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【 ORIGINAL ARTICLE 】

Reduced Rate of Disease Flares in Japanese Patients with Systemic Lupus Erythematosus: An Altered Balance between the Use of Glucocorticoids and Immunosuppressants in Recent Decades

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Abstract:

Objective This study examined whether or not the disease control in Japanese patients with systemic lupus erythematosus (SLE) had improved in recent years and its possible association with altered balance between the use of glucocorticoids and immunosuppressants.

Methods We enrolled Japanese patients with SLE who visited our medical center during 2013-2017 (Group A, 75 patients) and compared them with patients encountered during 1999-2003 (Group B, 69 patients; not overlapping with Group A). Patient background characteristics, doses of glucocorticoids, and the use of immunosuppressants at the times of SLE onset and disease flares were reviewed from the medical records. Disease flare was defined as new British Isles Lupus Assessment Group 2004 A or B scores in at least one system.

Results Lupus nephritis and neuropsychiatric manifestations were less frequently observed in Group A than in Group B (p=0.042 and p=0.045, respectively). Although the initial glucocorticoid dosage was similar between the groups, the inclusion rate of immunosuppressants in the initial SLE treatment was significantly higher in Group A than in Group B (56% vs. 6% in Group B, p<0.001). The median number of SLE flares per person-year was significantly lower in Group A than in Group B (0 vs. 0.3, respectively, p<0.001), and a propensity score-matched analysis indicated the association of SLE flare with the non-use of immunosuppressants in the initial treatment (p=0.012). The rates of infectious diseases and other complications were similar between the groups.

Conclusion The recent aggressive use of immunosuppressants in Japan resulted in a reduction in the rate of SLE flare.

Key words: flare, therapeutics, glucocorticoids, immunosuppressants, systemic lupus erythematosus

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Introduction

The outcomes for patients with systemic lupus erythematosus (SLE) have considerably improved from a 5-year survival rate of <50% at 60 years ago (1) to a 10-year survival rate of >90% in recent years (2-4). Several factors have contributed to the recent improvement in the SLE prognosis, including improvement in the classification of patients, earlier diagnoses, inclusion of milder cases, and advances in the management of SLE and renal failure, atherosclerotic events, infections, and cancers (3, 5, 6).

The current concept of the "treat-to-target" strategy for the management of rheumatoid arthritis has been applied to SLE as well (7), and very recent cohort studies have indeed demonstrated that better SLE disease control to prevent cu-

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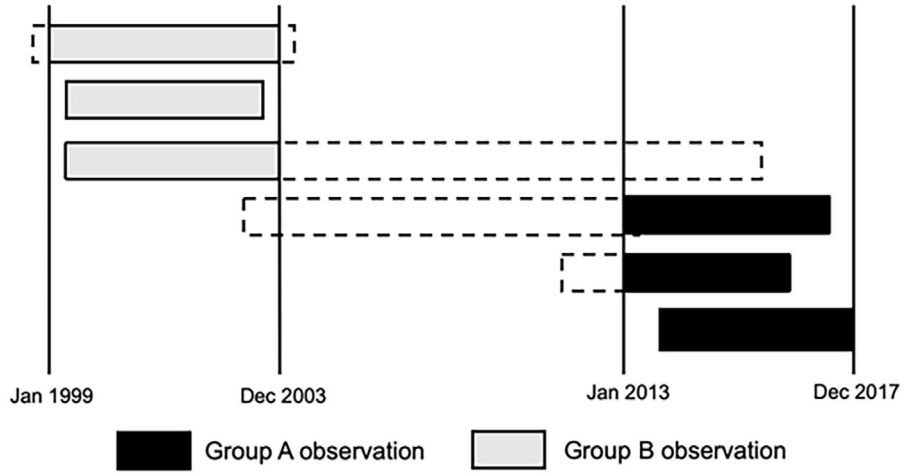

Figure 1. Patient inclusion in Groups A and B. Patients with more than six months of observation during the above period were enrolled, and inclusion in Group B from 1999 to 2003 (gray bars) preceded that in Group A from 2013 to 2017 (black bars). There was no overlap of cases between groups. Blank bars indicate observation periods other than those for Group A or B.

mulative organ damage is crucial for achieving better outcomes in SLE patients (8, 9). Because glucocorticoids (GCs) considerably affect the accrual of organ damage (10), there should be an optimal therapeutic balance between the risks and benefits of GCs and immunosuppressants for controlling disease activity and the subsequent course of SLE (7, 10, 11).

