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ORIGINAL ARTICLE

Steroid-free remission in lupus: myth or reality; an observational study from a tertiary referral centre

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Abstract

Objective Whether maintaining steroid-free remission is feasible in Indian patients with systemic lupus erythematosus (SLE).

Methods In 148 patients with SLE including 78 lupus nephritis (LN) previously put into remission, steroid therapy was gradually tapered off.

Results Patients received glucocorticoids for median 1855 days (interquartile range (IQR) 901–2834) before discontinuing. Median duration of follow-up was 539 days (IQR 266.25–840.75). Flare occurred in 31 patients (20.9%; 95% confidence interval (CI) 15.17–28.19, renal flare in 12.16% (18/148, 95% CI 7.83–18.41)). Most of the flares occurred in the first year of follow-up (41.9%, 13/31). Overall 93.5% (29/31) of flares occurred in those who received ≤ 8 years of glucocorticoids, compared to 6.5% (2/31) of flares in others ($p = 0.009$). Median flare-free survival was 611 days (95% CI 518–704). Multivariate Cox regression identified the following predictors of flare-free survival: duration of disease (hazard ratio (HR) 0.89, 95% CI 0.84–0.94, $p < 0.001$), duration of glucocorticoid before discontinuing (HR 1.000086, 95% CI 1.000047–1.00012, $p < 0.001$) and second immunosuppressive (HR 1.89, 95% CI 1.251–2.87, $p = 0.003$). Additional risk factors of a renal flare-free survival among patients with LN were initial dose of glucocorticoids (HR 0.97, 95% CI 0.94–0.99, $p = 0.005$) and presence of haemolytic anaemia (HR 2.43, 95% CI 1.067–5.54, $p = 0.035$).

Conclusions About 20% patients undergo exacerbation of disease activity after glucocorticoid withdrawal. Treatment for ≥ 8 years before discontinuing and an additional immunosuppressive agent improve the chance of flare-free survival.

Keywords Flare-free survival · Glucocorticoid · Lupus nephritis · Steroid-free-remission · Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multisystem immune-complex-mediated autoimmune disease with occasional waxing and waning. Over the past two decades, improved supportive care and aggressive immunosuppressive therapy early in the course of disease have resulted in a progressive improvement of disease outcome and reduced morbidity [1–3]. However, patients with lupus are exposed to prolonged treatment with glucocorticoids which may result in a number of serious adverse effects. EULAR/EDTA guideline on lupus nephritis has recommendations for the minimum duration of required immunosuppression (glucocorticoids and other immunosuppressant) for at least 3 years, with suggestion for individualization of duration of further continuation of glucocorticoids [4]. It is often reported that prolonged glucocorticoid treatment leads to short- and long-term increase in morbidity and mortality [5]. In the follow-up study of the Hopkins Lupus Cohort, multivariate analysis showed that the strongest predictors of

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Key messages
1. About 20% patients undergo disease-flare after glucocorticoid withdrawal, mostly within the first year
2. Glucocorticoid for ≥ 8 years before discontinuation and an additional immunosuppressive agent improve chance of flare-free survival
3. Neuropsychiatric flare is unlikely for a patient with baseline neuropsychiatric lupus, once in remission

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damage accrual were age and corticosteroid dose even after adjusting for lupus disease activity [6]. In the Systemic Lupus International Collaborating Clinics (SLICC) study, continued corticosteroid use and hypertension influenced future damage accrual in addition to disease activity [7]. Much of the increased morbidity and mortality related to the prolonged use of steroids owes to the development of premature atherosclerosis. Myocardial infarction and stroke are 8.5 and 10 times more prevalent, respectively, in SLE women than in the general population [8, 9]. Positive associations are reported between glucocorticoid use and dyslipidemia, arterial hypertension [10] and increased cardiovascular risk [11].

Following the first description of immunosuppressive withdrawal in lupus nephritis in 1988, studies have found that gradual tapering off of steroids in patients with lupus results in flares, varying from 38 to 50% [12–14]. All of these reports are from Caucasian populations.

Owing to the dearth of data on the feasibility of glucocorticoid withdrawal among Asian patients with SLE, we undertook this study aiming to look at the outcome of withdrawing glucocorticoid in Indian patients with lupus in clinical remission. Another objective of our study was to compare the rates of renal flares among patients with lupus nephritis (LN) achieving durable remission who are either with or without maintenance glucocorticoids.

Participants and methods

This retrospective longitudinal observational study was conducted in the Department of Rheumatology, Institute of Post Graduate Medical Education and Research, Kolkata, India. Patients with SLE, admitted and seen in the in-patient and out-patient (OPD) departments, were screened for inclusion in the study (from 1999 to 2006). All such patients' data are kept in OPD files and were accessed. These patients are being prospectively followed up in our clinic.

