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ORIGINAL ARTICLE

Steroid therapy still plays a crucial role and could serve as a bridge to the next promising treatments in patients with IgG4-related sclerosing cholangitis: Results of a Japanese nationwide study

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Abstract

Objective: The acceptable duration of steroid therapy for patients with IgG4-sclerosing cholangitis (SC) has been under debate. Our aim is to clarify the feasible duration of steroid treatment.

Design: We retrospectively reviewed the data of patients with IgG4-SC and analyzed the following: biliary status during the steroid therapy, incidence of remission, relapse, relapse-free survival rate, and steroid-related complications (SRCs).

Results: Remission was achieved in 99.5% (763/767) of patients who received steroid therapy, while the remission rate dropped to 63.6% (78/129) of patients who did not receive it. Relapse was noted in 19.7% (151/763) of the patients who received steroid. Besides, relapse rate went up 38.4% (30/78) of the counterpart. Normalization of the serum total bilirubin and serum alkaline phosphatase levels were achieved at 2 weeks regardless of biliary drainage. Multivariate analysis identified younger onset, MST less than 3 years, immunosuppressant, and steroid cessation as independent risk factors for relapse. Steroid-free was achieved in the patients underwent MST only 3.4% over 54 months. SRCs were recorded in a total of 99 patients (12.9%) despite sufficient preemptive medications. Multivariate analysis identified history of malignancy and immunosuppressant as independent risk factors for SRCs.

Conclusion: Steroid therapy should be continued for no <3 years to reduce the risk of relapse, with use of preemptive measures taken around 5 years. The biliary drainage might not be mandatory. Steroid as 1st line therapy could serve as a bridge to further promising treatments.

†Collaborators are given in the Appendix.

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1 | INTRODUCTION

IgG4-related diseases (RDs), such as autoimmune pancreatitis (AIP), have been treated by steroid monotherapy, including maintenance steroid therapy (MST).[1] Japanese researchers have indicated that MST could reduce the risk of relapse for a certain period.[2] The therapeutic strategy adopted for IgG4-related sclerosing cholangitis (IgG4-SC) is the same as that for AIP, because IgG4-SC is closely related to AIP.[3] However, there are yet no sufficient data based on multicenter studies to support this treatment strategy for patients with IgG4-SC. Additionally, the acceptable duration of steroid treatment, used as monotherapy, in patients with IgG4-SC remains unknown. The usefulness of repeat steroid treatment for patients with relapse also remains unknown. Steroid treatment is potent and effective to ameliorate the symptoms in patients with IgG4-RDs, but it does not serve as curative treatment for the disease.[4] Furthermore, adverse effects of steroids (AEs) are also a matter of concern.[5] Physicians in Europe and US hesitate to use MST for patients with IgG4-RDs,[6] owing to the concern that AEs of long-term steroid therapy may outweigh its therapeutic benefits, whereas MST is routinely administered to patients with IgG4-RDs in Japan.[7] The usefulness of biliary stent placement for patients with IgG4-SC has also been a controversial issue.[5,7,8] Under these circumstances, immunosuppressant drug use has been tried to enhance the effect of steroid treatment, while decreasing the steroid burden.[9] IgG4-bearing cell-depletion therapy has also been tried to achieve complete remission of IgG4-RDs.[9] Both therapies are promising. We conducted a Japanese nationwide survey of many patients with IgG4-SC who received steroid therapy alone,[10,11] to clarify the clinical profile of IgG4-SC, including the risks of relapse and AEs, the usefulness of MST, and the limitations of steroid therapy as monotherapy. The possibility of patients becoming steroid-free after MST was also evaluated. It would be time for us to rethink the roles and limitations of steroid treatment in patients with IgG4-SC, if there was no sufficient evidence of patients eventually becoming steroid-free. Our goal is to reveal the optimal duration of steroid treatment as 1st line. Consequently, we can deliver better treatment using steroids for patients with IgG4-SC based on rational evidence.

2 | METHODS

Firstly, we validate the effect of steroid treatment and the clinical course by comparing patients who received steroid treatment and patients who did not receive steroid treatment. Then, the feasible duration of steroid treatment is studied.

2.1 | Study population

A nationwide, hospital-based epidemiological survey was conducted according to the Nationwide Epidemiological Survey Manual issued by the Research Committee on the Epidemiology of the Intractable Diseases in 2019, to estimate the prevalence of IgG4-SC, and a total of 1096 cases were identified. Apart from clarifying the epidemiological features[10] and imaging features,[11] we investigated the therapeutic strategies adopted based on the same database. Out of the 1096 patients, 767 patients who had received steroid monotherapy, 52 patients who had undergone drainage without steroid treatment and 77 patients with wait and watch were enrolled in the present study, after excluding patients who had undergone surgical resection and patients with missing data, including data on the treatment outcome and follow-up period. As a result, 896 patients with IgG4-SC were studied (Figure S1). There were 24 patients who underwent surgical resection based on misdiagnosis as cancer. The rate of this misdiagnosis as biliary and/or pancreatic head cancer indicated 2.6% (24/920). The objective patients were collected from 150 institutes across Japan. The study was conducted with the approval of the Ethics Committee of Teikyo University (#18-237).

2.2 | Patient characteristics

The serological data, presence/absence of excessive alcohol consumption, presence/absence of underlying diabetes mellitus, presence/absence of a history of malignancy, presence/absence of AIP, including the type of AIP, presence/absence of proximal-type IgG4-SC (hilar

type, such as types 2,3,4), and presence/absence of other organ involvement (OOI) were reviewed. The patients who received steroid treatment were stratified into three groups depending on the initial steroid dose[12] (<0.39, 0.4-0.69, and >0.7 mg/kg), and the duration of steroid therapy, total dose of steroid used, and presence/absence of relapse were also recorded.

