IN THE NAME OF GOD

Update the Diagnosis and Treatment in Lupus Nephritis

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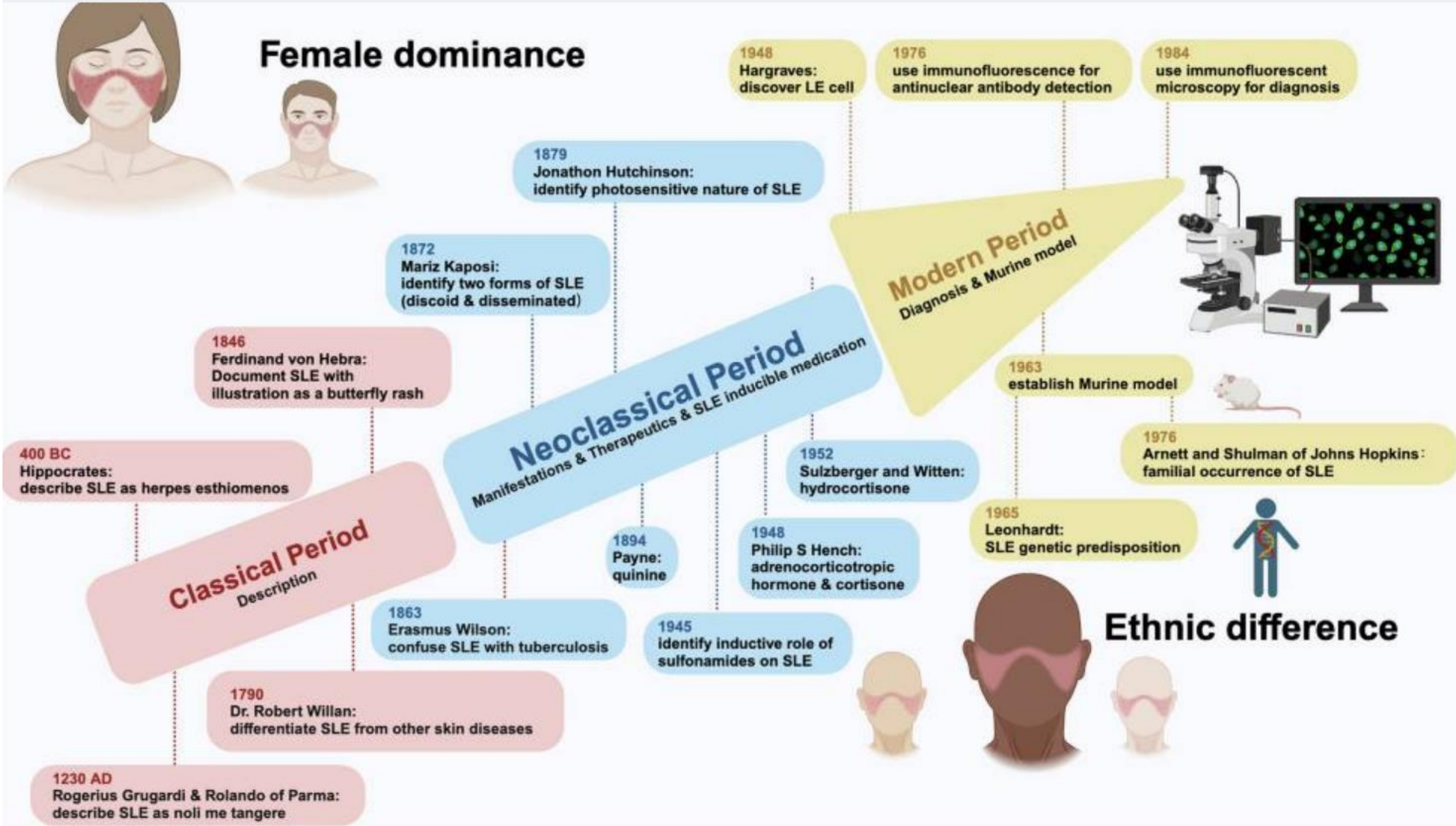
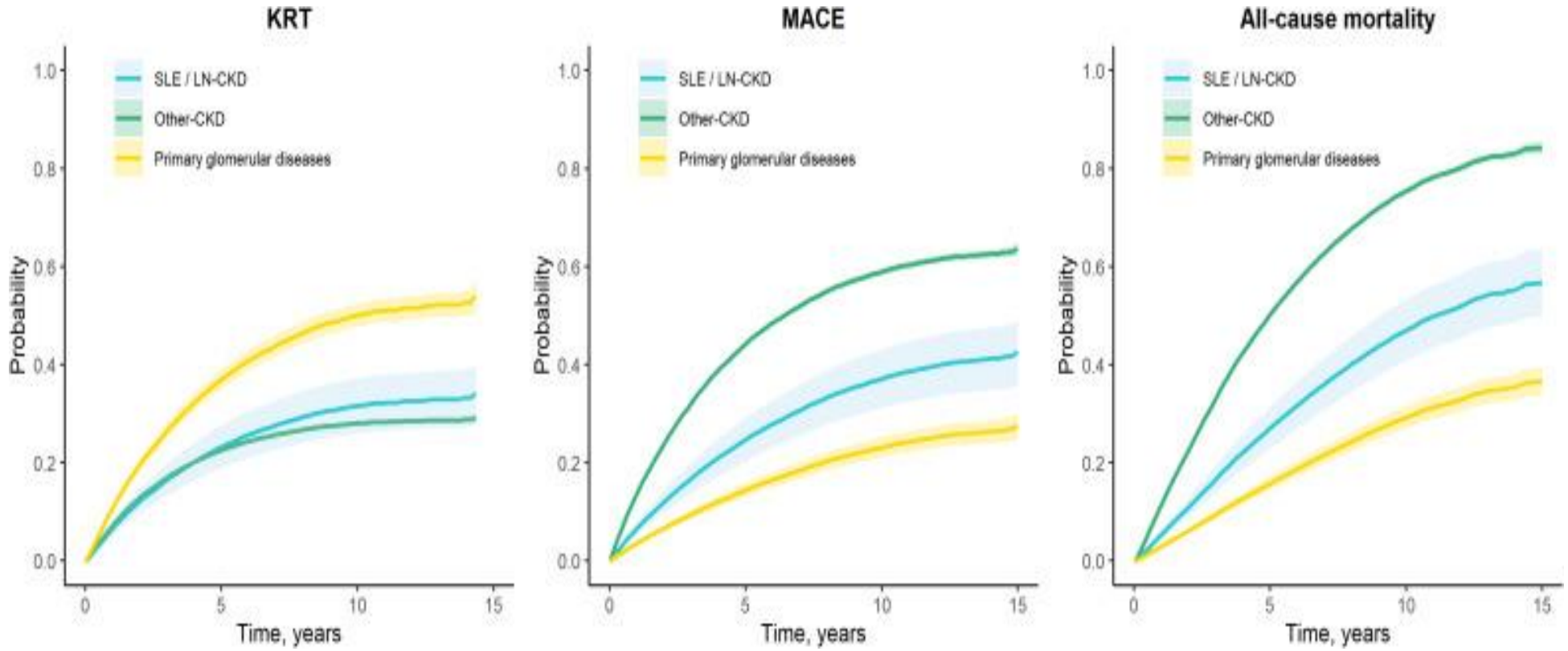
Professor of Nephrology in MUOMS.2025