Inclusion criteria were fulfilment of the SLICC 2012 criteria [15] and initiation of glucocorticoid therapy at any point of time between 1999 and 2006. At initiation of the study, diagnoses of lupus were revisited and included if SLICC 2012 criteria were fulfilled. As a part of institutional protocol, we taper glucocorticoids and other immunosuppressive agents after a patient is deemed in clinical remission (defined as clinical SLE disease activity index (SLEDAI-2K = 0) [16]. Those patients whose glucocorticoid therapy was completely discontinued were included for analysis. After discontinuation of glucocorticoid, the patients were further followed up on an average 3–4 months interval and additionally on SOS basis.

We excluded the following patients and did not include in the analysis: lost to follow-up for more than 6 months; no biochemical investigations done in the past 6 months and self-determination of immunosuppressive agents against physicians' advice.

Following data were recorded: age at SLE onset (juvenile- vs adult-onset SLE), age at the onset of glucocorticoid treatment, age at the end of follow-up, gender, duration of disease in years, duration of glucocorticoid therapy before discontinuing in days, type of SLE involvement at the onset of glucocorticoid initiation and use (if any) of other immunosuppressive agents .

Flares were defined using the SLEDAI-2K (≥ 4 point increase in SLEDAI-2K compared to previous visit) and recorded as individual organ system involvement. In particular, renal flare was defined as follows: presence of either proteinuric flare or nephritic flare. A proteinuric renal flare was defined as an increase in proteinuria to ≥ 2 g/day if the patient achieved a complete response after induction treatment of baseline lupus nephritis or doubling of proteinuria after a partial response. A nephritic flare was defined as recurrence of active urinary sediment with increase in plasma creatinine by ≥ 30% of baseline, with or without a concomitant increase in proteinuria [17]. However, if the patient did not have baseline lupus nephritis, then new fulfilment of any two of the four renal SLEDAI components would warrant a renal flare.

Flares were deemed major if it necessitated addition of prednisolone dose ≥ 0.5 mg/kg BW/day with or without addition or increment in dose of a second immunosuppressant agent other than hydroxychloroquine. All other flare episodes which were managed with local therapy, addition of nonsteroidal anti-inflammatory agents and steroids at a dose < 10 mg/day were deemed as minor flare.

We also performed a nested case-control study on patients with lupus nephritis. In one arm, we included all patients with lupus nephritis from our original cohort (described above) whose maintenance glucocorticoid was tapered off. The other arm consisted of longitudinally followed up patients with lupus nephritis, attending our clinic, who were on maintenance therapy after remission with low-dose prednisolone with or without any other immunosuppressive agents. Patients were included if they had achieved a durable complete renal remission (renal SLEDAI = 0), had been maintaining on a stable dose of low-dose glucocorticoid (prednisolone equivalent ≤ 7.5 mg/day), either without a second immunosuppressive agent or on a stable dose of the same (azathioprine, mycophenolate or tacrolimus) without a dose change in the past 6 months. This latter group of patients was selected matching for the number of patients with lupus nephritis in the original study (1:1 assignment), gender and age of onset of SLE. The same exclusion criteria, as in the main study, applied to these patients as well. The rates of development of renal flare in this group were noted and compared to those whose glucocorticoids had been stopped.

Statistical methods

Continuous variables were expressed as mean ± standard deviation (SD) when normally distributed or as median (interquartile range (IQR)) when otherwise. Categorical variables were expressed as number (percentage). Comparisons of means were done using Student's *t* test or Mann Whitney *U* test and comparison of proportions using the Chi squared test or Fisher's exact test as appropriate. Median flare-free survival was calculated from life tables. Univariate prediction of flare-free and renal flare-free survival was done with Cox proportional hazard regression analysis with days of follow-up time variable and censoring data points if and when a flare occurred. Variables with $p \leq 0.2$ in univariate survival analysis were analysed in a multivariate Cox regression. The results were reported as adjusted hazard ratios (aHR) and 95% confidence intervals (95% CI). All statistical analyses were done using the software package IBM SPSS v 21.

Ethical statement

All participants were informed of the study details and informed consents were taken. The study protocol was reviewed and approved by the Institutional Ethics Committee (Memo no IPGME&R/IEC/2018/043). Anonymity was maintained throughout the process.

