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The clinical course of patients with IgG4-related kidney disease

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Long-term follow-up for IgG4-related kidney disease, including relapse information, is sparse. To gather data on this we retrospectively examined the clinical course of 43 patients with IgG4-related kidney disease, in which most patients were treated with, and maintained on, corticosteroids. One month after the start of treatment, most of the abnormal serology and radiology parameters had improved. In 34 of the steroid-treated patients whose follow-up period was more than 12 months (median 34 months), excluding one hemodialysis patient, the estimated glomerular filtration rate (eGFR) before treatment was over 60 ml/min in 14 patients (group A) and under 60 ml/min in 20 patients (group B). In group A, there was no difference between the eGFR before therapy and at the last review. In group B, the mean eGFR before treatment (34.1 ml/min) was significantly improved after 1 month (45.0 ml/min), and renal function was maintained at a similar level through last follow-up. Among 24 evaluated patients at the last review, however, renal atrophy had developed in 2 of 9 in group A and in 9 of 15 in group B. Relapse of IgG4-related lesions occurred in 8 of 40 treated patients. Thus, the response of IgG4-related kidney disease to corticosteroids is rapid, not total, and the recovery of renal function persists for a relatively long time under low-dose maintenance. A large-scale prospective study to formulate more useful treatment strategies is necessary.

Kidney International (2013) **84,** 826–833; doi:10.1038/ki.2013.191; published online 22 May 2013

KEYWORDS: chronic kidney disease; corticosteroid therapy; follow-up; IgG4-related disease; tubulointerstitial nephritis

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Received 19 September 2012; revised 13 February 2013; accepted 7 March 2013; published online 22 May 2013

IgG4-related disease (IgG4-RD) is a newly recognized fibroinflammatory condition characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and an elevated serum IgG4 concentration.[1–4] The most common feature of the renal involvement in IgG4-RD is tubulointerstitial nephritis (TIN) with abundant IgG4-positive plasma cells, but glomerular lesions such as membranous glomerulonephritis have also been described.[5–10] In addition, several radiologically evident lesions within the kidney, including the renal parenchyma and the renal pelvis, occur in association with other manifestations of IgG4-RD and often resolve with corticosteroid therapy. Therefore, the kidney lesion associated with IgG4-RD is referred to collectively as 'IgG4-related kidney disease' (IgG4-RKD), including radiologically identified renal lesions in the setting of some other form of organ involvement that has been confirmed histopathologically.[7,11] Recent studies have revealed several characteristic clinical features of IgG4-related TIN (IgG4-TIN), including predominance in middle-aged to elderly men, frequent association with IgG4-related conditions in other organs, high levels of serum IgG and IgG4, a high frequency of hypocomplementemia, a high serum IgE level, eosinophilia, characteristic radiologic findings in the kidney, and a good initial response to corticosteroids.[5–10,12] However, longer follow-up data for IgG4-RKD, including relapse information, are still sparse. In this study, we retrospectively analyzed the longer-term clinical course of IgG4-RKD in detail in a larger cohort, including the responses to corticosteroid therapy.

RESULTS

Baseline characteristics

A total of 43 patients diagnosed as having definite IgG4-RKD according to the published diagnostic criteria[7] were assessed in this study. The baseline clinicopathological characteristics

of the patients are shown in Table 1. All of them were Japanese (33 men and 10 women) with an average age of 63.5 ± 12.3 (27–83) years at the time of diagnosis of renal disease. The follow-up period after diagnosis was 3–189 months (mean 44.0 ± 40.1), and 37 (86%) of the 43 patients were followed up for more than 12 months (Figure 1). Of the patients, 42 (97.7%) had accompanying IgG4-related extra-renal lesions. Computed tomography (CT) examinations were performed in all of the 43 patients, and these revealed characteristic renal features of IgG4-RKD[7] in 31 (72.1%) of them (Table 1). The serum creatinine level was 0.4–7.26 mg/dl and the estimated glomerular filtration rate (eGFR) was 124.4–6.6 ml/min per 1.73 m^2. Renal pathology data were available for 30 patients, and all of them were found to have characteristic IgG4-related TIN.[7] Glomerular lesions other than global sclerosis were evident in 10 of the 30 patients: Henoch–Schönlein purpura nephritis in two,[13,14] membranous glomerulonephritis in two,[10,15] focal and segmental endocapillary proliferative glomerulonephritis in two, mesangioproliferative glomerulonephritis (with mild IgG and IgA deposition in the glomeruli) in two, IgA nephropathy in one, and membranoproliferative glomerulonephritis in one patient. Four patients had a history of malignancy at the time of IgG4-RKD diagnosis (rectal cancer, breast cancer, urinary bladder cancer, and gastric cancer in one each, respectively).