2.3 | Diagnosis and classification of IgG4-SC

Diagnosis of IgG4-SC was made according to the diagnostic criteria proposed in 2012.[13] In 2009, Nakazawa et al.[14] classified patients with IgG4-SC into four types according to the stricture regions identified on cholangiography. Consequently, our subject population included patients with types 1-4 and unclassified type IgG4-SC. Unclassified type was regarded as type IV.[7] Definitive and/or probable diagnosis of IgG4-SC[13] was adopted in this study.

2.4 | Steroid administration

Most patients with IgG4-SC were initiated on treatment with oral prednisolone as monotherapy at the dose of 0.6 mg/kg/day after the diagnosis, because immunosuppressant other than steroid and rituximab (RTX) used were not yet covered by government insurance in Japan.[7] Regarding steroid therapy, prednisolone was mainly used, while methylprednisolone was adopted as steroid pulse treatment. Under the steroid pulse therapy, this dose converted to prednisolone dose for calculation (prednisolone 5 mg = methylprednisolone 4 mg). A higher steroid dose tended to be selected in some patients with severe disease.[2] After the initial steroid treatment, most of the patients received MST with prednisolone at the dose of 5-10 mg/day for an additional 3 years or so, to prevent relapse.[7] Along with the steroid therapy, the patients also received a bisphosphonate or active vitamin D preparation as prophylaxis against osteoporosis-related fractures.[7,15] Insulin was often administered to patients with deteriorated intolerance to glucose.[7] Biliary drainage, usually endoscopic drainage, was also performed at the discretion of the physician.[7] Thus, there were biases in terms of the indication for biliary stent placement in this study.

2.5 | Biliary improvement

The appropriateness of biliary stent placement for biliary drainage in patients with IgG4-SC also remains a controversial issue.[7,15] The effect of treatment in patients with IgG4-SC was evaluated based on both a 50% <improvement of the serum data and 50% <improvement of the bile duct abnormalities on cholangiography within 2 weeks after completion of the initial treatment, which indicated remission. Recovery was defined as normalization of the serum total bilirubin (TB) levels, serum alkaline phosphatase (ALP) levels and reversal of the bile duct abnormalities on imaging within 2 weeks after completion of the initial treatment. Normalization, namely, improvement of the serum TB levels, serum ALP levels and cholangiographic abnormalities at 2 weeks, 4 months and 1 year after completion of the initial treatment was investigated. The data remained abnormal at 4 months and 1 year after the treatment were studied since these variables were considered as a risk factor for relapse. The outcomes in the patient groups that received steroid treatment alone and steroid treatment plus biliary stenting were analyzed.

2.6 | Definition of relapse, prognosis, and follow-up information

Relapse of IgG4-SC was defined as a reappearance of symptoms after remission, with new development and/or aggravation of the biliary duct strictures, and/or OOI, appearance of new abnormalities on imaging, and/or elevation of the serum IgG4 levels.[7] Biliary type relapse was defined as relapse recognized in the biliary tree with/without OOI. Pancreatic type relapse was defined as relapse noted only in the pancreas with/without OOI. OOI type relapse was defined as relapse occurred in OOI without pancreato-biliary involvement.

Recurrent elevation of the serum IgG4 levels alone without symptoms or new appearance/worsening of biliary duct strictures was not considered as relapse.[7] The relapse-free survival (RFS) rates in patients with IgG4-SC who received steroid monotherapy was estimated by the Kaplan-Meier method.

2.7 | Steroid dosing period

Since steroid therapy is the standard treatment strategy for AIP,[2] a validation study to determine the usefulness of MST[16] for IgG4-SC was conducted. MST was defined as the prolongation of steroid therapy to more than 6 months after the initiation of steroid treatment. The steroid dosing period and proportions of patients who received steroid treatment for over 3 years, for 2-3 years, for 1-2 years, and for <1 year were compared.

2.8 | Speed of tapering of the initial dose of glucocorticoid

Rapid tapering of the initial dose of steroid is considered as a risk factor for relapse,[17] and the outcomes in patients in whom the dose began to be tapered after 2 weeks and 4 months after the start of steroid therapy were compared.

2.9 | Risk factors for relapse

Groups with/without relapse were compared based on age, gender, excess alcohol consumption, presence of malignancy, serological data (TB levels, ALP levels, IgG levels and IgG4 levels), presence of AIP, presence of proximal IgG4-SC, presence of OOI, administration of MST over 3 years, minipulse therapy, use of immunosuppressant, initial dose of steroid, reduction speed of steroid, steroid cessation and biliary stent placement (drainage). Univariate and multivariate analyses were performed to identify the risk factors for relapse.

2.10 | Steroid-free status after maintenance steroid treatment

While steroid therapy is potent treatment for IgG4-RD, whether the patients could become steroid-free after MST is a significant concern. The data of patients who received MST were scrutinized. The steroid dose used for MST was classified as 2.5 mg (range, 1-2.5 mg/day), 5 mg (range, 5-7 mg/day), and over 7.5 mg (range, 7.5-15 mg/day).

2.11 | Steroid-related complications

Steroid-related complications (SRCs) are a concern because they limit the duration of steroid treatment. Therefore, we also analyzed the frequencies of SRCs, based on the availability of the relevant data, including the duration of steroid administration, the total dose of steroid (TDS), and the adverse effects of steroids (AEs). Regarding osteoporosis, most of the patients with IgG4-SC in Japan suffer from osteoporosis and receive prophylactic treatment[7] against osteoporosis-related fractures, such as a bisphosphonate or active vitamin D preparation[15]; for this study, only serious complications, such as osteoporosis-related fractures that needed surgical intervention, cardiovascular disease that required intervention and severe infection were considered for the analyses. The rate of SRCs between the group with MST over 3 years and the other group was studied.