Results

Baseline characteristics

Overall, 148 patients (age: mean 32.5 ± 9.8 years; female: 95.9% (142/148)) could be followed up. Of these, 108/148 (73%) were adult-onset lupus patients (mean age of onset 26.4 ± 7.7; mean duration of disease 8.7 ± 4.7 years; female: 96.3%, 104/108) and 40/108 (27%) were of juvenile onset (mean age of onset 13.3 ± 5.4 years at disease onset, duration of disease 8.8 ± 4.8 years; female: 95%, 38/40). Baseline diagnosis of the included patients at the time of glucocorticoid initiation were as follows: lupus nephritis 52.7% (78/148); arthritis 37.2% (55/148); mucocutaneous 30.4% (45/148); haematological: autoimmune haemolytic anaemia (AIHA) 11.5% (17/148), thrombocytopenia 4.2% (6/144), leucopoenia 3.4% (5/148); neuropsychiatric lupus (NPLE) 10.1% (15/144); serositis 8.1% (12/148); myositis 6.8% (10/148); vasculitis 4.1% (6/148); enteritis 1.4% (2/148) and pneumonitis 0.7% (1/148). Mean SLEDAI-2K at the initiation of glucocorticoids was 12.55 ± 4.99. On an average, patients received glucocorticoids for 2317 ± 3490 days (median 1855; IQR 901–2834) before stopping. Initial prednisolone dose was 37 ± 16 mg per day (median 40 mg/day, IQR 25–50). Average age at steroid onset was 35.5 ± 9.1 years (median 35 years, IQR 30–41) for adult-onset patients and 20.9 ± 8.1 years (median 21 years, IQR 15–25 years) for juvenile-onset patients. All the patients were on hydroxychloroquine. No immunosuppressive agents other than glucocorticoids and hydroxychloroquine were given in 43.2% (64/148). Others received the following immunosuppressive agents: monthly IV cyclophosphamide followed by azathioprine (20.9%, 31/148); only azathioprine (13.5%, 20/148); mycophenolate mofetil (13.5%, 20/148); monthly IV cyclophosphamide followed by mycophenolate mofetil (7.4%, 11/148) and oral tacrolimus and IV rituximab in one patient each.

Follow-up

Mean duration of follow-up was 734 ± 737 days (median 539 days, IQR 266–841). Overall, 34 flare episodes occurred in 31 patients (31/148, 20.9%, 95% CI 15.17–28.19). Median duration of follow-up at flare was 400 days (IQR 232–724). The flare frequency according to the year of follow-up was as follows: in the first year: 41.9%, 13/31; 38.7% (12/31) in the second year; 9.7% (3/31) in the third year, and 6.5% (2/31) in the fourth year of follow-up. Only one flare occurred beyond the fourth year, a renal flare in the 8th year of follow-up. Flare frequency according to organ involvement were as follows: renal 12.16% (18/148, 95% CI 7.83–18.41), AIHA 3.4% (5/148, 95% CI 1.45–7.66), arthritis 2.7% (4/148, 95% CI 1.06–6.74), leucopenia and systemic 2% (3/148, 95% CI 0.69–5.79), mucocutaneous 1.4% (2/148, 95% CI 0.37–4.79) and neuropsychiatric and pulmonary arterial hypertension (PAH) in 0.7% (1/148, 95% CI 0.12–3.73). Flares were deemed major in 74.2% (23/31) and minor in 25.8% (8/31) of patients. Major flares occurred in 16.7% of (13/78) patients with LN, 11.8% (2/17) in AIHA, 33.3% (2/6) in vasculitis, 13.3% (6/45) in mucocutaneous lupus, myositis 20% (2/10), leucopenia 20% (1/5), serositis 8.3% (1/12), NPLE 35.7% (5/14) and none in thrombocytopenia, pneumonitis or enteritis as baseline diagnosis.

Overall, patients with mucocutaneous disease had the highest frequency of flare-free remission (84.4%). The flare-free remission according to baseline diagnosis is depicted in Fig. 1. In bivariate comparison, patients with baseline mucocutaneous disease had higher flare-free remission compared to baseline NPLE (difference 24.4%, 95% CI 0.27 to 49.88, $p = 0.049$) and vasculitis (difference 34.4%, 95% CI 0.47 to 66.60, $p = 0048$). Number of flare episodes with respect to baseline diagnosis is depicted in Fig. 2. Baseline LN patients suffered only LN as major flare ($n = 13$). None of the patients with baseline NPLE had any further flare of NPLE; rather they suffered from flares of LN ($n = 2$) and AIHA ($n = 3$).

