Risk factors of relapse following glucocorticoid tapering in IgG4-related disease

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ASBTRACT

Objective. *To identify risk factors of relapse in IgG4-related disease (IgG4-RD) during glucocorticoid (GC) tapering.*

Methods. *A total of 27 consecutive patients with IgG4-RD (7 with and 20 without relapse) treated with GC for more than 6 months were enrolled. Baseline characteristics were compared in patients with and without relapse. Longitudinal analysis was also performed.*

Results. *Patients with relapse had significantly higher levels of serum IgG4 (816.0 vs. 346.5 mg/dL, p=0.048) and number of organs involved (5 vs. 3, p=0.008) and lower levels of serum IgA (82 vs. 176 mg/dL, p=0.002) at baseline, compared to patients without relapse. The most useful cut-off value of baseline serum IgG4 to predictive relapse was 813 mg/dl with a sensitivity of 57.1% and a specificity of 95.0%. In longitudinal analysis, serum IgG4 decreased at 6 months after treatment in both groups, but was elevated at relapse in patients with relapse, while remaining low in those without relapse.*

Conclusion. *Higher levels of serum IgG4 at baseline were associated with relapse in IgG4-RD. Re-elevation of serum IgG4 levels during GC treatment reflected disease relapse.*

Introduction

IgG4-related disease (IgG4-RD) is a novel fibro-inflammatory systemic disease characterised by elevation of serum IgG4 levels and infiltration of $IgG4^+$ plasma cells into various affected organs (1, 2). A good initial response to glucocorticoid (GC) is one of the characteristics of IgG4-RD (3, 4) and it was proposed by some authors as a potential diagnostic criteria (2, 5). Despite the effectiveness of GC as induction therapy, one-third of IgG4-RD patients experience relapse during GC tapering (3, 4). However, little is known about the characteristics of relapse. The aim of this study was to clarify clinical and laboratory characteristics of relapse and identify predictors for IgG4-RD relapse.

Materials and methods

Patient inclusion

This study was approved by the ethics committee of our institution. Written informed consent was waived in accordance with regulations in Japan. All investigations were conducted according to the principles of the Declaration of Helsinki. Consecutive IgG4-RD patients who visited our Rheumatology Department between January 2000 and February 2017 were retrospectively reviewed. We included patients (i) who met the comprehensive diagnostic criteria for IgG4-RD (2), (ii) who did not receive any treatment at diagnosis, (iii) who received GC as induction therapy and were followed more than 6 months, (iv) who achieved disease response, which was a decline of IgG4-RD responder index (IgG4-RD RI) by ≥2 points after GC treatment (6). We defined complete response as IgG4-RD RI <3 and partial response as IgG4-RD RI ≥3 after the treatment (6). Patients were observed from GC initiation to disease relapse or to the last visit in those without relapse. Relapse was defined by a new lesion or return of abnormal findings on physical examination, laboratory test or imaging study. Isolated elevation of IgG4 did not include relapse (7). Patients were divided according to relapse or non-relapse in the analysis.

Data collection

Clinical information collected at initiation of GC treatment (baseline) included age, sex, body weight, follow up period, relapse duration, atopic history, distribution of organ involvement, laboratory findings, and treatment regimen from medical records. Organ involvement was assessed via physical examinations and systemic radiologic examinations, including

