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Outcomes following immunosuppressive therapy withdrawal after complete renal response in proliferative lupus nephritis

Paola Vidal-Montal ,[1,2] Javier Narváez ,[1,2] Xavier Fulladosa ,[2,3] Francesca Mitjavila,[2,4] Olga Capdevila ,[2,4] Joan Torras,[2,3] Montserrat Gomà,[2,5] Joan M Nolla[1,2]

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[1]Department of Rheumatology, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain
[2]Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain
[3]Department of Nephrology, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain
[4]Department of Internal Medicine, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain
[5]Department of Pathology, Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain

Correspondence to
Dr Javier Narváez; fjnarvaez@bellvitgehospital.cat

ABSTRACT

Objective To investigate the rate and factors influencing renal relapse (RR) in proliferative lupus nephritis (LN) patients who discontinued immunosuppressive therapy (IST), as well as the long-term renal outcomes following RR.

Methods Retrospective, single-centre study of biopsy-confirmed LN patients who had received IST for at least 36 months and maintained complete renal response (CRR) for a minimum of 12 months before therapy discontinuation.

Results Of a total of 106 patients meeting the inclusion criteria, 76 with proliferative classes were selected for analysis. The median duration of IST prior to discontinuation was 83.5 months (IQR 25th–75th: 53.5–120). Relapse occurred in 29 patients (38.2%) at a median of 26.5 months (IQR 25th–75th: 9.25–63.5 months) following IST withdrawal. Relapses were classified as severe in 9 cases (31%) and moderate in 16 cases (55.2%). Renal rebiopsy was performed in 25 of these patients (86.2%), with 80% retaining the same histological class.

Discontinuation of IST at ≤34 years of age significantly increased the risk of RR (adjusted HR: 3.5). In contrast, an IST duration exceeding 48 months prior to discontinuation (HR: 0.26), maintaining CRR for at least 48 months (HR: 0.32), achieving complete remission per DORIS (definition of remission in systemic lupus erythematosus) criteria at IST withdrawal (HR: 0.21) and gradual IST tapering (HR: 0.09) were associated with a reduced risk of RR.

Following reintroduction of IST, 20 out of 29 patients (68.9%) achieved CRR, 5 (17.2%) achieved a partial response and 4 (13.8%) did not respond; of these, 3 patients (10.3%) progressed to end-stage renal disease.

Conclusions Successful withdrawal of IST is possible in carefully selected patients with proliferative LN. If an RR occurs, most patients are able to remain in remission after resuming IST.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The optimal duration of immunosuppressive therapy (IST) for lupus nephritis (LN) remains uncertain. The 2023 EULAR (European League Against Rheumatism) and 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend a minimum of 36 months of IST, including induction and maintenance therapy, before considering withdrawal. While prolonged IST lowers the risk of relapse, it also increases the potential for adverse effects and long-term toxicity. Identifying factors that predict renal relapse after IST discontinuation could help optimise treatment strategies, reduce glucocorticoid exposure and minimise side effects.

WHAT THIS STUDY ADDS

⇒ This study reported a 38.2% relapse rate among proliferative LN patients who had received IST for at least 36 months and maintained complete renal response (CRR) for a minimum of 12 months before therapy discontinuation. Among those who experienced a relapse, most had moderate or severe renal relapses. Following IST reintroduction, the majority responded to treatment, achieving either complete or partial renal remission, with only 10.3% progressing to end-stage renal disease.

⇒ The study identified several factors influencing renal relapse (RR). An age of ≤34 years at IST discontinuation significantly increased the risk of RR, whereas an IST duration exceeding 48 months before discontinuation, maintaining CRR for at least 48 months, achieving complete remission according to the DORIS criteria at the time of IST withdrawal and gradual tapering of IST were associated with a reduced risk of relapse.