Treatment

Indications for treatment and the treatment regimen were decided according to the opinion of each attending physician. Among the 43 patients, 40 were treated with prednisolone (initial dose 20–60 mg/day; 0.35–1.0 mg/kg/day) for the lesions associated with IgG4-RD (Table 1 and Figure 1). The initial prednisolone dose had been reduced by ~10% at

Table 1 | Baseline characteristics of 43 patients with IgG4-related kidney disease

No.	Age	Sex	Follow-up (mo)	Extrarenal lesions	Renal radiology	Renal pathology	IgG4 ($N<105$)	Low-C	Cr (mg/dl)	eGFR (ml/min)	U-Pr/U-B	PSL Tx (mg/day)
1	54	F	35	Sa, La	A	NA	785	(−)	0.4	124.4	(−)/(−)	40
2	79	M	32	Ly	E	TIN + endocap	409	(+)	0.54	108.6	(−)/(+)	20
3	58	F	32	La, Lu	D	NA	606	(−)	0.55	86.0	(−)/(+)	20
4	76	F	36	Sa, Lu	A, D	TIN	769	(−)	0.59	73.7	(−)/(−)	20
5	35	F	83	Sa, La, RF	D	TIN	191	(−)	0.6	90.3	(−)/(−)	50
6	51	F	66	Sa, Pa	A	TIN	744	(−)	0.6	81.1	NA/NA	40
7	46	F	33	Sa	A, B	NA	751	(−)	0.6	83.6	(−)/(−)	40
8	56	M	27	Sa, Pa, Lu	A	NA	2169	(+)	0.7	90.3	(−)/(−)	35
9	76	M	72 (dead)	Sa, Ly, Pa, Lu	A	TIN	1030	(+)	0.71	81.4	(−)/(−)	0
10	58	F	45	Sa, La, Ly, Ma	D	NA	2150	(−)	0.73	63.1	(−)/(−)	0
11	27	M	47	Sa, La, Ly, Pa	A	NA	1200	(+)	0.8	96.2	(−)/(−)	50
12	72	M	30	Ly	B (plain)	TIN + HSPN	1100	(+)	0.8	72.5	(2+)/(2+)	30
13	77	M	26	Sa	D	NA	438	(−)	0.86	65.8	(−)/(−)	20
14	68	M	58	Sa, La, Ly	B (plain)	NA	2940	(+)	0.9	64.8	NA/NA	60
15	56	M	55	Sa, La, Ly	A	TIN + MGN	1920	(+)	0.9	68.6	(2+)/(±)	50
16	45	M	34	Sa, La, RF	A	NA	671	(+)	0.9	73.0	(−)/(−)	40
17	70	M	6	Pa	E	TIN	623	(+)	0.9	64.3	(±)/(−)	30
18	62	M	7	Sa, La, Ly, Pa, Pro, Ao, Lu	A	NA	1920	(+)	0.92	62.8	(3+)/(+)	40
19	61	M	189	Sa, Ly, Pa, Thr	C	TIN	730[a]	(+)	1.09	54.3	(+)/(+)	60
20	59	M	18	Sa, Pa, Pro, RF	A	TIN	734	(−)	1.1	54.2	(−)/(−)	40
21	42	M	29	Sa, La, Pa, Lu	A	NA	948	(−)	1.1	59.8	(−)/(−)	40
22	58	M	47	He, Neu	A	TIN	1470	(−)	1.15	51.9	(−)/(−)	30
23	65	M	19	Sa, Ly, Lu, Pro, RF, Ao	D	NA	1330	(−)	1.18	48.9	(±)/(−)	45
24	58	M	48	Sa, Ly, Lu	E (plain)	TIN	1204	(+)	1.2	49.6	(+)/(−)	30
25	67	F	19	Ly, Lu	E	TIN	738	NA	1.23	34.2	(±)/(+)	40
26	75	M	6 (dead)	Sa, Ly, Lu	A,B	TIN	587	(+)	1.34	40.8	(+)/(−)	30
27	63	M	13	Sa, Pa, Lu, Ao	A	TIN	408	(−)	1.36	42.2	(+)/(−)	20
28	68	M	66	Sa	E	TIN	670	(+)	1.37	41.0	(−)/(−)	40
29	83	M	51		E (plain)	TIN + MN	924	(+)	1.48	35.5	(3+)/(3+)	40
30	80	M	3 (dead)	Pa	E (plain)	TIN + MPGN	660	(+)	1. 6	33.0	(2+)/(+)	0
31	60	M	156	Sa, Ly	B	TIN + MGN	305[a]	(+)	1.75	32.5	(+)/(±)	50
32	60	M	16	Sa, La	E (plain)	TIN	886	(−)	1.82	31.1	(+)/(−)	30
33	68	M	24	Sa, Ly	A	TIN + IgAGN	736	(+)	1.9	28.6	(−)/(−)	30
34	55	M	124	Sa, Pa	A	TIN	1780	(−)	2.1	27.3	(+)/(−)	40
35	61	F	23	Ly, Lu	A	NA	152	(−)	2.22	18.4	(+)/(−)	30
36	75	F	31	Sa, Ly, Lu	B (plain)	TIN + HSPN	486	(+)	2.25	17.1	(2+)/(2+)	30
37	75	M	14	Sa	E (plain)	TIN	890	(−)	2.34	22.2	(+)/(+)	35
38	69	M	10 (dead)	Pa	E (plain)	TIN	1340	(+)	2.36	22.5	(2+)/(±)	30
39	64	M	132	Sa, La	A	TIN	1360	(−)	2.9	18.4	NA / NA	20
40	74	M	6	Sa, La, Ly, RF, Ao	E (plain)	TIN	1370	(+)	4.65	10.5	(2+)/(2+)	30
41	76	M	39	Sa	E (plain)	TIN	1800	(−)	5.4	8.9	(+)/(+)	40
42	78	M	55 (HD)	Pa	A	TIN + MN	1860	(+)	6.17	7.6	(3+)/(+)	20
43	69	M	31	Sa, La, Pa, Ly, Lu, Pro	B (plain)	TIN + endocap	1120	(+)	7.26	6.6	(2+)/(2+)	30