In Japan, mizoribine (MZR), an inhibitor of inosine monophosphate synthetase and guanosine monophosphate phosphatase (12), was approved for the treatment of lupus nephritis in 1990. Tacrolimus (TAC) was approved for lupus nephritis in 2007. Azathioprine (AZA) and cyclophosphamide (CYC) were approved in 2011. Hydroxychloroquine (HCQ) and mycophenolate mofetil (MMF) were approved for treatment of lupus nephritis in 2015, and the first biological agent belimumab was approved for SLE in 2017. Consequently, a trade-off between immunosuppressants and GCs has been aggressively attempted in our department in recent years to prevent the cumulative organ damage associated with GC use.

We therefore retrospectively examined whether or not disease control in Japanese patients with SLE had improved in the past 20 years. We also studied the possible associations of disease flare with the altered balance between the use of GCs and immunosuppressants.

Materials and Methods

Patients

We enrolled Japanese patients with SLE who visited Toho University Ohashi Medical Center from 2013 to 2017 (Group A, 75 patients) and compared them with patients who visited from 1999 to 2003 (Group B, 69 patients; not overlapping with Group A). We enrolled patients with more than six months of observation during the above period, and inclusion in Group B preceded that in Group A (Fig. 1). All patients met the 1997 revised criteria of the American College of Rheumatology for SLE classification (13).

Methods

Data on patient demographic and clinical characteristics and disease activity, SLE Disease Activity Index 2000 (SLEDAI-2K) (14), dose of GCs, and the use of immunosuppressants at the times of SLE onset and disease flare were retrospectively reviewed from the medical records. Disease flare was defined as new British Isles Lupus Assessment Group (BILAG) 2004 A or B scores in at least one system (15). Multiple flares observed within the observation period were counted separately. The propensity score was estimated using a multivariate logistic regression model predicting disease flare with the following key variables: age at the disease onset, age at enrollment, sex, observation period, disease duration at enrollment, presence of arthritis, and presence of lupus nephritis or neuropsychiatric manifestations.

The institutional ethical committee approved this study of Toho University Ohashi Medical Center (project approval number: H18004). The need for written informed patient consent was waived given the retrospective and observational nature of the study.

Statistical analyses

Statistical analyses were performed using the JMP Pro software program (version 14.2.0; SAS Institute Japan, Tokyo, Japan). Continuous variables were summarized as medians [interquartile range (IQR)] and analyzed using the Mann-Whitney U test. Binomial data were compared between the two groups using Fisher's exact test. p values < 0.05 were considered to be statistically significant.

Patients who experienced disease flare and those who did not were matched using the propensity score. Propensity

Table 1. Demographic and Clinical Features of the Patients.