Lupus nephritis

- incidence of lupus nephritis (LN) is 20%–60%, depending on the demographics of the population studied
- Kidney involvement in SLE has been associated with higher mortality, especially for patients progressing to kidney failure.
- The ultimate goal of treating LN is to preserve kidney function and reduce the morbidity and mortality associated with chronic kidney disease (CKD) and kidney failure, while minimizing medication-associated toxicities.


KRT
MACE
All-cause mortality
SLE / LN-CKD
Other-CKD
Primary glomerular diseases
Probability
Time, years
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15

who

Urine protein excretion greater than 500 mg/day.
An active urinary sediment with persistent hematuria (five or more RBC, most of which are dysmorphic) and/or cellular casts.
A rising serum creatinine

When to suspect LN :

an active urinary sediment with persistent hematuria (five or more RBC , most of which are dysmorphic) and/or cellular casts, proteinuria, and/or an elevated serum creatinine (or decrease in eGFR) in patients with known SLE.
Elevated anti-dsDNA titers and low complement (C3 and C4) levels

When to repeat the biopsy

An active sediment in someone with previously quiescent disease
a new elevation in serum creatinine and/or worsening of proteinuria despite treatment
Suspicion of possible kidney disease unrelated to LN (eg, drug-induced acute interstitial nephritis)

