RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Disease modification achievement in patients with lupus nephritis in a real-life setting: mission impossible?

Alexandros Panagiotopoulos,[1] Eleni Kapsia,[2] Ioannis Michelakis ,[3] John Boletis,[2] Smaragdi Marinaki,[2] Petros P Sfikakis,[1] Maria G Tektonidou [1]

To cite: Panagiotopoulos A, Kapsia E, Michelakis I, *et al*. Disease modification achievement in patients with lupus nephritis in a real-life setting: mission impossible?. *RMD Open* 2023;**9**:e003158. doi:10.1136/rmdopen-2023-003158

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003158).

AP and EK contributed equally.

Received 14 March 2023
Accepted 25 May 2023

Check for updates

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

[1]Rheumatology Unit, First Department of Propaedeutic Internal Medicine, Joint Academic Rheumatology Program, Laiko Hospital, Medical School, National and Kapodistrian University, Athens, Greece
[2]Department of Nephrology and Renal Transplantation, Laiko Hospital, Medical School, National and Kapodistrian University, Athens, Greece
[3]Medical School, National and Kapodistrian University, Athens, Greece

Correspondence to
Professor Maria G Tektonidou; mtektonidou@gmail.com

ABSTRACT

Objective A preliminary definition of disease modification (DM) in lupus nephritis (LN) was recently developed focusing on long-term remission and damage prevention, with minimal treatment-associated toxicity. We aimed to further specify aspects of DM criteria in LN, assess DM achievement in a real-world setting and examine potential DM predictors and long-term outcomes.

Methods We collected clinical/laboratory and histological inception cohort data from biopsy-proven LN patients (82% females) with ≥72 months follow-up at two joint academic centres. Specific criteria for 24-hour proteinuria, estimated glomerular filtration rate (eGFR), renal flares and glucocorticoids dose were set at three time frames (months 0–12, 13–60 and 72) to assess DM. In the first model, DM was achieved if patients fulfilled all four criteria at all three time frames (achievers). In the second model, the continued glucocorticoids reduction criterion was excluded. Logistic regression analyses were performed. Possible different trends in DM achievement between past and recent decades were also investigated.

Results DM was achieved by 60% of patients, increased to 70% when glucocorticoids excluded from DM criteria. 24-hour proteinuria at 9 months predicted DM achievement (OR 0.72, 95% CI 0.53 to 0.97, p=0.03), but none of baseline characteristics. Among patients with >72 month follow-up, non-achievers had worse renal outcomes (flares, >30% proteinuria increase, eGFR decline) than achievers at the end of follow-up (median 138 months). Patients diagnosed between 1992 and 2005 were found to have significantly lower percentages of DM achievement and met less often the glucocorticoids dose reduction criterion in all three time frames, compared with those diagnosed between 2006 and 2016 (p=0.006 and p<0.01, respectively).

Conclusions DM was achieved by only 60% of LN patients in a real-life setting, partly due to lack of glucocorticoids dose target attainment, while DM failure was associated with worse long-term renal outcomes. This may imply limitations in the effectiveness or implementation of current LN treatments, supporting the need for novel therapeutic strategies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Disease modification (DM) is an emerging concept in lupus nephritis (LN) management, following similar trends in other rheumatic and non-rheumatic chronic disorders.
⇒ A conceptual framework for defining DM in LN has been recently developed, seeking to catalyse further discussions.

WHAT THIS STUDY ADDS

⇒ We further specified some aspects of preliminary DM definition criteria in a clinically meaningful manner and assessed for the first time DM achievement in LN in a real-life setting.
⇒ Only 60% of LN patients achieved DM, increased to 70% when glucocorticoids excluded from DM criteria. A 24-hour proteinuria at 9 months was predictive of DM achievement at 72-month follow-up, while those not achieving DM (vs those who did) had worse outcomes for all renal parameters at the end of a long-term follow-up (median 138 months).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There is an evident need to develop more effective treatments to make DM in LN possible.
⇒ Further evaluation and validation is needed to establish DM criteria in LN, which can help to improve clinical trials' design and patient outcomes.

INTRODUCTION

Lupus nephritis (LN) is the most common serious manifestation in systemic lupus erythematosus (SLE), affecting 25%–60% of patients and jeopardising renal and patient survival.[1–4] Adverse renal outcomes, such as chronic kidney disease (CKD) and end-stage renal disease (ESRD), have been associated with multiple clinical, laboratory and histological factors.[5–11] Although ESRD risk has been gradually reduced over the past decades due to dramatic advances in LN treatment, a 15-year ESRD risk up to 44% has been reported in patients with its proliferative forms, especially among those from developed countries.[12] Preserving renal function

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

and preventing ESRD remains the primary goal in LN management.[13–15]

In this context, updated guidelines for the management of LN have been released by the European League against Rheumatism (EULAR) in collaboration with the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) in 2019, and by the Kidney Disease: Improving Global Outcomes in 2021.[16 17] In addition, treat-to-target (T2T) strategy approaches have been discussed.[18 19] One step forward, the concept of disease modification (DM) refers to interventions that can alter the natural course of the disease and prevent organ damage accumulation. Although DM definition has been applied in rheumatoid arthritis (RA),[20] systemic sclerosis[21] and other chronic non-rheumatic conditions (ie, neurodegenerative[22] and respiratory disorders[23]), it has not yet been established in SLE.

Recently, a conceptual framework for the definition of DM in SLE and in LN specifically was developed by a group of lupus experts.[24] The main considerations in defining DM in LN were the minimisation of disease activity with minimal treatment-associated toxicity and the prevention of organ damage progression (ie, ESRD). Ultimately, the significance of the definition of DM in LN is twofold, as it may both help to guide clinical practice and to improve clinical trials' endpoints by the demonstration of a drug's ability to modify the course of the disease.[25]

Here, we aimed to assess the extent to which DM can be achieved with the use of conventional therapies in a real-world setting. In order to inform the continuous refinement of DM definition in LN and based on recently proposed preliminary criteria, we aimed to further specify some aspects of the criteria in a clinically meaningful manner, and to assess potential predictors of DM and long-term outcomes.

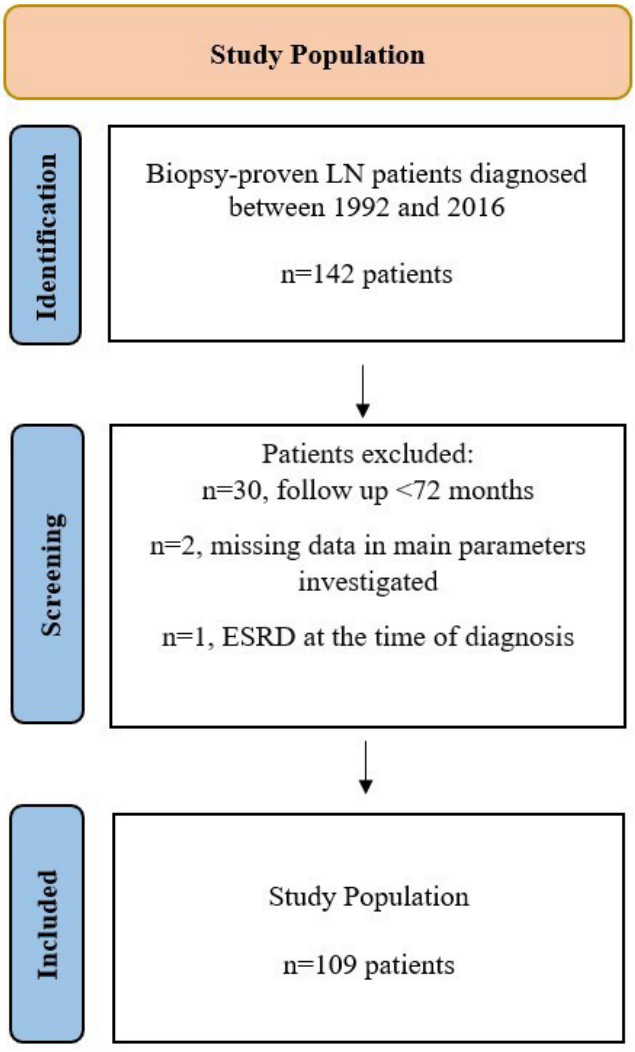

Figure 1 Flow chart: study population. ESRD, end-stage renal disease; LN, lupus nephritis.