Abbreviations: A, multiple low-density lesions on enhanced computed tomography; Ao, periaortitis; B, diffuse kidney enlargement; C, hypovascular solitary mass in the kidney; Cr, serum creatinine (mg/dl); D, hypertrophic lesion of renal pelvic wall without irregularity of the renal pelvic surface; E, normal; endocap, endocapillary hypercellularity; He, hepatopathy; HSPN, Henoch–Schonlein purpura nephritis; F, female; IgAGN, IgA nephropathy; IgG4, serum IgG4 (mg/dl); La, dacryoadenitis; Low C, low titer of serum complement; Lu, lung lesion; Ly, lymphadenitis; M, male; Ma, mastitis; MGN, mesangial proliferative glomerulonephritis; MN, membranous glomerulonephritis; Mo, month; MPGN, membranoproliferative glomerulonephritis; NA, not available; Neu, perineuritis; Pa, type 1 autoimmune pancreatitis; Pro, prostatitis; PSL Tx, initial dose of prednisolone; RF, retroperitoneal fibrosis; Sa, sialadenitis; Thr, thrombocytopenia; TIN, tubulointerstitial nephritis; U-B, hematuria; U-Pr, proteinuria.
[a]Value under steroid therapy.

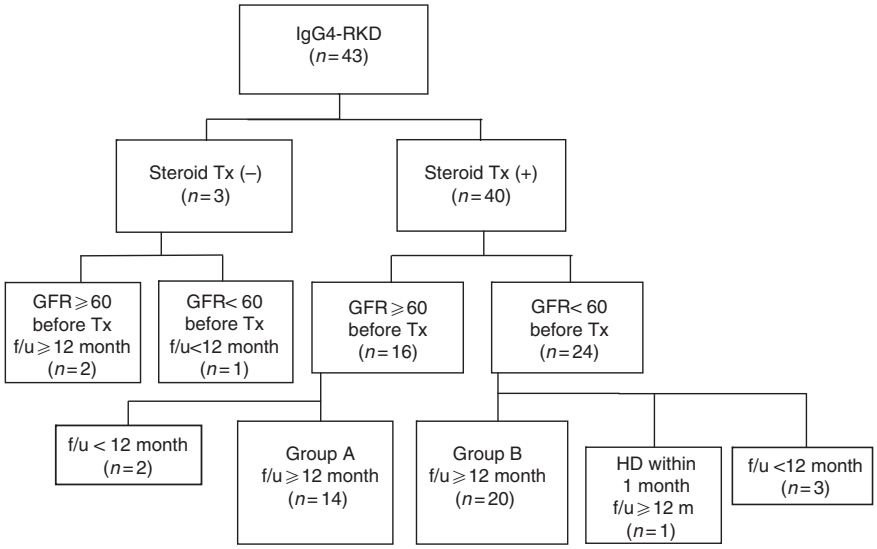

Figure 1 | Breakdown of the 43 patients with IgG4-related kidney disease (IgG4-RKD) according to treatment, estimated glomerular filtration rate (eGFR) before treatment, and follow-up period. f/u, follow-up period; GFR, glomerular filtration rate (ml/min); HD, hemodialysis; m, month; Tx, therapy.

1 month after the start of treatment, when most of the abnormalities of renal function, as well as serology and radiology parameters, had improved, and had been reduced to a maintenance dose by 12 months in most cases. Among the 35 patients who were treated and followed up for over 12 months, 33 (94.3%) were still being maintained on corticosteroids at the last review (mean prednisolone dose 5.8 ± 3.5 mg daily). Two patients (nos. 12 and 24) were weaned from corticosteroids 2 years after the start of treatment, and had been followed up without corticosteroids at the time of the last review. An immunosuppressant (azathioprine, cyclosporine A, or mizoribine) was added to the corticosteroids in four patients. Rituximab was used in one patient for frequent relapsing dacryoadenitis.

Table 2 | Characteristics of patients treated with corticosteroids and followed up for over 12 months

	Group A (eGFR before Tx ⩾60, *n* = 14)	Group B (eGFR before Tx <60, *n* = 20)	*P*-value
Age (year)	57.1 ± 15.9	64.4 ± 9.0	0.137
Male (%)	57.1 %	85.0 %	0.116
Follow-up (months)	42.4 ± 17.0	54.5 ± 52.4	0.381
Serum IgG4 before Tx (mg/dl)	1049.5 ± 774.7	969.2 ± 439.9	0.861
Hypocomplementemia (%)	50.0%	72.7 %	0.733
Renal imaging abnormality (%)	85.7 %	65.0 %	0.250
PSL dose (initial) (mg/day)	36.8 ± 13.2	36.0 ± 9.5	0.774
PSL dose (last) (mg/day)	5.5 ± 3.3	6.0 ± 3.7	0.482
eGFR before Tx (ml/min)	83.4 ± 16.0	32.5 ± 16.2	P < 0.0001

Abbreviations: eGFR, estimated glomerular filtration rate; PSL, prednisolone; Tx, corticosteroid treatment.