2.12 | Risk factors for steroid-related complications

Groups with/without SRCs were compared based on age, gender, excess alcohol consumption, presence of malignancy, serological data (TB levels, ALP levels, IgG levels and IgG4 levels), presence of AIP, presence of proximal IgG4-SC, presence of OOI, minipulse therapy, administration of MST over 3 years, total dose of steroid before relapse, use of immunosuppressant and incidence of relapse. Univariate and multivariate analyses were performed to identify the risk factors for SRCs.

2.13 | Statistical analysis

The data were analyzed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Categorical variables were compared by the χ^2 test or the Fisher exact test. Continuous variables that were not normally distributed were analyzed by Mann-Whitney's *U*-test. The primary outcome was the RFS. The RFS and cumulative survival rates were estimated by the Kaplan-Meier method and compared using the log-rank test. Multiple variable regression analyses were conducted to identify the factors associated with relapse. $P < .05$ was considered indicative of statistical significance.

3 | RESULTS

3.1 | Patient profile

A total of 896 patients with clear prognostic data were included in the study (Table 1). There were patients who received steroid treatment (n = 767) and patients who did not receive steroid treatment (n = 129). The median durations of follow-up are 54 months in steroid group and 45 months in non-steroid group, respectively. Significant differences between the groups were noted on the points of presence of AIP, the presence of OOI which is indicative of refractory disease.[18] Therefore, there were biased backgrounds between the groups. There were significant differences in the groups with/without steroid treatment on the points of remission rate (99.5% vs 63.6%) and relapse rate (19.7% vs 38.4%). As for the steroid dose, most patients (68.7%) received 0.4-0.69 mg/kg/day. The median duration of MST was 37 months. The median dose of steroid was 5400 mg. Figure S2 showed RFS duration in patients with IgG4-SC with/without steroid treatment. Although there were biased backgrounds, the group with steroid treatment indicated more favorable RFS than that with the counterpart ($P < .001$).

TABLE 1 Profile of the patients with IgG4-related sclerosing cholangitis who received/did not receive steroid therapy in this study (n = 896)

Groups	Steroid (n = 767)	Non-steroid (n = 129)	*P*
Variables			
Duration of follow-up; mean ± SD years	4.9 ± 3.8	5.2 ± 4.7	*.576.*
Duration of follow-up; median; months [range]	54 [6-250]	45 [6-240]	*NA*
Age (year-old<60) ±	597/172 (77.8)	98/31 (75.9)	.651
Sex; Male ±	615/152 (80.2)	102/27 (79.1)	.906
Excess alcohol consumption ±	206/561 (26.9)	37/92 (30.2)	.821
History of diabetes mellitus ±	241/526 (31.4)	34/95 (26.4)	.107
History of malignancy ±	81/686 (10.6)	18/111 (13.9)	.455
Serum Total Bilirubin 3 mg/dL < ±	224/543 (29.2)	30/99 (23.3)	.392
Serum Alkaline phosphatase; 2xUNL < ±	442/325 (57.6)	73/56 (42.3)	.923
Serum IgG;1800 mg/dL < ±	130/637 (16.9)	23/106 (17.8)	.899
Serum IgG4;135 mg/dL < ±	335/432 (43.7)	56/73 (43.4)	.694
Presence of autoimmune pancreatitis ±	587/180 (76.5)	64/65 (49.6)	.001<
Proximal type IgG4-SC ±	250/517 (32.6)	39/90 (30.2)	1
Other Organ Involvement 3 < ±	63/704 (8.2)	4/125 (3.1)	.0293
Remission ±	763/4 (99.5)	78/51 (63.6)	.001<
Relapse ±	151/621(19.7)	30/48 (38.4)	.001<
Initial dose of daily steroid			
<0.39 mg/kg/0.4-0.69 mg/kg/0.7 < mg/kg	71 (11.6)/419 (68.7)/140 (19.3)		
Duration of MST, months (median [range])	37 [6-202]		
Total dose of steroid, mg (median [range])	5400 [900-27 750]		
	(%)		

Note. Steroid: patients who received steroid therapy, Non-steroid: patients who did not receive steroid therapy. IgG4-SC: IgG4-related sclerosing cholangitis, ULN: upper limit of normal, SD: standard deviation, Other Organ Involvement 3<: other organ involvement recognized in more than four other organs, MST: maintenance steroid treatment. Italics values are indicated $p < .05$ statistically significant.

3.2 | Steroid treatment and treatment outcomes

Figure S3 shows the outcomes of steroid treatment in the patients. Initial treatment led to remission in 99.5% of patients, while four patients were refractory to treatment and needed increment of the steroid dose for achieving remission. Relapse was noted in 19.7% of patients. The relapse was of the biliary type in 81 patients (53.6%), of the pancreatic type in 16 patients (10.6%), and of the other OOI type in 54 patients (35.8%). Steroid was effective for relapse, with remission achieved in 96.7% of patients with relapse, while four dose increment and mini-steroid pulse therapy were conducted as additional treatment.

3.3 | Biliary recovery

As for biliary improvement, serological recovery, as attested by the serum TB and ALP levels, was obtained 89.6% of patients who did not undergo drainage and 87.1% of patients who underwent drainage, the difference between the two groups not being significant. Improvement of the cholangiographic abnormalities was obtained in 81.7% of patients who did not undergo drainage, and 89.2% of patients who underwent drainage, with the difference between the two groups not being significant. Moreover, regardless of whether biliary drainage was undertaken or not, near-normalization of the serum TB (79.8% in those who did not undergo drainage vs 67.4% in those who underwent drainage) and ALP (65.4% in those who did

not undergo drainage vs 58.7% in those who underwent drainage) were achieved at 2 weeks after the initiation of steroid treatment (Figure 1). Thereafter, almost complete normalization was recognized at 4 months after the treatment, although the data remained abnormal in under 10% of the patients (serum ALP remained abnormal), indicating the limitation of steroid treatment.