PATIENTS AND METHODS

Study population

We included data from two inception cohorts of LN patients diagnosed between 1992 and 2016 and followed up at two joint academic centres (Nephrology and Rheumatology Units, Laiko General Hospital of Athens) for at least 72 months. All patients met the 2019 SLE classification criteria[26] and had biopsy-proven LN (class II, III, IV, V, III/IV+V), according to the 2003 ISN/RPS LN classification system.[27]

Data collection

Clinical, laboratory, histological and treatment data were collected for each patient at the time of LN diagnosis (baseline); 12, 60 and 72 months afterwards; and, at the last follow-up visit. Patients with ESRD at the time of diagnosis (n=1) and those with less than 72 months follow-up (n=30) or missing data from the above time points (n=2), were excluded from the study (figure 1). Recorded data included: demographics (age, sex, race/ethnicity), laboratory measures [urine sediment, serum creatinine, estimated glomerular filtration rate (eGFR) based on the CKD Epidemiology Collaboration (CKD-EPI) formula, 24-hour proteinuria], histological characteristics [LN class, activity index, chronicity index, crescents, interstitial fibrosis/tubular atrophy (IF/TA), glomerulosclerosis and arteriosclerosis] and treatment regimens [hydroxychloroquine (HCQ), glucocorticoids (GCs), mycophenolic acid (MPA), cyclophosphamide (CYC), azathioprine, cyclosporine, tacrolimus and rituximab (RTX)].

Renal flares were defined according to the 2012 EULAR/ERA-EDTA recommendations[28] as an increase in glomerular haematuria by ≥10 red blood cells (RBCs)/hpf with or without a decrease in eGFR by ≥10%, irrespective of changes in proteinuria (nephritic flare), or as a reproducible doubling of proteinuria to >1000 mg/24 hours if a complete response had been previously achieved, or reproducible doubling of proteinuria to ≥2000 mg/24 hours if a partial response has been previously achieved (proteinuric flare).

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

Table 1 Disease modification criteria for LN

Outcomes	Months 0–12	Months 13–60	Months 60–72
24 hours proteinuria	Decrease ≥50%* and to subnephrotic level† OR <0.8 g/day‡ if baseline1–1.5 g/day OR Decrease ≥25% if baseline <1 g/day	≤0.5 g/day if at month 12 <0.8 g/day OR <1 g/day if nephrotic at baseline OR Further decrease of 25%	Sustained decrease
Renal flare	≤1 flare	≤1 flare	No flare
eGFR	Minimise decline ≤30%	Minimise further decline <30%	Minimise further decline <30% and No ESRD
GCs	7.5–10 mg/day	≤5 mg/day	<5 mg/day

*Based on the KDIGO 2021 definition of partial response.[17]
†If nephrotic range proteinuria at baseline.
‡Based on Dall'Era *et al*.[11]
eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GCs, glucocorticoids; KDIGO, Kidney Disease: Improving Global Outcomes; LN, lupus nephritis.

DM assessment

DM assessment in our study was based on the preliminary criteria proposed by van Vollenhoven *et al*.[24] In their call for formal criteria, the authors suggested three different time frames for the assessment of outcomes: (A) at year 1, (B) at years 2–5 and (C) >5 years. In the first time frame, DM criteria included a significant improvement in urinary protein-creatinine ratio (uPCR) or kidney activity index via biopsy, a significant reduction in renal flares, minimisation of eGFR decline (ie, ≤30%), and reduction in use of GCs and/or immunosuppressants. DM criteria at 2–5 years included a sustained improvement in uPCR or no worsening in kidney chronicity index via biopsy, prevention of flares, minimisation of further eGFR decline (ie,<30%) and continued reduction in GCs and/or immunosuppressants. Beyond 5 years, no change in Systemic Damage Index (SDI) or delayed progression was required.

We attempted to further specify the proposed criteria in a clinically meaningful manner, as shown in table 1. For patients with a renal flare, renal parameters (24 hours proteinuria, eGFR decline) and GCs dose were assessed 12 months after the flare. The target of flare minimisation was set at ≤1 flare for the first two time frames. For the third time frame, we believe that any renal flare at that longer period precludes the disease from being modified, therefore, 'absence of renal flare' was included in DM criteria for this time frame. For the 'beyond 5 years' time frame, we set month 72 as the timepoint of assessment. The kidney activity and chronicity index criteria were not included since per protocol kidney biopsies were not performed in our cohort. We implemented two models for DM achievement assessment. According to the first model, patients were considered to achieve DM (achievers of DM) if all four proposed criteria were attained at each time frame (12 out of 12 targets). In the second model, DM was achieved if patients fulfilled 24-hour proteinuria, flare and eGFR criteria at each time frame, excluding GCs dose target (9 out of 9 targets). Only patients fulfilling all the proposed criteria in a specific time frame were eligible to be assessed for DM in the next time frame.

In order to investigate possible different trends in DM achievement between recent and past decades, patients were classified in two subgroups based on the year of LN diagnosis, between 1992 and 2005 (period 1) and between 2006 and 2016 (period 2).

Statistical analysis

Continuous variables were expressed as the median value and IQR, whereas categorical variables as frequencies and percentages. The Mann-Whitney U test for independent samples for continuous variables and the χ^2 and Fisher's exact test for categorical variables were applied to test the differences in baseline demographic, clinical, laboratory and histological variables between achievers and non-achievers of DM. Logistic regression analysis was performed to evaluate potential determinants of DM achievement. Significance was set at α=0.05. The estimated ORs, as well as the related p values and 95% CIs, are presented. Data were analysed by using Stata V.17.0 software (Stata). All tests proceeded as two tailed.

