Deep remission within 12 months prevents renal flare and damage accrual in lupus nephritis

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Abstract

Objective

To evaluate the significance of achieving deep remission by induction therapy in lupus nephritis (LN) patients.

Methods

We assessed consecutive patients undergoing induction therapy for active LN. Achievement of complete renal response (CR) was defined as a urine protein creatinine ratio (UPCR) ≤0.5 g/gCr, and deep remission (DR) was defined as a UPCR ≤0.15 g/gCr with stabilisation of serum creatinine levels assessed every 2–3 months. We compared renal flare and damage accrual rates among patients with CR, CR without DR, and DR at 3, 6, and 12 months and later.

Results

Fifty-nine Asian patients were enrolled, and the median observation period was 48.6 months. Of these, 55 patients achieved CR, and 33 achieved DR within 12 months of receiving induction therapy. The patients with DR within 12 months experienced a significantly lower rate of subsequent renal flare ($p<0.001$) and damage accrual ($p=0.046$) than those without CR, those with DR after 12 months, and those with no DR but CR within 12 months.
In addition, younger age, shorter disease duration, lower urine protein at baseline, and earlier renal response were associated with DR within 12 months.

Conclusion

Achievement of DR within 12 months after induction therapy should be a treatment target for active LN, as it has implications for preventing renal flare and damage accrual.

Key words

lupus nephritis, remission induction, treatment outcome, outcome assessment

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Introduction

The treatment goal in systemic lupus erythematosus (SLE) management is to control the disease activity and prevent damage accrual (1). Remission and response criteria are often used as treatment targets, although definitions vary depending on research findings (2). The recommendation for lupus nephritis (LN) suggested that there is a complete clinical response if the urine protein creatinine ratio (UPCR) is below 0.5–0.7 g/gCr by 12 months after induction (3). However, mortality and morbidity remain high even if these criteria are met (4), and a more stringent treatment strategy may be appropriate to improve long-term outcomes. Deep remission (DR), defined as the reduction of UPCR to 0.15 g/gCr, has been reported to reduce subsequent renal flares (5, 6), however, the utility and associated factors of DR are not clearly understood.

The primary objective of this study was to clarify the clinical characteristics of patients with DR and evaluate the importance of DR achievement, especially within 12 months after induction for active LN.

Materials and methods

Patients and data collection

Consecutive patients who met the 1997 revised criteria of the American College of Rheumatology (ACR) or the 2010 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria were eligible for this study. Patients who underwent induction therapies for active LN, defined as a renal domain in the British Isles Lupus Assessment Group 2004 index of A or B with a severe flare by the Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index Flair Index, were recruited prospectively at Keio University Hospital between February 2015 and July 2019. Attending physicians decided on the treatment regimens based on the published recommendations for the management of LN (7). Demographic and clinical characteristics were recorded at least every three months from baseline until the most recent visit. Any and serious infectious events during the observation period were recorded as part of the safety profile. Ethics committee at Keio University School of Medicine (no. 2014-0093) approved this study conducting in accordance with the Declaration of Helsinki. All patients gave written consent.

Definition and statistical analysis

Complete renal response (CR) and DR were defined as stabilisation (within 25% increase in initial levels of Cr) in serum Cr with a reduction in UPCR to ≤0.5 g/gCr or reduction of UPCR to ≤0.15 g/gCr, respectively. Partial and no renal response, nephritic and proteinuric flare were defined in accordance with previous studies (Supplementary Table S1). Changes in the SLICC/ACR damage index (ΔSDI) from baseline to final visit were evaluated (8). The observation period was defined as the period from the initiation of induction to the final visit before June 2021. Used statistical analysis were shown in Supplementary Table S2.

Results

Patient baseline characteristics and treatments

Sixty Asian patients with active LN were identified, and 59 were enrolled after excluding one patient being transferred to another hospital (Table I). Cyclophosphamide, mycophenolate mofetil (MMF), and calcineurin inhibitors were administered in 40.7%, 40.7%, and 16.9% of patients, respectively, and there was no significant difference in their choice according to the pathological class. In the maintenance phase following 3–6 months of induction, MMF was frequently used for subsequent immunosuppression in 52.5%. The median observation period was 48.6 months.