3.4 | Relapse-free survival in the 767 patients

Figure S4 shows the RFS rate in the patients. After the start of steroid treatment, the 3-year RFS was 84.9%, the 5-year RFS was 74.5%, and the 7-year RFS was 67.3%.

3.5 | Relapse-free survival based on MST

Figure 2 shows the percentages of patients who received steroid therapy (n = 767) for over 3 years (over 3Y), for 2 to 3 years (<2-3Y), for 1 to 2 years (<1-2Y), and for less than a year (<1Y). The over 3Y group showed a significantly longer RFS rate than the other groups. Thus, the longer the duration of steroid therapy, the better the RFS rate was.

3.6 | Risk factors for relapse

Of the 767 patients who received steroid treatment, 151 (19.7%) developed relapse (Table 1). Besides, patients who did not receive steroid treatment experienced relapse in 38.4%. Multivariate analysis identified younger age <60 years old, without MST for more than 3 years, immunosuppressant and discontinuation of steroid therapy as independent risk factors for relapse (Table 2).

3.7 | Steroid-free status

Figure 3 shows the number of patients who became steroid-free after MST (n = 468). Immunosuppressants

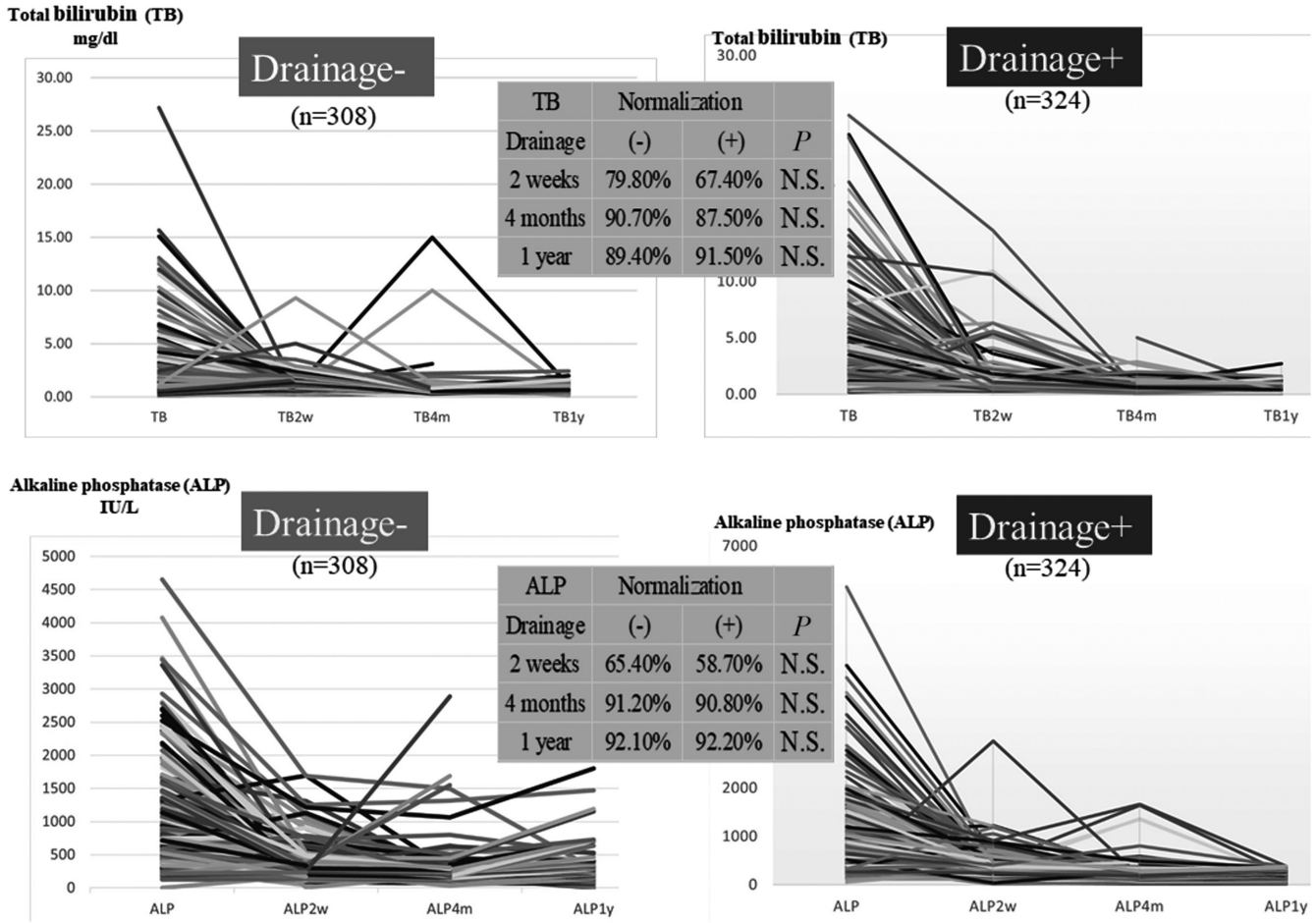

FIGURE 1 Normalization of data in patients with IgG4-related sclerosing cholangitis who received steroid therapy (n = 632). Regardless of whether the patients underwent biliary drainage or not, normalization of the serum TB and ALP levels was achieved in nearly 90% of all patients at 4 months after the initiation of steroid therapy