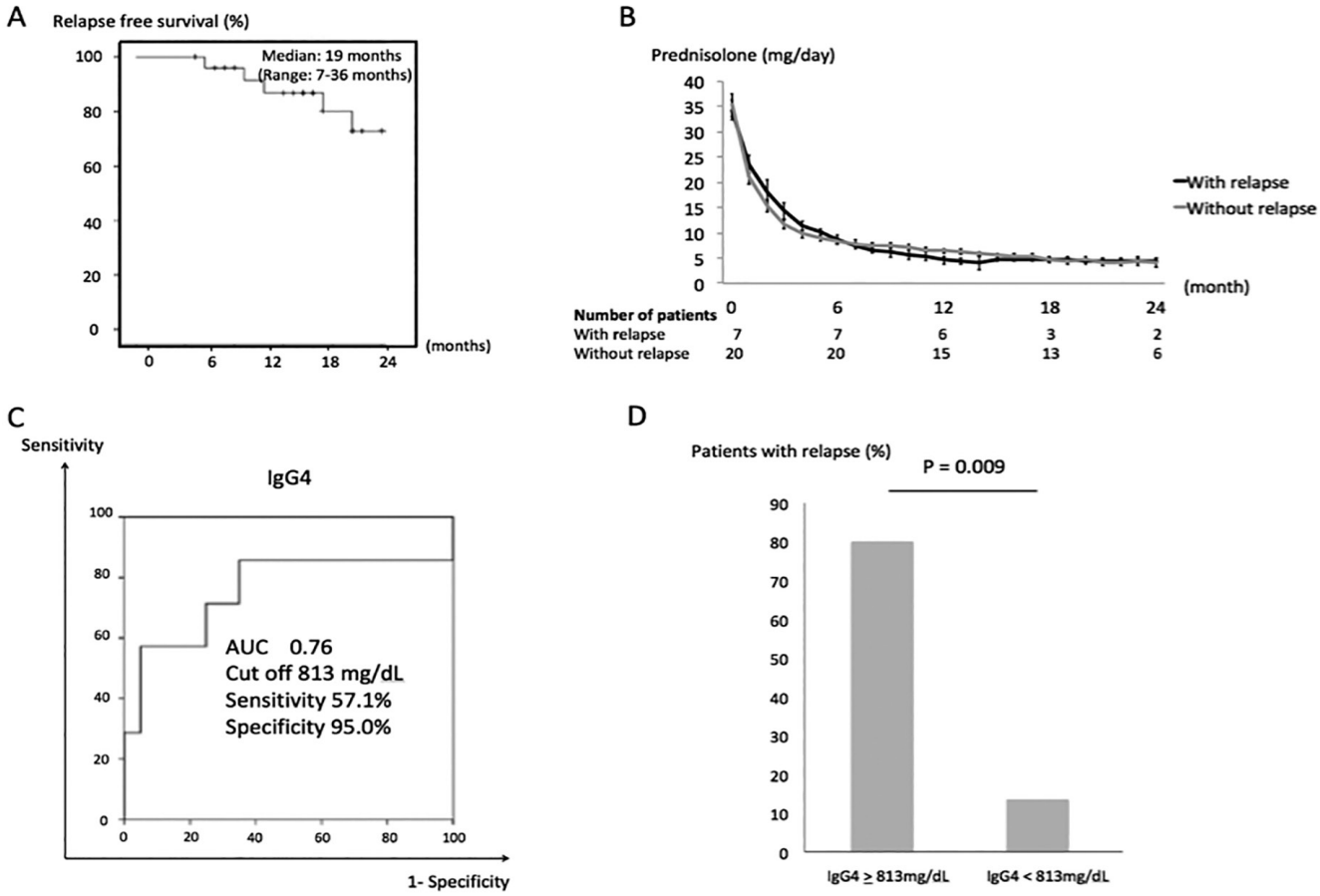

Fig. 1. (**A**) Kaplan-Meier curve for relapse-free survival through 24 months. (**B**) Comparison of time course of glucocorticoid dose between patients with and without relapse. (**C**) Receiver operating characteristic curve analysis of serum IgG4 level. (**D**) Comparison of occurrence of relapse between high IgG4 level group and low IgG4 level group.

computed tomography (CT), magnetic resonance imaging, and/or fluoro-D-glucose positron emission tomography. The involvement of lymph nodes was defined as abnormal lymphadenopathy by whole body CT, which was clinically distinguished from other causal diseases. Atopic history was defined as having allergic rhinitis, asthma, and/or atopic dermatitis. Disease duration was the time from the first symptom to the diagnosis. Longitudinal data of serum IgG4 were also collected at every 3 months until the time of the relapse or last observation.

Statistical analysis

Continuous variables were described as median (range), and categorical variables were described as numbers and percentages. Time course of glucocorticoid dose were expressed as mean ± standard error (SE). Statistical differences for continuous variables were assessed using appropriate non-parametric tests. Categorical variables were analysed using Fisher's exact test. The predictive ability of IgG4 for relapse and cut-off values were calculated with a receiver operating characteristic (ROC) curve. Longitudinal data were analysed using Wilcoxon's signed rank test. $P<0.05$ (two-sided) was considered significant. SPSS v. 23.0 (IBM, Armonk, NY, USA) was used for all statistical analysis.