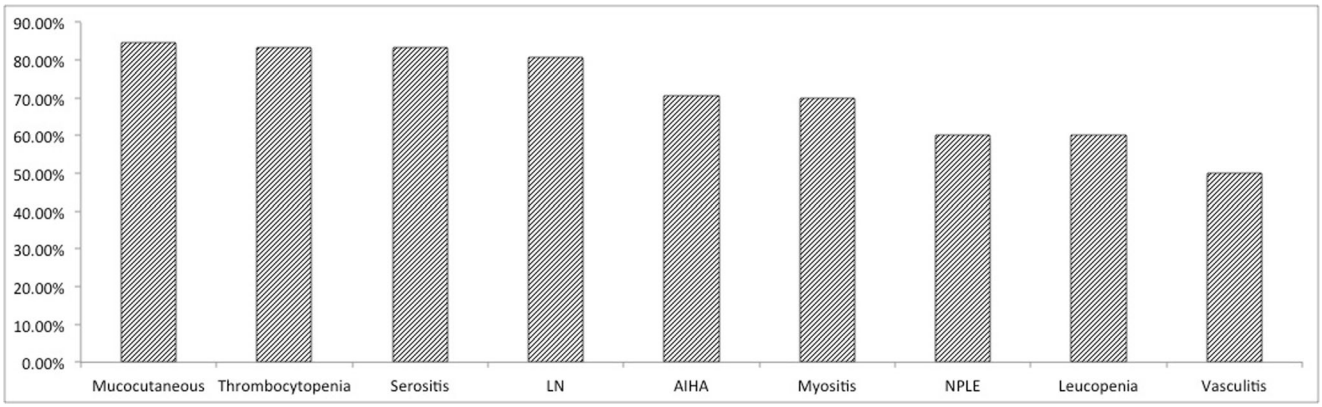

Fig. 1 Comparison of flare-free remission in the glucocorticoid-off group. Rates of flare-free remission in decreasing frequency were as follows: mucocutaneous (84.4%), thrombocytopenia and serositis (83.3%), lupus nephritis (80.77%), autoimmune haemolytic anaemia (70.59%), myositis (70%), neuropsychiatric lupus and leucopenia (60%) and vasculitis (50%). In bivariate comparison, patients with baseline mucocutaneous disease had higher flare-free remission compared to baseline NPLE (difference 24.4%, 95% CI 0.27 to 49.88, $p = 0.049$) and vasculitis (difference 34.4%, 95% CI 0.47 to 66.60, $p = 0048$). Abbreviations used: AIHA, autoimmune haemolytic anaemia; LN, lupus nephritis; NPLE, neuropsychiatric lupus

The flare frequency according to number of years on glucocorticoids before discontinuation is displayed in Fig. 3. Least number of flares occurred in those with ≥ 8 years of glucocorticoid exposure. Overall, 93.5% (29/31) of flares occurred in those with ≤ 8 years of treatment, whereas only 6.5% (2/31) of flares occurred in those with > 8 years of treatment before discontinuation ($p = 0.009$).

Survival analysis

The median flare-free survival was 611 days (95% CI 518–704). The median major flare-free survival was 586 days (95% CI 505–667). Cox hazard analyses of baseline predictors of having a flare-free survival are given in Tables 1 and 2. Duration of disease (HR 0.91, 95% CI 0.87–0.95, $p < 0.001$), receipt of a second immunosuppressive agent (HR 1.77, 95% CI 1.22–2.57, $p = 0.003$) and presence of myositis at baseline (HR 1.17, 95% CI 1.104–5.32, $p = 0.027$) predicted flare-free survival in univariate Cox regression. In multivariate Cox regression, the following predictors of flare-free survival were identified: duration of disease (HR 0.89, 95% CI 0.84–0.94, $p < 0.001$), duration of treatment with glucocorticoid before discontinuing (HR 1.000086, 95% CI 1.000047–1.00012, $p < 0.001$) and receipt of a second immunosuppression (HR 1.89, 95% CI 1.251–2.87, $p = 0.003$). This translates to a 3.18% increased chance of flare-free survival after one more year of continued glucocorticoids after achieving remission. Predictors of renal flare-free survival among patients with baseline lupus nephritis are given in Table 3. In multivariate analysis, renal flare-free survival was predicted by duration of

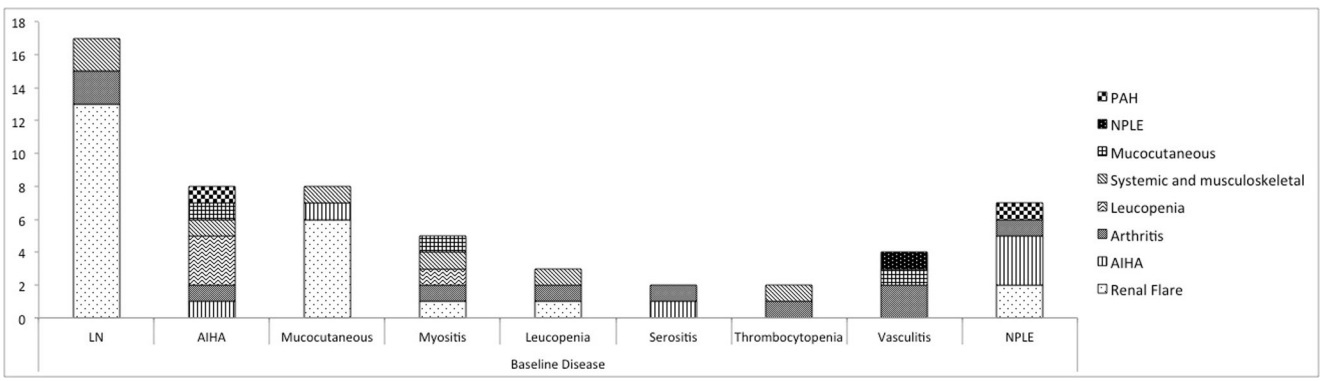

Fig. 2 Number of flare episodes with respect to baseline diagnosis. Baseline LN patients suffered only LN as major flare ($n = 13$). Patients with AIHA suffered from AIHA flare ($n = 1$) and leucopenia ($n = 3$). Patients with baseline myositis had one episode of LN and another leucopenia. One episode of AIHA occurred in a patient with baseline serositis. One patient with baseline vasculitis developed an episode of NPLE. None of the patients with baseline NPLE had any further flare of NPLE; rather they suffered from flares of LN ($n = 2$) and AIHA ($n = 3$). Baseline diagnostic groups, which never had relapse, in the same group were as follows: mucocutaneous, myositis, leucopenia, thrombocytopenia, vasculitis and NPLE. Abbreviations used: AIHA, autoimmune haemolytic anaemia; LN, lupus nephritis; NPLE, neuropsychiatric lupus; PAH, pulmonary arterial hypertension