Renal responses after induction therapy

Fifty-five (93.2%) patients experienced CR during the observation period (CR-ever) (Figure 1), with median time to the achievement of 2.6 months (IQR; 0.6–5.5). Forty-nine (83.1%) patients achieved CR within 12 months after induction (CR ≤12), and among them, 33 (55.9%) achieved DR within 12 months (DR ≤12), and 16 (27.1%) did not achieve DR within 12 months (non-

Table I. Demographics and treatment response of patients.

Clinical characteristics at baseline and final visit in all patients, n=59		
At baseline		
Age, years	39.0	(33.0–50.0)
Female, n (%)	50	(84.7)
Disease duration, months	45.0	(2.0–131.0)
Newly onset, n (%)	22	(37.3)
Classification of renal pathology	24	(40.7), 16 (27.1),
(III/IV, III/IV+V, V, N/A), n (%)	8	(13.6), 11 (18.6)
Neuropsychiatric, n (%)	6	(10.2)
Cardiopulmonary, n (%)	5	(8.5)
Serositis, n (%)	13	(22.0)
Gastrointestinal, n (%)	3	(5.1)
Rash, n (%)	31	(52.5)
Alopecia, n (%)	12	(20.3)
Mucosal ulcers, n (%)	7	(11.9)
Musculoskeletal, n (%)	15	(25.4)
Fever, n (%)	16	(27.1)
Leukocytopenia, n (%)	16	(27.1)
Thrombocytopenia, n (%)	12	(20.3)
Haemolytic anaemia, n (%)	5	(8.5)
Anti-dsDNA antibodies, IU/mL	46.1	(15.7–359.0)
Hypocomplementaemia, n (%)	46	(78.0)
Immune complex-C1q, μg/mL	4.5	(0.0–9.3)
Anti-Sm antibodies, n (%)	28	(49.1)
Anti-RNP antibodies, n (%)	30	(57.7)
Anti-SS-A/Ro antibodies, n (%)	41	(69.5)
Anti-SS-B/La antibodies, n (%)	11	(18.6)
Anti-cardiolipin antibodies, n (%)	22	(37.3)
Positive direct Coombs' test without haemolytic anaemia, n (%)	35	(77.8)
C-reactive protein, mg/dL	0.1	(0.0–0.4)
eGFR, ml/min/1.73m^2	77.0	(54.0–101.0)
UPCR, g/gCr	1.54	(0.54–2.62)
SLEDAI	20.0	(15.0–25.0)
PSL before induction therapy, mg/day	3.8	(0.0–10.0)
Treatments		
Starting dose of PSL, mg/day	50	(40–60)
Starting dose of PSL, mg/kg/day	0.95	(0.78–1.04)
Use of steroid pulse therapy, n (%)	14	(23.7)
Use of mycophenolate mofetil as induction therapy, n (%)	24	(40.7)
Use of intravenous cyclophosphamide as induction therapy, n (%)	24	(40.7)
Use of tacrolimus as induction therapy, n (%)	10	(16.9)
Use of mycophenolate mofetil as subsequent therapy, n (%)	31	(52.5)
Use of azathioprine as subsequent therapy, n (%)	12	(20.3)
Use of tacrolimus as subsequent therapy, n (%)	16	(27.1)
Cumulative dose of cyclophosphamide, mg	4750	(3000–6300)
Dose of mycophenolate mofetil as induction therapy, mg/day	2000	(1625–2000)
Dose of mycophenolate mofetil as subsequent therapy, mg/day	1500	(1000–1750)
Renal response		
Renal response at 3 months, CR/PR/NR, n (%)	26	(44.1)/13 (22.0)/20 (33.9)
Renal response at 6 months, CR/PR/NR, n (%)	37	(62.7)/9 (15.3)/13 (22.0)
Renal response at 12 months, CR/PR/NR, n (%)	44	(74.6)/6 (10.2)/9 (15.3)
At final visit		
Observational period, months	48.6	(37.6–62.0)
eGFR at final visit, ml/min/1.73m^2	79.0	(60.0–94.0)
Δ eGFR from baseline to final visit, ml/min/1.73m^2	1.0	(-13.0–16.0)
30% decline in eGFR from baseline to final visit, n (%)	4	(6.8)
40% decline in eGFR from baseline to final visit, n (%)	1	(1.7)
UPCR at final visit, g/gCr	0.1	(0.0–0.2)
Δ SLICC/ACR damage index from baseline to final visit	0	(0–0)
Δ SLICC/ACR damage index from baseline to final visit ≥1, %	13	(22.0)
Dose of PSL at final visit, mg/day	4.0	(1.0–6.0)
Dose of PSL at 12 months, mg/day	7.0	(5.0–9.0)
Cumulative dose of PSL until final visits, mg	11370	(7780–15591)

