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REVIEW

Disease-Modifying Therapies in Lupus Nephritis: A Narrative Review Evaluating Currently Used Pharmacologic Agents

Anca D. Askanase · Richard Furie · Maria Dall'Era · Andrew S. Bomback · Andreas Schwarting · Ming-Hui Zhao · Ian N. Bruce · Munther Khamashta · Bernard Rubin · Angela Carroll · Roger Abramino Levy · Ronald van Vollenhoven · Murray B. Urowitz

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ABSTRACT

As more lupus nephritis (LN) medications become available, identifying treatments that are disease-modifying is critical in making treatment decisions. Based on our 2022 published working definition of LN disease modification as '*minimizing disease activity with the fewest treatment-associated toxicities and slowing progression to end-stage kidney disease*' (ESKD), the objective of this review was to classify current LN treatments according to the proposed kidney disease modification criteria, excluding toxicities. Based upon a selection of LN clinical trial ($n=27$) and observational study ($n=20$) publications, as well as the authors' clinical experiences, we evaluated the disease modification potential for

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A. D. Askanase · A. S. Bomback
Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA

R. Furie
Division of Rheumatology, Northwell Health, Great Neck, NY, USA

M. Dall'Era
Division of Rheumatology, University of California San Francisco School of Medicine, San Francisco, CA, USA

A. Schwarting
Rheumatology Center Rhineland Palatinate, Bad Kreuznach, Germany

A. Schwarting
University Medical Centre, Johannes Gutenberg University Mainz, Mainz, Germany

M.-H. Zhao
Renal Division, Peking University First Hospital, Beijing, China

I. N. Bruce
The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

M. Khamashta
Medical Affairs, GSK, Dubai, UAE

B. Rubin · A. Carroll
US Medical Affairs, GSK, Durham, NC, USA

R. A. Levy (✉)
Specialty Care, Global Medical Affairs, GSK, 1250 S Collegeville Rd, Collegeville, PA 19426, USA
e-mail: roger.x.levy@gsk.com

16 LN treatments (inclusive of antimalarials, glucocorticoids, immunosuppressants, calcineurin inhibitors and biologics) according to the proposed kidney disease activity and organ damage criteria at year 1, years 2–5, and > 5-year time points. Fulfilling criteria at year 1 and years 2–5 was considered evidence for disease modification potential. Satisfying criteria at > 5 years (slowing or preventing progression in SLICC/ACR Damage Index [SDI] and ESKD, and/or doubling of serum creatinine) was used to confirm disease modification. Each treatment was designated as one of the following at each time point: (a) criterion met; (b) inconclusive; (c) no available supportive data. This review excluded an assessment of potential toxicities. All LN treatments met at least one of the potential kidney disease-modification criteria at any time point, but limited relevant data in the literature meant disease modification > 5 years could only be confirmed for cyclophosphamide. Belimumab met more criteria across the three time points than any other biologic treatment but lacked > 5-year data to confirm disease modification. Further research is needed to support the classification of LN treatments as disease modifiers, particularly for > 5 years. We discuss considerations for future studies, challenges to the classification, and possible updates to published criteria.

Keywords: Biological products; Glucocorticoids; Lupus erythematosus; Systemic; Lupus nephritis

Key Summary Points

We previously proposed a working definition of disease modification in lupus nephritis (LN) as: 'the minimization of disease activity with the fewest treatment-associated toxicities and slowing progression to end-stage kidney disease'.

We searched the available literature for 16 currently administered LN treatments to determine which therapies fulfil the proposed disease modification criteria. Outcomes at year 1 and years 2–5 indicated disease modification potential, with disease modification confirmed beyond year 5 by evidence of delayed organ damage accrual and slowing or preventing end-stage kidney disease and/or doubling of serum creatinine.

Based on the available literature, cyclophosphamide is the only treatment for LN that currently satisfies the confirmed disease modification criteria.

Belimumab met more criteria across the three time points than any other biologic treatment, but lacked sufficient data beyond year 5 to confirm disease modification.

All LN treatments had data indicating disease modification potential, and these will need formal evaluation in longer-term studies to confirm their disease modification status and to aid informed treatment decisions by physicians and patients.