INTRODUCTION

Determining the optimal duration of maintenance immunosuppressive therapy (IST) remains a significant challenge in the management of lupus nephritis (LN).[1–3] As highlighted in the 2023 European League Against Rheumatism (EULAR) recommendations, one of the key issues for future SLE research is establishing the optimal duration of therapy and the appropriate timing for discontinuing IST in both renal and extrarenal diseases.[4]

The latest guidelines for LN management, including the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines, advocate for a minimum total duration of 36 months for the combination

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Successful withdrawal of IST is feasible in carefully selected LN patients. Our study provides insights into the optimal timing for IST tapering and discontinuation in LN patients. It identifies predictors of safe withdrawal, which can support clinicians in their decision-making process when considering this option, and clarifies the associated risks, including the likelihood of renal relapse and long-term renal prognosis.

of initial IST and maintenance therapy.[5 6] Similarly, the 2019 update from the Joint EULAR/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) recommends considering the gradual withdrawal of IST 3 to 5 years after the diagnosis of LN in patients who have achieved a sustained complete renal response (CRR).[7] Nonetheless, reported rates of renal response (RR) following IST tapering or discontinuation in LN range from 9.6% to 38.5% in the literature.[8–14]

Deciding whether to withdraw IST after achieving CRR poses a significant clinical challenge.[15 16] While prolonged IST can reduce the risk of RR, it also increases the patient's exposure to potential adverse effects and long-term toxicity associated with immunosuppression. Therefore, identifying reliable predictors of disease progression, particularly predictors of RR after IST withdrawal, may help guide therapeutic decisions. Additionally, the emergence of novel approaches, such as protocol renal biopsies, highlights the need for more nuanced strategies in decision-making regarding the duration of IST in patients with LN.[17–19]

Nevertheless, there is still limited knowledge regarding the optimal timing for IST tapering and discontinuation, the predictors of safe withdrawal, the risk of RR following IST cessation and the renal outcomes in relapsed patients. These outcomes include the frequency of progression to a more severe grade of nephritis, the response to the reintroduction of IST and the risk of progression to end-stage renal disease (ESRD).

In light of these considerations, the present study aimed to assess the rate and determinants of RR in proliferative LN patients who discontinued IST after completing at least 36 months of treatment and maintaining sustained CRR for a minimum of 12 months before therapy withdrawal, as well as to evaluate the long-term renal outcomes following RR.

METHODS

Study population

We retrospectively reviewed our hospital databases to identify all patients with SLE and renal biopsy-proven LN from the Departments of Internal Medicine, Nephrology and Rheumatology who were treated between 1988 and 2023. LN was confirmed according to the WHO classification for biopsies performed before 2003 and according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification for those performed after that date.[20 21]

From an initial cohort of 272 patients, 106 met the criteria of having received IST for at least 36 months and achieving sustained CRR for a minimum of 12 months prior to its withdrawal. Of these, 76 had proliferative classes (III, IV or mixed III/IV+V) and were included in the analysis.

Patients with ESRD at the time of diagnosis and those treated only with glucocorticoids were excluded from the study.

The study was approved by our institutional ethics committee and did not include any identifiable patient data.

Data collection

Data were retrospectively collected from patients' medical records using a specifically designed protocol, which included the following:

- Sociodemographic data: age, sex, ethnicity and body mass index.
- Comorbidities: smoking history and cardiovascular risk factors.
- Clinical data: date of SLE diagnosis, date of nephritis diagnosis and clinical manifestations, including alopecia, oral and nasal ulcers, acute/subacute cutaneous lupus, pleural and pericardial effusion, joint involvement, myositis, vasculitis neuropsychiatric SLE, leucopenia, thrombocytopenia and autoimmune haemolytic anaemia. The date of the last visit and the year and cause of death (if applicable) were also recorded.
- Laboratory data: antinuclear antibody patterns, antiphospholipid antibodies (anti-cardiolipin, anti-beta2-glycoprotein and lupus anticoagulant) and anti-C1q antibodies. Serum creatinine, estimated glomerular filtration rate (eGFR), proteinuria over 24 hours of collection, microhaematuria, dysmorphic erythrocytes and leucocyturia were assessed at baseline and at the time of biopsy.
- Number of renal relapses: patients with multiple relapses were included. This antecedent ('Previous LN: Yes/No') was considered as a variable in analysing risk factors for LN recurrence.
- Nephritis episode: histological class, activity and chronicity indices,[21] grade of interstitial inflammation, tubular atrophy, interstitial fibrosis and the presence of thrombotic microangiopathy lesions. Additionally, the presence of nephrotic syndrome, secondary arterial hypertension and acute renal failure were recorded.
- Treatment: details of initiation and follow-up, including the dates of IST initiation, discontinuation and total duration. We documented whether treatment was stopped abruptly or gradually. Abrupt discontinuation was defined as the complete cessation of IST within a short period (<12 months), whereas gradual discontinuation involved slow tapering of IST

over 12 months or more. We also noted whether a biopsy was performed before treatment withdrawal. Additionally, assessments were made to determine if patients met the DORIS 2021[22 22] and Low Lupus Disease Activity State (LLDAS) criteria[23] and the prednisone dose at the time of immunosuppression withdrawal.