Changes in eGFR after treatment

Before treatment, eGFR had decreased to <60 ml/min (31.8 ± 16.3 ml/min) in 24 of 40 treated patients (Figure 1), and the renal dysfunction was suggested to be caused by IgG4-TIN on the basis of the findings of renal biopsy. At 1 month after the start of treatment, it was significantly improved (43.5 ± 14.0 ml/min, $P<0.01$), although maintenance hemodialysis became necessary in one patient (no. 42) with renal failure.[15] Among the 34 patients who were treated with corticosteroids and followed up for over 12 months, excluding one hemodialysis patient, the eGFR before treatment was ⩾60 ml/min in 14 patients (group A) and <60 ml/min in 20 patients (group B) (Figure 1). There was no significant difference in baseline characteristics and corticosteroid treatment between the two groups, except for eGFR before therapy (Table 2). Immunosuppressive drugs were added in three patients (nos. 5, 11, and 15) in group A for steroid-dependent extrarenal lesions, and in one patient (no. 33) in group B because of fluctuation in the level of creatinine during maintenance steroid therapy. In group A, there was no difference between the eGFR before therapy and that at 1 month after the start of treatment, 12 months after the start of treatment, and at the last review (84.2 ± 17.0, 82.4 ± 16.1, 83.5 ± 14.0, and 82.9 ± 19.1 ml/min, respectively; Figure 2). In group B, eGFR before treatment (34.1 ± 15.8 ml/min) was significantly improved at 1 month after the start of treatment (45.0 ± 13.8 ml/min, $P<0.01$), and renal function was maintained at a similar level at both 12 months (46.8 ± 12.2 ml/min) and the last review (44.4 ± 11.0 ml/min; Figure 2). Except for one patient in whom maintenance hemodialysis became necessary within 1 month after the start of treatment (no. 42), no patient showed progression to end-stage renal disease during follow-up.

Changes in urinalysis parameters after treatment

Proteinuria and hematuria before treatment were absent or mild ('−' to '+' by qualitative analysis) in 28 of the 40 treated patients (Table 1), and none of them developed apparent proteinuria or hematuria (2+ to 3+ by qualitative analysis) during follow-up. Proteinuria or hematuria was

apparent before therapy in 9 of the 40 treated patients, and most of them had accompanying glomerular lesions. Among eight of nine patients (excluding the hemodialysis patient), protein excretion and hematuria remained unchanged in three (nos. 12, 18, and 40), improved (but persisted) in four (nos. 29, 36, 38, and 43), and disappeared in one (no. 15) at 1 month after the start of therapy, when renal dysfunction, radiological abnormalities, and hypocomplementemia had improved in all patients. In groups A and B, serial urinalysis data were available for five patients. In the patient with membranous glomerulonephritis (no. 29), protein excretion gradually decreased (2.3 g/g cr before treatment, 1.0 g/g cr at 1 month, 0.4 g/g cr at 12 months, and 0.3 g/g cr at the last review) (hematuria was transient because it had been caused by transurethral resection of the prostate for prostatic hypertrophy).[10] In the remaining patients, proteinuria and hematuria were absent or mild at 12 months after the start of treatment and at the last review.

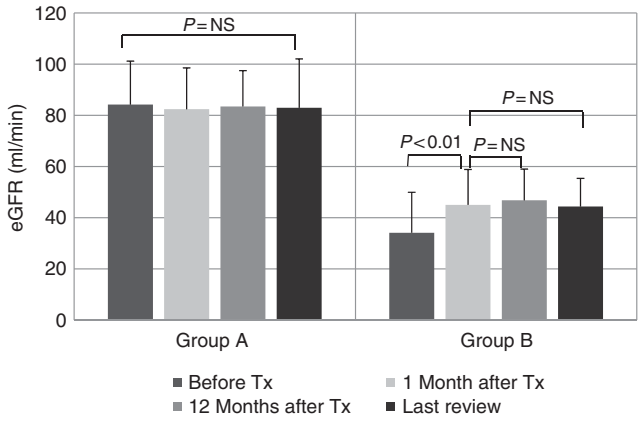

Figure 2 | Response to corticosteroid therapy (Tx) in terms of estimated glomerular filtration rate (GFR). In group A, there was no difference between the estimated GFR (eGFR) before therapy and that at 1 month after the start of treatment, 12 months after the start of treatment, and at the last review (84.2 ± 17.0, 82.4 ± 16.1, 83.5 ± 14.0, and 82.9 ± 19.1 ml/min, respectively). In group B, eGFR before treatment (34.1 ± 15.8 ml/min) was significantly improved at 1 month after the start of treatment (45.0 ± 13.8 ml/min, $P < 0.01$), and renal function was maintained at a similar level at both 12 months (46.8 ± 12.2 ml/min) and the last review (44.4 ± 11.0 ml/min). NS, not significant.