	Group A n=75	Group B n=69	p value
Age at disease onset, year	35 (24-51)	30 (22-44)	0.11
Age at enrollment, year	44 (36-58)	38 (27-48)	0.006
Female	63 (84)	62 (90)	0.33
Observation period during enrollment, year	5.0 (3.3-5.0)	5.0 (4.8-5.0)	0.015
Disease duration at enrollment, year	4.0 (0.1-8.9)	3.2 (0.7-9.2)	0.96
SLEDAI-2K at disease diagnosis	8 (4-12)	10 (6-13)	0.24
Overlap/secondary systemic autoimmune diseases			
Rheumatoid arthritis	6 (8)	2 (3)	0.28
Systemic sclerosis	4 (5)	2 (3)	0.68
Polymyositis/dermatomyositis	2 (3)	1 (1)	1.0
Sjögren syndrome	11 (15)	5 (7)	0.19
Antiphospholipid antibody syndrome	4 (5)	7 (10)	0.35
Clinical features			
Rash	55 (73)	60 (87)	0.060
Arthritis	43 (57)	42 (61)	0.74
Serositis	22 (29)	19 (28)	0.86
Neuropsychiatric manifestations	5 (7)	13 (19)	0.042
Lupus nephritis	31 (41)	41 (59)	0.045
ISN/RPS Class I/II	5	8	
Class III/IV/V	17	18	
Undetermined	9	15	
Leukopenia†	34 (45)	38 (55)	0.32
Thrombocytopenia‡	13 (17)	18 (26)	0.23
Initial treatment			
Initial dose of oral PSL, mg/day	30 (26-50)	30 (20-50)	0.59
Total PSL dosage in the initial 16 weeks, mg§	2,275 (1,292-4,747)	2,660 (1,705-4,795)	0.66
Immunosuppressants in the initial treatment	41 (56)	4 (6)	<0.001
Disease flare	34 (45)	52 (75)	<0.001
Rate of flare per patient	0 (0-0.2)	0.3 (0.2-0.4)	<0.001

Values are expressed as median (IQR) and number (%). Fisher's exact test or Mann-Whitney U test was used for group comparisons. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, ISN/RPS: International Society of Nephrology/Renal Pathology Society, PSL: prednisolone

†Leukopenia: white blood cell <4,000/μL, ‡Thrombocytopenia: platelet $<10.0\times10^4$/μL, §n=58 and 49, respectively, for Groups A and B.

score matching used the nearest-neighbor method with a caliper distance of 0.2. A matching ratio of 1:1 was used. Matching covariates included variables with p values less than 0.2 before matching and the variables considered confounders based on existing literature and clinical judgment.

Results

Demographic and clinical features of the patients

The demographic and clinical features of the patients are shown in Table 1. The age at the disease onset, sex, disease duration on study enrollment, and the SLEDAI-2K at the disease diagnosis were comparable between the two groups; however, the age at enrollment was higher in Group A than in Group B (median 44 vs. 38 years old, respectively, p=0.006), and the observation period was shorter in Group A than in Group B (median 5.0 years for both, IQR 3.3-5.0 vs. 4.8-5.0, respectively, p=0.015).

Comparable portions of patients showed overlap syndrome with rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis (PM/DM), or secondary Sjögren syndrome or antiphospholipid syndrome (APS). Positive clinical features were comparable except for a lower prevalence of neuropsychiatric manifestations (7% vs. 19%, respectively, p=0.042) and lupus nephritis (41% vs. 59%, respectively, p=0.045) in Group A than in Group B.

Although the median initial dosage of oral prednisolone (PSL) was equivalent in both groups (median; 30 mg/day, p=0.59), and the total GC dosage in the initial 16 weeks was also comparable, the concomitant use of immunosuppressants in the initial treatment was more frequent in Group A (56%) than in Group B (6%; p<0.001).

Disease flare

Because disease flares are associated with damage accrual

Table 2. Comparison of Flare Events and Treatments before and after the Events.

	Group A n=47	Group B n=90	p value
Flare events			0.71
BILAG A event	19 (40)	33 (37)	
BILAG B event	28 (60)	57 (63)	
Rate of flare, per total person-year	0.16	0.29	<0.001
Clinical manifestations			
Rash	16 (34)	40 (44)	0.28
Arthritis	18 (38)	24 (27)	0.18
Lupus nephritis	7 (15)	20 (22)	0.37
Serositis	6 (13)	11 (12)	1.0
Neuropsychiatric manifestations	0 (0)	3 (3)	0.55
PSL at disease flare, mg/day	5 (2-6)	5 (0-9)	0.20
Hydroxychloroquine at disease flare	7 (15)	0 (0)	<0.001
Immunosuppressants at disease flare	37 (79)	10 (11)	<0.001
PSL after SLE flare, Δmg/day	5 (0-24)	14 (7-26)	0.005
Addition or alteration of immunosuppressants	39 (83)	22 (24)	<0.001