Results

Patient inclusion

Sixty-one patients with IgG4-RD were identified. Nine patients with an follow up period of 6 months or less, nine with no medication during observation, 11 with treatment at diagnosis, 4 with receiving immunosuppressants other than GC and 1 whose IgG4-RD RI was not assessed after the treatment were excluded, resulting in 27 IgG4-RD patients enrolled in the present analysis. Among them, 7 patients (25.9%) experienced relapse during GC tapering. In both groups, most of the patients met definite diagnosis in comprehensive diagnostic criteria (Supplementary table I). All relapses showed re-enlargement of involved organs (Supplementary Table II). Median time of relapse was 19 months (range: 7–36), as shown in Figure 1A.

Patient demographics and clinical data

Table I shows clinical characteristics of the relapse and non-relapse groups. No difference was found in age, sex, body weight, treatment response, follow up periods, disease duration, initial prednisolone dose and frequency of atopic history between the two groups. The relapse group showed significantly higher levels of serum IgG4 at treatment initiation (816.0 vs. 346.5 mg/dL, p=0.048), number of organs involved (5 *vs*. 3, p=0.008), and lower levels of serum IgA (*82 vs*. 176 mg/dL, p=0.002), compared to the non-relapse group.

The statistically significant difference of number of organs involved was also observed when excluding lymphonodal involvements (Supplementary Table III). Other laboratory findings were not statistically different between the two groups. GCs were tapered at comparable rates (Fig. 1B). Supplementary table IV shows initial and re-induction treatment in patients with relapse. In all cases, the size of relapsed organs decreased again by the re-induction treatment.

Utility of IgG4 for predicting relapse

As the level of IgG4 was higher in relapse group, we investigated utility of IgG4 for predicting relapse. The optimal cut-off values of IgG4, and its area under the curve, sensitivity and specificity were 813 mg/dl, 0.76, 57.1%, and 95.0%, respectively (Fig. 1C). Patients with IgG4 ≥813 mg/dl relapsed approximately six times more frequently than patients with IgG4 <813 mg/dl (80.0% *vs*. 13.6%, p=0.009, Fig. 1D).

Supplementary figure 1 shows the chronological changes in the levels of serum IgG4 until the time of relapse or last observation in patients whose IgG4 levels were followed at every 3 months. Initial treatment decreased serum IgG4 levels in both groups, however, after 3–6 months of initial treatment, the serum IgG4 levels in the patients with relapse gradually increased while those in the patients without relapse did not. Serum IgG4 at the time of relapse in the relapse group was significantly higher than at 6 months (254.6 *vs*. 178.2 mg/dL, p=0.043). The IgG4 levels in the non-relapse group remained at the same level throughout the observation.

Table I. Characteristics of the patients with relapse and those without.

Clinical characteristics	Relapse (n=7)	Non-relapse (n=20)	p-value
At treatment initiation			
Demographics and initial treatment			
Age (years)	61 (37-75)	61 (36-79)	0.725
Male : female ratio	3:4 9: 11	1.000	
Body weight (kg)	58.0 (48.0-70.0)	58.5 (42.0-90.0)	0.978
Disease duration (month)	13 (3-97)	11 (1-288)	0.431
Atopic history (%) (n)	85.7 (6)	85.0 (17)	1.000
Initial prednisolone dose (mg/day)	30 (30-40)	30 (25-60)	0.725
Baseline IgG4-RD RI	18 (9-21)	12 (6-21)	0.081
Organ involvement (%) (n)			
Number of organ involvements	5 (3-6)	3 (1-6)	0.008*
Multi-organ (≥3 organs)	100.0 (7)	60.0 (12)	0.057
Pachymeninges	14.3 (1)	0 (0)	0.286
Orbits and lacrimal glands	85.7 (6)	80.0 (16)	1.000
Salivary glands	85.7 (6)	75.0 (15)	1.000
Lymph nodes	71.4 (5)	30.0 (6)	0.084
Lungs	71.4 (5)	25.0 (5)	0.065
Aorta and large blood vessels	14.3 (1)	5.0 (1)	0.459
Retroperitoneum	28.6 (2)	10.0 (2)	0.269
Pancreas	28.6 (2)	30.0 (6)	1.000
Bile duct and liver	0.0 (0)	5.0 (1)	1.000
Kidney	42.9 (3)	45.0 (9)	1.000
Skin	0 (0)	10.0 (2)	1.000
Laboratory findings			
WBC (cells/μL)	6100 (3700-10000)	5900 (4200-8500)	0.498
Hb (g/dL)	13.8 (11.4-16.2)	13.8 (9.7-16.8)	0.978
Plt ($\times 10^4$/μL)	27.6 (15.3-45.6)	24.3 (14.2-35.3)	0.725
Eosinophil (cell/μL)	372.7 (92.4-1425.0)	204.0 (50.0-1567.7)	0.179
IgG (mg/dL)	1920 (1305-4431)	1675 (1077-3031)	0.130
IgA (mg/dL)	82 (71.0-164.0)	176.0 (121.0-331.0)	0.002*
IgM (mg/dL)	44.0 (27.0-173.0)	83.5 (29.0-188.0)	0.179
IgE (IU/mL) [A]	480.0 (210.0-610.0)	230.0 (38.0-2700.0) (n=15)	0.266
IgG4 (mg/dL)	816.0 (65.0-2110.0)	346.5 (172.0-904.0)	0.048*
CH50 (U/mL)	50.2 (30.2-55.7)	54.3 (14.4-60.0)	0.219
CRP (mg/dL)	0.04 (0.02-0.30)	0.07 (0.01-2.61)	0.862
Treatment response			
Complete response	71.4 (5)	90.0 (18)	
Partial response	28.6 (2)	10.0 (2)	0.269
At relapse or last observation			
Follow up period (month)	19 (7-36)	18 (7-112)	0.935
PSL dose	5 (0-9)	5 (0-10)	0.725
Discontinuation of PSL (%) (n)	28.6 (2)	5.0 (1)	0.156
Duration of receiving PSL (month)	19 (7-32)	18 (7-112)	0.978

