initial diagnosis.

Statistical analysis

Statistical analysis was performed using SPSS version 19 software (IBM SPSS, Chicago, IL, USA). The significance of differences between groups was determined using Mann–Whitney *U* test or Wilcoxon signed-rank test, and the significance of differences in frequencies was analyzed with Fisher's exact probability test. Data are presented as means ± SD. Significant differences were defined as $P < 0.05$.

Results

Baseline characteristics

The baseline clinical characteristics of 40 patients are shown in Table 1. Our patient group was composed of 37 men and 3 women with an average age of 66.4 ± 7.1 years (age range, 44 to 75). One patient (patient 9 in Table 1) had been treated with prednisolone (PSL) at a dose of 5.0 mg/day for type 1 AIP. None of the other 39 patients had been treated with any immunosuppressants, including corticosteroids, before their diagnosis. Thirty-six patients (90.0%) had more than one IgG4-related extravascular lesion (average, 2.3 ± 1.5 organs; range, 0 to 6 organs). Involvement of the salivary gland was observed in 25 patients (62.5%), lacrimal gland in 14 (35.0%), pancreas in 14 (35.0%), kidney in 13 (32.5%), retroperitoneum in 13

(32.5%), prostate in 6 (15.0%), lung in 3 (7.5%) and hepatobiliary tract and hypophysis in 2 each (5.0%). The frequency of subjective symptoms was low (fever, 10.0%; abdominal pain, 12.5%; general malaise, 12.5%). Moreover, five of seven patients with luminal dilatation of the affected lesions at the time of diagnosis complained of no subjective symptoms. With regard to the major risk factors of atherosclerosis, diabetes mellitus (DM) was present at the time of diagnosis in 20 patients (50.0%), hypertension (HT) in 17 (42.5%), dyslipidemia (DL) in 18 (45.0%), current smoking in 9 (22.5%) and past smoking in 15 (37.5%). The mean follow-up period of all 40 patients after diagnosis was 33.9 ± 39.8 months (range, 1 to 204 months).

At diagnosis, 37 (92.5%) of 40 patients showed elevated serum IgG4 levels exceeding 135 mg/dl (average, 815 ± 771 mg/dl; range, 105 to 3,100 mg/dl). Thirty-one (77.5%) of forty patients showed elevated serum IgG levels (average, 2,551 ± 1,543 mg/dl; range, 1,200 to 10,121 mg/dl; normal range, 870 to 1,700 mg/dl). Twenty-three (60.5%) of thirty-eight evaluated patients showed elevated serum IgE levels (average, 403 ± 398 IU/ml; range, 7.9 to 1,760 IU/ml; normal range, <250 IU/ml). Although none of the patients had leukocytosis, 16 (41.0%) of 39 evaluated patients had eosinophilia (eosinophils >5%). Six (15.4%) of thirty-nine evaluated patients had hypocomplementemia. Antinuclear antibodies were positive in 16 (40.0%) of 40 patients and the rheumatoid factor in only 3 (8.1%) of 37 evaluated patients. Myeloperoxidase antineutrophil cytoplasmic antibodies (ANCAs) and proteinase 3 ANCAs were not observed in any of the evaluated patients (21 and 14 patients, respectively). Only six (15.0%) of forty patients had elevated serum C-reactive protein (CRP) level (CRP >1 mg/dl).

Treatment

The respective attending physicians decided the indications for treatment and the treatment regimen. Thirty-six of forty patients were treated with PSL at an average initial dose of 32.6 ± 9.7 mg/day (range, 15 to 50 mg/day) for the lesions associated with IgG4-RD. Only one patient (patient 1 in Table 1) received cyclophosphamide in addition to PSL. Endovascular aortic repair (EVAR) was performed for the periaortic lesions with marked luminal dilatation before corticosteroid therapy in one patient (patient 18) to prevent rupture. We excluded five patients (patients 1, 2, 21, 39 and 40) from the analysis of the clinical course because their follow-up imaging data were not available. During the clinical course of the other 31 patients, the initial PSL dose was generally continued until 2 to 4 weeks after the start of therapy and then gradually tapered. The PSL dose was tapered to 5 to 10 mg/day by 12 months in 18 (94.7%) of 19 patients whose follow-up period was more than 12 months. The average PSL dose at the last review was 10.0 ± 9.2 mg/day. Because one patient (patient 12) showed strong positivity in the tuberculin skin test and interferon γ release assays, he was treated with antituberculosis therapy only. The other three patients (patients 20, 33 and 37) were observed without any treatment (Figure 1).