- Renal response: classified as complete, partial or no response. The date of achieving complete response, the duration of remission at IST discontinuation and the date of recurrence, along with subsequent biopsy results, were documented. According to the EULAR/ERA-EDTA criteria, CRR was defined as proteinuria reduced to <0.5 g/24 hours, accompanied by a stable or near-normal eGFR.[7] In patients with baseline nephrotic-range proteinuria, achieving this milestone may require additional time beyond 12 months of therapy. Partial renal response (PRR) was defined as a reduction in proteinuria by at least 50% from baseline within 6 months of therapy. For patients with nephrotic-range proteinuria, a reduction to below 3.5 g/24 hours was indicative of a partial response. Stabilisation or improvement in eGFR was also required.[7]
- RR: defined as the need to reinstate IST due to clinico-analytical abnormalities, usually confirmed by renal biopsy. The occurrence and date of a renal flare after IST withdrawal, the severity of the relapse and the treatment and response to the relapse were documented. RR was classified as mild, moderate or severe based on the following criteria:[24] (1) Mild relapse: an increase in red blood cells in urinary sediment from <5 to >15 per sample, with 2 or more dimorphic red cells per high-power field, or the presence of 1 or more casts or leucocyte counts without significant changes in creatinine or proteinuria; (2) Moderate relapse: if baseline creatinine<2 mg/dL, an increase of 0.2–1 mg/dL; if baseline creatinine≥2 mg/dL, an increase of 0.4–1.5 mg/dL. Protein/creatinine ratio increases from <0.5 to ≥1 or from 0.5 to 1 by ≥2; and (3) Severe relapse: if baseline creatinine<2 mg/dL, an increase of >1 mg/dL; if baseline creatinine≥2 mg/dL, an increase of >1.5 mg/dL. The protein/creatinine ratio exceeds 5 in the absence of urinary infection.
- Outcomes: serum creatinine and eGFR at the last visit, progression to ESRD (eGFR<15 mL/min/1.73 m^2), initiation of dialysis and/or renal transplantation and their respective dates were recorded.

Statistical analysis

A descriptive analysis of the data was performed. Continuous variables are expressed as mean±SD or median with IQRs (25th–75th percentiles), while qualitative variables are presented as counts and percentages.

To investigate factors associated with RR, independent Cox regression analyses were conducted for each risk factor, with RR as the dependent variable. Models were adjusted for age and sex. HRs with 95% CIs are reported. Assumptions for the Cox models were evaluated to ensure validity. Statistical significance was defined as an alpha level of <0.05.

RESULTS

Patient characteristics

Table 1 summarises the main clinical features, laboratory data and treatments received by the 76 included patients. The majority were women (82.9%), with a median age of 30.5 years (IQR 25th–75th: 25–39.2) at the time of LN diagnosis. The median follow-up duration was 19.9 years (IQR 25th–75th: 13.1–29.9 years) from LN diagnosis and 10.2 years (IQR 25th–75th: 6.2–15.9 years) from the date of IST discontinuation.

With respect to LN classification, 16 patients (21%) were classified as class III or mixed III+V, while 60 (79%) were class IV or mixed IV+V. The median duration of IST at the time of discontinuation was 83.5 months (IQR: 53.5–120). Only 6.6% of patients (5 out of 76) underwent a renal biopsy prior to stopping treatment. A protocol-mandated repeat biopsy before IST discontinuation is not standard practice at our centre; instead, the decision to perform a biopsy was left to the discretion of the treating clinician.

Renal relapse occurrence

Among the 76 patients who discontinued IST due to sustained CRR, 29 patients (38.2%) experienced RR after a median of 26.5 months (IQR: 9.25–63.5) following treatment discontinuation. The relapses were classified as severe in 9 cases (31%), moderate in 16 cases (55.2%) and mild in 4 cases (13.8%).

Among the 29 patients who relapsed, 25 (86.2%) underwent a renal biopsy after relapse, with 20 (80%) retaining the same renal class as in their initial biopsy. In the remaining 5 cases, 2 transitioned from class III to class IV, while 3 shifted from class IV to class III, including one with a mixed III and V classification.

Following the reintroduction of IST after relapse, 20 patients (68.9%) achieved CRR, 5 (17.2%) achieved PRR and 4 patients (13.8%) did not respond; of these, 3 patients (10.3%) progressed to ESRD.