RESULTS

One hundred and nine LN patients were included in the study [82% females, median age: 32 years (IQR 19)]. The median 24-hour proteinuria at the time of diagnosis was 3 g (IQR 4.2) and the median eGFR was 96 mL/min/1.73 m^2 (IQR 43). Seventy-two patients (66%) had a proliferative class of LN (III, IV, III/IV+V), 26% (28/109) had membranous LN (class V) and 8% (9/109) class II. Three out of nine patients (33%) with class II have experienced a class switch into proliferative classes (III, III+V) in a

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

median time of 64 months. Induction treatment included CYC in 57% (62/109) of patients (in combination with RTX in 7/62), and MPA in 32% (35/109) of patients (in combination with RTX in 6/35). RTX in combination with GCs alone was given as induction therapy in two patients. Eight patients (7.5%) did not receive any induction treatment; six of them had class V and proteinuria <3 g/day, which was not an indication for immunosuppressive treatment according to the existing at the time (diagnosis from 2005 to 2018) guidelines; the other two had class II. The majority of patients (71.5%) were treated with MPA as maintenance therapy. Nine patients (8%) did not receive any maintenance treatment; one patient due to non-compliance; the other eight patients have not received induction treatment either, as described above. Two of the patients who received GCs monotherapy as maintenance treatment were treated with combination of RTX and GCs as induction therapy. Ever use of HCQ was recorded in 85.3% (93/109) of patients, at different time points of follow-up; 37 patients (34%) were on HCQ before LN diagnosis, and 12 patients (11%) started HCQ treatment at the time of LN diagnosis. Persistent use (for more than two-thirds of the follow-up time) was documented in 62.5% (68/109). HCQ use at the time of LN diagnosis as well as persistent HCQ use were more frequent during period 2 compared with period 1 (49.4% vs 29.1%, p=0.08 and 71.5% vs 32%, p<0.001, respectively). The baseline demographic, clinical, laboratory and histological characteristics of the patients, as well as the treatment regimens applied, are presented in online supplemental table 1.

At the end of the first time frame (months 0–12), a total of 85/109 (78%) patients fulfilled all four criteria. None of the patients had an eGFR decline greater than 30% of the baseline levels (eGFR variation range: −29.2%, +606%). Only one patient relapsed (6 months after the diagnosis), but finally achieved all four targets at the 12-month timepoint. The 24-hour proteinuria target was achieved by 97/107 (91%) patients. More specifically, 47/53 (88.7%) of patients with nephrotic range proteinuria at baseline attained a >50% decrease to subnephrotic levels. Furthermore, for non-nephrotic patients at baseline, 24-hour proteinuria target was achieved by 18/22 (82%) patients with 1.5–3 g/day; 8/8 (100%) patients with 1–1.5 g/day and 24/26 (92%) patients with <1 g/day baseline proteinuria. In total, 86% reached the GCs target (prednisolone <7.5 mg/day), 14/103 patients (14%) were on GCs dose ≥10 mg/day and 2/14 were on 25 and 30 mg of prednisolone daily, respectively, due to extrarenal manifestations [central nervous system involvement and gastrointestinal vasculitis (diagnosed simultaneously with LN)].

During the second time frame (months 13–60), among 85 patients eligible for DM assessment, 77.6% (66/85) met all the four criteria. No flare was recorded for 66 (77.5%) patients, while 14 patients relapsed once, 3 patients twice and 2 patients three times. The vast majority (79/85, 93%) met the target for eGFR; 41/85 patients improved their renal function and 38/85 had less than 30% eGFR decline at 60 months of follow-up compared with month 12. Only three patients progressed to ESRD. The 24-hour proteinuria target was achieved by 75/85 (88.2%) patients by month 60. More specifically, 61/68 (89.7%) patients with <0.8 g/day proteinuria at month 12 achieved further decrease to <0.5 g/day, 10/13 patients with nephrotic range proteinuria at baseline achieved a decrease to <1 g/day and 4/4 non-nephrotic patients at baseline achieved further decrease of >25%. Six patients (7%) were still on GCs dose ≥5 mg/day. To note, 3/6 (50%) were receiving a higher than desired GCs dose due to extrarenal manifestations (arthritis flare at the time of the assessment), 2/6 due to a previous renal flare, and 1 patient was on prednisolone 7.5–10 mg/day tapering.

At the third time frame (months 60–72), only 1 patient relapsed once, while 65/66 (98.5%) patients met all four necessary criteria.

The number of patients who attained each of the proposed DM criteria in a specific time frame is shown in figure 2. Finally, 60% of patients (65/109) reached all proposed criteria in all three time frames and were considered achievers of DM (figure 3). The percentage of DM achievers increased to 70% (76/109) when GCs dose reduction criterion was excluded.

Interestingly, DM achievement differed significantly between patients diagnosed in years 1992–2005 (period 1) and those diagnosed in years 2006–2016 (period 2), with a higher percentage of achievers in period 2 (9/25 (36%) vs 56/84 (67%), p=0.006, figure 3). When GCs dose was not a prerequisite to determine DM, 14/25 (56%) of patients achieved DM in period 1 vs 62/84 (74%) in period 2 (p=0.089). During the assessment up to month 72, use of higher doses of GCs was more frequent in period 1 compared with period 2 (>10 mg/day at month 12: 39% vs 6%; >5 mg/day at month 60: 25% vs 7%; and >5 mg/day at month 72: 25% vs 6%, respectively, p<0.01).

The minimum number of achieved targets in all three time frames (with or without GCs dose target) is shown in online supplemental tables 2A,B.

Differences in characteristics between achievers and non-achievers of DM are shown in table 2. No difference was shown between achievers and non-achievers of DM in median baseline 24 hours proteinuria (2.5 g/day vs 3.5 g/day, p=0.23), renal function at the time of diagnosis (median eGFR 97 mL/min/1.73 m^2 vs 96 mL/min/1.73 m^2, p=0.75) and LN histological classes (p=0.95). Histological findings of glomerulosclerosis were comparable among the two study groups, regarding both globally (8.5% vs 10%, p=0.6) and segmentally (8.5% vs 9%, p=0.67) sclerotic glomeruli. None of DM achievers had evidence of severe IF/TA in renal biopsies, while in the non-achievers group there were two such cases (4.5%, p=0.16). Of note, no difference was found in induction treatment regimens (CYC or MPA) between patients with and those without DM achievement (p=0.14), nor in HCQ use (table 2). Interestingly, patients who did