Changes in renal CT findings after treatment

Among the 40 treated patients, renal radiologic features characteristic of IgG4-RKD that had been evident in 29 patients were improved at 1 month after the start of treatment in all of the 18 patients evaluated. Although, on the whole, contrast enhancement of the renal cortex demonstrated resolution of multiple low-density lesions on enhanced CT, scar-like focal cortical atrophy with decreased enhancement was found to have progressed in some patients a few months after the start of treatment.[12] The CT findings at the last review were evaluable for 24 patients (9 (64.3%) of 14 patients in group A and 15 (75.0%) of 20 patients in group B, $P = 0.500$). There was no significant difference in age or follow-up period between the 9 patients in group A and the 15 patients in group B. Although renal atrophy was not evident in any of the patients before treatment, atrophy had developed in 2/9 (22.2%) in group A and 9/15 (60.0%) in group B ($P = 0.084$) at the last review. Among 11 patients diagnosed as having renal atrophy at the last review, 8 showed bilateral focal atrophy (two in group A (nos. 6 and 11) and six in group B (nos. 19, 22, 28, 32, 35, and 36)), and 3 patients in group B (nos. 31, 33, and 41) showed bilateral global atrophy (Figure 3). There was no significant difference in pretreatment eGFR between the group with focal atrophy and the group without atrophy. In three patients who

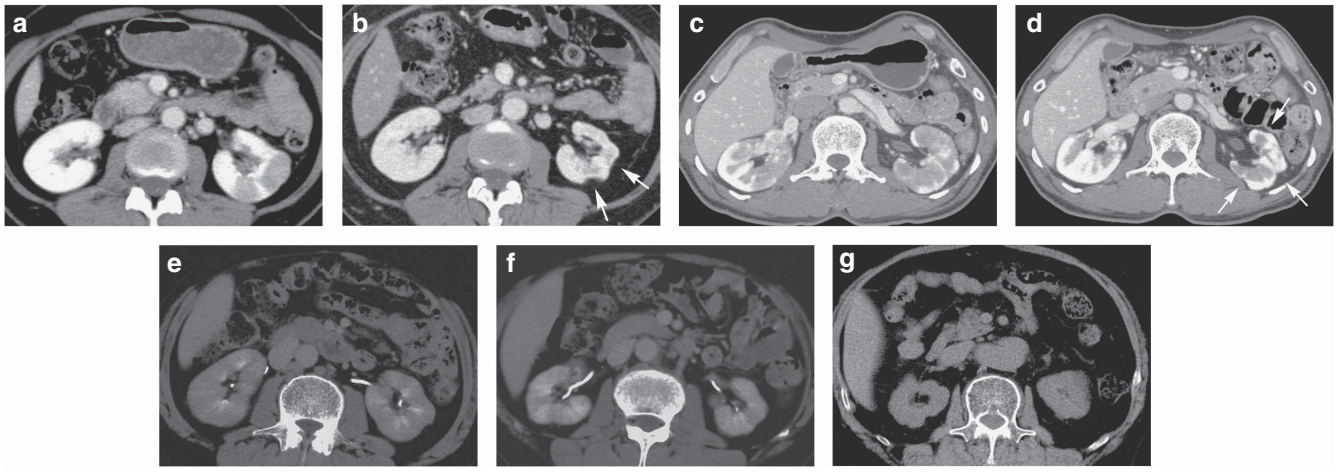

Figure 3 | Changes in computed tomography (CT) findings resulting from corticosteroid therapy. (**a**, **b**) CT findings in patient 6 (in group A) (**a**) before therapy (estimated glomerular filtration rate (eGFR) 81.1 ml/min) and (**b**) at the last review (eGFR 78.9 ml/min), and (**c**, **d**) those in patient 22 (in group B) (**c**) before therapy (eGFR 51.9 ml/min) and (**d**) at the last review (eGFR 63.1 ml/min). In both patients, multiple low-density lesions were evident on enhanced CT before therapy, and focal atrophy (arrows) had developed at the last review. (**e**–**g**) CT findings in patient 31 (in group B). (**e**) Before therapy, bilateral renal swelling with decreased contrast enhancement was observed (eGFR 32.5 ml/min). (**f**) At 1 month after the start of treatment, the bilateral renal swelling had improved, and contrast enhancement of the renal cortex had also ameliorated (eGFR 37.1 ml/min). (**g**) At the last review, bilateral global atrophy was shown by nonenhanced CT (eGFR 45.6 ml/min).

developed global atrophy, eGFR before treatment was <40 ml/min (32.5, 28.6, and 8.9 ml/min, respectively). In the hemodialysis patient (no. 42), CT at the last review demonstrated marked global atrophy of both kidneys.

Changes in serum IgG4 level and hypocomplementemia after treatment

The serum IgG4 level at 1 month after the start of treatment was decreased in all of 16 evaluated patients (842 ± 383 mg/dl before therapy and 325 ± 104 mg/dl at 1 month after treatment, $P<0.01$). Among the patients in groups A and B, data from serial examinations of the serum IgG4 level were available for 28 patients, of whom 13 (46.4%) showed re-elevation of the serum IgG4 level during follow-up. The serum IgG4 level at the last review of the 24 evaluated patients in groups A and B was 62–555 mg/dl (mean 208 ± 140 mg/dl), and it remained elevated (>135 mg/dl) in 17 (70.8%) of these patients. Hypocomplementemia was improved at 1 month after the start of treatment in all but 1 of the 11 patients evaluated. Although the complement level remained improved during follow-up in 11 of the 14 patients evaluated, 3 patients showed a decrease again, and all of them were diagnosed as having IgG4-RD relapse at that time (see section referring to relapse). In patients without hypocomplementemia before treatment, hypocomplementemia did not develop during follow-up.