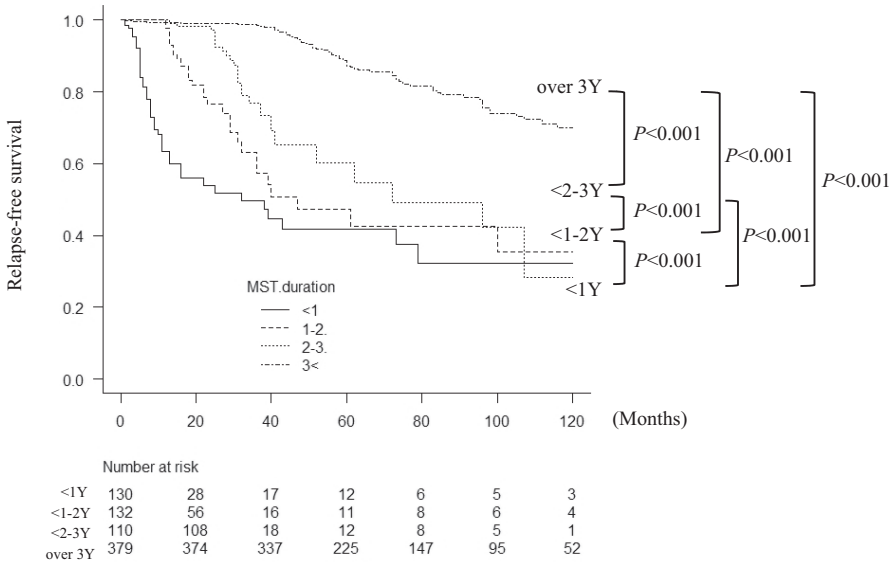

FIGURE 2 Relapse-free survival duration in patients with IgG4-related sclerosing cholangitis according to the steroid dosing period (n = 767). This figure shows the percentages of patients who received steroid therapy (n = 767) for over 3 years (over 3Y), for 2 to 3 years (<2-3Y), for 1 to 2 years (<1-2Y), and for less than a year (<1Y). The patient group that received steroid therapy for over 3Y showed a significantly longer RFS duration as compared with the other groups

were used in 19 patients (2.5%) with refractory disease, to maintain their condition.[9] There were only 16 patients (including five patients in the 2.5- mg dose group, 10 patients in the 5-mg dose group, and one patient in the 7.5-mg dose group) who became steroid-free, corresponding to only 3.4% of all patients who received MST. Immunosuppressant helped only one patient to become steroid-free. We tried steroid-free trial (SFT) in 48 out of 468 patients. Consequently, 16 patients achieved steroid-free (33.3%; 16/48), while the remaining patients could not be tried SFT mainly due to their instability. As a result, the rate of SFT was 3.4% (16/468).

3.8 | The details of immunosuppresant

Immunosuppresant (IS) was given in 19 patients. Azathioprine (AZT) was administered in 16 patients. The maintenance dose (MD) was 50 mg and median duration was 22 months [1.136]. The remaining three patients were received Methotrexate, Ciclosporin and Mycophenolate Mofetil, respectively.

3.9 | Steroid-related complications

Steroid-related complications were recorded in a total of 99 patients during the median steroid dosing period of 54 months (12.9%). The most frequent were impaired glucose tolerance (n = 64), osteoporosis (n = 9), viral infection (n = 5), and others. Severe complications (n = 16; 2%) of osteoporosis necessitating emergency admission, such as osteoporosis-related fractures, developed in five patients. Other severe complications included acute pancreatitis (n = 1), acute hepatitis (n = 1), acute myocardial infarction (n = 1), fungal infection (n = 2), bacterial pneumonia (n = 2), deep vein thrombosis (n = 1), and mental disorder (n = 2). Total dose of steroid (TDS) was not affecting the incidence of SRCs (Table 3). The area under the ROC curve (AUROC) for the TDS was 0.508, 95% CI: 0.413-0.604, indicated low accuracy. The optimal cut-off value was 5850 mg showing 0.564 in specificity 0.521 in sensitivity, indicated with low accuracy. The rate of SRCs between the group with MST over 3 years and the other group was also studied. The time dependency of SRCs was not validated since there were no significant differences in the rate of SRCs between groups (Figure S5). Multivariate analysis identified history of malignancy and immunosuppressant as independent risk factors for SRCs (Table 3).

4 | DISCUSSION

Steroid therapy is accepted as the 1st line treatment for IgG4-RDs, as attested in an international consensus meeting.[19] Although steroid therapy yields a favorable remission rate and is affordable treatment, it is associated with a high relapse rate of around 30%.[3,18] This study revealed that steroid therapy is still feasible as 1st line treatment, since MST for over 3 years was effective for achieving remission and against 1st relapse. This also validates the Japanese guideline published in 2019,[7] especially providing evidence of the effectiveness of MST. However, there are limitations such as the short-term data based on no more than 54 months of surveillance. Furthermore, there were few patients who became steroid-free. Under this situation, supportive or alternate treatment should be used to reduce the risk of steroid toxicity and overcome the drawbacks of steroid therapy. To some extent, steroid

TABLE 2 Risk factors for relapse in patients with IgG4-related sclerosing cholangitis who received steroid therapy (n = 767)