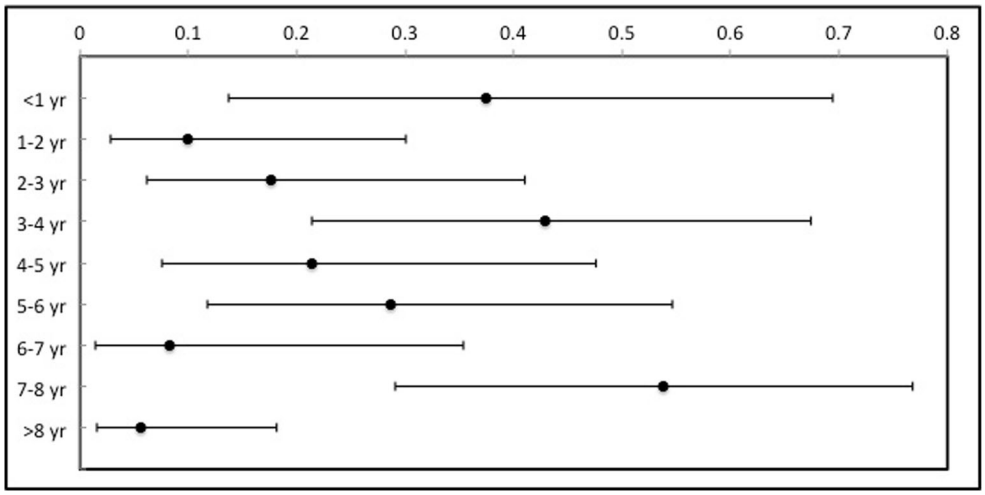

Fig. 3 Comparison of flare frequency (as percentage on x-axis) according to number of years on glucocorticoids before discontinuation (y-axis). The observed frequency (central black dot) and 95% confidence intervals are depicted as a forest plot. On direct bivariate comparison of flare frequency with different intervals of glucocorticoid duration, compared to those with > 8 years of glucocorticoid exposure, the following results were obtained (expressed as mean difference with 95% confidence interval): vs 7–8 years: 48.3 (20.6–71.6), $p < 0.0001$; 6–7 years: 2.8 (− 11.5014 to 30.1400), $p = 0.7$; 5–6 years: 23.1 (2.0700 to 49.4794), $p = 0.02$; 4–5 years: 15.9 (− 2.7983 to 42.3620), $p = 0.09$; 3–4 years: 37.4 (12.5064 to 62.2670), $p = 0.001$; 2–3 years: 12.1 (− 4.8913 to 35.8155), $p = 0.1$; 1–2 years: 4.5 (− 9.9914 to 24.9950), $p = 0.53$; < 1 year: 32 (5.0714 to 64.1738), $p = 0.01$. Least number of flares occurred in those with ≥ 8 years of glucocorticoid exposure. Overall 93.5% (29/31) of flares occurred in those with ≤ 8 years of treatment, whereas only 6.5% (2/31) flares occurred in those with > 8 years of treatment before discontinuation ($p = 0.009$)

disease (HR 0.85, 95% CI 0.78–0.93, $p < 0.001$), duration of treatment with glucocorticoid before discontinuing (HR 1.000094, 95% CI 1.000004–1.00014, $p < 0.001$), receipt of a second immunosuppression (HR 3.2, 95% CI 1.39–7.33, $p = 0.006$), initial dose of glucocorticoids (HR 0.97, 95% CI 0.94–0.99, $p = 0.005$) and presence of AIHA (HR 2.43, 95% CI 1.067–5.54, $p = 0.035$). Again, this would mean a 3.49% increased chance of renal flare-free survival with one more year of continued glucocorticoid after achieving remission.