*Numbers are shown by median (interquartile range) unless otherwise specified.
CR: complete renal response; DR: deep remission; eGFR: estimated glomerular filtration rate; NR: no renal response; PR: partial renal response; PSL: prednisolone; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR: Systemic Lupus International Collaborating Clinics/American College of Rheumatology; UPCR: urine protein creatinine ratio.

DR in CR ≤12). In total, 44 (74.6%) patients experienced DR during the observation period (DR-ever), with median time to the achievement of 5.8 months (IQR; 2.4–12.9). No patient had developed end-stage renal disease by the final visit.

Renal flares and damage accrual

Renal flares were observed in 14 (23.7%) patients with proteinuric flares in 11 and proteinuric plus nephritic flares in three. Among patients with CR-ever and DR-ever, 13 (23.6%) and 3 (6.8%) patients experienced renal flares, with median time of 4.2 and 28.1 months after CR achievement and 2.8 months after DR. The cumulative renal flare-free rate was significantly higher in the DR-ever than in the non-DR in CR-ever (p<0.001) (Fig. 2A).

Thirteen (22.0%) patients had ΔSDI ≥1 before the final visit (Suppl. Table S3). Among the non-CR patients, three (75.0%) developed damage with an estimated glomerular filtration ratio (eGFR) <50%. Ten (18.2%) patients with CR-ever and eight (18.2%) with DR-ever developed damage accrual.

Timing of complete renal response and deep remission

We divided the patients by the timing of achievement of CR or DR (Suppl. Figure S1). Achievement of DR at 6–12 months was associated with low rates of renal flare compared to non-DR in CR at 6–12 months (p=0.023) (Suppl. Fig. S2, S3). Achievement of DR at ≤3 months was associated with prevention of ΔSDI ≥1 compared to non-DR in CR ≤3 months (p=0.032) (Suppl. Fig. S4). Furthermore, achievement of DR ≤6 or DR ≤12 was associated with higher cumulative renal flare-free rates compared to non-DR in CR ≤6 (p=0.008) or non-DR in CR ≤12 (p<0.001) (Table II, Fig. 2B). Achievement of CR-ever and DR ≤12 was associated with prevention of ΔSDI ≥1 compared with non-CR (p=0.031) and non-DR ≤12 (p=0.012).

Clinical outcomes in patients with a complete renal response or deep remission within 12 months