For the 47 patients who did not experience a relapse, the median follow-up time after IST withdrawal was 113.5 months (IQR 25th–75th: 65–131.3).

Factors influencing RR

The independent Cox regression analyses for each risk factor are summarised in table 2 and figure 1. Patients who received IST for more than 48 months had a significantly lower risk of RR compared with those treated for 36 to 48 months, with a HR of 0.31 (95% CI 0.14 to 0.69) and an adjusted HR of 0.20 (95% CI 0.08 to 0.48).

Similarly, patients who maintained CRR for more than 48 months before discontinuing IST were less likely to experience RR compared with those with remission durations of less than 36 months, with an HR of 0.33 (95% CI 0.14 to 0.81) and an adjusted HR of 0.31 (95% CI 0.12 to 0.77).

Table 1 Main clinical features, laboratory data and treatments received by the study cohort

	Total sample, n=76	Without renal relapses, n=47	With renal relapses after IST discontinuation, n=29
Age at SLE onset, years, median (IQR 25–75)	25 (20–33)	25 (19–27.3)	26 (20–35)
Age at LN diagnosis, years, median (IQR 25–75)	30.5 (25–39.2)	32 (25.2–41.8)	29 (23.2–34)
Women/men	63 (82.9%)/13 (17.1%)	36 (76.6%)/11 (23.4%)	27 (93.1%)/2 (6.9%)
Age at IST discontinuation, years, median (IQR 25–75)	41 (32–52)	44.5 (35.2–52.8)	34.5 (27.2–45)
Histological class			
Class III (pure or mixed III+V)	16 (21.1%)	10 (21.3%)	6 (20.7%)
Class IV (pure or mixed IV+V)	60 (78.9%)	37 (78.7%)	23 (79.3%)
Activity index, mean±SD	9.36±4.2	9.6±4.4	8.9±3.9
Chronicity index, mean±SD	1.32±1.5	1.4±1.6	1.2±1.4
Serum creatinine at LN onset, µmol/L, mean±SD	92.9±30.5	93.7±31.9	91.5±28.7
Proteinuria at LN onset, g/24 hours, mean±SD	2.9±2.2	2.8±1.8	2.9±2.8
Nephrotic syndrome at LN onset	35 (46.1%)	21 (44.7%)	14 (48.3%)
Acute renal failure at LN onset	18 (23.7%)	12 (25.5%)	6 (20.7%)
Hypertension at LN onset, n (%)	19 (25%)	12 (25.5%)	7 (24.1%)
Induction immunosuppressive therapy			
CYC	29 (38.2%)	19 (40.4%)	10 (34.5%)
MMF	28 (36.8%)	19 (40.4%)	9 (31%)
AZA	19 (25%)	9 (19.1%)	10 (34.5%)
Maintenance immunosuppressive therapy			
MMF	38 (50%)	26 (55.3%)	12 (41.3%)
AZA	32 (41%)	16 (34%)	16 (55.2%)
MMF+AZA	6 (9.52%)	5 (10.6%)	1 (3.4%)
Maintained use of antimalarials	43 (56.6%)	31 (65.9%)	12 (41.4%)
Total treatment duration, months, median (IQR 25–75)	83.5 (53.5–120)	94 (60.8–175.3)	61.5 (43.8–93.3)
Remission duration at IST discontinuation, months, median (IQR 25–75)	54 (36.8–95)	71 (47–119.8)	36 (25.3–68.5)
Time to achieve CRR, months, median (IQR 25–75)	12 (6–30)	12 (6–42.3)	13 (6.5–25)
Mode of IST discontinuation			10 (34.5%) 15 (51.7%)
Abrupt cessation	14 (21.9%)	4 (8.5%)	
Progressive	50 (78.1%)	35 (74.5%)	
Fulfilling DORIS/LLDAS criteria at IST discontinuation			
No	26 (34.2%)	8 (17%)	18 (62%)
LLDAS	17 (22.4%)	12 (25.5%)	5 (17.2%)
DORIS+LLDAS	33 (43.4%)	27 (57.4%)	6 (20.7%)
Prednisone dose at IST discontinuation, mg/day median (IQR 25–75)	5 (0–10)	5 (0–5)	7.5 (5–10)
Date of renal biopsy, before/after the year 2000	32 (42.1%)/44 (57.9%)	17 (36.2%)/30 (63.8%)	15 (51.7%)/14 (48.3%)

AZA, azathioprine; CRR, complete renal response; CYC, cyclophosphamide; DORIS, definition of remission in systemic lupus erythematosus; ESRD, end-stage renal disease; HCQ, hydroxychloroquine; IST, immunosuppressive therapy; LLDAS, lupus low disease activity state; LN, lupus nephritis; MMF, mycophenolate.