Comparison of renal flare rates between the groups of lupus nephritis with or without glucocorticoid withdrawal

We prospectively followed up a cohort of 88 patients with lupus nephritis, treated at our centre, who had achieved a complete renal remission and maintained on low-dose glucocorticoids. Comparison of these patients with those who had their glucocorticoids stopped is given in Table S1. Overall, patients continuing on glucocorticoids were younger (26.8 ± 9 years vs 32.2 ± 9.6, $p < 0.001$), had a shorter duration of disease (6.1 ± 3.8 years vs 9.2 ± 4, $p < 0.001$) and had a shorter duration on glucocorticoids (1366 ± 821 days vs 2647 ± 4526 days, $p < 0.001$). In all other respects, these two groups were comparable. Rate of renal flare was higher in the glucocorticoid-off group (13/78, 16.67%, 95% CI 10.01–26.45 vs 5/88, 5.68%, 95% CI 2.45–12.62, $p = 0.023$). Patients with renal flare in the continued glucocorticoid group had lower initial prednisolone dose (30 ± 17.7 vs 44.6 ± 12.7 mg/day, $p = 0.035$) and shorter duration of disease (5 ± 2.2 vs 8.8 ± 3.7 years, $p = 0.035$) compared to the patients whose glucocorticoids were stopped (Fig. 3). In multivariate logistic regression (Table S2), protection from renal flare was associated with continued glucocorticoid use (odds ratio (OR) 0.16, 95% CI 0.03–0.74, $p = 0.02$) and more than 8 years of glucocorticoid therapy (OR 0.53, 95% CI 0.003–8.78, $p = 0.02$). The groups had comparable frequency of glucocorticoid related adverse effects (Table S1).

Discussion

In this study we observed that withdrawal of glucorticoids is feasible in Indian patients with SLE even with proliferative lupus nephritis. However, flare of disease activity was not uncommon and occurred in 20.9% (95% CI 15.17–28.19) after a median of 400 days of follow-up. Around 42% flares occurred in the first year of follow-up and all except one flare occurred in the first 4 years of follow-up. Most renal flares had necessitated induction therapy again. Flare-free survival was predicted by shorter duration of disease, longer duration of treatment with glucocorticoid before discontinuing and receipt of a second immunosuppressive agent. Additional predictors of renal flare-free survival were lower initial dose of glucocorticoids and presence of AIHA.

Drenkard et al. [18], from a cohort of 667 patients, out of which 156 had at least one period of ≥ 1 year of treatment-free clinical remission, reported 48% flare rate. Available data on

Table 1 Comparison of demographics and baseline diagnostic classes between those who had a flare versus those who did not

Dependent variables	No flare $n = 117$	Flare occurred $n = 31$	p value[a]	HR	95% CI	p value[b]
Age in years at the end of follow-up	33.2 ± 10.3	29.6 ± 7.3	0.089	0.98	0.96–1.001	0.057
Age in years at GC onset	32.7 ± 11.2	27.3 ± 8.9	0.013*	0.98	0.97–1.004	0.13
Age of onset of disease	23.5 ± 9.7	20.4 ± 6.9	0.144	1.001	0.98–1.02	0.93
Duration of disease in years	8.8 ± 4.9	8 ± 3.5	0.99*	0.91	0.87–0.95	< 0.001
Female gender	95.7 (112)	96.8 (30)	0.99#	1.18	0.75–1.85	0.48
Juvenile onset disease	27.4 (32)	25.8 (8)	0.86	0.91	0.60–1.38	0.67
Duration of GC treatment before stopping in days	2478 ± 3880	1710 ± 994	0.26	1.00004	0.999–1.00008	0.088
Initial dose of GC (mg/day)	37.1 ± 15.8	36.8 ± 17.7	0.91	0.99	0.98–1.005	0.28
Prescription of other immunosuppressive agent	58.1% (68)	51.6% (16)	0.52	1.77	1.22–2.57	0.003
Days of follow-up after steroid withdrawal	1124.27 ± 3813.12	533.69 ± 491.6	0.17			
Baseline diagnosis						
LN	53.8 (63)	48.4 (15)	0.58	1.06	0.73–1.53	0.76
NPLE	7.7 (9)	19.4 (6)	0.056	0.59	0.30–1.19	0.14
AIHA	10.3 (12)	16.1 (5)	0.36	1.25	0.68–2.28	0.47
Leucopenia	2.6 (3)	6.5 (2)	0.28#	1.45	0.45–4.64	0.53
Thrombocytopenia	4.7 (5)	3.2 (1)	0.99#	2.29	0.91–5.74	0.077
Mucocutaneous	32.5 (38)	22.6 (7)	0.28	1.08	0.73–1.61	0.69
Arthritis	35.9 (42)	41.9 (13)	0.54	1.54	0.75–3.18	0.24
Vasculitis	2.6 (3)	9.7 (3)	0.107#	1.005	0.32–3.19	0.99
Myositis	6 (7)	9.7 (3)	0.46	2.42	1.104–5.32	0.027
Serositis	8.5 (10)	6.5 (2)	0.7	1.17	0.61–2.24	0.64
SDI ≥ 1	15.4 (18)	19.4 (6)	0.594	0.771	0.465–1.278	0.313
Serological activity at steroid withdrawal[c]	16.2 (19)	29 (9)	0.106	0.845	0.516–1.384	0.505
SLEDAI at GC inception	12.35 ± 4.99	13.32 ± 4.99	0.268	1.016	0.977–1.056	0.434

AIHA autoimmune haemolytic anaemia, *CI* confidence interval, *GC* glucocorticoid, *HR* hazard ratio, *LN* lupus nephritis, *NPLE* neuropsychiatric lupus, *SDI* Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K)