INTRODUCTION

Lupus nephritis (LN), the most common severe manifestation of systemic lupus erythematosus (SLE), affects approximately 50% of patients and can progress to end-stage kidney disease (ESKD) [1, 2]. In an observational cohort, only ~ 60% of

R. van Vollenhoven
Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, Amsterdam University Medical Centers, Amsterdam, The Netherlands

M. B. Urowitz
Professor Emeritus, Department of Medicine, University of Toronto, Toronto, ON, Canada

patients with LN achieved remission (defined as a return to normal serum creatinine and urine protein ≤ 0.5 g/day) 2 years after standard induction therapy with cyclophosphamide, mycophenolate mofetil (MMF), azathioprine or rituximab [3]. Furthermore, in one retrospective analysis, 32% of those achieving remission subsequently relapsed and had a kidney flare during a median follow-up period of 138 months, which was associated with an increased risk of progression to advanced chronic kidney disease (CKD) [4]. These data suggest further efforts are required to improve rates of LN remission achievement and long-term remission without relapse. With the increasing number of LN medications and treatment regimens available [5, 6], the characterization of treatments as disease-modifying will enable more informed treatment decisions by physicians and patients with LN.

The concept of disease modification in SLE and LN is based on the ability of a therapy to impact disease activity and outcomes, indicating a modification of the natural course of the disease [7]. The following working definition of kidney disease modification in LN was proposed: *'minimizing disease activity with the fewest treatment-associated toxicities and slowing or preventing the progression to ESKD'* [7]. A framework was constructed to apply this definition, which included proposed criteria for three specific time points: year 1, years 2–5, and > 5 years, as detailed in Table 1. In this review, we explored the available literature and applied the proposed kidney disease modification criteria to LN treatments. The assessment of toxicities is excluded, with the focus instead on previously defined kidney criteria and damage progression.

METHODS

We considered 16 LN treatments currently used in routine practice across the following treatment classes: antimalarials, glucocorticoids, immunosuppressants, calcineurin inhibitors and biologic therapies. Medications used predominantly for managing comorbidities (e.g., lipid-lowering agents and antihypertensives) were not included. This article is based on previously conducted studies and contains no new studies with human participants or animals performed by any of the authors. Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

We searched PubMed in April and May 2022 for clinical trials and clinical practice studies that investigated the 16 selected LN treatments. Screening for relevance to this analysis was initially based upon their title and abstract, and publications containing data deemed relevant to the kidney disease modification criteria were selected. Additional relevant publications known to the authors were also included. We identified 27 LN clinical trial and 20 clinical practice/observational study publications and summarized the study outcomes. Evidence from the identified studies was supplemented with the authors' clinical experiences to determine whether the treatments met the criteria of the published disease modification framework at three time points [7]. Specific criteria used to determine disease modification potential included a treatment's capacity to: (1) improve urine protein/creatinine ratio (uPCR); (2) minimize estimated glomerular filtration rate (eGFR) decline; (3) reduce kidney flares or relapses; (4) reduce glucocorticoid use; (5) delay organ damage progression and increase nephroprotection by preventing ESKD and/or doubling of serum creatinine. Criteria 1–4 were assessed at year 1 and at years 2–5, and when at least one criterion was met, were considered evidence for long-term disease modification potential. Criterion 5 was used to confirm disease modification at > 5 years. Each treatment received one of three mutually exclusive designations at each time point: (a) criterion met; (b) inconclusive; (c) no available supportive data. When evaluating studies that included two treatment arms, rather than a placebo arm, if there was no clear improvement with one therapy over the other, the evidence was classified as inconclusive. While aspects of safety and toxicity were included within the broader disease modification framework [7], the focus of this review was the kidney disease activity components and clinical outcomes of the disease modification definition only.