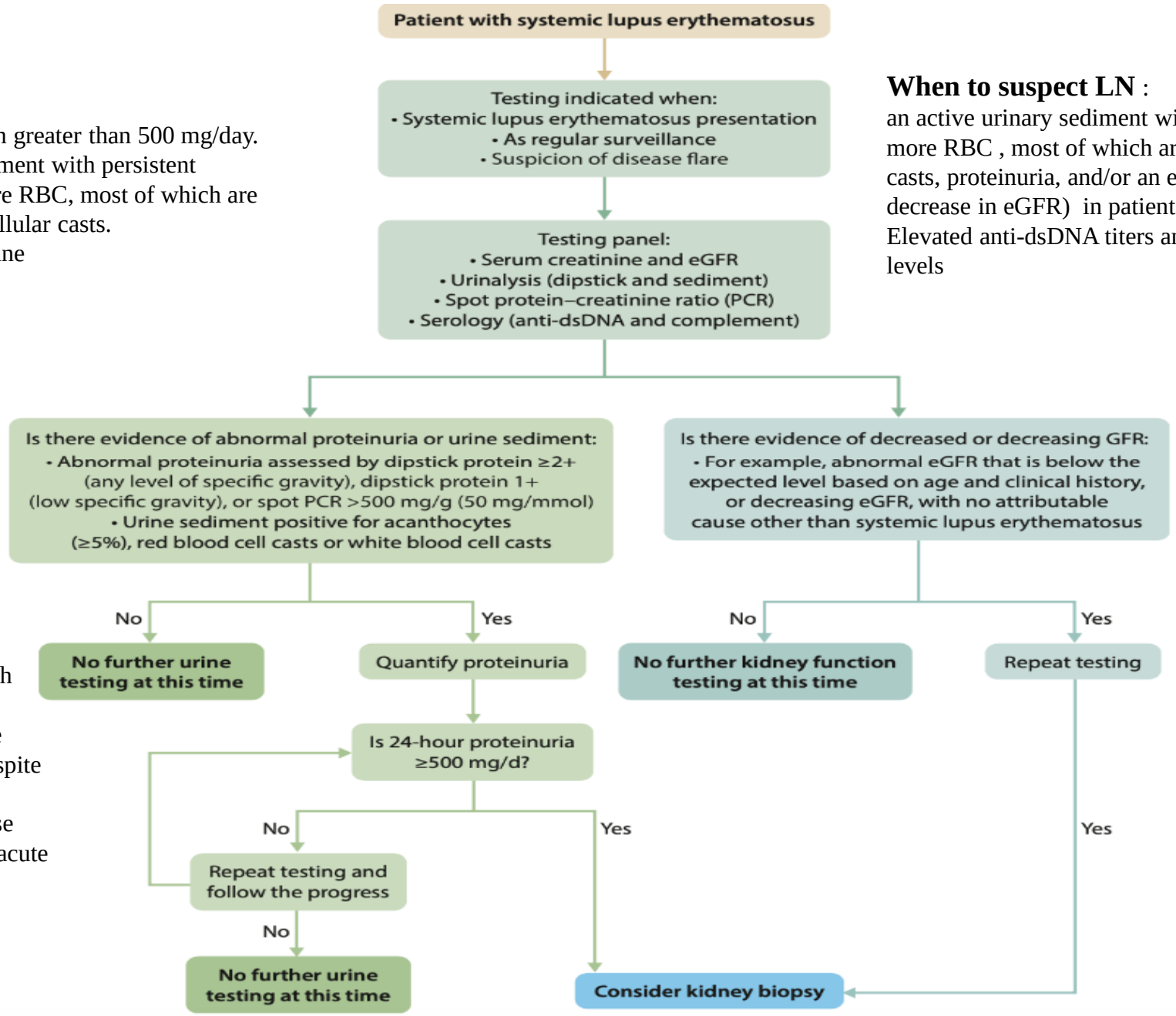


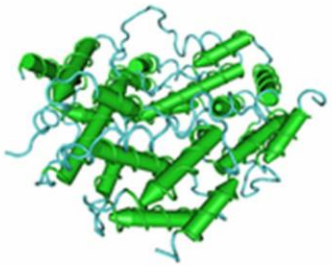
Figure 1 | Diagnosis of kidney involvement in systemic lupus erythematosus. anti-dsDNA, anti-double-stranded deoxyribonucleic acid; eGFR, estimated glomerular filtration rate.

Activity and chronicity items included in lupus nephritis kidney biopsy report. NIH

Components of the activity index	Score	Calculating the activity score Extent of lesion — Points
• Endocapillary hypercellularity • Neutrophils and/or karyorrhexis • Fibrinoid necrosis • Hyaline deposits (wire loop and/or hyaline thrombi) • Cellular/fibrocellular crescents • Interstitial inflammation (interstitial leukocytes)	0–3 0–3 (0–3) × 2 0–3 (0–3) × 2 0–3 **Total: 0–24**	Not present — 0 Present in <25% — 1 Present in 25%–50% — 2 Present in >50% — 3
Items included in the NIH chronicity score	**Score**	**Calculating the chronicity score** **Extent of lesion — Points**
• Total glomerulosclerosis (global + segmental) • Fibrous crescents • Interstitial fibrosis • Tubular atrophy	0–3 0–3 0–3 0–3 **Total: 0–12**	Present in <10% — 0 Present in 10%–25% — 1 Present in 25%–50% — 2 Present in >50% — 3
Other histologic findings not included in the activity or chronicity score		
• Foot process effacement (lupus podocytopathy) • Collapsing lupus glomerulopathy • Vascular lesions (arteriosclerosis, non-inflammatory vascular immune complex deposits, thrombotic microangiopathy, non-inflammatory necrotizing vasculitis, true renal vasculitis)		