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

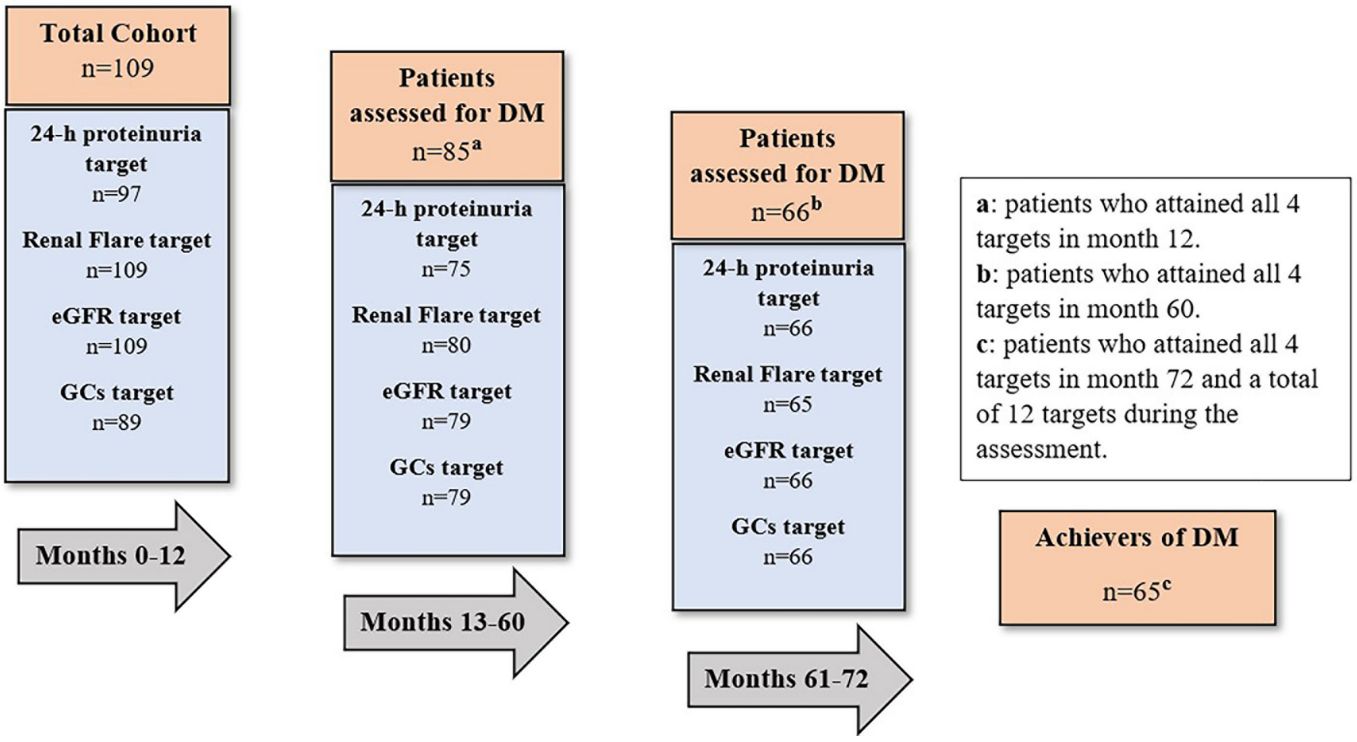

Figure 2 Patients attaining each of the proposed disease modification (DM) targets* in a specific time frame. *Targets as defined in table 1. GCs, glucocorticoids; eGFR, estimated glomerular filtration rate.

not attain DM, considerably improved their 24 hours proteinuria by month 12, but DM achievers reached more substantial improvement versus non-achievers (90% vs 77%, p=0.005). In addition, an increase in eGFR levels from month 0 to month 72 was observed in DM achievers (median % eGFR change: +9.9) versus a reduction in eGFR levels over time in non-achievers (median % eGFR change: −5.3) (p=0.0046). For patients with baseline eGFR<60 mL/min/1.73m^2 an eGFR increase of +115% was reported for DM achievers versus +118%

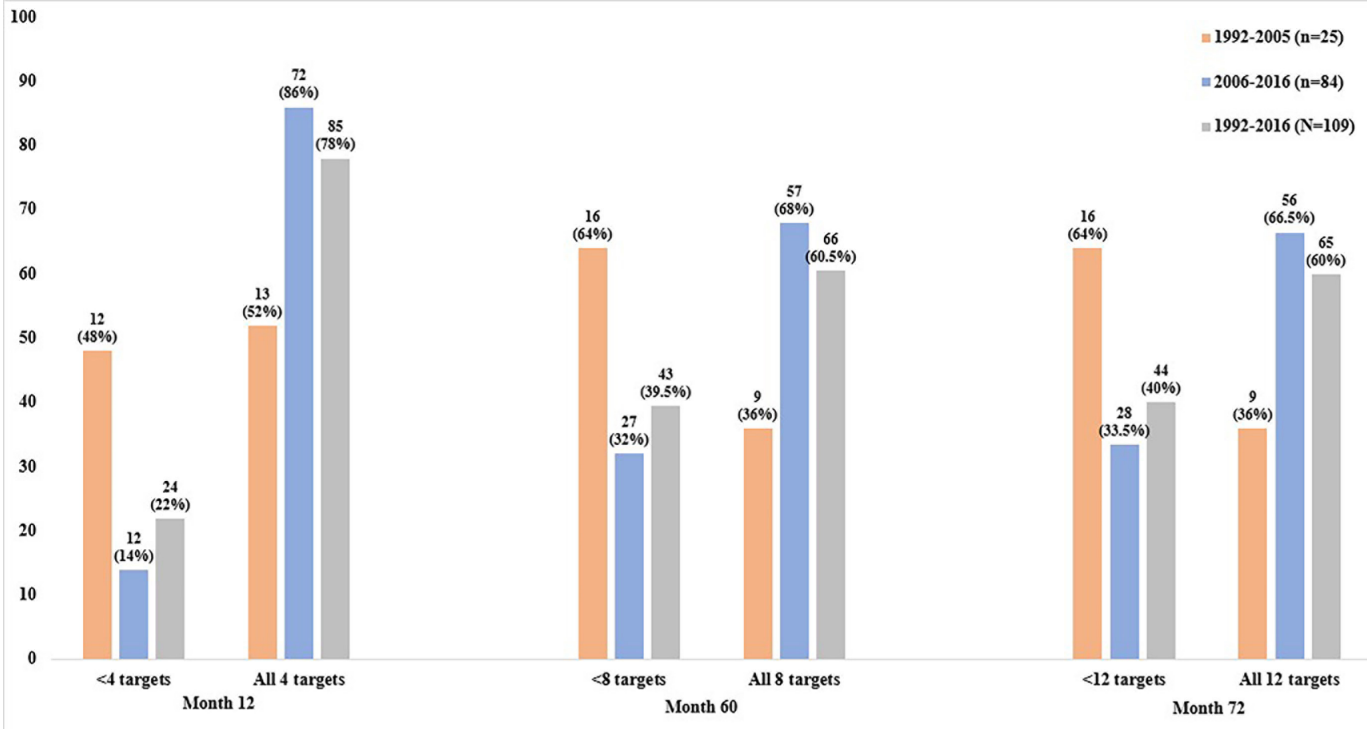

Figure 3 Number and percentage of patients attaining or not all proposed disease modification criteria in a specific time frame.

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

Table 2 Differences in patient characteristics between achievers and non-achievers of disease modification (DM)

Characteristics	Achievers of DM (n=65)	Non-achievers of DM (n=44)	P value
	Median [IQR] - N (%)		
Age (years)	33 [16]	30 [23]	0.43
Median proteinuria at diagnosis (g/day)	2.5 [4.1]	3.5 [4.2]	0.23
Proteinuria >3 g/day	29 (45)	24 (54.5)	0.58
Proteinuria 1–3 g/day	19 (29)	11 (25)	
Proteinuria <1 g/day	17 (26)	9 (20.5)	
Median eGFR at diagnosis (mL/min/1.73m^2)	97 [41]	96 [46]	0.75
eGFR>60	53 (82)	35 (80)	0.84
eGFR 30–60	8 (12)	5 (11)	
eGFR<30	4 (6)	4 (9)	
LN class at diagnosis			
Class II	6 (9.5)	3 (6.5)	0.95
Class V	17 (26)	11 (25)	
Class III	15 (23)	10 (23)	
Class IV	21 (32)	14 (32)	
Class III/IV+V	6 (9.5)	6 (13.5)	
Number of crescents	0 [2]	0 [2]	0.34
IF/TA			
None/mild/moderate	65 (100)	42 (95.5)	0.16
Severe	0	2 (4.5)	
Arteriosclerosis (moderate/severe)	12 (18.5)	11 (26)	0.34
Sclerotic glomeruli (%)	13.5 [17.5]	11 [16.5]	0.92
Globally sclerotic (%)	8.5 [11.5]	10 [13]	0.6
Segmentally sclerotic (%)	8.5 [12]	9 [13]	0.67
Induction treatment			
CYC	33 (58)	29 (72.5)	0.14
MPA	24 (42)	11 (27.5)	
HCQ treatment			
Before LN diagnosis	20 (30.7)	17 (38.6)	0.39
Initiation on LN diagnosis	9 (20.9)	3 (11.5)	0.31
Persistent use*	40 (61.5)	28 (63.5)	0.82
Median proteinuria at month12 (g/day)	0.17 [0.23]	0.46 [1.6]	**0.0001**
% reduction of median 24 hours proteinuria between baseline and month 12	90 [24]	77 [55.5]	**0.005**
Median eGFR at month 12 (mL/min/1.73m^2)	112 [23]	104 [37.5]	0.29
Median % eGFR change between baseline and month 12	+4.7 [29.7]	0 [26.8]	0.25
Median % eGFR change between baseline and month 72	+9.9 [39.9]	−5.3 [51.2]	**0.0046**