Table 1 Application of the proposed matrix for kidney-specific disease activity and organ damage disease modification criteria

Product	DISEASE MODIFICATION POTENTIAL		DISEASE MODIFICATION CONFIRMED (BEYOND 5 YEARS)
	Outcomes Year 1	Outcomes Years 2–5	Outcomes >5 years
	❶ Significant improvement in uPCR or kidney activity index via biopsy ❷ Minimise eGFR decline (i.e., ≤30%) ❸ Significant reduction in kidney flare ❹ Reduction in use of glucocorticoids[a]	❶ Sustained improvement in uPCR ❷ Minimise decline in eGFR (i.e., ≤30%) ❸ Reduction in kidney flare/relapse rate ❹ Continued reduction in use of glucocorticoids[a] and/or immunosuppressants **Provisional:** no worsening in kidney chronicity index via biopsy	No change or delayed progression in SDI + Slowing or preventing ESKD and/or doubling of serum creatinine
Glucocorticoids [21-25, 60, 61]	1 2 3 4	1 2 3 4	✕
Hydroxychloroquine [26, 40-42]	1 2 3 4	1 2 3 4	●
Immunosuppressants			
Azathioprine [15, 43-45]	1 2 3 4	1 2 3 4	●
Cyclophosphamide [16, 17, 27, 28, 48, 50, 62]	1 2 3 4	1 2 3 4	b
Leflunomide [38, 46]	1 2 3 4	1 2 3 4	●
Mizoribine [35-37]	1 2 3 4	1 2 3 4	●
Mycophenolate mofetil [15-19]	1 2 3 4	1 2 3 4	●
Calcineurin inhibitors			
Cyclosporine [15, 20]	1 2 3 4	1 2 3 4	●
Tacrolimus [18, 19, 63]	1 2 3 4	1 2 3 4	●
Voclosporin [6, 64]	1 2 3 4	1 2 3 4	●
Biologics			
Belimumab [5, 12, 39]	1 2 3 4	1 2 3 4	c
Rituximab [30-34]	1 2 3 4	1 2 3 4	●
Obinutuzumab [29]	1 2 3 4	1 2 3 4	●
Anifrolumab [12]	1 2 3 4	1 2 3 4	●
Ocrelizumab [13]	1 2 3 4	1 2 3 4	●
Abatacept [14]	1 2 3 4	1 2 3 4	●

●, criterion met; ●, data inconclusive; ●, data not available in the literature to support the criterion; ✕, negative impact on criterion

Table 1 continued

DORIS definition of remission in SLE, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *EULAR* European Alliance of Associations for Rheumatology, *LLDAS* Lupus Low Disease Activity State, *LN* lupus nephritis, *SDI* Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, *SLE* systemic lupus erythematosus, *uPCR* urine protein/creatinine ratio

[a] ≤7.5 mg/day per 2019 EULAR SLE treatment guidelines and LLDAS [9, 10]; ≤5 mg/day per DORIS remission definition

[b] Cyclophosphamide designation based on pivotal trials that showed reduced ESKD progression over >5 years, together with the authors' collective expert opinions and clinical experiences that cyclophosphamide has long-term LN disease-modifying effects, despite an absence of available long-term SDI cyclophosphamide data

[c] Although relevant >5-year SDI and ESKD data for belimumab in LN are lacking, there are indications towards long-term disease modification

RESULTS

Treatments with Disease-Modifying Potential—Year 1 Outcomes

Outcomes at year 1 required the fulfillment of at least one of the following criteria to demonstrate kidney disease modification potential: (1) significantly improved uPCR or kidney biopsy activity index; (2) reduced eGFR decline (i.e., decline no greater than 30% from baseline); (3) significantly reduced kidney flare rates; or (4) reduced use of glucocorticoids. We adopted a glucocorticoid threshold of ≤ 7.5 mg/day according to the 2019 EULAR SLE treatment guidelines (NB: updated 2023 EULAR recommendations that suggest a taper to ≤ 5 mg/day became available after the disease modification criteria were proposed [8]) and the Lupus Low Disease Activity State (LLDAS) definition [9, 10], or ≤ 5 mg/day per Definitions Of Remission In SLE (DORIS) [7], which aligns with the 2024 Kidney Disease Improving Global Outcomes (KDIGO) LN treatment guidelines to reduce maintenance glucocorticoid use to ≤ 5 mg/day prednisone-equivalent [11] and the 2023 EULAR recommendations for SLE [8].