We focused on the patients with CR ≤12 and DR ≤12. The CR-ever group showed

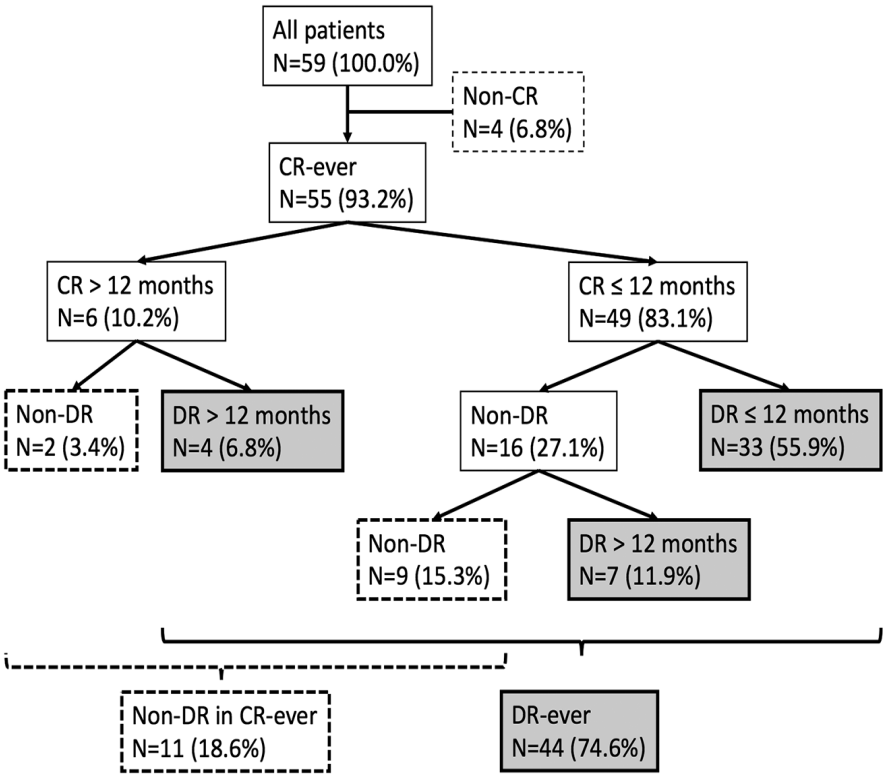

Fig. 1. Patient flow diagram and overview of the achievement of complete renal response (CR) and deep remission (DR). Overview of the numbers and proportions of the patients who experienced CR and DR during the observational period (CR-ever and DR-ever) and those who achieved or did not achieve CR and DR within or after 12 months after induction therapy initiation (CR ≤12, DR ≤12, CR>12, DR >12, non-CR, and non-DR).

a higher eGFR (p=0.003) and lower UPCR at the final visit (p=0.008), and lower proportions of ΔSDI ≥1 (p=0.008) than the non-CR group (Suppl. Table S4). The CR ≤12 group had lower UPCR at the final visit than CR >12 (p=0.030), although renal flares and damage accrual did not significantly differ.

Next, the DR-ever group had lower rates of renal flares and a 30% decline in eGFR and lower UPCR at the final visit than the non-DR group (p=0.002, p<0.001, and p<0.001, respectively) (Suppl. Table S5). Patients with DR ≤12 had lower rates of renal flares (p=0.011), lower UPCR at the final visit (p=0.011), and lower ΔSDI (p=0.007) than DR >12.

Finally, patients with DR ≤12 had lower UPCR (p=0.006), lower rates of renal flares (p<0.001), and lower ΔSDI (p=0.046) compared with non-DR in CR ≤12 (Table III).