Variables	Univariate analysis			Multivariate analysis		
	With relapse (n = 176)	Without relapse (n = 591)	*P* value	Hazard ratio	95% confidence interval	*P* value
Age (year-old<60)	129 (73.2)	465 (78.7)	.028	0.53	0.33-0.85	.008
Sex; Male	146 (83)	462 (78.2)	.52			
Excess alcohol consumption; ±	37/110 (25.2)	121/267 (31.2)	.203			
History of diabetes mellitus	59 (33.5)	185 (31.3)	.783			
History of malignancy; ±	22/143 (13.3)	56/395 (12.4)	.785			
Serum Total Bilirubin 3 mg/dL <	55 (31.3)	167 (28.3)	.569			
Serum Alkaline phosphatase; 2xUNL<; ±	117/59 (66.4)	317/263 (55.6)	<.001	1.36	0.863-2.15	.184
Serum Alkaline phosphatase remained abnormal/4 months; ±	6/128 (4.5)	10/376 (2.6)	.26			
Serum Alkaline phosphatase remained abnormal/1 year; ±	8/128 (5.9)	3/347 (0.9)	.037	2.3	0.757-6.99	.142
Serum IgG;1800 mg/dL <; ±	44/117 (27.3)	131/392 (30.9)	.606			
Serum IgG4;135 mg/dL <; ±	80/9 (89.9)	247/41 (86)	.374			
Presence of autoimmune pancreatitis; ±	130/19 (87.2)	444/67 (86.9)	1			
Proximal type Igg4-SC; ±	56/107 (34.4)	176/364 (32.6)	.704			
Other Organ Involvement 3<; ±	7/151 (4.4)	12/413 (2.8)	.43			
Maintenance steroid treatment 3 years<	67 (38.1)	312 (52.8)	<.001	0.333	0.216-0.514	<.001
Minipulse; ±	13/153 (7.8)	31/403 (6.9)	.73			
Immunosuppressant; ±	15/156 (8.8)	6/451(1.3)	<.001	4.9	1.54-15.5	.007
Initial dose of steroid						
<0.39 mg/kg/day; ±	13/153 (7.8)	56/399 (12.3)	.149	0.59	0.301-1.16	.124
0.4-0.69 mg/kg/day; ±	115/52 (68.8)	299/156 (65.7)	.503			
0.7 < mg/kg/day; ±	39/128 (23.2)	100/355 (23)	.745			
Reduction speed of initial dose of steroid for 2 weeks (mg/day) o.5<; ±	39/107 (26.7)	88/318 (20.4)	.251			
Reduction speed of initial dose of steroid for 4 months (mg/day) 0.2<; ±	75/87 (46.3)	210/217 (49.2)	.579			
Steroid cessation; ±	64/109 (37)	106/343 (23.6)	.0012	1.61	1.01-2.54	.043
Drainage; ±	109/61 (64.1)	241/214 (53)	.014	1.44	0.914-2.27	.117
	(%)					

Note. Other organ involvement 3<: other organ involvement recognized within less than three lesions. Italics values are indicated $p < .05$ statistically significant.

Abbreviations: CI, confidence interval; IgG4-SC, IgG4-related sclerosing cholangitis; UNL, Upper normal limit.

use around 5 years, with preemptive medication to counter the adverse effects of steroids would be suitable for patients to maintain their condition and safety. Steroid treatment would be useful as interim strategy and serve as a bridge to adjunctive immunosuppressant and/or the B-cell depletion therapy in the future.

The precise pathogenetic mechanisms of IgG4-RD are still unclear, although a recent study validated the suggestion that increasing B cells and plasma blasts, which constitute major inflammatory cell populations that are believed to cause organ damage and tissue fibrosis, underlie the development of IgG4-SC[20]; these cells would be primary target for treatment, which cannot be completely covered by steroid monotherapy. Steroid therapy is effective for preventing relapse to some extent[2,3,18]; in refractory cases, a repeat course of steroid therapy is usually sufficient, as indicated by our data, however immunosuppressants are sometimes needed as adjunctive drugs to decrease the steroid burden.[5,9,21] Rituximab (RTX), a B-cell-depleting anti-CD monoclonal antibody,[22]