Table 2 Independent Cox regression results for each risk factor

		No renal relapse, n=47	Renal relapse, n=29	Unadjusted HR	HR adjusted by sex, age and renal histological class
Sex, n (%)	Male	11 (23.4)	2 (6.9)	Ref.	
	Female	36 (78.3)	27 (90)	2.04 (0.62–6.74)	
Age at LN diagnosis, years		32 (25.2–41.8)	29 (23.2–34)	0.99 (0.96–1.03)	
Age at IST discontinuation, years		44.5 (36.0–52.8)	34.5 (27.2–45.0)	0.98 (0.95–1.01)	0.91 (0.83–1)
Age at IST discontinuation, years, n (%)	>34	38 (80.8)	14 (48.2)	Ref.	Ref.
	≤34	9 (19.6)	15 (50)	2.27 (1.09–4.74)	3.65 (1.28–10.42)
Proteinuria at LN onset, mg/day		2200 (1400–3500)	2255 (1498–3322)	1.00 (1.00–1.00)	1 (1.00–1.00)
Nephrotic syndrome at LN onset, n (%)	No	26 (55.3)	15 (51.7)	Ref.	Ref.
	Yes	21 (44.7)	14 (48.3)	0.72 (0.35–1.48)	0.7 (0.33–1.46)
Hypertension at LN onset, n (%)	No	35 (74.5)	22 (75.9)	Ref.	Ref.
	Yes	12 (25.5)	7 (24.1)	0.76 (0.32–1.80)	0.73 (0.3–1.77)
Acute renal failure at LN onset, n (%)	No	35 (74.5)	23 (79.3)	Ref.	Ref.
	Yes	12 (25.5)	6 (20.7)	0.55 (0.22–1.37)	0.5 (0.2–1.29)
Histological class, n (%)	Class IV	37 (78.7)	23 (79.3)	Ref.	Ref.
	Class III	10 (21.3)	6 (20.7)	1.21 (0.49–2.99)	
Activity index		10.00 (6.00–13.0)	9.00 (7.00–12.0)	0.94 (0.85–1.04)	0.92 (0.82–1.02)
Chronicity index		1.00 (0.00–2.50)	1.00 (1.00–2.00)	1.05 (0.80–1.37)	1.1 (0.82–1.48)
Induction treatment, n (%)	AZA	9 (19.1)	10 (34.5)	Ref.	Ref.
	MMF	19 (40.4)	9 (31)	0.99 (0.4–2.46)	1.07 (0.41–2.77)
	CYC	19 (40.4)	10 (34.4)	0.59 (0.25–1.39)	0.58 (0.24–1.43)
Maintenance treatment, n (%)	AZA	16 (34)	16 (55.2)	Ref.	Ref.
	MMF	26 (55.3)	12 (41.3)	0.96 (0.44–2.08)	1.04 (0.46–2.35)
	AZA+MMF	5 (10.6)	1 (3.4)	0.49 (0.06–3.73)	0.47 (0.06–3.63)
Date or renal biopsy, months, n (%)	<2000	17 (36.2)	15 (51.7)	Ref.	Ref.
	≥2000	30 (63.8)	14 (48.3)	1.18 (0.56–2.51)	1.29 (0.58–2.87)
Previous episode of LN, n (%)	No	31 (65.9)	18 (62)	Ref.	Ref.
	Yes	16 (34)	11 (37.9)	1.55 (0.73–3.29)	1.58 (0.73–3.4)
Maintenance of antimalarials, n (%)	Retired	16 (34)	17 (58.6)	Ref.	Ref.
	Maintained	31 (65.9)	12 (41.4)	0.49 (0.23–1.01)	0.51 (0.24–1.07)
Time to achieve CRR, months, n (%)	<12	26 (55.3)	14 (31)	Ref.	Ref.
	≥12	21 (44.6)	15 (51.7)	1.19 (0.52–2.73)	1.09 (0.46–2.56)
Total treatment duration, months, n (%)	(36–48)	4 (8.5)	8 (27.5)	Ref.	Ref.
	>48	43 (91.5)	21 (72.4)	0.31 (0.14–0.69)	0.2 (0.08–0.48)
Remission duration at IST discontinuation, months, n (%)	<48	18 (38.3)	22 (75.8)	Ref.	Ref.
	≥48	29 (61.7)	7 (24.1)	0.33 (0.14–0.81)	0.31 (0.12–0.77)
Fulfilling DORIS/LLDAS criteria at IST discontinuation, n (%)	No	8 (17)	18 (62)	Ref.	Ref.
	LLDAS	12 (25.5)	5 (17.2)	0.39 (0.14–1.05)	0.36 (0.13–1.01)
	DORIS+LLDAS	27 (57.4)	6 (20.7)	0.24 (0.10–0.63)	0.24 (0.09–0.63)
Mode of IST discontinuation, n (%)	Abrupt cessation	4 (8.5)	10 (34.5)	Ref.	Ref.
	Progressive	35 (74.5)	15 (51.7)	0.29 (0.13–0.64)	0.28 (0.12–0.66)