Characteristics with complete renal response and deep remission within 12 months

Patients with DR ≤12 were younger (p=0.034), had a shorter disease du-

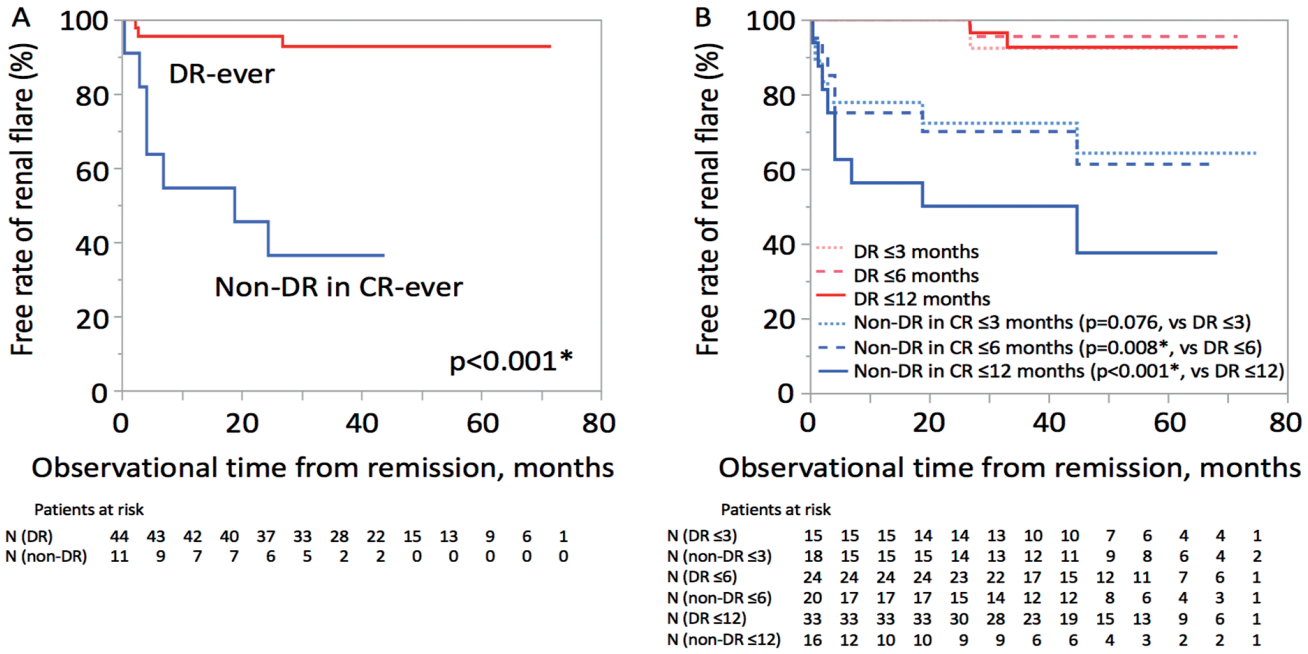

Fig. 2. Cumulative renal flare-free rate after achieving complete renal response (CR) and deep remission (DR).
Comparison of flare-free rate between the patients who experienced CR during the period but did not achieve DR (non-DR in CR-ever) and those experienced DR during the period (DR-ever) **(A)**. Comparison of flare-free rate between the patients achieved CR within 3, 6 and 12 months but did not achieve DR within respective months (non-DR in CR ≤3, 6, and 12) and those who achieved DR within 3, 6, and 12 months (DR ≤3, 6, and 12), respectively **(B)**. Log-rank test was used for the analysis. * p<0.05.

Table II. The complete renal response and deep remission timing are associated with renal flare and damage accrual.

Timing of achievement of CR and DR	Free from renal flare			Damage accrual (ΔSDI ≥1)		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
Achievement of CR within 3 months (*vs*. non-CR ≤3)	1.368	0.411–4.558	0.609	1.344	0.382–4.733	0.645
Achievement of CR within 6 months (*vs*. non-CR ≤6)	1.944	0.530–7.132	0.316	0.444	0.119–1.662	0.228
Achievement of CR within 12 months (*vs*. non-CR ≤12)	1.481	0.327–6.701	0.611	0.338	0.079–1.449	0.144
Achievement of CR during observational period (CR-ever) (*vs*. non-CR)	1.077	0.103–11.260	0.951	**0.074**	**0.007–0.788**	**0.031**
Achievement of DR within 3 months (*vs*. non-DR ≤3)	5.871	0.698–49.384	0.103	0.190	0.023–1.610	0.128
Achievement of DR within 6 months (*vs*. non-DR ≤6)	**5.739**	**1.151–28.626**	**0.033**	0.357	0.087–1.470	0.154
Achievement of DR within 12 months (*vs*. non-DR ≤12)	**13.286**	**2.617–67.440**	**0.002**	**0.160**	**0.038–0.666**	**0.012**
Achievement of DR during observational period (DR-ever) (*vs*. non-DR)	**7.238**	**1.913–27.382**	**0.004**	0.444	0.119–1.662	0.228

*Numbers are shown by median (interquartile range) unless otherwise specified. Bold text indicates a statistically significant difference ($p<0.05$).
CR: complete renal response; DR: deep remission.

Table III. Comparison in demographics and outcomes between DR and non-DR in CR within 12 months.