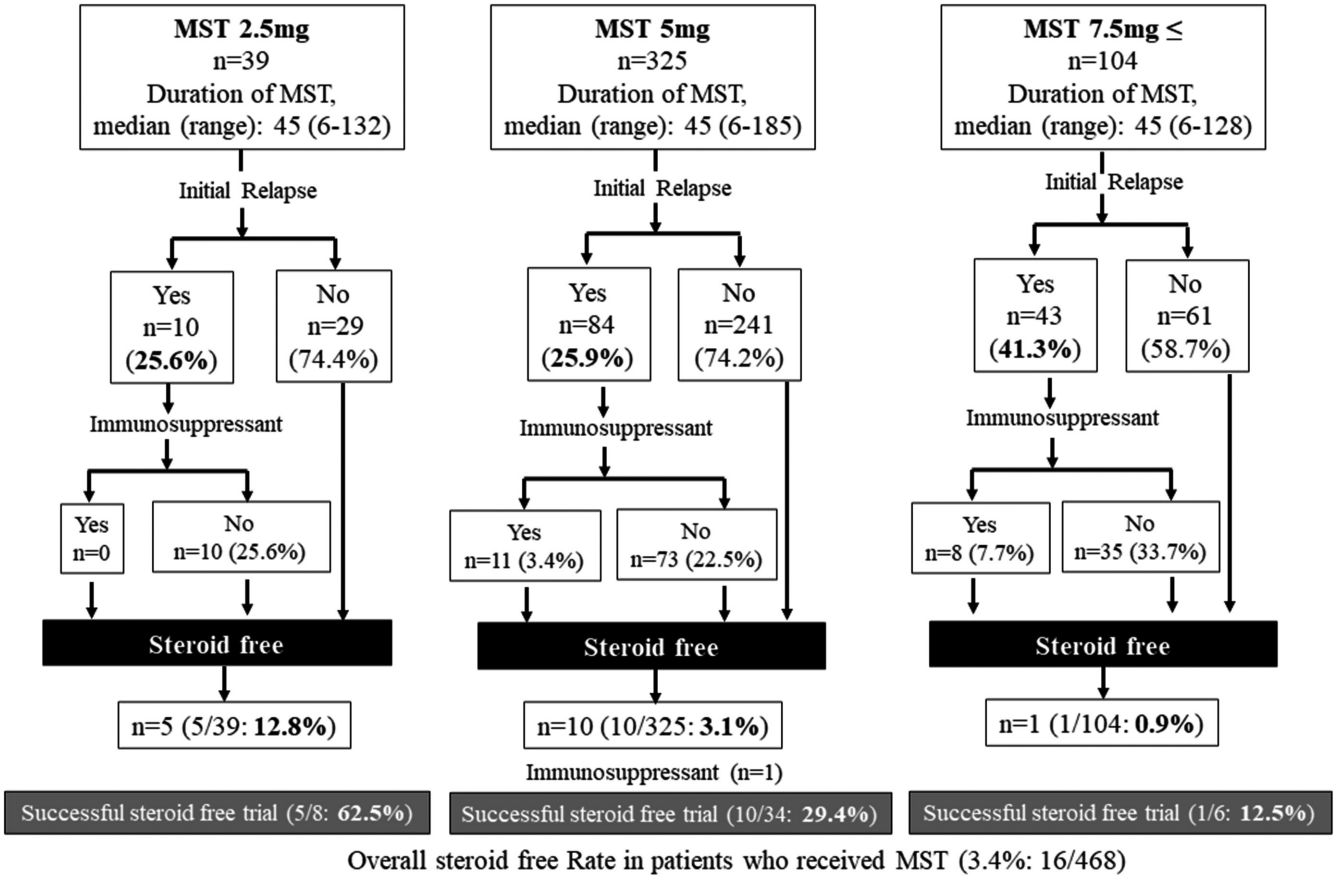

FIGURE 3 Flow chart of the treatment outcomes in patients with IgG4-related sclerosing cholangitis who received maintenance steroid treatment (MST) (n = 468). This diagram indicates how many patients became steroid-free after MST (n = 468). Of all the patients, 19 patients (2.5%) also received immunosuppressants. We tried steroid-free trial (SFT) in 48 out of 468 patients. Consequently, 16 patients achieved steroid-free (33.3%, 16/48), while the remaining patients could not be tried SFT mainly due to their instability. As a result, the rate of SFT was 3.4% (16/468)

is a promising agent to reduce the risk of relapse, and at the same time, can counter steroid dependence of the patients. However, there are concerns; one is the risk of viral leukoencephalopathy, a critical side effect of RTX, and the other is the high cost. Some political strategy and consideration to facilitate RTX treatment would be desirable.

Steroid treatment could yield remission and reduce the risk of relapse over the short term; however, steroid therapy cannot be continued permanently, because of its severe toxicities and incomplete effectiveness.[6,20,21] Steroids can only alleviate symptoms, and make the disease dormant; therefore, it could serve as a safe bridge to further radical treatments. Our data indicated that a steroid-free status may not be obtained even in patients who strictly adhere to MST (steroid-free status was achieved in only 3.4% of patients overall). B cell depletion has also been found to induce remission in patients with steroid-resistant disease and has also been used as a steroid-sparing agent for patients with relapsing disease.[23] However, it would be impractical to administer RTX to all patients because of the high cost and concern of serious adverse effects, and a comprehensive balanced strategy combining steroid and RTX regimens would be needed. At the same time, steroid treatment should be administered in an interim manner while being fully aware of its limitations.

Infiltration of IgG4-bearing plasma lymphocytes causes biliary damage and jaundice, and steroid treatment is effective for ameliorating such damage. However, there is no reliable evidence yet about the time needed for the biliary system damage to reverse completely, not only in terms of the serological data, but also in terms of cholangiographic evidence. Biliary stenting has been used to counter biliary damage.[7] Recently, a paper suggested that patients with IgG4-SC do not necessarily need biliary drainage.[8] In the absence of life-threatening cholangitis, steroid therapy alone could lead to biliary recovery in patients with IgG4-SC and might represent the optimal treatment. As the biliary parameters improved within 2 weeks to 4 months of the start of treatment, even in the absence of biliary stenting, the biliary drainage might not be mandatory. However, there are cases where short-term biliary stent placement

TABLE 3 Risk factors for the development of steroid adverse effects in patients with IgG4-related sclerosing cholangitis receiving steroid therapy (n = 767)

Variables	Univariate analysis			Multivariate analysis		
	With AEs (n = 99)	Without AEs (n = 476)	*P*-value	Hazard ratio	95% confidence interval	*P*-value
Age (year-old<60)	75 (77.8)	358 (75.2)	.898			
Sex; Male	84 (84.8)	375 (78.8)	.173			
Excess alcohol consumption	24 (24.2)	119 (25)	1			
History of diabetes mellitus	35 (35.4)	187 (39.3)	.498			
History of malignancy	17 (17.2)	52 (10.9)	.088	1.86	1.020-3.41	.043.
Serum Total Bilirubin 3 mg/dL <	30 (30.3)	134 (28.2)	0.903			
Serum Alkaline phosphatase; 2xUNL<	56 (56.6)	282 (59.2)	*0.911*			
Serum IgG 1800 mg/dL <; ±	17 /70 (19.5)	94/336 (21.9)	.671			
Serum IgG4 135 mg/dL <; ±	32/2 (94.1)	185/34 (84.5)	.187			
Presence of autoimmune pancreatitis; ±	79/10 (88.8)	347/50 (87.4)	.859			
Proximal type IgG4-SC; ±	30/61 (40)	148/293 (33.6)	1			
Other Organ Involvement 3<; ±	2/92 (2.2)	15/431 (3.4)	.749			
Minipulse; ±	5/91 (5.2)	38/416 (8.4)	.403			
Maintenance steroid treatment 3 years<	54 (54.5)	237 (49.8)	.439			
Total steroid dose before relapse 7000 mg<; ±	18/30 (37.5)	97/183 (34.6)	.744			
Total steroid dose before relapse 8000 mg<; ±	16/32 (33.3)	82/198 (29.3)	.609			
Total steroid dose before relapse 9000 mg<; ±	0/33 (0)	1/209 (0.4)	1			
Immunosuppressant; ±	6 (6)	12/462 (2.5)	.103	2.8	1.020-7.69	.046.
Relapse; ±	35/62 (36.1)	120/355 (25.3)	.033	1.43	0.876-2.340	.153.
	(%)					

Note. Other organ involvement 3<: other organ involvement recognized within less than three lesions. Italics values are indicated $p < .05$ statistically significant.