New LN biomarkers

Genetic factors

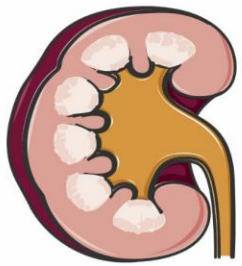


Interferon Type I

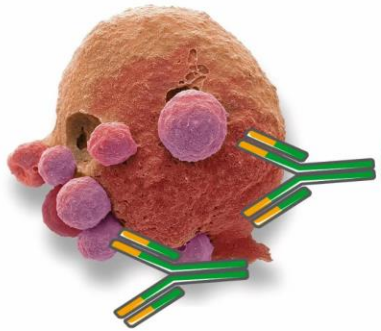
Macrophages M2 (CD163+)

Classical LN biomarkers

Kidney biopsy

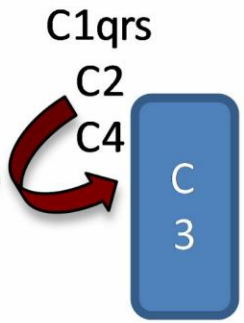


Immune complexes



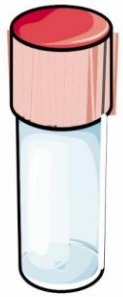
anti-dsDNA

Complement pathway

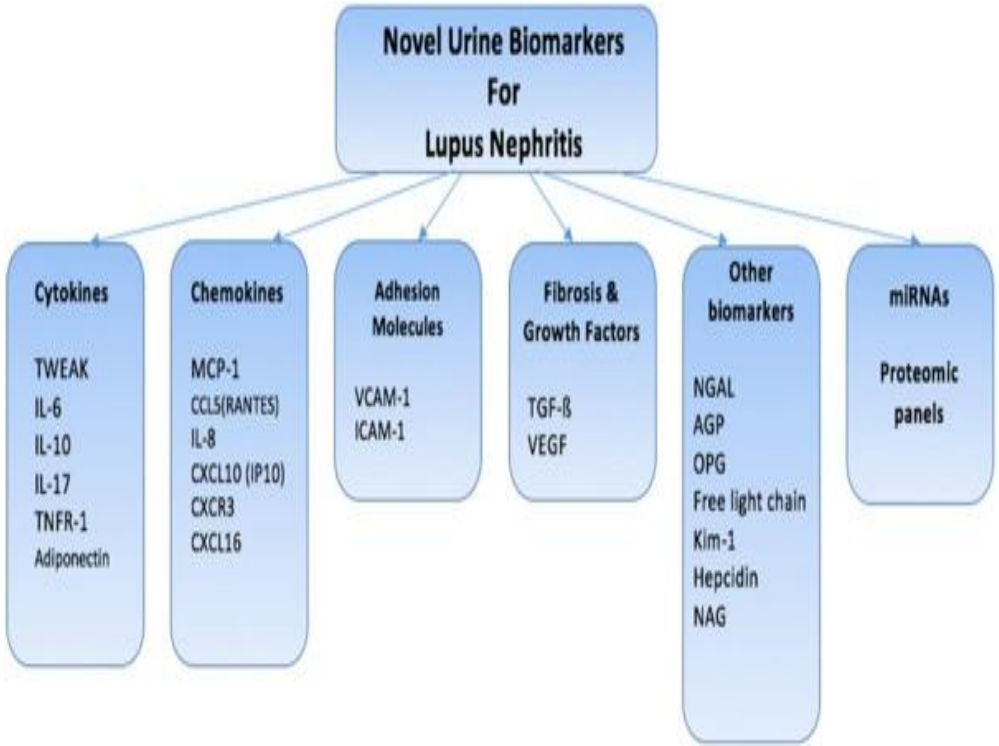


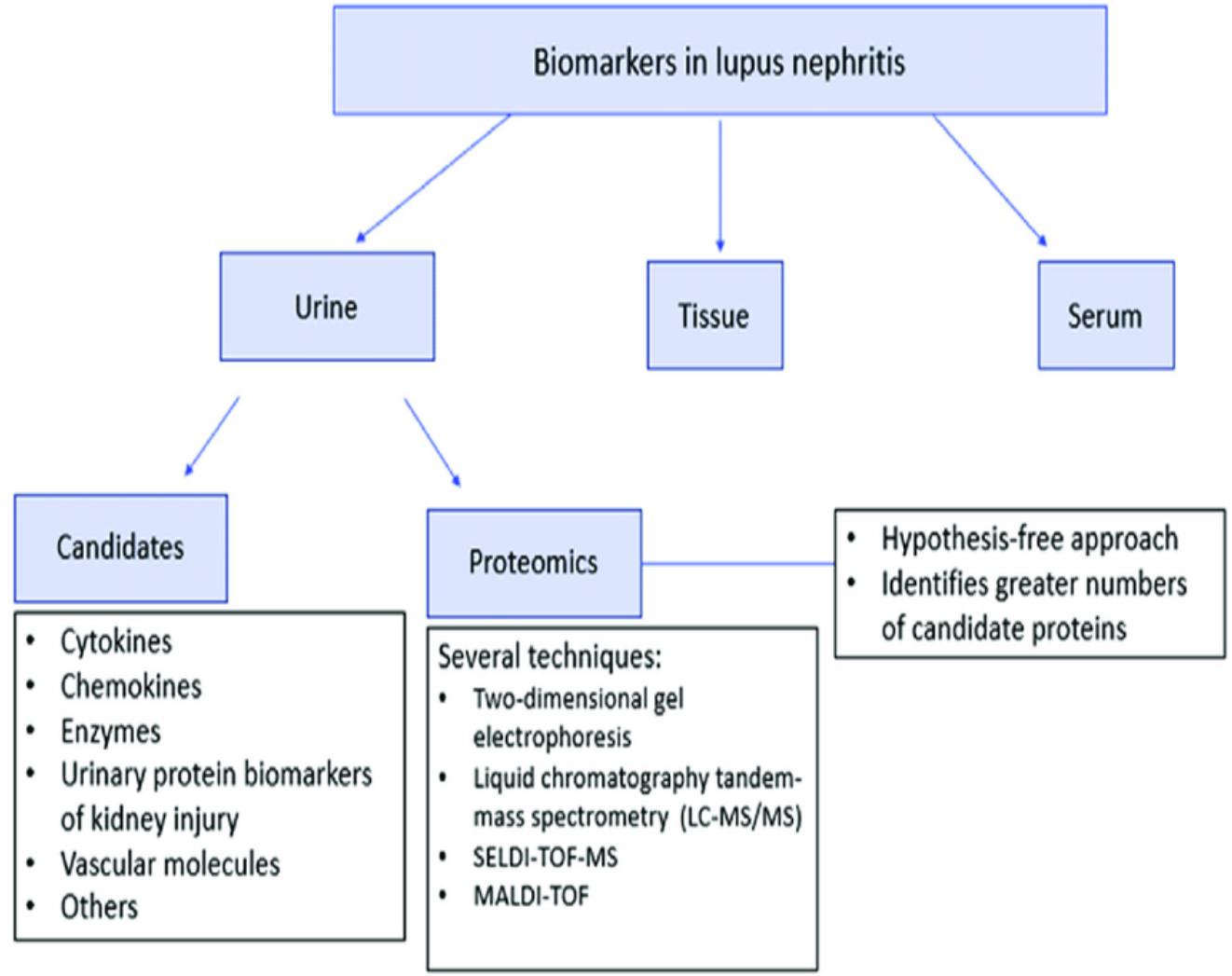
Anti-C1q

Urinary biomarkers



24h-proteinuria


Novel Urine Biomarkers For Lupus Nephritis
Cytokines
TWEAK
IL-6
IL-10
IL-17
TNFR-1
Adiponectin
Chemokines
MCP-1
CCL5(RANTES)
IL-8
CXCL10 (IP10)
CXCR3
CXCL16
Adhesion Molecules
VCAM-1
ICAM-1
Fibrosis & Growth Factors
TGF-ß
VEGF
Other biomarkers