*Student's *t* test

Fisher's exact test

[a] The first *p* value is the result of univariate comparison between the two groups (either comparison of means or comparison of proportions for a single dependent variable)

[b] The second *p* value is the result of univariate Cox proportional hazard logistic regression and the HRs are unadjusted taking each dependent variable once at a time

[c] Serological activity was defined as presence of low serum complement activity and/or positive anti-dsDNA antibody at the time of steroid withdrawal

lupus nephritis are few. Majority reported high flare rates (36–50%) [14, 19, 20]. A single Italian centre reported on structured therapy withdrawal in lupus nephritis. In 1988, Moroni et al. reported that complete withdrawal of immunosuppressive agents after a long period of inactive disease is well-tolerated in lupus nephritis [12]. In their 2006 paper on lupus nephritis ($n = 32$), after median follow-up of 203 months following complete discontinuation of corticosteroids and cytotoxic agents, almost half experienced a flare (17/32). They had shorter duration of treatment before stopping corticosteroids than those who never experienced a flare (30 vs 57 months) [21]. Later in 2013, they reported on 52 patients out of which 20 relapsed (38%) after a median of 37 months. Patients experiencing relapse had worse baseline proteinuria (4.75 vs 2.77 g/day, $p = 0.04$), shorter duration of therapy before discontinuing (31 vs 98 months, $p = 0.01$) and lower frequency of use of second immunosuppressive agent (25 vs 62.5%, $p = 0.019$). Overall, patients who stopped therapy had lower frequency of chronic kidney disease, hypertension, cardiovascular events and dyslipidemia. However, no obvious survival advantage could be demonstrated [13]. Two thirds of our patients with lupus nephritis received a second immunosuppressant compared to just less than half in the Italian studies. This is not surprising as with time, the use of these agents is increasing and has contributed to progressively reduced need for glucocorticoids.

Table 2 Result of multivariate Cox proportional hazard logistic regression for not experiencing a flare

Parameters[a]	SE	Wald	aHR	95% CI	*p* value
Age in years at the end of follow-up	0.01	0.138	1.004	0.98–1.023	0.711
Duration of disease in years	0.029	17.05	0.89	0.84–0.94	< 0.00001
Duration of GC treatment before stopping in days	0.00002	18.74	1.000086	1.000047–1.00012	0.000014
Prescription of other immunosuppressive agent	0.21	9.1	1.89	1.251–2.87	0.003
Myositis	0.41	2.04	0.81	0.8–4.1	0.153
NPLE	0.37	0.009	1.036	0.510–2.141	0.925
Thrombocytopenia	0.48	0.24	1.26	0.49–3.23	0.625

aHR adjusted hazard ratio, *CI* confidence interval, *GC* glucocorticoid, *NPLE* neuropsychiatric lupus, *SE* standard error

[a] Stability parameters (tolerance, variance inflation factor, respectively) for the listed parameters: age (0.83, 1.19), duration of disease (0.73, 1.37), duration of GC treatment (0.84, 1.18), other immunosuppressive (0.89, 1.11), myositis (0.95, 1.05), NPLE (0.95, 1.05), thrombocytopenia (0.97, 1.02)

Previous experiences have shown that an abrupt discontinuation of immunosuppressive agents often lead to severe disease exacerbation [17, 22]. Gradual withdrawal of glucocorticoid with optimization of remission is generally the norm. However, optimal duration of maintenance therapy before safe discontinuation is not clearly known. It appears from our data that at least 8 years of treatment with steroids before discontinuing decreases the chance of future relapses especially in patients with lupus nephritis. We used Cox survival analysis, suited to the genre of analysis where data censoring occurs. In case of lupus nephritis, we observed that lower initial dose of prednisolone and concomitant AIHA were associated with better renal flare-free survival. This is possibly related to a more benign initial disease, which was treated with lower

Table 3 Result of univariate and multivariate Cox proportional hazard logistic regression for not experiencing a renal flare among patients with lupus nephritis at baseline

Parameters[a]	Unadjusted HR	95% CI	*p* value[b]	Adjusted HR	95% CI	*p* value[c]
Age in years at the end of follow-up	0.97	0.95–0.99	0.04	1.002	0.97–1.03	0.89
Age in years at GC onset	0.98	0.96–1.001	0.065			
Age of onset of disease	0.99	0.98–1.013	0.3			
Duration of disease in years	0.89	0.83–0.96	0.002	0.85	0.78–0.93	0.00029
Female gender	1.19	0.71–1.99	0.49			
Juvenile onset disease	0.93	0.53–1.63	0.8			
Duration of GC treatment before stopping in days	1.000036	0.999–1.000083	0.13	1.000094	1.00004–1.00014	0.00026
Initial dose of GC (mg/day)	0.98	0.95–1.004	0.09	0.97	0.94–0.99	0.005
Prescription of other immunosuppressive agent	2.21	1.10–4.42	0.02	3.2	1.39–7.33	0.006
Baseline diagnosis:						
LN	0.91	0.64–1.29	0.6			
NPLE	1.12	0.44–2.81	0.81			
AIHA	2.62	01.21–5.65	0.015	2.43	1.067–5.54	0.035
Leucopenia	1.64	0.38–6.91	0.5			
Thrombocytopenia	2.85	0.85–9.55	0.089	1.45	0.29–7.05	0.64
Mucocutaneous	0.54	0.07–3.93	0.54			
Vasculitis	1.93	0.26–14.18	0.51			
Myositis	6.15	1.83–20.64	0.003	4.083	0.82–20.48	0.08
Serositis	0.95	0.41–2.23	0.91			