Values are expressed as median (IQR) and number (%). Fisher's exact test or Mann-Whitney U test was used for group comparisons. Rates were compared using the mid-p exact test. BILAG: British Isles Lupus Assessment Group, PSL: prednisolone, SLE: systemic lupus erythematosus

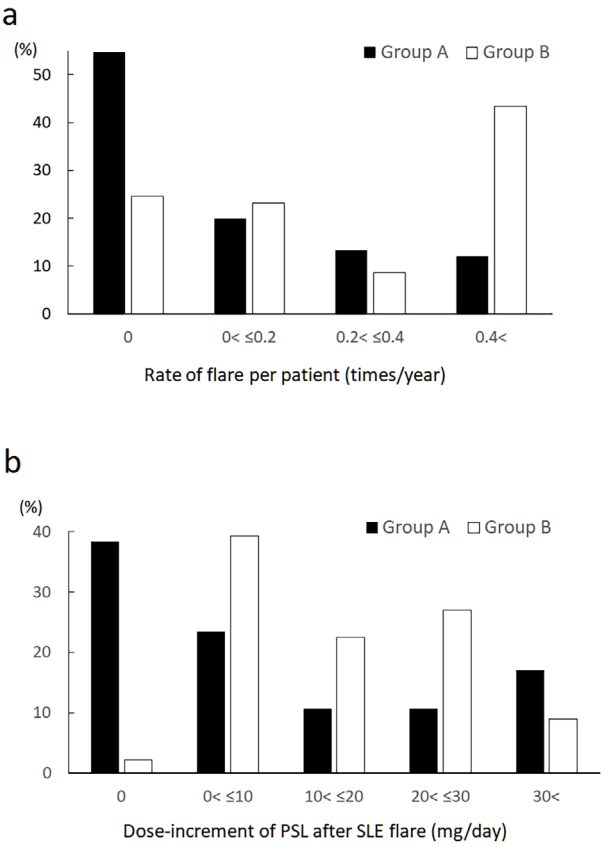

Figure 2. The comparison of the distribution (%) of yearly flare rate per patient (A) and of the PSL dose-increase (mg/day) upon SLE flare (B) between Groups A and B.

leading to a poor outcome (16-18), and treat-to-target recommendations include the prevention of flares as a therapeutic goal (7), we compared the frequency and severity of SLE flare between Groups A and B. We found a total of 47 flare events in 34 patients (45%) in Group A and 90 events in 52 patients (75%, p<0.001 vs. Group A) in Group B, with a significantly lower rate of flares per total person-year in Group A than in Group B (0.16 vs. 0.29, respectively, p< 0.001; Table 2). The reduced flare rate in Group A compared to Group B was confirmed by an individual person-year analysis (0 vs. 0.3, respectively, p<0.001; Table 1), and the distribution of the yearly flare rate demonstrated that more than half of the patients in Group A did not experience disease flares, while nearly half of the patients in Group B showed flare rates greater than 0.4/year (Fig. 2a).

BILAG A and B flare distribution and clinical manifestations of flare were comparable between groups (Table 2). The dosage of PSL at the time of disease flare was similar (median 5 mg/day) in both groups (p=0.20). However, the dose-increment of PSL was smaller in Group A than in Group B (median 5 vs. 14 mg/day, respectively, p=0.005), and the continuation of the same dose of PSL was observed in 38% of flare events in Group A, while it was very rare (2%) in Group B (Fig. 2b). In contrast, the addition or alteration of immunosuppressants was more frequent in Group A than in Group B (83% vs. 24%, respectively, p<0.001). However, immunosuppressants had already been received by the time of disease flare at 79% of flare events in Group A (11% of patients in Group B, p<0.001).

The comparison between patients who did and did not experience disease flare

We then compared the demographic and clinical features of patients who experienced disease flares (n=86) with those

Table 3. Comparison of Demographic and Clinical Features between the Patients who Experienced Disease Flare and Those Did Not with and without Propensity Score Matching.