For each treatment, Table 1 shows the outcomes of our analyses of individual year 1 kidney disease modification criteria. Most treatments ($n = 13/16$) satisfied at least one criterion at year 1. However, data did not support the attainment of any year 1 (or beyond) disease modification criteria for anifrolumab [12], ocrelizumab [13], or abatacept [14]. The author group notes that there were indications towards improved attainment of complete renal response and glucocorticoid dose reductions in the Treatment of Uncontrolled Lupus via the Interferon Pathway (TULIP)-LN Phase 2 trial; however, the study did not meet its primary uPCR endpoint and these reductions were only observed in the intensified regimen cohort [12]. As no differences were noted in the 300-mg anifrolumab dose that is approved in SLE, there is not currently sufficient evidence to support the attainment of the year 1 criteria for disease modification potential [12].

MMF [15–19] and cyclosporine [15, 20] fulfilled all four year 1 kidney disease modification criteria, indicating disease modification potential. Glucocorticoids [21–25], hydroxychloroquine [26], azathioprine [15], cyclophosphamide [16, 17, 27, 28], voclosporin [6], obinutuzumab [29], belimumab [5, 12] and rituximab [30–34] met two or three of the year 1 kidney disease modification criteria. Glucocorticoids met criteria 1 [23, 24] and 2 [22] for disease modification potential at year 1, a designation which also took into account the authors' clinical experiences and treatment recommendations for their use as first-line treatment for LN in combination with MMF or cyclophosphamide [9]. Mizoribine met the criteria for reduced eGFR decline; however, data for reduction in kidney flare were inconclusive [35–37]. Obinutuzumab met the criteria for both reduced eGFR decline and significant improvement in uPCR [29]. Leflunomide [38] and tacrolimus [19] only met the

criteria for significant improvement in uPCR or kidney activity index via biopsy.

For a full list of publications examined, please refer to Tables S1–S5.

Treatments with Disease-Modifying Potential—Years 2–5 Outcomes

To demonstrate kidney disease modification potential during years 2–5, at least one of the following criteria was required to be fulfilled: (1) sustained improvement in uPCR; (2) reduced decline in eGFR (i.e., decline no greater than 30% from baseline); (3) reduction of kidney flare rates; and 4) continued reduction in glucocorticoids and/or immunosuppressants.

Only belimumab met all four criteria for kidney disease modification potential at years 2–5, although the expert group notes that this was based on 2-year data [5, 12, 39]. Hydroxychloroquine [26, 40–42], azathioprine [15, 43–45], leflunomide [38, 46], and MMF [15–19] met three of the years 2–5 criteria for kidney disease modification potential. Of these, azathioprine was the only treatment with supportive data for the fourth criterion, though it was inconclusive for data pertaining to the continued reduction in glucocorticoids and/or immunosuppressants [15, 43–45].

Confirmed Disease-Modifying Treatments for LN—Outcomes Beyond Year 5

Confirmed disease modification in LN at > 5 years was defined as slowing or preventing organ damage assessed by total SDI, ESKD, and/or doubling of serum creatinine to indicate nephroprotection, per the proposed criteria [7]. Supportive > 5-year data for leflunomide, mizoribine, voclosporin, rituximab, anifrolumab, obinutuzumab, ocrelizumab, and abatacept were not available; therefore, the long-term LN disease modification status of these treatments could not be evaluated. Although there are no > 5-year SDI, ESKD or serum creatinine data available in LN for belimumab, the authors note that the positive > 5-year SDI data for belimumab in SLE [47], as well as belimumab having met seven of the eight LN disease modification criteria at years 1–5 (Table 1), indicate that belimumab is likely to also have disease modification potential beyond year 5 in LN. However, additional long-term data are required for this to be confirmed, and so belimumab is currently designated as inconclusive for outcomes after 5 years.

Of the treatments with available and relevant long-term data, only cyclophosphamide was deemed to meet the full criteria for confirmed LN disease modification beyond year 5 (Table 1) [27, 28, 48]. While 10-year follow-up data from the Euro-Lupus Nephritis trial found the probability of ESKD was not significantly different between low and high-dose cyclophosphamide groups [27], data from several National Institutes of Health (NIH) studies indicate significant long-term reductions in the risk of ESKD with cyclophosphamide [48–50]. For example, a 1986 study [48] found a significant difference in rates of ESKD between the cyclophosphamide group ($n = 1/20$) and the high-dose prednisone group ($n = 10/28$; $p = 0.027$), with similar results observed in a subsequent study [49]. Despite a lack of long-term SDI data for patients with LN receiving cyclophosphamide, given the positive ESKD data from the NIH studies in conjunction with the authors' collective clinical experiences and expertise, it was deemed that there is sufficient evidence to support a long-term disease-modifying effect of cyclophosphamide in LN.