Statistical significance (p<0.05) is shown in bold
*More than two-thirds of the follow-up time.
CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; IF/TA, interstitial fibrosis/tubular atrophy; LN, lupus nephritis; MPA, mycophenolic acid.

for non-achievers (p=0.60). Of note, this eGFR increase was mainly achieved during the first 12 months. On the other hand, for patients with baseline eGFR>60 mL/min/1.73m^2, there was no eGFR change between month 0 and month 72 for DM achievers, while non-achievers suffered an eGFR decrease of −6.5% (p=0.005).

In 45 patients (41.3%), a repeat kidney biopsy was performed due to renal flare (41/45, 91%) or due to non-response to treatment (4/45, 9%). Median time

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

from initial to repeat biopsy was 40 months (IQR 62) in DM achievers and 36.5 months (IQR 41) in non-achievers (p=0.40). We reported a median increase by 3 points in chronicity index in non-achievers of DM compared with a median increase of 1 in DM achievers (p=0.23).

To note, when GCs dose was not a prerequisite to determine DM, those attaining DM were 7 years older than those in the opposite group (34 years vs 27 years, p=0.03). Non-achievers of DM had more severe 24 hours proteinuria at baseline, but not significantly different than that of achievers (3.5 g/day vs 2.7 g/day, p=0.40) and were evenly treated with CYC or MPA (p=0.93, table 3). In DM achievers, eGFR levels increased from month 0 to month 72 (median % eGFR change: +10.3), while non-achievers had a significant reduction in eGFR levels over time (median % eGFR change: −8.7) (p=0.0015). For patients with baseline eGFR<60 mL/min/1.73 m^2, an eGFR increase of +118% was reported for DM achievers versus +96% for non-achievers (p=0.59), while for patients with baseline eGFR>60 mL/min/1.73 m^2, there was an eGFR change of +0.8% between month 0 and month 72 for DM achievers and an eGFR decrease of −9.3% for non-achievers (p=0.0004).

We further performed a logistic regression analysis in which DM was the dependent variable and baseline clinical, laboratory, histological and treatment characteristics, as well as 24 hours proteinuria levels at 3, 6 and 9 months of follow-up, were the independent variables (table 4). Proteinuria at month 12 was not examined as possible predictor of DM, since this parameter is included in the definition of DM. In univariate analysis, no baseline characteristic was found to be predictive of DM, except 24 hours proteinuria at 9 months (OR 0.72, p=0.03), therefore, multivariate analysis was not implemented. IF/TA was not included in the analysis as an independent variable since all patients with severe IF/TA were non-achievers of DM.

We performed a separate analysis considering as DM achievers all patients who attained the three DM targets (24 hours proteinuria, eGFR decline, flares) at all time frames, irrespective of GCs dose (table 5). Since no baseline characteristic, nor 24 hours proteinuria at 3, 6 and 9 months were found to predict DM attainment, multivariate analysis was not performed.

Since the vast majority (90/109) of patients in our cohort had a follow-up greater than 72 months, we extended our analysis to the end of follow-up for these patients [median follow-up 138 months (IQR 83)]; 51/90 (57%) had been classified as DM achievers and 39/90 (43%) as non-achievers. Four patients progressed to ESRD, all non-achievers of DM by month 72 (p=0.03). Moreover, non-achievers had a further median decline by 9 mL/min/1.73 m^2 in eGFR after month 72, while achievers preserved a stable renal function (no eGFR decline, p=0.0047). An increase >30% in 24 hours proteinuria was observed in 25% (13/51) of DM achievers vs 38% (14/39) of non-achievers (p=0.2), with a trend for a higher median proteinuria increase in non-achievers [69% (IQR 125) vs 115% (IQR 550), p=0.06]. Moreover, a higher percentage of (at least one) flares was observed among non-achievers of DM vs achievers after month 72 (31% vs 12%, p=0.03) and 2% (1/51) of achievers vs 7.7% (3/39) of non-achievers were on a prednisolone dose >5 mg/day (p=0.31).

DISCUSSION

In the current study, we assessed for the first time the extent of DM achievement in LN patients by implementing and further specifying evaluation criteria for DM working definition in LN.[24] We found that only 60% of LN patients followed in two joint academic centres and treated with conventional therapies, achieved DM.

DM refers to interventions that alter the natural course of a disease, improve signs, symptoms and quality of life and slow or prevent the progression of organ damage.[20–23] The implementation of the concept of DM is important not only for designing clinical trials that will test new disease-modifying treatments, but also for the everyday clinical practice in the context of a T2T approach. International recommendations for the management of LN focus on the achievement of renal response which, however, may constitute a temporary or short-term goal.[29] DM, on the other hand, reflects a more holistic and long-term approach of consistent disease activity minimisation with the fewest treatment-associated toxicities.

A pioneer attempt to define DM in LN patients was recently made by a group of international lupus experts[24] who proposed a set of preliminary criteria assessed in three different time frames. In order to inform the continuous work and refinement of DM definition in LN, we endorsed the main components of DM definition (ie, sustained proteinuria decrease, flares reduction, minimisation of eGFR decline and reduction in GCs use), since proteinuria levels indicate renal damage risk, reduction of renal flares prevents kidneys from further nephron loss, while slowing or preventing eGFR decline is the ultimate goal in LN, along with minimisation of drug-induced toxicity.[16 17] In the current study, we further specified some aspects of these criteria in a clinically meaningful way and in accordance with the existing literature on factors affecting the short-term and long-term renal survival in LN patients.[6 9–11 30] For the first time frame (months 0–12), we proposed specific targets to define proteinuria improvement based on the baseline proteinuria levels (ie, ≥50% decrease and to subnephrotic levels if nephrotic range proteinuria was documented at baseline, or <0.8 g/day if the baseline proteinuria was 1–1.5 g/day, or ≥25% decrease if the baseline proteinuria was <1 g/day) and we set the target of ≤1 flare and of 7.5–10 mg/day prednisolone equivalent at 12 months for the definition of 'reduction of flares' and 'GC use decrease', incorporating the ≤30% eGFR decline target from the previous criteria. For the second time frame (months 13–60), we suggested targets for the 'sustained proteinuria improvement' depending on its

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

Table 3 Differences in characteristics between achievers and non-achievers of disease modification (DM), when glucocorticoids dose was not a prerequisite to determine DM