Clinical characteristics	DR ≤12, n=33	Non-DR in CR ≤12, n=16	*p*-value
At baseline			
Age, years	**38 (26.5–45)**	**44 (37.5–53.8)**	**0.034**
Female, n (%)	28 (84.9)	15 (93.8)	0.373
Disease duration, months	**20 (0–97)**	**117 (23–212.3)**	**0.011**
Newly onset, n (%)	16 (48.5)	4 (25.0)	0.117
Classification of renal pathology (III/IV, III/IV+V, V, N/A), n	14, 7, 4, 8	6, 4, 4, 2	0.374
Neuropsychiatric, n (%)	3 (9.1)	1 (6.3)	0.733
Cardiopulmonary, n (%)	2 (6.1)	1 (6.3)	0.979
Serositis, n (%)	9 (27.3)	3 (18.8)	0.515
Gastrointestinal, n (%)	2 (6.1)	1 (6.3)	0.979
Rash, n (%)	20 60.6)	7 (43.8)	0.266
Alopecia, n (%)	8 (24.2)	2 (12.5)	0.339
Mucosal ulcers, n (%)	5 (15.2)	1 (6.3)	0.373
Musculoskeletal, n (%)	12 (36.4)	3 (18.8)	0.210
Fever, n (%)	12 (36.4)	2 (12.5)	0.083
Leukocytopenia, n (%)	11 (33.3)	2 (12.5)	0.121
Thrombocytopenia, n (%)	6 (18.2)	4 (25.0)	0.579
Haemolytic anaemia, n (%)	4 (12.1)	0 (0.0)	0.146
Anti-dsDNA antibodies, IU/mL	98.4 (14.4–4000.0)	27.5 (13.5–44.4)	0.068
Hypocomplementaemia, n (%)	25 (75.8)	13 (81.3)	0.666
Immune complex-C1q, μg/mL	7.2 (0–12.2)	1.0 (0–4.6)	0.051
Anti-Sm antibodies, n (%)	15 (46.9)	7 (43.8)	0.838
Anti-RNP antibodies, n (%)	17 (60.7)	6 (40.0)	0.194
Anti-SS-A/Ro antibodies, n (%)	23 (69.7)	13 (81.3)	0.390
Anti-SS-B/La antibodies, n (%)	6 (18.2)	5 (31.3)	0.304
Anti-cardiolipin antibodies, n (%)	13 (39.4)	7 (43.8)	0.771
Positive direct Coombs' test without haemolytic anaemia, n (%)	22 (84.6)	10 (100.0)	0.188
C-reactive protein, mg/dL	0.15 (0.04–0.49)	0.16 (0.05–0.35)	0.873
eGFR, ml/min/1.73m^2	81 (56.5–101.5)	82.5 (59.3–116.5)	0.741
UPCR, g/gCr	**1.31 (0.42–1.74)**	**1.86 (1.11–3.00)**	**0.025**
SLEDAI	20 (16–28)	18.5 (12–21.8)	0.162
PSL before induction therapy, mg/day	0 (0–8)	5 (0–10)	0.236
Observational periods, months	48.6 (37.2–65.8)	43.3 (37.2–56.3)	0.382
Treatments			
Starting dose of PSL, mg/day	**50 (42.5–60)**	**42.5 (30–53.8)**	**0.044**
Starting dose of PSL, mg/kg/day	0.96 (0.87–1.04)	0.88 (0.61–1.03)	0.254
Use of steroid pulse therapy, n (%)	10 (30.3)	1 (6.3)	0.058
Use of mycophenolate mofetil as induction therapy, n (%)	17 (51.5)	5 (31.3)	0.182
Use of intravenous cyclophosphamide as induction therapy, n (%)	13 (39.4)	7 (43.8)	0.771
Use of tacrolimus as induction therapy, n (%)	4 (12.1)	3 (18.8)	0.534
Use of mycophenolate mofetil as subsequent therapy, n (%)	20 (60.6)	7 (43.8)	0.266
Use of azathioprine as subsequent therapy, n (%)	8 (24.2)	4 (25.0)	0.954
Use of tacrolimus as subsequent therapy, n (%)	7 (21.2)	4 (25.0)	0.766
Cumulative dose of cyclophosphamide, mg	93.8 (82.0–110.6)	95.7 (73.5–98.9)	0.821
Dose of mycophenolate mofetil as induction therapy, mg/day	2000 (1750–2000)	2000 (1500–2000)	0.306
Dose of mycophenolate mofetil as subsequent therapy, mg/day	1500 (1000–1688)	1500 (1250–2000)	0.727

Clinical characteristics	DR ≤12, n=33	Non-DR in CR ≤12, n=16	*p*-value
Renal response			
Renal response at 3 months, CR/PR/NR, n (%)	**21 (63.6)/8 (24.2)/4 (12.1)**	**5 (31.3)/4 (25.0)/7 (43.8)**	**0.031**
Renal response at 6 months, CR/PR/NR, n (%)	**31 (93.9)/0 (0.0)/2 (6.1)**	**6 (37.5)/6 (37.5)/4 (25.0)**	**<0.001**
At final visit			
Renal flares during observational periods, n (%)	**2 (6.1)**	**9 (56.3)**	**<0.001**
eGFR at final visit, ml/min/1.73m^2	86 (63.5–99.5)	88.5 (66.8–109.5)	0.536
Δ eGFR from baseline to final visit, ml/min/1.73m^2	1.0 (-11.0–18.3)	-5 (-17.5–12.5)	0.565
30% decline in eGFR from baseline to final visit, n (%)	0 (0.0)	1 (6.3)	0.147
40% decline in eGFR from baseline to final visit, n (%)	0 (0.0)	0 (0.0)	–
UPCR at final visit, g/gCr	**0.05 (0.00–0.12)**	**0.14 (0.08–2.01)**	**0.006**
Δ SLICC/ACR damage index from baseline to final visit	**0 (0–0)**	**0 (0–1)**	**0.046**
Δ SLICC/ACR damage index from baseline to final visit ≥1, %	**3 (9.1)**	**5 (31.3)**	**0.049**
Dose of PSL at final visit, mg/day	5 (0.5–6.5)	4 (2.7–7.5)	0.723
Dose of PSL at 12 months, mg/day	7 (5.0–9.0)	8 (6.3–9.0)	0.463
Cumulative dose of PSL until final visits, mg	10600 (7826–16065)	11630 (7330–14932)	0.509