For hydroxychloroquine, long-term data were inconclusive. A real-world study showed that the cumulative probability of developing kidney damage at 5 years was 20% with hydroxychloroquine versus 47% without hydroxychloroquine and 38% vs. 70% at 10 years, respectively (both $p < 0.0001$) [40]. However, the lack of robust long-term SDI or ESKD data available in LN precluded a confirmed classification of hydroxychloroquine as LN disease-modifying. Conversely, glucocorticoids did not meet the disease modification criteria beyond 5 years, given their negative impact on long-term organ damage accrual, regardless of whether the damage was in the kidney [9].

The LN disease modification status beyond 5 years of azathioprine [15, 45] and MMF [15] was considered inconclusive. In one study, time

to ESKD did not differ between groups treated with azathioprine and MMF [45], and another study found no significant difference in the proportion of patients with advanced CKD between MMF, cyclosporine and azathioprine-treated patients [15].

Data for cyclosporine [15] and tacrolimus [18] at > 5 years were also considered inconclusive. In an open-label randomized controlled trial comparing tacrolimus with MMF as induction therapy, there was no difference between groups in terms of accrual of new organ damage over time (47% with tacrolimus vs. 45% with MMF; $p = 0.75$), and there was no significant difference in the proportion of patients with eGFR decline by ≥ 30%, CKD stage 4/5 progression or death at 5 (17% vs. 24%) and 10 years (33% vs. 33%; $p = 0.90$).

DISCUSSION

The prevalence of CKD has not decreased despite many advances in LN treatment [51]. Defining disease modification criteria in LN and classifying treatments accordingly might allow physicians to make better therapeutic choices to prioritize nephroprotection such as by preventing CKD and ESKD. This review is the first attempt to examine the existing literature for the kidney disease modification potential of LN therapies at 1, 2–5 and > 5 years using the proposed criteria [7]. The criteria allowed for differentiation between LN therapies at each of the three time points. However, applying the proposed criteria to the existing literature was challenging because studies used various combinations of agents and had inconsistent designs, patient populations, and renal response definitions.

Of the 16 LN treatments evaluated, disease modification beyond 5 years could be confirmed only for cyclophosphamide based on currently available data. Although long-term SDI data in patients with LN were not available for this treatment, the author group felt that cyclophosphamide should not be excluded from disease-modifying status given that the SDI was first proposed in 1996 [52], after the majority of the pivotal cyclophosphamide trials had been conducted. Instead, the strong evidence that cyclophosphamide reduces the long-term risk of ESKD progression [48–50, 53, 54], together with the authors' clinical experiences and expertise, were deemed sufficient to designate cyclophosphamide as meeting the criteria > 5 years. However, the authors acknowledge that this raises the question of whether more established treatments that have been part of LN standard therapy for many years may be at a disadvantage if measures used to assess disease modification (e.g., SDI and SLEDAI) were not routinely used or available when these treatments were first studied. Indeed, we emphasize that our previously proposed matrix for applying disease modification criteria was not intended to be definitive, and it may be appropriate for clinicians and investigators to substitute or adapt the criteria as necessary when evaluating disease modification.

Despite only cyclophosphamide having been confirmed as possessing LN disease modification capacity, all treatments evaluated aside from anifrolumab, ocrelizumab, and abatacept met at least one of the kidney disease modification criteria at any time point to suggest disease modification potential. It is very likely that several treatments other than cyclophosphamide are LN disease-modifying, but confirmatory studies are required. Generally, there was a lack of supportive long-term clinical and/or real-world data > 5 years, or inconclusive data, which prevented some treatments that showed promising < 5-year data from being confirmed as disease-modifying. For example, belimumab met seven of the eight year 1–5 criteria to indicate disease modification potential, but a lack of > 5-year SDI or ESKD data in an LN population precluded classification of belimumab as a confirmed LN disease-modifier. However, we note that belimumab was approved for LN in 2020 and, as such, there are scarce long-term data in LN. Therefore, given the promising year 1–5 data together with the strength of indirect evidence from SLE, we believe there are indications that belimumab is disease-modifying in LN, but additional belimumab data for 5 years

and beyond are needed to confirm if this is the case.