Characteristics	Achievers of DM (n=76 pts)	Non-achievers of DM (n=33 pts)	P value
	Median [IQR] – N (%)		
Age (years)	34 [17]	27 [23]	**0.03**
Median proteinuria at diagnosis (g/day)	2.7 [3.9]	3.5 [4.8]	0.40
Proteinuria >3 g/day	34 (45)	19 (57.5)	0.31
Proteinuria 1–3 g/day	24 (31.5)	6 (18)	
Proteinuria <1 g/day	18 (23.5)	8 (24.5)	
Median eGFR at diagnosis (mL/min/1.73 m^2)	97 [40]	96 [60]	0.96
eGFR>60	63 (83)	25 (75)	0.68
eGFR30-60	8 (10.5)	5 (15)	
eGFR<30	5 (6.5)	3 (9)	
LN class at diagnosis			
Class II	6 (8)	3 (9.1)	0.68
Class V	20 (26.5)	8 (24.2)	
Class III	15 (19.5)	10 (30.5)	
Class IV	27 (35.5)	8 (24.2)	
Class III/IV+V	8 (10.5)	4 (12)	
N of crescents	0 [2.5]	0 [2]	0.39
IF/TA			
None/mild/moderate	76 (100)	31 (94)	0.09
Severe	0	2 (6)	
Arteriosclerosis (moderate/severe)	14 (18.5)	9 (28)	0.27
Sclerotic glomeruli (%)	13.5 [17.5]	11 [16.5]	0.98
Globally sclerotic (%)	8.5 [10]	11.5 [13.5]	0.3
Segmentally sclerotic (%)	8.5 [12.5]	8 [5.5]	0.47
Induction treatment			
CYC	43 (64)	19 (63.5)	0.93
MPA	24 (36)	11 (36.5)	
HCQ treatment			
Before LN diagnosis	23 (30.2)	14 (42.4)	0.21
Initiation on LN diagnosis	11 (21.5)	1 (5.5)	0.12
Persistent use*	48 (63)	20 (60.5)	0.80
Median proteinuria at month 12 (g/day)	0.18 [0.23]	0.6 [2.3]	**<0.001**
% reduction of median 24 hours proteinuria between baseline and month 12	91 [23]	68 [80]	**0.001**
Median eGFR at month 12 (mL/min/1.73m^2)	111 [25.5]	105 [37]	0.76
Median % eGFR change between baseline and month 12	0 [24.8]	+3.7 [37.5]	0.92
Median % eGFR change between baseline and month 72	+10.3 [39.7]	−8.7 [46.5]	**0.0015**

statistical significance (p<0.05) is shown in bold
*More than two-thirds of the follow-up time.
CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; IF/TA, interstitial fibrosis/tubular atrophy; LN, lupus nephritis; MPA, mycophenolic acid.

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

Table 4 Determinants of disease modification achievement

Parameters	Univariate model		
	OR	95% CIs	P value
Age (years)	1.009	0.98 to 1.04	0.54
eGFR at diagnosis (mL/min/1.73 m^2)	0.99	0.98 to 1.01	0.88
Proteinuria at diagnosis (g/day)	0.93	0.83 to 1.03	0.19
Proteinuria <1 g/day	Reference group		
Proteinuria 1–3 g/day	0.9	0.3 to 2.73	0.87
Proteinuria >3 g/day	0.63	0.24 to 1.7	0.37
LN class			
Membranous*	Reference group		
Proliferative†	0.85	0.37 to 1.92	0.7
No of crescents	1.03	0.92 to 1.16	0.6
Arteriosclerosis			
None/mild	Reference group		
Moderate/severe	0.63	0.25 to 1.6	0.34
Sclerotic glomeruli (%)	1.56	0.03 to 62	0.81
Induction treatment			
CYC	Reference group		
MPA	1.91	0.8 to 4.57	0.14
Persistent use of HCQ‡	0.91	0.41 to 2.01	0.82
Proteinuria at month 3 (g/day)	0.99	0.81 to 1.2	0.94
Proteinuria at month 6 (g/day)	0.79	0.61 to 1.01	0.06
Proteinuria at month 9 (g/day)	0.72	0.53 to 0.97	**0.03**

statistical significance (p<0.05) is shown in bold
*Refers to LN class V.
†Refers to LN class III, IV, III/IV+V.
‡More than two-thirds of the follow up time.
.CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; LN, lupus nephritis; MPA, mycophenolic acid.

baseline levels (ie, a reduction in proteinuria levels to ≤0.5 g/day, if proteinuria at month 12 was <0.8 g/day, or <1 g/day if nephrotic levels were documented at baseline, or a further decrease by 25%). We also specified the target for renal flares to ≤1 flare and the target for GCs dose to ≤5 mg/day prednisolone equivalent, keeping the target of <30% further eGFR decline. As for the third time frame (months 60–72), common DM criteria for SLE and LN were proposed by van Vollenhoven *et al*, namely 'no change in SDI' or 'delayed progression'. We suggested targets for the four main topics of DM definition in LN (proteinuria, renal flares, eGFR, GCs dose) corresponding to this specific time frame: a sustained decrease in proteinuria, no renal flares, <30% further GFR decline (without occurrence of ESRD) and a further GCs dose reduction to <5 mg/day.

Among 109 LN patients with at least 72 months follow-up who had been treated with conventional therapies (primarily CYC or MPA), only 60% achieved DM, as defined by the fulfilment of all criteria (24 hours proteinuria, flares, eGFR, GCs dose) at all three time frames (months 0–12, 13–60, 60–72). Furthermore, patients defined as non-achievers of DM at month 72, presented in the long-term a further decline in renal function, a greater increase in proteinuria and a higher frequency of flares compared with achievers. These observations highlight the unmet need of sustained renal response achievement in LN and raise the question of the effectiveness of current LN management.[14 31 32] It may be that current treatments reduce disease activity but do not alter the underlying pathophysiologic mechanisms of the disease and, therefore, its progression.[33 34] In this context, new treatments or better implementation of available treatment strategies are needed, especially for patients with more severe or frequently relapsing disease. Data from recent trials of add-on therapies in LN have shown favourable short-term results in terms of remission and relapse, but their potential role in DM remains unknown.[35–40]

Emphasis should also be given on adjunctive interventions, that can help to slow or prevent disease progression and facilitate DM goal in LN, such as the optimal

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

Table 5 Determinants of disease modification achievement, when glucocorticoids dose was not a prerequisite

Parameters	Univariate models		
	OR	95% CIs	P value
Age (years)	1.03	0.99 to 1.06	0.07
eGFR at diagnosis (mL/min/1.73 m^2)	1	0.99 to 1.01	0.82
Proteinuria at diagnosis (g/day)	0.95	0.85 to 1.06	0.41
Proteinuria <1 g/day	Reference group		
Proteinuria 1–3 g/day	1.77	0.52 to 6	0.35
Proteinuria >3 g/day	0.79	0.29 to 2.1	0.65
LN class			
Membranous*	Reference group		
Proliferative†	0.96	0.4 to 2.2	0.93
No of crescents	1.03	0.91 to 1.18	0.57
Arteriosclerosis			
None/mild	Reference group		
Moderate/severe	0.58	0.22 to 1.53	0.27
Sclerotic glomeruli (%)	0.98	0.02 to 48	0.99
Induction treatment			
CYC	Reference group		
MPA	0.96	0.4 to 2.36	0.93
Persistent use of HCQ‡	1.11	0.48 to 2.58	0.80
Proteinuria at month 3 (g/day)	1.02	0.82 to 1.27	0.84
Proteinuria at month 6 (g/day)	0.87	0.69 to 1.09	0.23
Proteinuria at month 9 (g/day)	0.82	0.63 to 1.06	0.13