Radiological findings at diagnosis

CT images revealed thickened lesions surrounding the aorta/artery in all patients. The affected aorta/artery data were for two thoracic aortas (Figure 2A), thirty-three abdominal aortas (Figure 2C), twenty-three iliac arteries (Figure 2E), one superior mesenteric artery (Figure 2G) and one inferior mesenteric artery. All 33 abdominal aortic lesions affected the infrarenal abdominal aorta, and only 6 lesions also affected the suprarenal abdominal aorta. CT also revealed typical extravascular lesions, mainly in the salivary glands, lacrimal glands, pancreas and kidney. Sixteen of twenty patients who underwent FDG-PET/CT, and only four of twelve patients who underwent gallium scintigraphy, showed significant uptake of the periaortic/periarterial lesions detected by CT.

Changes in radiological findings of periaortic/periarterial lesions after corticosteroid therapy

After corticosteroid therapy, reduction in the thickness of the periaortic/periarterial lesions was observed during an average follow-up period of 30.1 ± 26.2 months (range, 1 to 96 months) in 30 (96.8%) of 31 patients whose clinical course was analyzed (Figure 2), although 1 patient (patient 9 in Table 1) experienced relapse during PSL tapering at a dose of 7.0 mg/day. The average vascular wall thickness of the 34 periaortic/periarterial lesions of 31 patients at the time of diagnosis (7.1 ± 3.0 mm; range, 3 to 18 mm) significantly decreased after corticosteroid therapy (2.7 ± 2.0 mm; range, 1 to 9 mm) (Figure 2I). Generally, obvious radiographic improvement of more than 50% reduction in thickness was observed by 2 months after the start of therapy, after which point some patients showed further improvement and others showed almost no change (Figure 3). Eighteen of the thirty-four lesions had almost completely disappeared by the time of the last review. The rate of improvement, relapse or complete disappearance of the perivascular lesions did not differ significantly between the patients with multiple versus single vascular involvement, between those with versus without a specific other organ involvement such as AIP or between the presence or absence of any of the specific risk factors of atherosclerosis.

Luminal changes after corticosteroid therapy

Of the 31 patients whose clinical course was analyzed after corticosteroid therapy, 5 (patients 4, 9, 10, 18 and 29 in Table 1) had luminal dilatation of the periaortic/