The disease modification framework for LN is consistent with the approach of recent 2023 EULAR recommendations for kidney involvement in SLE and the 2024 KDIGO guidelines for LN [8, 55]. Both task forces emphasize the importance of reducing treatment-associated toxicity and preserving kidney function, which are central to the LN disease modification working definition. Importantly, both EULAR and KDIGO now encourage the consideration of advanced therapies (such as voclosporin or belimumab) earlier in the disease course, including as initial therapy alongside antimalarials and classic immunosuppressants [8, 55]. This represents a shift in the approach of LN management towards earlier and more intensive treatment to help slow long-term kidney damage progression. It is encouraging that several LN treatments show strong disease-modifying potential during years 1–5, indicating that the disease modification framework could be used alongside treatment guidelines to help clinicians achieve the best long-term outcomes for their patients.

As with our previous evaluation of SLE treatments for extra-renal disease modification [47], a key consideration when applying and interpreting the proposed framework in LN is whether any, or all, of the individual criteria were mandatory for disease modification potential to be fulfilled at the early time points. This may be especially relevant for LN, given that tacrolimus has been associated with eGFR decline but may still prevent overall progression to ESKD [56]. As we noted for extra-renal SLE disease-modifying treatments [47], this topic should be addressed using a consensus approach with a larger group of rheumatology and nephrology experts. We also suggest that a more formal consideration of the efficacy data for each LN treatment is made based on the strength of available evidence. This could use, for example, a Delphi-based consensus approach and an expanded panel of rheumatology and nephrology experts. Further to this point, a recent real-world study applied the kidney disease modification potential to patients with LN, where all four criteria were required to progress to the next stage. Only 60% of the patients achieved disease modification, and failure to meet the disease modification criteria was associated with worse long-term outcomes [57].

Our attempt to apply the proposed framework also raises the question of whether treatments could be considered as LN disease-modifying at the earlier time points (i.e., < 5 years), rather than only having potential as disease modifiers during these earlier years. In this review, many of the LN treatments met individual criteria < 5 years to indicate kidney disease modification potential, but long-term disease modification was not able to be confirmed due to a lack of supportive data at > 5 years. The ability to do so could be beneficial in determining whether additional measures need to be implemented during the early LN disease course. In addition, treatments generally did not have supportive data for all four criteria at the earlier time points, either due to outcomes not being reported per the specific criterion, or data being considered inconclusive. For instance, some studies reported SLE flares, rather than kidney flares as specified in the criteria, and uPCR was often reported as part of a composite endpoint rather than as a standalone endpoint.

There is also a need to consider whether confirmed disease modification in LN should require evidence of delayed progression in both SDI and ESKD, or only one. Extra-renal damage (e.g., as measured using SDI) should be considered when evaluating the disease-modifying potential of LN treatments; however, these broader outcomes are not consistently reported in studies specific to LN and kidney outcomes. For example, a real-world study in patients with LN illustrated the benefits of hydroxychloroquine treatment for delaying kidney damage progression [40]; however, disease modification at > 5 years could not be confirmed for hydroxychloroquine because the total SDI score was not evaluated. This raises the question of whether the total SDI score should be required when confirming disease modification in LN, or if kidney-specific outcomes alone are sufficient. In the authors' experiences, if kidney manifestations are under control, it is unlikely that new damage is occurring in other areas. However, if some

new extra-renal damage has occurred (e.g., cataracts), there is an argument that this should not prevent a treatment from being considered LN disease-modifying. Conversely, if the focus is too narrow on the kidney, this may weaken the disease modification criteria; thus, total SDI was included in the proposed criteria and this evaluation, but this topic requires further consideration.