The results are expressed as medians (ranges) or numbers (%).
AZA, azathioprine; CRR, complete renal response; CYC, cyclophosphamide; DORIS, definition of remission in systemic lupus erythematosus; ESRD, end-stage renal disease; HCQ, hydroxychloroquine; HR, hazard ratio; IST, immunosuppressive therapy; LLDAS, lupus low disease activity state; LN, lupus nephritis; MMF, mycophenolate; Ref, reference group.

Patients who achieved clinical remission according to the[22] criteria showed a significantly reduced risk of RR compared with those who did not, with an HR of 0.24 (95% CI 0.10 to 0.63) and an adjusted HR of 0.24 (95% CI 0.09 to 0.63). While patients meeting only the LLDAS criteria demonstrated a tendency toward a lower risk of

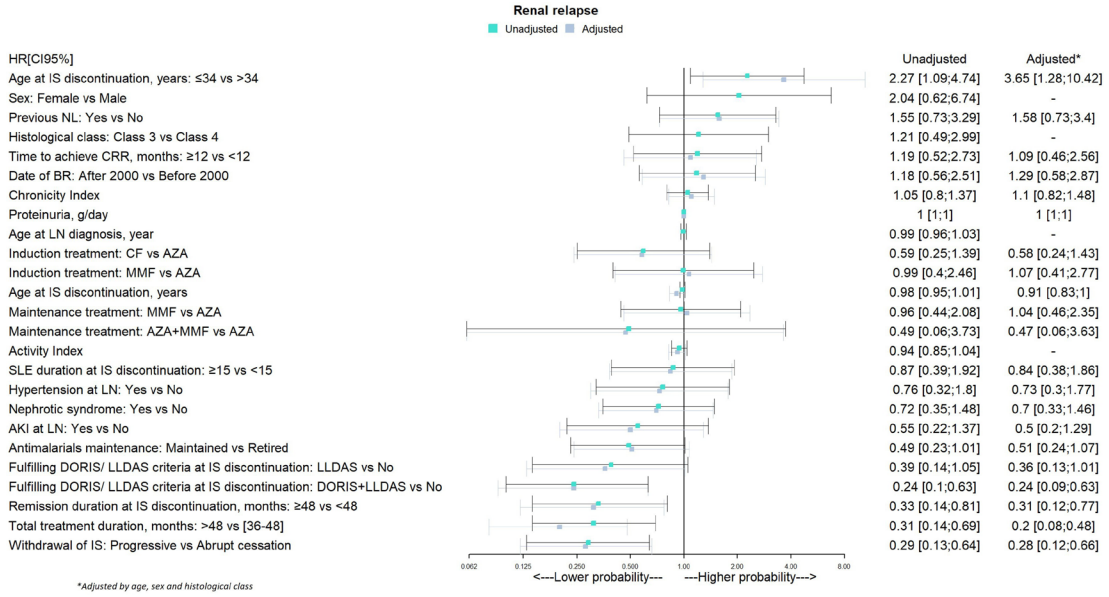

Figure 1 Factors influencing renal relapses. *HR: Adjusted by sex, age and renal histological class. AKI, acute renal failure at LN onset; AZA, azathioprine; BR, renal biopsy; CF, cyclophosphamide; CRR, complete renal response; DORIS, definition of remission in systemic lupus erythematosus; HR, hazard ratio; IS, immunosuppressive; LLDAS, lupus low disease activity state; LN, lupus nephritis; MMF, mycophenolate.