NGAL
AGP
OPG
Free light chain
Kim-1
Hepcidin
NAG
miRNAs
Proteomic panels


Biomarkers in lupus nephritis
Urine
Tissue
Serum
Candidates
Cytokines
Chemokines
Enzymes
Urinary protein biomarkers of kidney injury
Vascular molecules
Others
Proteomics
Several techniques:
Two-dimensional gel electrophoresis
Liquid chromatography tandem-mass spectrometry (LC-MS/MS)
SELDI-TOF-MS
MALDI-TOF
Hypothesis-free approach
Identifies greater numbers of candidate proteins

Blood/serum novel biomarkers for LN

- Anti-C1q antibodies
- MCP-1
- NGAL
- TNF-Like weak inducer of apoptosis(TWEAK)
- VCAM-1
- miRNA

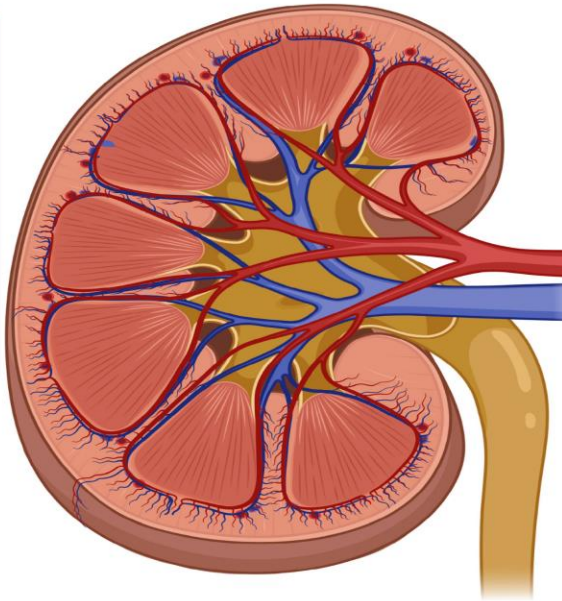
Urinary Biomarkers for Lupus Nephritis: A Systems Biology Approach