WBC: white blood cell; Hb: haemoglobin; Plt: platelet; CRP: C-reactive protein; PSL: prednisolone. A: Available patient numbers. Eelapse: 5; Non-relapse:15.

Discussion

In this study, we found that patients with higher baseline levels of serum IgG4 had a higher risk of relapse during tapering of GC. The large number of affected organs, and low levels of serum IgA at baseline were also characteristics for patients with relapse. The re-elevation of serum IgG4 reflected disease relapse.

A few studies reported that lower levels of serum IgG (8), a greater number of organs involved (10), and higher levels of serum IgG4, IgE, and blood eosinophils (7) were predictive factors for relapse during GC and rituximab treatment. Our study also found that lower levels of serum IgA at baseline as well as higher levels of serum IgG4 were distinctive features of IgG4-RD with relapse. These findings suggest that greater skewing toward IgG4 class-switching is associated with disease relapse. In addition, we demonstrated for the first time that not only baseline levels of serum IgG4 but also re-elevation were associated with disease relapse. Previously, Carruthers *et al*. revealed that the levels of IgG4 in multiorgan patients were significantly higher than those in single-organ patients. In this context, we believe that the level of IgG4 is useful for predicting the number of organ involvements during treatment as well as those at baseline. However, our results might be influenced by the patient characteristics unique to Japanese population. Yamada *et al*. recently reported that the rates of patients with IgG4 elevation, single-organ and relapse were different between Japanese and Western populations (11). This

should be further validated in the future. We previously reported the role of follicular helper T cells in the disease process of IgG4-RD, particularly in IgG4 class-switching and plasmablast differentiation (12, 13). The elevation of circulating activated follicular helper T cells and plasmablasts coincided with disease relapse (12, 14), suggesting that these lymphocytes can be useful as a biomarker for relapse. However, the frequent measurement of these lymphocytes is not feasible; therefore, serum IgG4 levels are useful in daily clinical practice.

Recognising the characteristics of IgG4-RD patients who are inclined to relapse is essential for determining an appropriate treatment approach. The Japanese consensus guidelines for IgG4-related pancreatitis recommend that after induction therapy using a moderate dose, prednisolone should be tapered to 2.5-5 mg/day (15). Although all IgG4-RD patients in our study received recommended dose of GC for induction and maintenance, one-fourth experienced disease relapse. Our study suggests that patients with baseline serum IgG4 levels ≥813mg/dL, who are inclined to relapse during GCs tapering, may need more intensive induction therapy.

Our study has a number of limitations. First, there could be a diagnostic bias in this study. For example, the timing of follow-up imaging evaluation depended on the clinician's judgement which might be influenced by the IgG4 levels. Second, the number of patients was relatively small because of the rarity of this disease. To validate the results, a larger prospective cohort study is needed.

In conclusion, a greater number of organs involved, higher levels of serum IgG4, and lower levels of serum IgA at baseline were risk factors for disease relapse. Re-elevation of serum IgG4 levels during GC tapering can be associated with disease relapse in IgG4-RD.

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Competing interests

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