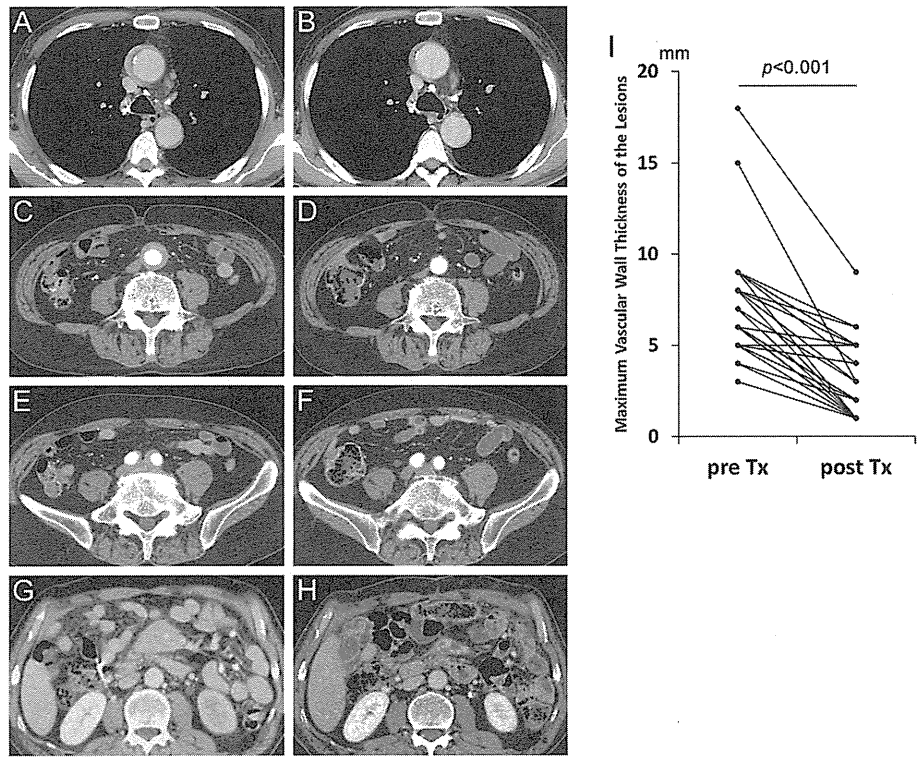

Figure 2 Contrast-enhanced computed tomography findings of periaortic/periarterial lesions and changes after corticosteroid therapy. A thoracic aortic lesion **(A)** had slightly improved 1 month after corticosteroid therapy **(B)**, an abdominal aortic lesion **(C)** and an iliac arterial lesion **(E)** had almost disappeared 10 months after therapy (**D** and **F**, respectively) and a superior mesenteric arterial lesion **(G)** showed fair improvement 2 months after therapy **(H)**. Significant pre- to posttherapy decreases in maximum wall thickness of periaortic/periarterial lesions were observed **(I)**. Tx, Treatment.

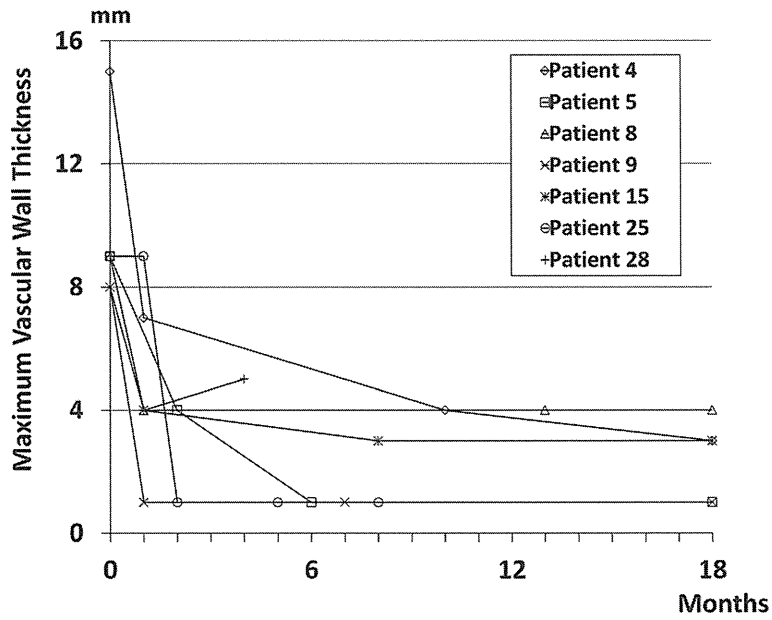

Figure 3 Changes in maximum vascular wall thickness of periaortic/periarterial lesions after the start of corticosteroid therapy. Data for patients who underwent follow-up computed tomography within 2 months after the start of therapy are shown.

periarterial lesions at the time of the initial CT (Figures 4A, 4C and 4E) and three (patients 10, 18 and 29) of them were diagnosed as having inflammatory aneurysm. One (patient 18) of them was treated with EVAR and PSL administration and did not have exacerbation of the luminal dilatation during the follow-up. The other four patients received PSL administration alone, in two (patients 9 and 10) of whom (50%) the luminal dilatation was exacerbated 28 and 46 months after the start of therapy, respectively (Figures 4B, 4D, 4F and 4G). Throughout the clinical course, patient 9 did not have hypertension and patient 10 received antihypertensive agents, which achieved good blood pressure control (below 140/90 mmHg). The luminal diameter was stable after corticosteroid therapy in the 26 patients without luminal dilatation at diagnosis (Figure 4H).

Outcome of patients without corticosteroid therapy

Four patients (patients 12, 20, 33 and 37 in Table 1) did not receive corticosteroid therapy. One patient (patient 12) treated with antituberculosis therapy had gradual improvement of serum IgG4 level, periaortic/periarterial lesions and retroperitoneal fibrosis. In another untreated patient (patient 20), periaortic/periarterial lesion showed no change during the 24-month follow-up period. No new appearance of luminal dilatation was observed in these two patients. Because follow-up imaging data of the other patients were lacking, we excluded them from the analysis of the clinical course.

Discussion

We analyzed the clinical course after corticosteroid therapy in patients with IgG4-related PAo/PA. To our knowledge, this study is the largest to evaluate corticosteroid safety and effectiveness in preventing new aneurysm formation in patients without luminal dilatation of periaortic/periarterial lesions, as well as the risk for exacerbation of luminal dilatation of such lesions in patients with it before therapy.