J clin Med 2024

Overview of Urinary microRNAs associated with Lupus Nephritis

Multimarker panel composed of miRNA135b−5p, miRNA−107, and miRNA−31

- Significantly different amongst treatment responders and non responders
- Able to accurately predict response to therapy disease activity and progression during flare up periods and one year after initial flare up with an AUC of 0.73−0.78



miRNA−21

- Critical mediator of inflammation and lymphocyte signalling
- Able to discriminate between active and inactive LN (AUC 0.89) in addition to LN and healthy controls (AUC 0.91)

miRNA−146a

- Modulator of the NF-κB inflammatory pathway
- Able to discriminate between LN and healthy controls
- Correlates with disease activity and capable of predicting clinical progression

Multimarker panel composed of miRNA−21, miRNA−150, and miRNA−29c

- Able to identify evidence of early renal fibrosis and able to assess disease severity

miRNA−29c

- Modulator of renal fibrosis
- Able to determine disease chronicity
- Able to predict renal fibrosis and disease severity with sensitivity and specificity rates >80%

The 6 Urinary Protein Biomarkers Utilized in the RAIL score

NGAL

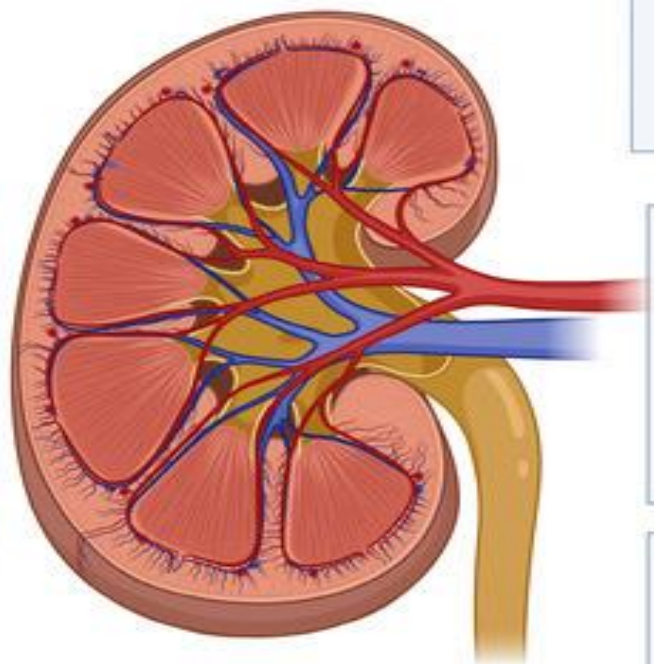
- Found in the distal and proximal nephron
- Nephroprotective molecule that is upregulated in a variety of renal disorders including LN

MCP-1

- Found in renal epithelial cells, fibroblasts, endothelial and mesangial cells
- Chemokine molecule that modulates the infiltration of inflammatory cells into the kidney

KIM-1

- Found in the proximal nephron
- Nephroprotective molecule which modulates the clearance of damaged cells



Adiponectin

- Found in adipocytes
- A molecule that suppresses inflammatory responses and modulates ongoing inflammation

Hemopexin

- Accumulates in the proximal nephron
- Anti-oxidant molecule that is involved in iron metabolism

Ceruloplasmin

- Found in glomerular epithelial cells
- Plays various roles as a modulator of inflammation and an anti-oxidant molecule

Treatment of LN

Measures to minimize the risk of complications related to lupus nephritis or its treatment.

Risk	Risk attenuation
Cardiovascular risk	• Lifestyle modifications – smoking cessation, body weight optimization, exercise • Dyslipidemia management • Low-dose aspirin during pregnancy • Blood pressure control
Proteinuria and CKD progression (refer to Chapter 1)	• Avoid high-sodium diet • Optimize blood pressure • Renoprotective medications, such as RAAS blockade, SGLT2 inhibitor, etc., in stable patients without AKI • Avoid nephrotoxic insult • Prevent AKI
Infection risk	• Assess medical history of herpes zoster and tuberculosis • Screening for HBV, HCV, HIV, and HBV vaccination • *Pneumocystis jirovecii* prophylaxis (issue of potential adverse drug reaction discussed below) • Influenza and pneumococcal vaccination • Individualized consideration for recombinant zoster vaccine • Individualized consideration for other infectious organisms as dictated by public health concerns at the time of treatment
Bone injury	• Bone mineral density and fracture risk assessment • Calcium and vitamin D supplementation • Bisphosphonates when appropriate
Ultraviolet light exposure	• Broad-spectrum sunscreen • Limit ultraviolet light exposure

Premature ovarian failure	• Gonadotropin-releasing hormone agonists (i.e. leuprolide) • Sperm/oocyte cryopreservation
Unplanned pregnancy	• Individual evaluation and counselling for contraception type (preference, thrombosis risk, age)
Cancer	• Evaluate individual risk factors for malignancies • Age-specific malignancy screening • Minimize lifetime cyclophosphamide exposure to <36 g

progestin-only contraceptives are preferable in patients with a moderate or high level of disease activity.