Outcome of patients without treatment

Among the 43 patients, three were untreated, two patients (nos. 9 and 10) were followed up without treatment, and steroid treatment was avoided in 1 patient (no. 30) because of serious infection. In patient 9, swelling of the submandibular glands, and radiological abnormalities of the pancreas and the kidney had improved spontaneously by 6 months after the diagnosis of IgG4-TIN, and this condition was maintained during follow-up, although the lung lesions fluctuated. The serum IgG4 level was high (850–1050 mg/dl), and the serum CH50 level remained low (9–21 U/ml; normal 30–45 U/ml) during follow-up, despite fluctuation. Although the IgG4-RD status remained unchanged, this patient developed lung and colon cancers at 72 months after the diagnosis of IgG4-TIN, and these ultimately proved fatal. In patient 10, hypertrophy of the renal pelvic wall remained unchanged at 12 months after the diagnosis of IgG4-RKD, but had improved at the last review. The serum IgG4 level also decreased spontaneously (2150 mg/dl at diagnosis, 1160 mg/dl 12 months later, and 667 mg/dl at the last review). Patient 30 died of pneumonia 3 months after the diagnosis of IgG4-TIN.

Relapse of IgG4-RD after treatment

Among the 40 treated patients, 8 (20.0%) were diagnosed as having IgG4-RD relapse. Relapse occurred in the kidney ($n=3$) and also extrarenally ($n=5$: sialadenitis, dacryoadenitis, autoimmune pancreatitis, lymphadenopathy, and retroperitoneal fibrosis in one case each) during maintenance corticosteroid therapy (2.5–15 mg prednisolone daily, median 5 mg) at 12–66 (median 24.5) months after the start of treatment. There were no striking clinicopathological features at the time of diagnosis in the patients with relapse. In six of the eight relapsed patients, the dose of corticosteroids was increased and the increased corticosteroid dose was effective for all of the relapsed lesions. Two patients (one with sialadenitis and one with hypertrophy of the renal pelvic wall) were followed up without any increase in the dose of corticosteroids, and their condition remained unchanged. The levels of serum IgG and/or IgG4 at relapse were higher than those before relapse in six of the relapsed patients. The level of serum complement at relapse was examined in four patients, and a re-decrease was evident in three patients who had shown hypocomplementemia before therapy. In two of these three patients, relapses occurred in the kidney: TIN with infiltration of numerous mononuclear cells demonstrated by renal rebiopsy with re-elevation of the serum IgG4 level (no. 33) and a rapid rise in the serum creatinine level (1.25 to 1.84 mg/dl) with a re-increase of the serum IgG4 level (no. 43). At that time, a re-decrease of the serum CH50 level (38–14 U/ml, normal range 32–47 U/ml) was evident in patient 33, and a re-decrease of the serum C3 level (47 to 16 mg/dl, normal range 60–135 mg/dl) was evident in patient 43. Patient 31 showed re-enlargement of systemic lymph nodes, with a re-decrease of the serum CH50 level (53.9 to 25 IU/ml), although the kidney lesions were unchanged. In all patients, the re-decrease of the complement level improved as the dose of corticosteroids was increased. In one patient without hypocomplementemia before therapy, no decrease in the serum complement level was evident at relapse.

Adverse events after treatment

None of the patients required drug discontinuation because of adverse events. Although development or worsening of diabetes mellitus after corticosteroid therapy occurred in several patients, this was controlled by oral antidiabetic medication or insulin therapy. Avascular necrosis of the femoral head was evident in two patients. Two patients developed infection (diverticulitis in one and unknown origin in one), but were improved by antibiotic treatment. One patient developed steroid-induced psychosis, and one developed a compression fracture of a lumbar vertebra. Two patients were diagnosed as having gastric cancer within 1 month after the diagnosis of IgG4-RKD, and three patients were diagnosed as having cancer at over 12 months after the diagnosis of IgG4-RKD (gastric cancer, pharyngeal cancer, and rectal cancer in one patient each, respectively). Four of these five patients were still alive without relapse at the last review, but the other (no. 26) died of gastric cancer.

DISCUSSION

Responsiveness to corticosteroid therapy is a characteristic feature of IgG4-RD and consistently leads to improvement of most lesions, at least in the short term.[1,3,5–9,12,16,17] Type 1

autoimmune pancreatitis, the pancreatic manifestation of IgG4-RD, is the first recognized form of organ involvement,[18] and the long-term outcome of IgG4-RD has been most extensively examined in terms of the pancreatic lesions. Kamisawa *et al.*[19] retrospectively examined the outcome of 563 patients with autoimmune pancreatitis in Japan. In that study, the remission rate in steroid-treated patients (98%) was significantly higher than that in patients without steroid treatment (74%). The relapse rate in patients receiving steroid maintenance therapy (23%) was significantly lower than that in patients who stopped maintenance treatment (34%), and steroid re-treatment was effective in 97% of those who relapsed. Because tumefactive or hyperplastic lesions are characteristic, and many of the symptoms are caused by such morphologic changes in the affected organ, the effectiveness of corticosteroids in IgG4-RD is usually recorded in terms of the radiologic resolution and disappearance of clinical symptoms.[19,20] Chari and Murray[20] reported that remission (and also relapse) of IgG4-RD could refer to symptoms, serology, radiologic changes, or histology. On the other hand, treatment response and relapse in patients with renal disease is usually estimated in terms of improvement in renal function or urinary abnormalities.[21]