RR, this difference did not achieve statistical significance, with an HR of 0.39 (95% CI 0.14 to 1.05) and an adjusted HR of 0.36 (95% CI 0.13 to 1.01).

Gradual IST withdrawal, as opposed to abrupt discontinuation, was associated with a significantly lower likelihood of RR, with an HR of 0.29 (95% CI 0.13 to 0.64) and an adjusted HR of 0.28 (95% CI 0.12 to 0.66).

Maintenance of antimalarials was associated with a non-significant trend toward reduced relapse risk (HR: 0.49, 95% CI 0.23 to 1.01; adjusted HR: 0.51, 95% CI 0.24 to 1.07).

In contrast, younger age at the time of IST discontinuation was identified as a significant risk factor for relapse. Patients aged ≤34 years were more likely to experience RR compared with those older than 34 years, with an HR of 2.27 (95% CI 1.09 to 4.74) and an adjusted HR of 3.65 (95% CI 1.28 to 10.42). A prior episode of LN showed a trend toward a higher risk of relapse, though this difference was not statistically significant (HR: 1.55, 95% CI 0.73 to 3.29; adjusted HR: 1.58, 95% CI 0.73 to 3.4).

No other factors analysed in our cohort, including the presence of nephrotic syndrome at the time of LN diagnosis, were significantly associated with the risk of RR

DISCUSSION

Whether, when and how complete withdrawal of IST is feasible in patients with LN remain controversial.[15 16] In managing LN, the risk of RR is a significant concern. Flare rates reported in the literature vary widely, ranging from 8% at 1 year to 48% at 10 years and from 9.6% to 38.5% following IST tapering or discontinuation.[8–16] Notably, RR is associated with reduced renal function, an increased risk of progression to ESRD, the need for intensified treatment and a lower health-related quality of life.[8–16] On the other hand, prolonged IST exposure can lead to severe or even life-threatening side effects. Therefore, deciding whether to discontinue or continue IST after achieving a prolonged CRR remains a clinical challenge.

The optimal duration of IST for the LN continues to be uncertain. The updated 2023 EULAR[4] and 2024 KDIGO guidelines recommend a minimum of 36 months of total IST before considering withdrawal.[5–7] The American College of Rheumatology has emphasised the need for evidence-based data to establish the optimal duration of maintenance therapy.[25] There is still uncertainty about the best timing for IST tapering and discontinuation, the factors that predict a safe withdrawal, and the long-term prognosis of LN patients if treatment is stopped and relapse occurs.

In our study, we confirm that successful withdrawal of IST is feasible in proliferative LN. Notably, 61.8% of patients remained flare-free and off immunosuppressants for a median of 113.5 months following treatment discontinuation. Previous studies have reported success rates for IST withdrawal in patients with LN in remission ranging from 61% to 77.1%.[8 9 11]

The key challenge in ensuring successful withdrawal is identifying and selecting patients who can be safely weaned off therapy. In this context, we identified a patient profile associated with a low risk of relapse: patients who received IST for 48 months, maintained CRR for at least 36 months (ideally 48 months) and were in complete remission according to the DORIS criteria at the time of treatment discontinuation. To optimise outcomes, gradual tapering of IST is recommended.

Several studies have highlighted the additional benefits of extending IST beyond 3 years after an LN diagnosis. Ten *et al* reported a significant reduction in relapse rates when IST was maintained for at least 3 years after achieving remission, rather than starting at the time of LN diagnosis.[8] Similarly, Moroni *et al* found that patients who remained flare-free after discontinuing therapy had received longer maintenance IST after induction treatment compared with those who experienced relapses, with median treatment durations of 90 months versus 30 months, respectively.[10] Furthermore, Das *et al* examined the relationship between sustained CRR and histological remission in patients with quiescent proliferative LN through repeat kidney biopsies. Their study revealed that maintaining CRR for more than 48 months was a strong predictor of achieving histopathological remission, with 100% of patients in this group reaching it, compared with 84% in the group of 24–48 months.[26] These findings, which align with our study, suggest that maintenance IST should be extended for at least 48 months after achieving CRR.