Estrogen-containing contraceptives should be avoided in patients with antiphospholipid antibodies or a history of thrombosis

For patients who prefer oral hormonal contraception, estrogen–progestin contraceptives with ethinyl estradiol dose not higher than 30 micgr may be used in patients who are negative for antiphospholipid antibodies and with stable low disease activity

The benefits and harms of antimalarial use in SLE

- Recommendation 10.2.1.1: We recommend that patients with SLE, including those with LN, be treated with **hydroxychloroquine** or an equivalent antimalarial unless contraindicated (1C).
- lower flare rates (including kidney)
- higher response rates to therapy
- Slower progression of kidney disease
- lower incidence of CV and thrombotic events in patients with antiphospholipid antibodies
- less organ damage
- improved lipid profile
- and better preservation of bone mass
- protective effects against infection, and may increase complete remission rate
- In pregnancy : decrease in lupus activity and a satisfactory safety profile in both the mother and the fetus

- Significant side effects are uncommon but include skin rash, increase in skin pigmentation, muscle weakness, and visual change or loss of vision.
- The recommended starting dose of hydroxychloroquine is around 5 mg/kg/d (#2.3 mg/kg/d for chloroquine).
- Doses of 2–3 mg/kg/d may not achieve adequate blood levels and could be associated with higher flare rates.
- G6PD
- ocular toxicity
- Cardiotoxic, manifesting as cardiomyopathy or conduction abnormalities in patients with a high cumulative exposure.