In IgG4-TIN, similar to autoimmune pancreatitis, a rapid response to steroid has been demonstrated.[5–9,12] In our earlier study, decreased renal function, hypocomplementemia, or abnormal renal radiologic findings were rapidly improved at 1 month after the start of corticosteroid therapy in 18 (94.7%) of 19 patients with IgG4-TIN.[5] The Japanese standard steroid treatment for autoimmune pancreatitis[22] involves oral administration of prednisolone (0.6 mg/kg/day) as induction therapy for 2–4 weeks, and then the dose is gradually tapered to a maintenance dose of 2.5–5 mg/day over a period of 2–3 months. Maintenance therapy with low-dose prednisolone is recommended to prevent relapse, but withdrawal of maintenance therapy within at least 3 years is also recommended for patients showing radiological and serological improvement. In the present retrospective study of IgG4-RKD, in which most of the renal dysfunction and renal parenchymal radiological abnormalities are responsible for IgG4-TIN, the induction regimen was similar to that for autoimmune pancreatitis, although the initial prednisolone dose varied somewhat in each case, and low-dose corticosteroid therapy had been maintained in most of the patients at the last review. Under these conditions, steroid therapy elicited rapid, but not total, improvement of renal function in patients whose eGFR had been <60 ml/min before therapy, and this effect persisted for a relatively long period. On the other hand, CT at the last review demonstrated that renal atrophy had developed in a considerable proportion of the patients, especially those in whom advanced renal damage had already been evident before therapy (22.2% in group A and 62.5% in group B, although the difference was not statistically significant). These results suggested that, although the response of IgG4-TIN to corticosteroids is certainly rapid, recovery may not be total and irreversible lesions may remain, especially in patients with advanced renal damage. In a study involving re-renal biopsy after treatment, Mizushima *et al.*[12] showed that regional fibrosis developed in the renal interstitium, even though the area of cell infiltration decreased, and suggested that these histologically evident fibrotic lesions might correspond to the focal atrophic lesions demonstrated by imaging. Accordingly, early treatment of IgG4-TIN appears to be necessary.

Spontaneous improvement or remission has been documented in IgG4-RD.[17] Indeed, in two of the present study patients, renal radiological abnormalities resolved spontaneously without renal dysfunction, suggesting that spontaneous improvement of radiologic parameters can also occur in IgG4-RKD. However, renal function did not recover completely in patients with advanced renal damage. Although the indications for corticosteroid therapy in IgG4-RKD have not been established, patients with renal dysfunction should receive it, and careful attention should be paid to renal function during follow-up without therapy.

In IgG4-RD, disease relapse is common and can occur in various organs irrespective of the clinical form evident at the first visit.[16,17,19,20,23] In this study, relapses occurred in 8 (20%) of 40 treated patients with IgG4-RKD including kidney lesions, similar to those in patients with autoimmune pancreatitis receiving maintenance treatment.[19] In autoimmune pancreatitis, withdrawal of maintenance therapy within at least 3 years is recommended for patients in remission to prevent steroid-related complications.[22] However, as relapse of renal disease probably leads to deterioration of renal function, which may irreversibly progress to end-stage renal disease, withdrawal of maintenance therapy for IgG4-TIN should be considered very carefully. In this study, renal atrophy had developed in a significant number of patients at the last review and relapse occurred in 20% of treated patients, suggesting that maintenance corticosteroid therapy under the present system may still be insufficient for treatment of IgG4-TIN. A large-scale prospective study is necessary to determine a more useful treatment strategy for IgG4-TIN, including a review of the need for maintenance corticosteroid therapy. Interestingly, a re-decrease of the serum complement level in three patients who had shown hypocomplementemia before therapy was associated with IgG4-RD relapse in all of them, suggesting that such a re-decrease of the serum complement level may be useful for prediction of relapse in IgG4-TIN patients. Kawa *et al.*[24] demonstrated that immune complexes appeared to be a useful marker of relapse of autoimmune pancreatitis. In IgG4-TIN, the frequency of hypocomplementemia is high and immune-complex deposition is a significant feature of renal histology.[5,6,25] Although the pathogenesis of immune-complex formation in IgG4-RD has not been elucidated,[3] changes in complement levels should be followed up carefully in patients with IgG4-TIN.

In contrast to the uniform rapid response in terms of renal function, radiology, and serology, the response in terms of

urinalysis parameters after therapy seemed to vary. In IgG4-RKD, TIN is the most common feature, and certain common pathologic features are shared between IgG4-TIN and extrarenal organs affected by IgG4-RD.[5,26] However, urinary abnormalities were usually associated with glomerular lesions, and the relationship between glomerular lesions and IgG4-RD has not been elucidated. Membranous glomerulonephritis is the most commonly observed glomerular lesion in IgG4-RKD and is thought to be associated with IgG4-RD.[9–11] However, even in membranous glomerulonephritis, the response of proteinuria to corticosteroid therapy varies from rapid[27] to gradual (patient 29 in this study), or almost none.[28] Changes in urinalysis parameters may not reflect the disease activity of IgG4-RKD precisely, and their significance should be considered carefully.