	Unmatched			Matched		
	Flare (+) n=86	Flare (-) n=58	p value	Flare (+) n=46	Flare (-) n=46	p value
Age at disease onset, year	33 (23-43)	34 (22-51)	0.53	33 (24-42)	35 (23-51)	0.65
Age at enrollment, year	39 (30-49)	44 (31-57)	0.10	40 (33-50)	42 (30-56)	0.84
Female	73 (85)	52 (90)	0.46	44 (96)	42 (91)	0.68
Observation period, year	5.0 (4.0-5.0)	5.0 (2.9-5.0)	0.031	5.0 (4.1-5.0)	5.0 (4.0-5.0)	0.56
Disease duration, year	3.2 (0.4-8.1)	4.0 (0.6-9.0)	0.60	6.1 (0.5-9.8)	3.6 (0.7-8.7)	0.53
SLEDAI-2K at disease diagnosis	9 (6-12)	10 (4-13)	0.97	8 (5-11)	9 (4-12)	0.59
Clinical features						
Rash	71 (82)	44 (77)	0.53	37 (80)	35 (76)	0.80
Arthritis	55 (64)	30 (52)	0.17	23 (50)	27 (59)	0.53
Serositis	25 (29)	16 (28)	1.0	12 (26)	14 (30)	0.82
Neuropsychiatric manifestations	13 (15)	5 (9)	0.31	8 (17)	3 (7)	0.20
Lupus nephritis	40 (47)	32 (55)	0.40	23 (50)	23 (50)	1.0
Leukopenia†	42 (49)	30 (52)	0.87	25 (54)	27 (59)	0.83
Thrombocytopenia‡	19 (22)	12 (21)	1.0	9 (20)	9 (20)	1.0
Neurological or renal disorder	46 (54)	33 (57)	0.74	26 (57)	24 (52)	0.82
Initial treatment						
Initial dose of oral PSL, mg/day	30 (20-44)	40 (30-50)	0.17	30 (24-43)	40 (30-50)	0.072
Total PSL dosage in the initial 16 weeks, mg§	2,573 (1,554-4,235)	2,494 (816-5,019)	0.78	2,741 (1,761-4,373)	2,802 (1,381-5,019)	0.99
Immunosuppressants in the initial treatment‖	22 (26)	23 (40)	0.10	8 (18)	20 (44)	0.012

Values are expressed as median (IQR) and number (%). Fisher's exact test or Mann-Whitney U test was used for group comparisons. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, ISN/RPS: International Society of Nephrology/Renal Pathology Society, PSL: prednisolone

†Leukopenia: white blood cell <4,000/μL, ‡Thrombocytopenia: platelet <10.0×10^4/μL, §Unmatched date: n=63 and 44, Matched date: n=30 and 36, respectively, for flare and non-flare groups.

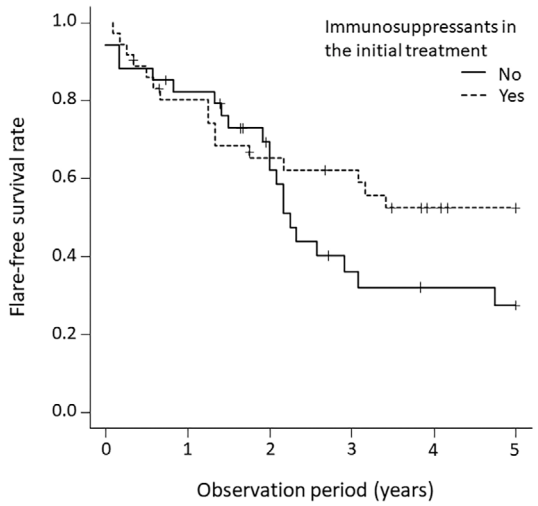

Figure 3. The comparison of disease flare between patients with and without immunosuppressants in the initial treatment after propensity score matching (n=36 for each group). Kaplan-Meier plots during the observation period were presented.

of the patients who did not (n=58; Table 3). A statistically significant between-group difference was observed only in the observation period (p=0.031). However, there was a trend favoring the use of immunosuppressants in the initial treatment for preventing disease flare (p=0.101). After propensity score matching by age at the disease onset, age at enrollment, sex, observation period, disease duration at enrollment, presence of arthritis, and presence of lupus nephritis or neuropsychiatric manifestations (n=46 for both groups), the use of immunosuppressants in the initial treatment was identified as the only factor significantly different between patients who did and did not experience disease flare (p=0.012).