Biopsy of periaortic/periarterial lesions may cause massive hemorrhage. In our study, we could not perform histopathological examinations of these lesions, with the single exception of patient 37, whose specimens obtained by incisional biopsy of periaortic mass lesions showed only findings compatible with IgG4-related retroperitoneal fibrosis because of a lack of vasculature structures. To compensate for this difficulty, the presence of IgG4-related extravascular lesions, in addition to serological and typical radiological findings, was helpful in making a diagnosis of IgG4-related PAo/PA.

In contrast to our present study, the frequency of extravascular lesions was low in several previous studies. In those studies, periaortic/periarterial lesions were at an advanced stage with frequent aneurysmal formation, and the diagnosis was based mainly on the histopathological findings of the periaortic/periarterial lesions themselves because surgical treatment was selected [4,6,7,18,19]. In contrast, our cases seem to have been at an earlier stage, attributable to the fact that the identification of extravascular lesions

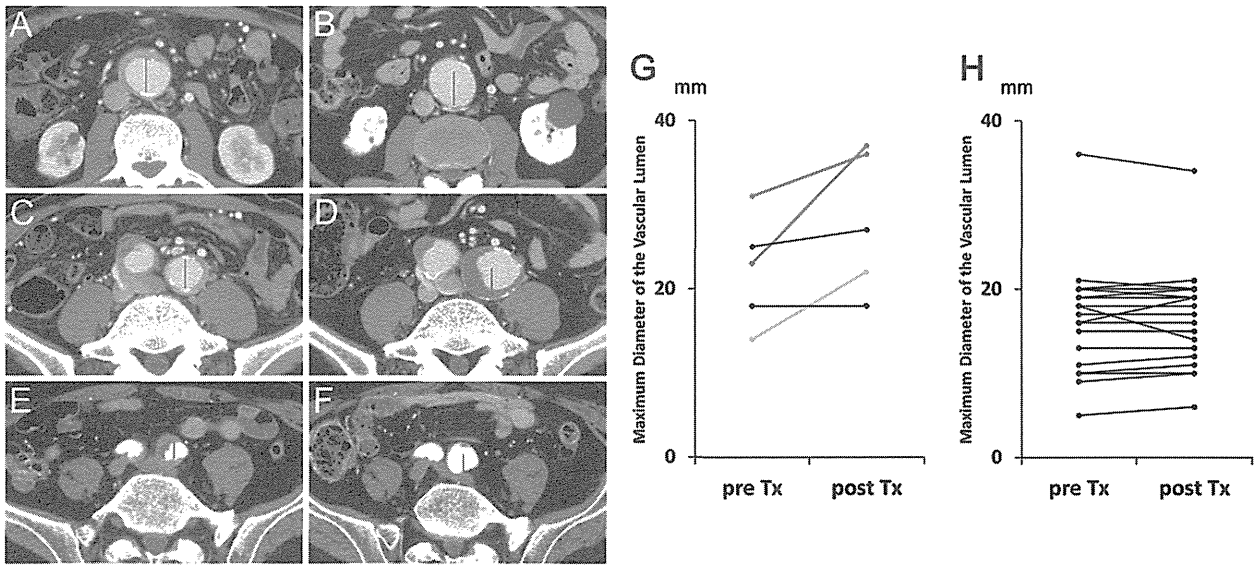

Figure 4 Exacerbation of luminal dilatation after corticosteroid therapy. Luminal dilatation (**A** and **C**, patient 10 in Table 1; **E**, patient 9) of the periaortic/periarterial lesions at the time of diagnosis was exacerbated after corticosteroid therapy (**B**, **D** and **F**, respectively). Red lines in each of the three paired images (**A** and **B**, **C** and **D**, and **E** and **F**, respectively) have the same length. Of five lesions from four patients with luminal dilatation, three lesions from two patients (red and yellow) in the maximum luminal diameter increased **(G)**, whereas no obvious increase was observed in the 28 lesions of the 26 patients without luminal dilatation **(H)**. Tx, Treatment.

and the recent greater awareness of these lesions facilitated the making of an early diagnosis.

Accordingly, in vasculature-restricted cases, the correct diagnosis of IgG4-RD is much more difficult to make. To diagnose such patients early, the indications and accuracy of CT-guided biopsy of periaortic/periarterial lesions should be investigated, the risks and benefits of a diagnostic trial of corticosteroid therapy should be evaluated and a search for other valuable and less-invasive diagnostic markers should be undertaken. In such cases, it is of great importance to exclude other differential diagnoses, such as malignancy, infections, autoimmune disease and drug reactions, which can mimic IgG4-related PAo/PA [20,21].