In patients with IgG4-RD, the risk of malignancies has been discussed.[16,29] In the present series of 43 patients with IgG4-RKD, 4 had a history of malignancy, and 7 malignancies were diagnosed in 6 patients after the diagnosis of IgG4-RKD; 2 patients died of their malignancies. Careful examination and long-term follow-up of IgG4-RKD patients for complications or the development of malignancies is therefore required.

In conclusion, IgG4-RKD shows rapid, but not total, improvement with corticosteroid therapy, and the recovery of renal function persists for a relatively long period under low-dose maintenance. However, a large-scale prospective study to formulate a more useful treatment strategy will be necessary.

MATERIALS AND METHODS

Patients

Among patients with suspected IgG4-RD seen at Nagaoka Red Cross Hospital, Kanazawa University Hospital, Sapporo Medical University Hospital, Niigata University Hospital, and Fukuoka University Hospital between January 2004 and March 2012, we identified 43 patients as having definite IgG4-RKD according to the published diagnostic criteria.[7] All of these patients showed elevation of the serum IgG4 level (>135 mg/dl). Renal pathology data were available for 30 patients, and all of them had the tubulointerstitial features characteristic of IgG4-RKD: dense lymphoplasmacytic infiltration with >10 infiltrating IgG4-positive plasma cells per high-power field and/or a IgG4 + /IgG + plasma cell ratio of $>40\%$ with fibrosis. In the other 13 patients, the diagnosis of IgG4-RKD was based on both the renal radiologic findings characteristic of IgG4-RKD (multiple low-density lesions on enhanced CT, diffuse kidney enlargement, a hypovascular solitary mass in the kidney, or a hypertrophic lesion in the renal pelvic wall without irregularity of the renal pelvic surface) and histologic findings in extrarenal organ(s) that were equivalent to those described above for the kidney. Among the 43 patients, 39 patients had been included in our earlier study (nos. 4, 9, 15, 17, 19, 22, 26, 28, 29, 31, 34, 38, 39, 41–43 were described in ref. 5).[5,7,10,12–15,30] Four of the 43 patients had been followed up for primary Sjögren's syndrome before 2004. The diagnosis of extrarenal lesions was made on the basis of physical findings and the results of imaging studies (CT and gallium citrate scintigraphy) and/or biopsy, in addition to exclusion of other diseases. Diagnosis of autoimmune pancreatitis was made in accordance with the 2006 Japan Pancreas Society revised criteria.[31] We retrospectively examined the treatment, renal function, urinalysis, and serological data, as well as renal CT findings, before therapy, 1 month after the start of treatment, 12 months after the start of treatment, at the last review, and at relapse. We also examined malignancies and adverse events during the treatment.

The study was approved by the review board of Nagaoka Red Cross Hospital and the boards of the collaborating institutions. All data and samples from patients were collected with their informed consent, and the study was conducted in compliance with the Declaration of Helsinki Principles.

Renal imaging and definition of renal atrophy

Whole-body CT imaging was evaluated in all patients before treatment, and follow-up CT data were available for 30 patients. The renal CT findings at the time of diagnosis of IgG4-RKD, changes during follow-up, and the presence of renal atrophy were based on information supplied by experienced radiologists at each of the institutions. Renal atrophy was classified as either focal or global.[32] Global renal atrophy was defined as an apparent reduction in renal length judged by each radiologist in consideration of the age and physique of each patient, and not simply as a decline in renal size before treatment. Focal renal atrophy was defined as loss of renal parenchyma with no apparent reduction in renal length. The renal length was measured on the long axis of the kidney on a CT workstation.

Definition of improvement and relapse

For extrarenal lesions, improvement of the organ involvement was decided according to changes in symptomatic, radiologic, serologic, or histologic features.[20] In IgG4-RKD, improvement of renal function (in terms of serum creatinine level or eGFR) was also considered.[21] Relapse of extrarenal lesions was decided on the basis of reappearance or worsening of symptomatic, radiologic, serologic, or histologic features.[20] In IgG4-TIN, a rapid rise in the serum creatinine level, after careful exclusion of other renal diseases, was also considered as relapse.[21] Re-elevation of the serum level of IgG or IgG4 alone was not considered to be relapse.[19] Because the relationship between IgG4-RD and glomerular lesions has not been fully clarified, and cases in which the glomerular lesion is the sole kidney lesion (without TIN) are not included in IgG4-RKD,[11] worsening of urinalysis parameters alone was not considered to be relapse of IgG4-RKD.

Statistics

Statistical analysis was performed using the paired Student's *t*-test, Wilcoxon signed rank test, Mann–Whitney *U*-test, and Fisher's exact probability test as appropriate. Data are presented as means ± s.d. A probability of $P<0.05$ was considered to indicate statistical significance.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This work was supported in part by grants from Health and Labour Sciences Research Grants for the Study of Intractable Disease from Ministry of Health, Labor and Welfare, Japan and 'IgG4-related Kidney Disease' working group of the Japanese Society of Nephrology.

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