In addition, to further elucidate the effectiveness of immunosuppressants, we compared patients with (n=45) and without (n=97) use of immunosuppressants in the initial treatment. Disease flare was numerically more frequent in patients who did not use immunosuppressants than in those receiving immunosuppressants (64% vs. 49%, respectively, p =0.10). We therefore performed propensity score matching by age at the disease onset, age at enrollment, sex, observation period, disease duration at enrollment, and presence of neuropsychiatric manifestations (n=36 for both groups). The flare-free survival rate during the observation period was calculated by the Kaplan-Meier method and compared between the patients with the presence and absence of immunosuppressants in the initial treatment by the log-rank test (p=0.17, Fig. 3).

Table 4. Complications.

	Group A n=75	Group B n=69	p value
Serious infection†	12 (16)	13 (19)	0.67
Pneumonia (bacterial)	1 (1)	4 (6)‡	0.19
Fungal infection	1 (1), Aspergillosis	1 (1), Cryptococcosis	1.0
Skin infection	1 (1)	4 (6)	0.19
Urinary tract infection	1 (1)	0 (0)	1.0
Enteritis	1 (1)	0 (0)	1.0
Herpes zoster	1 (1)	1 (1)	1.0
Cytomegalovirus infection	1 (1)	2 (3)	0.61
Diabetes	2 (3)	2 (3)	1.0
Osteonecrosis of the femoral head	4 (5)	6 (9)	0.52
Cerebrovascular disease	0 (0)	2 (3)	0.23
Cardiovascular disease	1 (1)	1 (1)	1.0
Malignancy	0 (0)	2 (3)	0.23

Values are expressed as number (%). Fisher's exact test was used for group comparisons.
†Admission to hospital for an infection, ‡One patient died of sepsis following bacterial pneumonia.

Complications

Finally, we compared the complications between Groups A and B to elucidate the safety profiles of aggressive use of immunosuppressants with rapid tapering and limited dose-increment of GCs (Table 4). The rates of severe infections requiring hospitalization were similar between the groups (p =0.67). One patient in Group B died of sepsis following pneumonia. The development of diabetes mellitus, osteonecrosis of the femoral head, cerebrovascular disease, cardiovascular disease, and malignancy were also comparable between Groups A and B.

Discussion

In the present study, we demonstrated a reduction in the rate of SLE flare with aggressive use of immunosuppressants and minimal dose-increment of GCs after the initial treatment in the past 5 years compared with the period 14 years earlier, which may have led to better long-term outcomes for Japanese patients with SLE.

Given the excellent short-term or intermediate outcome of a 5-year survival rate of ≥95% seen in recent years, the current approach to managing SLE patients appears to be successful, except for in a very small portion of patients with refractory diseases, such as those with diffuse pulmonary hemorrhage and pulmonary arterial hypertension (2, 4); however, the long-term outcome remains insufficient due to damage accrual associated with recurrent disease flare and the cumulative dose of GCs (9, 10, 16-18).

SLE flares after the achievement of a low disease activity or remission are commonly observed, even in recent clinical trials (19-22). Therefore, the prevention of disease flare and subsequent damage accrual is crucial for improving the long-term outcome of SLE patients. Reducing the cumulative dose of GCs is necessary because a large number of reported cohort studies in SLE have demonstrated a significant dose-related association between exposure to GCs and damage accrual (10, 17, 18). Although current evidence supporting the GC-sparing effect of immunosuppressants is not solid (7, 11), the present study findings suggest that aggressive use of immunosuppressants in the initial treatment and treatment of disease flare may be associated with a reduction in the SLE flare rate and the dose of GCs.