A definitive therapeutic strategy for IgG4-related PAo/PA has not been established, and to date indications for treatment and the type of treatment regimen have been decided by the respective attending physician. In type 1 AIP (IgG4-related pancreatitis), the pancreatic manifestation of IgG4-RD, consensus guidelines for treatment, which are based on copious clinical experience [22], have been available since 2010 [23]. In AIP patients, corticosteroid administration should be employed for patients with symptoms such as obstructive jaundice and abdominal and back pain. The initial oral PSL dose of 0.6 mg/kg/day, continuation of the initial dose for 2 to 4 weeks and tapering by 5 mg every 1 to 2 weeks to a maintenance dose (2.5 to 5 mg/day) over a period of 2 to 3 months are recommended. In our study, corticosteroid therapy was started at an initial PSL dose of less than 30 mg/day for eight patients, 30 to 40 mg/day for twenty-four patients and over 40 mg/day for four patients. In most of the patients whose follow-up period was more than 12 months, the PSL dose was tapered to 5 to 10 mg/day by 12 months. In this way, the initial therapy generally following the guidelines of AIP and maintenance therapy with relatively slow tapering were performed in our study, with good efficacy attained on the whole.

The results of this study suggest that luminal dilatation of affected lesions may actually occur during corticosteroid therapy in patients with IgG4-related PAo/PA. In past studies [5,8,10], it was speculated that corticosteroid and other immunosuppressive therapies might increase the risk of aneurysm rupture. Actually, an IgG4-RD patient with multiple aneurysms who died of aneurysm rupture after high-dose corticosteroid therapy has been reported [24]. In our present study, of 31 patients treated with corticosteroid, exacerbation of luminal dilatation were observed in only 2 who had already had it before therapy. Because blood pressure was maintained below 140/90 mmHg in these patients throughout their clinical course, hemodynamics seemed not to have influenced the exacerbation of luminal dilatation in any obvious fashion. In contrast, no patient without luminal dilatation showed a new appearance of it after therapy. These results suggest that more careful observation during corticosteroid therapy may be necessary to detect further luminal dilatation early in IgG4-related PAo/PA patients with preexisting luminal dilatation. However, because no patient with luminal dilatation and only one patient without luminal dilatation were observed without corticosteroid therapy, the natural course of the disease or of preexisting dilatation was not clarified. Moreover, the small number of patients with luminal dilatation precluded statistical analysis of the influence of independent risk factors on the luminal dilatation in IgG4-related PAo/PA. Therefore, whether preexisting luminal dilatation, corticosteroid therapy or some other factor is an independent risk factor for the aneurysm formation or exacerbation in IgG4-related PAo/PA patients will have to be clarified through multivariate analysis in a larger prospective study.

This study's results appear to support the contention that corticosteroid therapy can prevent new appearance of luminal dilatation in patients without it before therapy. In two case reports of IgG4-related aortitis/periaortitis patients with ruptured aortic aneurysms [25,26], immunosuppressive agents, including corticosteroids, had not been administered before aneurysm rupture. These case reports suggest that IgG4-related PAo/PA is itself a risk for aneurysm formation resulting in rupture when the lesions are left untreated. However, considering that no patient without luminal dilatation showed new appearance of it after therapy in our study, it is reasonable to surmise that corticosteroid therapy improves periaortic/periarterial lesions and prevents aneurysm formation at the affected site.

Therapeutic alternatives to corticosteroids have not been well-established in IgG4-RD. In some case reports and small case series, some oral immunosuppressive drugs, including azathioprine [27], methotrexate [28] and mycophenolate mofetil [29], have been reported to be effective. In addition, good effectiveness of rituximab, which eliminates B cells by binding the cell-surface marker CD20, has been described [30,31]. However, the efficacy of these drugs remains to be evaluated with regard to their effectiveness for periaortic/periarterial lesions and their influence on luminal dilatation in IgG4-related PAo/PA.

This study has a few limitations. First, the treatment regimen and follow-up protocols were inconsistent between patients because of its retrospective and multi-institutional nature. Second, although this study included more patients than past ones, the number of patients with luminal dilatation at the time of diagnosis was small. Third, the association between histopathological findings and clinical features could not be evaluated, because biopsy specimens for histopathological analysis of the periaortic/periarterial lesions could not be procured. Fourth, no patient with luminal dilatation at the time of diagnosis was observed without corticosteroid therapy.