*Refers to LN class V.
†Refers to LN class III, IV, III/IV+V
‡More than two-thirds of the follow up time.
. CYC, cyclophosphamide; eGFR, estimated glomerular filtration rate; HCQ, hydroxychloroquine; LN, lupus nephritis; MPA, mycophenolic acid.

management of hypertension, diabetes and obesity, the implementation of low-salt and low-protein diets, and smoking cessation.[41 42] It is well known that renin-angiotensin-aldosterone system (RAAS) blockade has a significant renoprotective effect mediated by systemic and intraglomerular pressure control and other pleiotropic effects (antifibrotic, antihyperplastic, anti-inflammatory).[43] Recently, a novel class of antidiabetic drugs, the SGLT2 inhibitors, have shown to delay CKD progression in patients with non-diabetic kidney disease, including also those with LN.[44 45]

It is noteworthy that, in our study, the percentage of DM achievers raised from 60% to 70% when the GCs dose target was excluded from all three timepoints of DM evaluation. Furthermore, the goal of GCs dose reduction was met less often than the other three renal outcome targets (24 hours proteinuria, eGFR, flares) in all time points. Significantly higher percentages of DM achievement were found in patients diagnosed in the second (2006–2016) than in the first (1992–2005) time period (p=0.006), which can be explained by the advances in LN treatment over the past decades and a better management of comorbidities. Notably, patients diagnosed before 2006 were exposed more often to higher doses of GCs, compared with patients diagnosed afterwards. Interestingly, no significant difference in DM achievement was observed between the two time periods when GCs dose was excluded from the DM criteria, supporting the impact of GCs on DM. In general, we can conclude that DM in the entire cohort has been significantly affected by the failure to achieve the GCs dose target. Future disease-modifying interventions should also aim to protect patients from long-term use of GCs and its side effects.

Regarding DM attainment determinants, no baseline clinical, laboratory, histological or therapeutic parameter was found to predict DM achievement at 72 months of follow-up. This finding may imply that assessment of these parameters at later time points in the course of the disease may be more predictive of DM attainment.[6 46] Indeed, we observed that 24 hours proteinuria at 9 months after diagnosis was predictive of DM. It is also noteworthy that there was no difference in DM achievement between patients with pure membranous LN (26% in our cohort), who are supposed to have better renal

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

prognosis, than those with proliferative classes. This may be due to the fact that we followed in some of these patients (depending on the time of their diagnosis) previous guidelines on LN management which restricted subnephrotic patients with pure membranous LN from immunosuppressive therapy.[28 47]

Concerning the histological lesions, we examined LN class, number of crescents, percentage of glomerulosclerosis and IF/TA. Among vascular lesions, we included data on arteriosclerosis, although it would be important to examine also how thrombotic microangiopathy/antiphospholipid syndrome nephropathy lesions correlate to DM outcomes. This would demand a more detailed re-evaluation of all renal biopsies based on current efforts for recharacterisation of antiphospholipid syndrome (APS) nephropathy lesions,[48] that was not feasible in the current study, especially for biopsies of previous decades.

The main strengths of the current study include the first implementation of recently proposed criteria for DM in a real-life setting with an effort to further specify some of the criteria, the inclusion of data from two inception cohorts and the availability of a large set of clinical, laboratory and treatment data from multiple regular visits during a median follow-up time of 138 months. We acknowledge that our study has certain limitations. Repeat biopsies in our cohort were performed based on clinical/laboratory indications of renal flare or in cases of no response to treatment, therefore, the time of repeat biopsies differed among patients. Per-protocol biopsies performed at prespecified time points can be of major importance in evaluating DM in LN,[49] but such biopsies were only recently introduced in our units and were not available in our cohort at the examined time periods. Other limitations of this study are its retrospective nature and the inclusion of exclusively Caucasian patients. Of note, all patients of our cohort were managed within a supportive and easily accessible public health system providing a free hospital care, therefore, our results may differ from those in other countries.

Conclusions

In conclusion, in this first attempt to assess whether DM in LN is possible in a real-life setting, we found that DM was achieved in only 60% of LN patients, commonly due to the failure to reduce GCs exposure. This may suggest limitations in the effectiveness of current LN management strategies or in their implementation. Further evaluation and validation in large multicentre and multiethnic cohorts is needed to establish DM criteria in LN, which will help to improve treatment efficacy assessment in clinical trials and in clinical practice.

Contributors Conception and design: MGT. Data collection: EK, AP and MGT. Data analysis: IM and MGT. Data interpretation: AP, EK, IM and MGT. Manuscript drafting: AP, EK, IM and MGT. Critical revision of the manuscript and approval of the final version: AP, EK, IM, JB, SM, PPS and MGT. Guarantor: MGT

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Institutional Review Board (protocol number 14697/08-11-2022) of Laiko General Hospital of Athens and does not contain any identifiable patient data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Ioannis Michelakis http://orcid.org/0000-0002-3314-3329
Maria G Tektonidou http://orcid.org/0000-0003-2238-0975

REFERENCES

1 Hanly JG, O'Keeffe AG, Su L, *et al*. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology (Oxford)* 2016;55:252–62.
2 Yap DYH, Tang CSO, Ma MKM, *et al*. Survival analysis and causes of mortality in patients with lupus nephritis. *Nephrol Dial Transplant* 2012;27:3248–54.
3 Tektonidou MG, Lewandowski LB, Hu J, *et al*. Survival in adults and children with systemic lupus erythematosus: a systematic review and Bayesian meta-analysis of studies from 1950 to 2016. *Ann Rheum Dis* 2017;76:2009–16.
4 Petri M, Barr E, Magder LS. Risk of renal failure within 10 or 20 years of systemic lupus erythematosus diagnosis. *J Rheumatol* 2021;48:222–7.
5 Gatto M, Radice F, Saccon F, *et al*. Clinical and histological findings at second but not at first kidney biopsy predict end-stage kidney disease in a large Multicentric cohort of patients with active lupus nephritis. *Lupus Sci Med* 2022;9:e000689.
6 Kapsia E, Marinaki S, Michelakis I, *et al*. Predictors of early response, flares, and long-term adverse renal outcomes in proliferative lupus nephritis: A 100-month median follow-up of an inception cohort. *J Clin Med* 2022;11:5017.
7 Pirson V, Enfrein A, Houssiau FA, *et al*. Absence of renal remission portends poor long-term kidney outcome in lupus nephritis. *Lupus Sci Med* 2021;8:e000533.
8 Moroni G, Gatto M, Tamborini F, *et al*. Lack of EULAR/ERA-EDTA response at 1 year predicts poor long-term renal outcome in patients with lupus nephritis. *Ann Rheum Dis* 2020;79:1077–83.
9 Tamirou F, Lauwerys BR, Dall'Era M, *et al*. A proteinuria cut-off level of 0.7 G/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN nephritis trial. *Lupus Sci Med* 2015;2:e000123.
10 Parikh SV, Nagaraja HN, Hebert L, *et al*. Renal flare as a Predictor of incident and progressive CKD in patients with lupus nephritis. *Clin J Am Soc Nephrol* 2014;9:279–84.
11 Dall'Era M, Cisternas MG, Smilek DE, *et al*. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-lupus nephritis cohort. *Arthritis & Rheumatology* 2015;67:1305–13.
12 Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971-2015: A systematic review and Bayesian meta-analysis. *Arthritis & Rheumatology* 2016;68:1432–41.
13 Yu C, Li P, Dang X, *et al*. Lupus nephritis: new progress in diagnosis and treatment. *J Autoimmun* 2022;132:S0896-8411(22)00079-8.
14 Porta SV, Enfrein A, Houssiau F, *et al*. Controversies in systemic lupus erythematosus 2021. *J Clin Rheumatol* 2022;28:229–33.
15 Mok CC, Teng YKO, Saxena R, *et al*. Treatment of lupus nephritis: consensus, evidence and perspectives. *Nat Rev Rheumatol* 2023;19:227–38.