Abbreviations: AEs, steroid adverse effects; CI, confidence interval; IgG4-SC, IgG4-related sclerosing cholangitis; UNL, upper normal limit.

would be needed to avoid acute side effects following biliary examinations, such as biopsy and intraductal ultrasound, to rule out malignancy.

Identification of the risk factors for relapse is an important matter, since patients without relapse could be tried steroid-free, while patients with relapse would be candidate for re-administration of steroid or other alternatives including RTX. In our survey, multivariate analysis identified younger onset, MST for over 3 years, immunosuppressant, and steroid cessation as independent risk factors for relapse. As for younger onset, it was compatible with previous data.[7] Regarding MST for over 3 years, it can reduce the relapse rate (Figure 2) as previous mentioned,[16] therefore, MST for over 3 years should be recommended, while the risk of AEs could be addressed by preemptive use of countermeasures around 5 years. The presence of immunosuppressant indicated refractory disease with repeated relapses. Immunosuppressant plays a supportive role in patients receiving steroid therapy.[9,21] Steroid discontinuation was identified as a risk factor for relapse,[24] because while MST could maintain an asymptomatic condition of the patients, steroids do not address the underlying pathology. Thus, we believe that an awareness of the risks and limitations of steroid therapy would be useful for the development of better treatment strategies for patients with IgG4-SC in the long run.

Adverse effects of steroids (AEs) are a matter of concern in these patients. Steroid toxicity, such as impaired glucose tolerance, osteoporosis and immunocompromise are serious AESs. In previous studies, a TDS of over 6405 mg[25] or over 8694 mg[26] was associated with an increased risk of severe AEs.[24] In this survey, the patients had received a median steroid dose of 5400 mg over a period of 54 months, and 12.9%, which

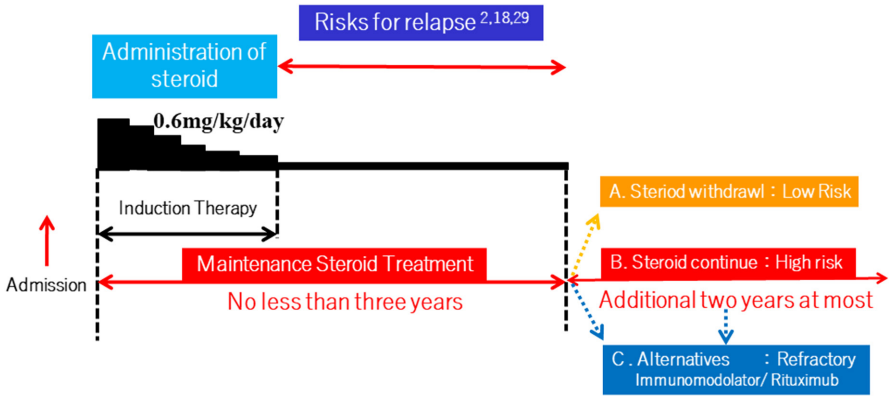

FIGURE 4 A proposal therapeutic strategy for patients with IgG4-related sclerosing cholangitis. Steroid treatment should be continued for no <3 years to reduce the risk of disease relapse, with preemptive measures to lessen steroid toxicity taken around 5 years. Steroid withdrawal would be appreciated in patient with low risk for relapse, while high-risk patients[2,18,28] could be continued safely steroid additional 2 years at most to avoid steroid toxicity. Immunosuppressant and B-cell depletion therapy have been shown to be promising for inducing remission in steroid-resistant patients and have also been used as steroid-sparing agents in patients with relapsing disease. High-risk patients should be identified carefully, and personalized treatment could be considered in such refractory patients

is a relatively small percentage, of the patients developed AEs.[27] Although dose-dependent toxicity could not be validated in the present study, MST for more than 3 years could be administered on the condition that preemptive measures are taken to minimize the risk of AEs. However, MST for over 5 years could be challenging, and for such patients, supportive or replacement therapy would be prerequisite. History of malignancy and immunosuppressant were identified as risk factors for AEs in the present study. In the case of the latter factor, it is possible that people who were started on immunosuppressant were refractory cases who needed high steroid doses. As for malignancy, it is speculated that these patients have weakened immune systems and may be more vulnerable to drug toxicity. The TDS would not increase the risk of SRCs provided that adequate preemptive measures are taken to minimize the risk of steroid toxicity and that the steroid treatment is discontinued within 5 years.

There were some limitations of this study. Firstly, it was based on retrospective data, and a prospective study is needed. In terms of evaluation of the therapeutic strategy, data on the long-term prognosis (over at least a decade) was lacking in some patients; in addition, there was a deviation: based on the discretion of the attending physician, some patients underwent biliary drainage along with the steroid treatment, while others did not. As biliary drainage was performed at the discretion of the physician, there were biases in terms of the indication for biliary stent placement in this study. In addition, the cumulative negative effects of steroid treatment in individuals could not be fully investigated in this study. Fourth, there could be some bias from some patients who could have received continuous steroid treatment for an excessively long duration, despite no longer needing steroid treatment.

In conclusion, as biliary recovery in patients with IgG4-SC is achieved mainly by steroid treatment (within 2 weeks to 4 months of the start of treatment), the biliary drainage might not be mandatory. Steroid treatment should be continued for no less than 3 years to reduce the risk of disease relapse, with preemptive measures to lessen steroid toxicity taken around 5 years. Steroid withdrawal would be appreciated in patient with low risk for relapse, while high-risk patients could be continued safely steroid additional 2 years at most to avoid steroid toxicity. Immunosuppressant and B-cell depletion therapy have been shown to be promising for inducing remission in steroid-resistant patients and have also been used as steroid-sparing agents in patients with relapsing disease. High-risk patients should be identified carefully, and personalized treatment could be considered in such refractory patients (Figure 4).

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX A

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