It should be noted that the major differences between Groups A and B include the recent approval of various immunosuppressants for SLE by the Japanese Pharmaceuticals and Medical Devices Agency, as described previously. Thus, the use of immunosuppressants for SLE patients has been promoted by the disease state (Fig. 4). For example, AZA was actively included in the initial treatment of non-severe SLE manifestations in Group A. MMF tended to be used for BILAG A flares, and TAC was used for BILAG B flares. In Group B, intravenous CYC pulse therapy (IV-CYC) was mainly applied for BILAG A diseases, such as neuropsychiatric manifestations or severe lupus nephritis, and cyclosporin A (CsA) and MZR were used for BILAG B diseases, such as rash and arthritis. Thus, the recent decrease in the flare rate (Table 1, 2) may be partly attributable to the increased treatment choice for immunosuppressants, such as the new approval of MMF.

While most SLE patients show a good initial response to an adequate dose of GCs, the clinical response to any immunosuppressants is varied and unpredictable. For this reason, GCs have been the first choice of therapy for moderate to severe SLE, with the use of immunosuppressants limited (7, 11, 23). However, the long-term safety of immunosuppressants, except for CYC, is regarded as better than that of GCs (11, 24-26). Thus, immunosuppressants with or without the lowest possible dose of GCs may be the mainstay treatment for maintaining remission of moderate to severe SLE, and HCQ may eventually be needed for all patients with SLE (7, 11, 27).

The limitations of this study are the limited sample size,

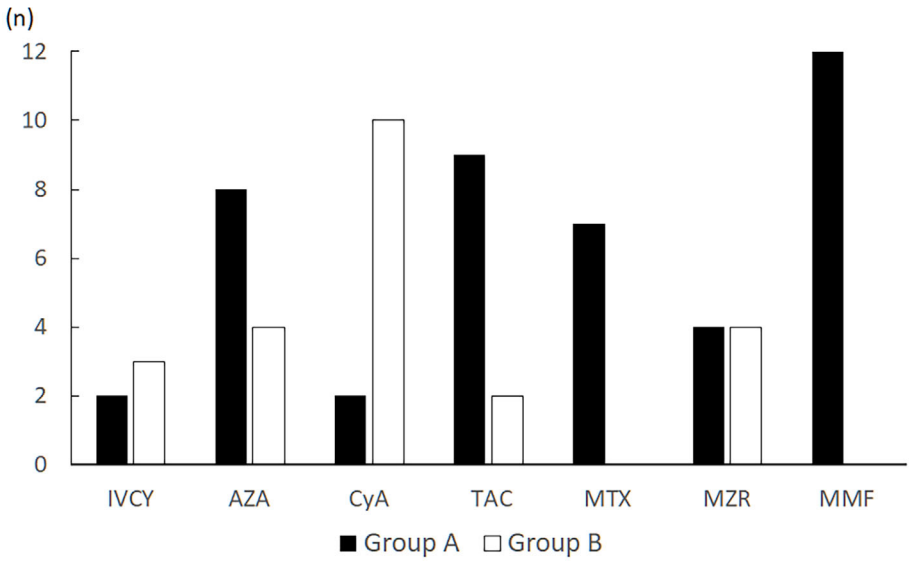

Figure 4. **The total use of immunosuppressants for the treatment of SLE flare. n: number of patients experiencing each treatment, AZA: azathioprine, CsA: cyclosporine A, IV-CYC: intravenous cyclophosphamide, MMF: mycophenolate mofetil, MTX: methotrexate, MZR: mizoribine, TAC: tacrolimus**

single-center setting, and the retrospective, limited period of observation. Therefore, this study suggested but did not verify the effectiveness of immunosuppressants in preventing disease flare.

In conclusion, the recent aggressive use of immunosuppressants resulted in a reduction in the rate of SLE flares and the rate of dose-increment of GCs. Such a trade-off between GCs and immunosuppressants may improve the long-term outcomes of SLE, although this should be confirmed in an extended observational study.

Author's disclosure of potential Conflicts of Interest (COI).
Takehisa Ogura: Honoraria, AbbVie. Hideto Kameda: Honoraria, AbbVie, Asahi-Kasei Pharma, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly Japan, Gilead, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, Novartis, Pfizer Japan, Sanofi and UCB Japan.

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