AIHA autoimmune haemolytic anaemia, *CI* confidence interval, *GC* glucocorticoid, *HR* hazard ratio, *LN* lupus nephritis, *NPLE* neuropsychiatric lupus

[a] Stability parameters (tolerance, variance inflation factor, respectively) for the listed parameters: age (0.69, 1.44), duration of disease (0.69, 1.45), duration of GC treatment (0.87, 1.15), initial dose of GC (0.87, 1.14), other immunosuppressive (0.74, 1.35), AIHA (0.89, 1.12), thrombocytopenia (0.85, 1.17), myositis (0.84, 1.19)

[a] The first *p* value is the result of univariate Cox proportional hazard logistic regression and the HRs are unadjusted taking each dependent variable once at a time

[b] The second *p* value is the result of multivariate Cox proportional hazard logistic regression taking variables with *p* value < 0.2 from the univariate Cox regression

initial dose of prednisolone and higher rate of second immunosuppression use in case of concomitant AIHA.

Maintenance phase of management of lupus is often confronted by episodes of relapse and sometimes, major relapses. Lupus nephritis is known to relapse even after 10 years of remission [23]. Each renal flare results in further irreversible loss of nephrons, and resultant fibrosis and heightened risk of loss of renal function [24]. Relapse rates even with ongoing immunosuppressive therapy after achievement of remission range from 10 to 66% [5]. Mok et al. reported a relapse rate as high as 38% after median of 32 months on concurrent immunosuppressive agents. Higher chronicity score and absence of a second immunosuppressive agent predicted relapse [25]. The major concern with a new flare is progressive damage accrual. For example, the Ohio SLE study showed that spending > 30% of time in renal flare (OR 20, 95% CI 4.6–91.3, $p < 0.001$) and age > 35 years (OR 69, 95% CI 6.3–753.6, $p < 0.001$) were independent predictors of new or progressive CKD [26]. Therefore, every attempt at therapy withdrawal should be properly planned and closely followed up, ensuring that the patient understands and weighs the risks of both the drug and a flare. It should also be noted that studies focusing on long-term durable drug-free remission of lupus show that only a small fraction of patients achieve this state. In the GLADEL cohort, 20.2% of SLE patients were able to completely withdraw therapy for 1 year, and only 9.7% for 3 years [27]. Other reports showed that around 2–16% of all lupus patients might have long-term drug-free remission [28–30].

Therefore, it appears that only in a minority of patients with lupus, and perhaps even in lesser number of patients with lupus nephritis glucocorticoids may actually be withdrawn. We report a lower figure of flare rate post-withdrawal (around 20% compared to 36–50% in Caucasian patients). There may be factors other than Indian ethnicity or genetics. Our patients received longer duration of steroid treatment before discontinuing, on an average 2317 days or 77 months, whereas previous reports of steroid withdrawal reported shorter durations (38–77 months). Second immunosuppressive agent was given in 57% of our patients compared to 48% in the Italian cohort [13, 21]. Among patients with lupus nephritis, this figure goes up to 67%. These factors might have resulted in a better outcome in our cohort. However, in comparison to the parallel cohort of patients with lupus nephritis who were maintained on low-dose prednisolone, higher rate of renal flare was observed in the glucocorticoid withdrawal group.

Many of our patients who did not have a flare had mucocutaneous disease at baseline and this group had the highest frequency of flare-free survival. They might represent a more benign group of lupus as compared to lupus nephritis. Most flares were lupus nephritis and many of them had baseline lupus nephritis. However, none of our patients with NPLE had a neuropsychiatric flare.

This report had a few limitations: heterogeneous disease activity parameters at baseline, non-randomised design, single centre and open label design, a relatively shorter duration of follow-up; we did not report on cardiovascular outcome of our patients at the end of follow-up and did not calculate cumulative dose of glucocorticoid. As the study population was heterogeneous, we could not strictly follow a uniform glucocorticoid tapering regimen for each and every patient.

To conclude, this study demonstrates that a subset of patients with Indian SLE, though small, may enter stable and prolonged remission after glucocorticoid withdrawal. Risk of flare especially renal flare remains but appears to be smaller compared to Caucasian patients. Attempting discontinuation of glucocorticoids in selected patients, especially those who have been treated for ≥ 8 years along with concomitant second immunosuppressive agent might be feasible.

Compliance with ethical standards

Disclosures None.

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