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.

16 Fanouriakis A, Kostopoulou M, Cheema K, *et al*. Update of the joint European League against rheumatism and European renal Association–European dialysis and transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis. *Ann Rheum Dis* 2020;79:713–23.
17 Rovin BH, Adler SG, Barratt J, *et al*. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney International* 2021;100:S1–276.
18 Mok CC. Is treat-to-target in lupus nephritis realistic in clinical practice *CRR* 2018;15:2–6.
19 van Vollenhoven RF, Mosca M, Bertsias G, *et al*. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;73:958–67.
20 Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum Dis Clin North Am* 2006;32:9–44.
21 Nagaraja V, Matucci-Cerinic M, Furst DE, *et al*. Current and future outlook on disease modification and defining low disease activity in systemic sclerosis. *Arthritis Rheumatol* 2020;72:1049–58.
22 Cummings J. Disease modification and Neuroprotection in neurodegenerative disorders. *Transl Neurodegener* 2017;6:25:25.:.
23 Halpin DMG, Tashkin DP. Defining disease modification in chronic obstructive pulmonary disease. *COPD* 2009;6:211–25.
24 van Vollenhoven R, Askanase AD, Bomback AS, *et al*. Conceptual framework for defining disease modification in systemic lupus erythematosus: a call for formal criteria. *Lupus Sci Med* 2022;9:e000634.
25 Houssiau FA. Why will lupus nephritis trials not fail anymore *Rheumatology* 2016:kew252.
26 Aringer M, Costenbader K, Daikh D, *et al*. European League against rheumatism/American college of rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol* 2019;71:1400–12.
27 Weening JJ, D'Agati VD, Schwartz MM, *et al*. The classification of glomerulonephritis in systemic lupus erythematosus Revisited. *J Am Soc Nephrol* 2004;15:241–50.
28 Bertsias GK, Tektonidou M, Amoura Z, *et al*. Joint European League against rheumatism and European renal Association–European dialysis and transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and Paediatric lupus nephritis. *Ann Rheum Dis* 2012;71:1771–82.
29 Weeding E, Fava A, Magder L, *et al*. One-third of patients with lupus nephritis classified as complete responders continue to accrue progressive renal damage despite resolution of proteinuria. *Lupus Sci Med* 2022;9:e000684.
30 Anders H-J, Saxena R, Zhao M, *et al*. Lupus nephritis. *Nat Rev Dis Primers* 2020;6:7.
31 Pakchotanon R, Gladman DD, Su J, *et al*. Sustained complete renal remission is a Predictor of reduced mortality, chronic kidney disease and end-stage renal disease in lupus nephritis. *Lupus* 2018;27:468–74.
32 Davidson JE, Fu Q, Ji B, *et al*. Renal remission status and longterm renal survival in patients with lupus nephritis: A retrospective cohort analysis. *J Rheumatol* 2018;45:671–7.
33 Lichtnekert J, Anders HJ, Lech M. Lupus nephritis: Current perspectives and moving forward. *J Inflamm Res* 2022;15:6533–52.
34 Obrișcă B, Sorohan B, Tuță L, *et al*. Advances in lupus nephritis pathogenesis: from bench to bedside. *Int J Mol Sci* 2021;22:3766.
35 Parodis I, Houssiau FA. From sequential to combination and Personalised therapy in lupus nephritis: moving towards a paradigm shift. *Ann Rheum Dis* 2022;81:15–9.
36 Furie R, Rovin BH, Houssiau F, *et al*. Two-year, randomized, controlled trial of Belimumab in lupus nephritis. *N Engl J Med* 2020;383:1117–28.
37 Furie R, Rovin BH, Houssiau F, *et al*. Safety and efficacy of Belimumab in patients with lupus nephritis. *CJASN* 2022;17:1620–30.
38 Rovin BH, Teng YKO, Ginzler EM, *et al*. Efficacy and safety of Voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, Multicentre, placebo-controlled, phase 3 trial. *Lancet* 2021;397:2070–80.
39 Aringer M, Alarcón-Riquelme ME, Clowse M, *et al*. A glimpse into the future of systemic lupus erythematosus. *Ther Adv Musculoskelet Dis* 2022;14:1759720X221086719.
40 Yap DYH, Mok CC. Novel and emerging treatment strategies for lupus nephritis. *Expert Rev Clin Pharmacol* 2022;15:1283–92.
41 Cheung AK, Chang TI, Cushman WC, *et al*. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int* 2021;99:559–69.
42 Rossing P, Caramori ML, Chan JCN, *et al*. Executive summary of the KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease: an update based on rapidly emerging new evidence. *Kidney International* 2022;102:990–9.
43 Bakris G. Are there effects of renin–angiotensin system antagonists beyond blood pressure control. *Am J Cardiol* 2010;105:21A–9A.
44 Säemann M, Kronbichler A. Call for action in ANCA-associated vasculitis and lupus nephritis: promises and challenges of SGLT-2 inhibitors. *Ann Rheum Dis* 2022;81:614–7.
45 Wang H, Li T, Sun F, *et al*. Safety and efficacy of the Sglt2 inhibitor Dapagliflozin in patients with systemic lupus erythematosus: a phase I/II trial. *RMD Open* 2022;8:e002686.
46 Cooper Blenkinsopp S, Fu Q, Green Y, *et al*. Renal response at 2 years post biopsy to predict long-term renal survival in lupus nephritis: a retrospective analysis of the Hopkins lupus cohort. *Lupus Sci Med* 2022;9:e000598.
47 Cattran DC, Feehally J, Cook HT. Notice. *Kidney International Supplements* 2012;2:139.
48 Barbhaiya M, Erkan D, Zuily S, *et al*. Characterization of Antiphospholipid antibody-associated nephropathy: an international survey of renal pathology society members - ACR meeting abstracts. *Arthritis Rheumatol* 2020;72. Available: https://acrabstracts.org/abstract/characterization-of-antiphospholipid-antibody-associated-nephropathy-an-international-survey-of-renal-pathology-society-members/
49 Parodis I, Adamichou C, Aydin S, *et al*. Per-protocol repeat kidney biopsy portends relapse and long-term outcome in incident cases of proliferative lupus nephritis. *Rheumatology* 2020;59:3424–34.

RMD Open: first published as 10.1136/rmdopen-2023-003158 on 12 June 2023. Downloaded from http://rmdopen.bmj.com/ on April 4, 2024 by guest. Protected by copyright.