*Numbers are shown by median (interquartile range) unless otherwise specified. Bold text indicates a statistically significant difference ($p<0.05$).
CR: complete renal response; DR: deep remission; eGFR: estimated glomerular filtration rate; NR: no renal response; PR: partial renal response; PSL: prednisolone; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR: Systemic Lupus International Collaborating Clinics/ American College of Rheumatology; UPCR: urine protein creatinine ratio.

Table IV. Comparison of infections between the patients with or without deep remission within 12 months and during the period.

	All, n=59	Non-DR, Nn=15	DR-ever, n=44	*p*-value Non-DR *vs*. DR	DR >12, n=11	DR ≤12, n=33	*p*-value DR ≤12 *vs*. DR >12
Any infections, n (%)	47 (79.7)	13 (86.7)	34 (77.3)	0.435	10 (90.9)	24 (72.7)	0.213
Number of any infections	2 (1–3)	2 (1–3)	2 (1–3)	0.832	3 (1–4)	2 (0–3)	0.195
Serious infections, n (%)	9 (15.3)	2 (13.3)	7 (15.9)	0.811	3 (27.3)	4 (12.1)	0.234
Number of serious infections	0 (0–0)	0 (0–0)	0 (0–0)	0.812	0 (0–1)	0 (0–0)	0.240

*Numbers are shown by median (interquartile range) unless otherwise specified. DR, deep remission

ration (p=0.011), and lower UPCR (p=0.025) at baseline, compared with non-DR in CR ≤12 (Table III). The induction therapy regimens were not different, however, the renal response at 3 and 6 months was better in patients with DR ≤12 (p<0.001).

Safety profile in patients with DR and with non-DR

Forty-nine (79.7%) and 9 (15.3%) patients experienced any and serious infections (Table IV, Suppl. Table S6). The incidence of any and serious infections did not significantly differ between the patients with non-DR and DR-ever, as well as between those with DR >12 and DR ≤12.

Discussion

Renal flare is an important predictor of progressive chronic kidney disease (CKD) which associated with risks for mortality in SLE (9, 10). Since most patients are young-onset and will have chronic morbidity, more stringent management of CKD may further improve long-term prognosis (11). Our prospective study demonstrated that the renal flare rate was lower in patients with DR achievement than only CR achievement, and ΔSDI ≥1 was observed in 18.2% of the CR-ever group over the 48.6-month, suggesting that there is scope for more stringent targets than only CR.

The present study also suggests that the earlier DR achievement, the more favourable the outcome. Lack of differences in the frequency of infections between patients with DR ≤12 and later, suggested that immunosuppression was not excessively intensive in those with DR achievement. The importance of DR ≤12 was in line with our previous report that achieving the lupus low disease activity state within 12 months was associated with favourable outcomes (12).

The first limitation of this study is a small Asian cohort from a single centre, and the limited duration of observation, although the median period was more than four years. During this, no patients developed ESRD, and the rates of 30% and 40% decline in eGFR (13), were low. Second, our real-world cohort included first-onset and relapse patients with various treatment histories. Third, no significant difference was reached by histological classification between DR and non-DR in CR, although previous reports suggested that histology was associated with renal response (14, 15). The reasons could be that renal biopsies were not performed in some cases and the small numbers.

In conclusion, DR achievement within 12 months after induction therapy is associated with preventing renal flares and damage accrual better than later DR achievement or CR achievement without DR and is a more suitable treatment target of induction therapy for LN. Younger age, shorter disease duration, lower urine protein level at baseline, and earlier renal response are favourable predictors of DR achievement within 12 months.

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