The duration of CRR at the time of IST discontinuation has been identified as another independent protective factor against renal relapse, as has been described previously. In the study by Zen *et al*,[8] a 3-year remission reduced the risk of relapse by 71%. However, our data suggest that a longer duration, specifically at least 48 months, is preferable to further minimise this risk. In this regard, Moroni *et al* reported that patients without RR after IST discontinuation had a median CRR duration of 53 months.[9] Similarly, data from the Toronto Lupus cohort revealed that sustaining a CRR for at least 5 years was associated with lower rates of flares, chronic kidney disease, ESRD and mortality.[27] A recent study highlighted the potential impact of the time required to achieve CRR, suggesting that earlier achievement may reduce the risk of relapse;[11] however, this finding has not been consistently reported in previous studies.

Treat-to-target strategies for SLE include achieving LLDAS and DORIS remission. Achieving DORIS remission before IST discontinuation appears to be a key factor in minimising the risk of renal relapse. In a recent study by Panagiotopoulos *et al*, patients who reached DORIS complete remission at the initiation of IST tapering experienced fewer renal and extrarenal flares compared with those who did not.[11] They also found that lower SLEDAI-2K scores were protective against any flares (renal and/or extrarenal). Several observational studies have shown that patients who achieve this target have lower rates of organ damage accrual and fewer flares. According to Pitsigavdaki *et al*, achieving DORIS remission for at least 24 months demonstrates high specificity (>80%) for reduced damage accrual.[28] A recent study of 3000 SLE patients, 46.8% of whom had LN, found that achieving DORIS complete remission at the start of IST tapering was linked to lower flare rates and a longer time to flare.[29]

Beyond accurately identifying the best candidates for successful IST withdrawal, therapy discontinuation should be performed gradually, as recommended in some guidelines.[7 22] Tapering the dosage until complete discontinuation may take several months (at least 12, according to our experience) and should be carried out under strict medical supervision. Abrupt discontinuation of treatment can lead to severe and potentially irreversible renal failure, as demonstrated in earlier studies.[30–32]

As risk factors associated with a higher risk of RR, our study identified only age younger than 34 years at the time of IST discontinuation. Specifically, patients aged 34 years or younger at the time of IST discontinuation had a significantly higher risk of RR compared with those older than 34 years. This finding is consistent with the study by Zen *et al*,[8] which also reported that younger age at IST discontinuation was associated with an increased risk of RR.

Finally, maintenance therapy with antimalarials, unless contraindicated, provided protection against disease relapse in our cohort, consistent with findings from previous studies in patients with LN.[8 9 11]

Discontinuation of IST should be approached with caution, carefully weighing the risks and benefits. The primary risk is RR, which we observed in 38.2% of our patients. Reported frequencies in the literature range from 9.6% to 38.5%, as previously mentioned.[8–14] Although most relapses are moderate to severe, the prognosis after restarting treatment is generally good, with most patients achieving remission again after resuming IST.[8 9 11] The frequency of progression to ESRD in these cases ranges from 7.9% to 10.8%.[8]

When interpreting the results of our study, it is important to consider the inherent limitations of a retrospective analysis, the relatively small sample size, which predominantly consists of white Europeans, and the fact that a protocol-mandated repeat biopsy before IST discontinuation was performed in only five patients, limiting the availability of histological data at that time. Additionally, there is some heterogeneity in the IST strategies used throughout the study period, as patients were treated between 1988 and 2023. During this time, clinical practice evolved from intravenous CYC, the standard IST in the early years to the more commonly adopted MMF and AZA, following evidence of a more favourable benefit-risk ratio for these therapies. This shift in IST approaches may have introduced variability in both initial and maintenance therapies, potentially influencing the risk of relapse among patients.

To assess the potential impact of this treatment heterogeneity, we examined whether there was an association between the time of diagnosis, initial and maintenance therapy and the risk of LN relapse. No significant association was found between these variables and relapse risk.

Despite these limitations, our data reflect real-world clinical practice outcomes and provide valuable insights into the optimal timing for IST discontinuation in patients with proliferative LN. The study identifies

predictors of safe withdrawal and clarifies the associated risks, including the likelihood of renal relapse and the long-term renal prognosis in these cases.

In summary, successful withdrawal of IST is possible in carefully selected LN patients. Our study identifies key factors associated with a reduced risk of relapse, which can aid clinicians in their decision-making process when evaluating this option. If a relapse occurs, most patients are able to achieve remission after resuming IST.

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ORCID iDs
Paola Vidal-Montal http://orcid.org/0009-0003-0034-2270
Javier Narváez http://orcid.org/0000-0002-1614-8064
Xavier Fulladosa http://orcid.org/0000-0003-1974-9874
Olga Capdevila http://orcid.org/0000-0002-5517-7482

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