As with our prior evaluation of SLE treatments for extra-renal disease modification [47], adjustments to the proposed kidney disease modification definition may be required. Alterations to the individual time point criteria may also be warranted. For example, the current criteria do not necessarily require sustained improvements in proteinuria, which means that a kidney flare could still occur. Similarly, as GFR continues to decline even after a single LN episode without further inflammation [58], both eGFR and histological chronicity findings may be expected to worsen in the long term. If the chronicity index inevitably worsens, LN disease modification can only aim to slow this progression. Given these considerations, the chronicity index may not need to be a major factor when determining LN disease modification, and such issues require further debate. Additionally, eGFR stability and kidney flare rates are best determined over many years; therefore, assessing this at a 1-year time point may not be appropriate.

Limitations of this review include the narrative approach of the analysis, which did not systematically analyze the differing levels of evidence between identified studies. In addition, the timing of treatments (such as induction versus maintenance) should also be considered when categorizing treatments as LN disease-modifying. We emphasize that clinicians should follow the latest disease management guidelines when determining the timing (such as initial vs. maintenance therapy and the use of combination therapy) and duration of treatment, outside of the disease modification designation. As noted previously, this analysis also did not consider toxicity of treatments in the disease modification classification, although toxicity was a component of the 2022 working definition; rather, we focused on the kidney criteria. In addition, this analysis also did not consider health-related quality of life, patient-reported outcome measures, and biomarkers or other measures of immunological activity (e.g., histological evaluation), which were suggested as supportive elements to the proposed working definition [7]. Furthermore, we note that the treatments evaluated are not used as monotherapy in clinical practice and are instead used as one component alongside other treatments and LN management modalities; this makes it difficult to conclusively attribute any disease-modifying effects observed to the investigational drug alone. This applies both to LN therapies as well as other background medications, such as renin–angiotensin–aldosterone system (RAAS) inhibitors. The use of combination therapies has recently been reinforced by the 2024 ACR Guideline for the Screening, Treatment, and Management of Lupus Nephritis, which recommends 'triple therapy', comprising glucocorticoids plus two immunosuppressants (typically either MMF plus belimumab, MMF plus a calcineurin inhibitor, or low-dose CYC [MMF maintenance] plus belimumab) for new-onset LN or flares [59]. Although we assessed individual treatments, future research would be needed to evaluate the disease modification potential of combination therapies. These elements should be considered in future studies. Finally, this evaluation was funded by GSK, the manufacturer of belimumab, which is the only FDA-approved biologic for LN to date. However, we attempted to mitigate any potential unconscious bias towards belimumab by involving numerous prominent rheumatology and nephrology experts as authors, who each contributed significantly to the approach, the study selection, data evaluation and application of the criteria.

CONCLUSIONS

This was the first attempt to classify existing LN treatments in accordance with the 2022 working definition of kidney disease modification in LN [7]. Based on the available evidence,

only cyclophosphamide could be confirmed as disease-modifying in LN, and we provide insights into the considerations and challenges when evaluating disease modification for LN treatments. It is likely that other therapies are indeed LN disease-modifying, but longer-term studies in patients with LN are first needed before these treatments can be designated as such.

We identified and discussed several considerations in the implementation of the working definition and suggested further work to help clarify the disease-modifying status of existing treatments. Future studies could evaluate the minimum number of criteria required to designate disease modification at each of the three time points so that disease modification can be considered in LN trial design and the care of patients with LN. In addition, we suggest a future consensus publication involving a larger group of rheumatology and nephrology experts be considered to fully determine classification of disease-modifying therapies in LN.

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Declarations

Conflict of Interest. Anca D Askanase has received consulting fees from AbbVie, Amgen, Aurinia, AstraZeneca, BMS and GSK; and has been an investigator for GSK, Janssen, Pfizer, UCB, Vielo, AstraZeneca and Eli Lilly. Anca D Askanase is an Editorial Board member of *Rheumatology and Therapy*. Anca D Askanase was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Richard Furie has received research support from GSK and is an advisory board member for GSK. Maria Dall'Era has received consulting fees from Aurinia, AstraZeneca, Biogen, Gilead, Pfizer and GSK. Andrew S Bomback has received consulting fees from

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