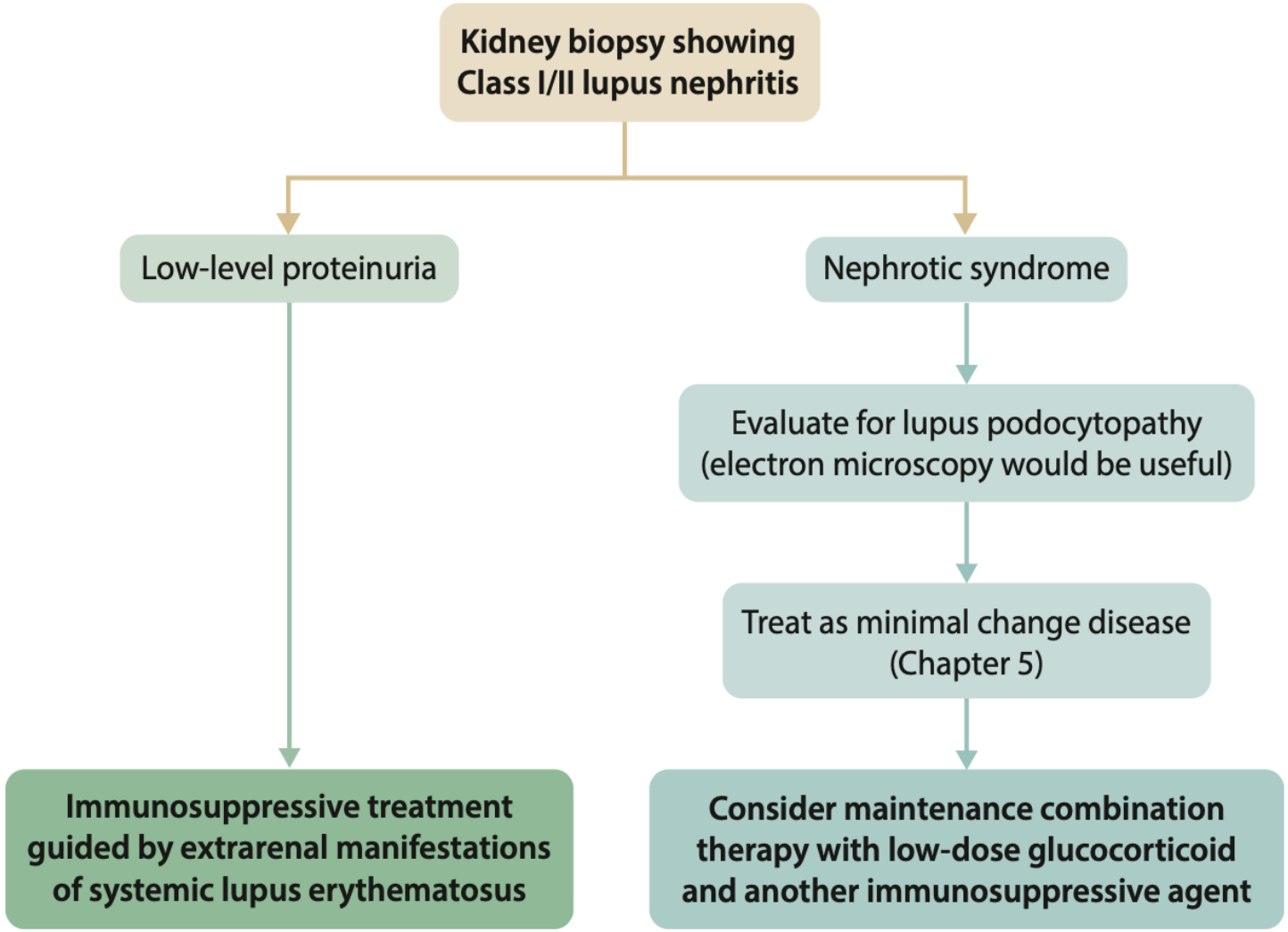
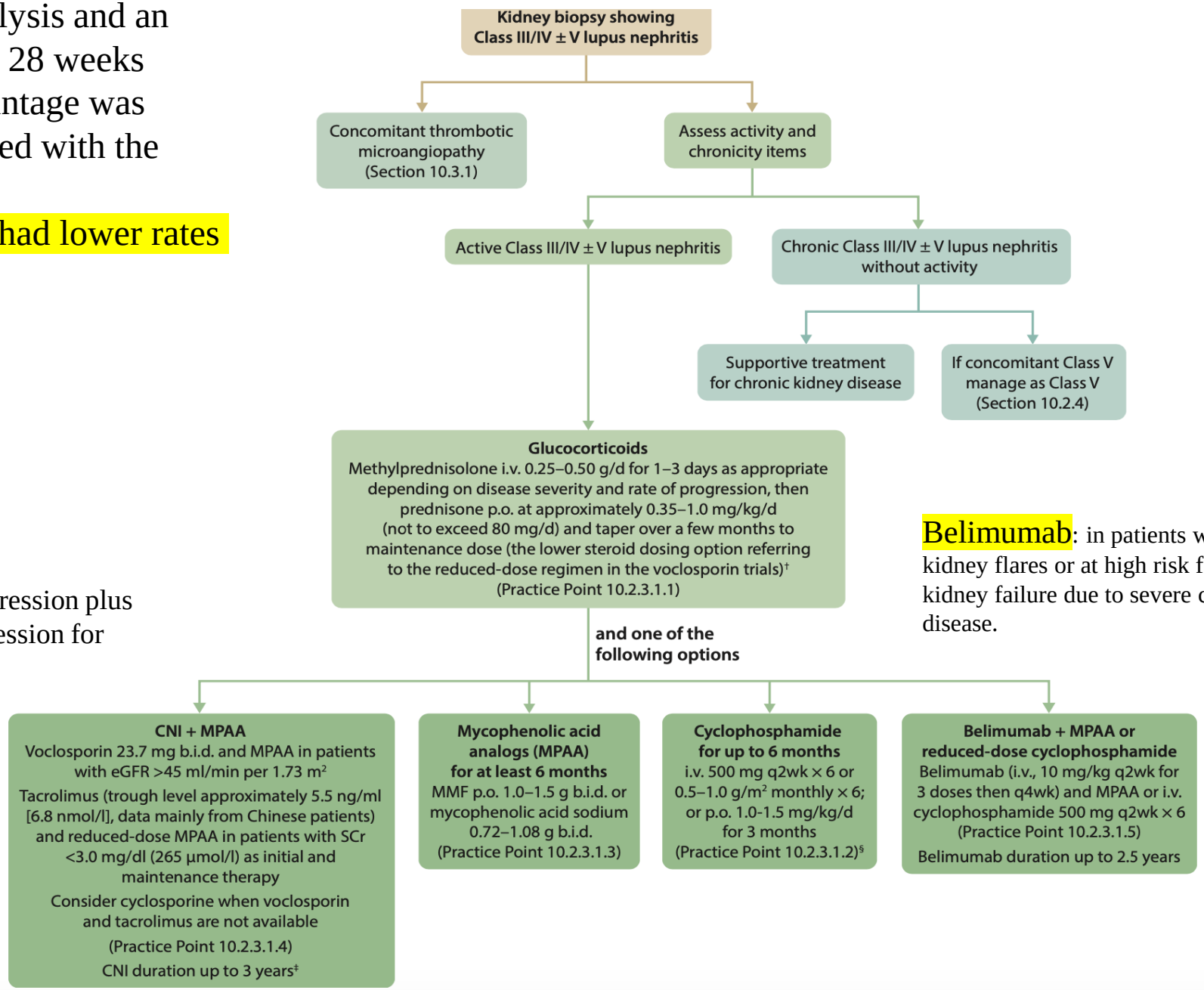


Figure 4 | Immunosuppressive treatment for patients with Class I or Class II lupus nephritis. Note: Chapter 5 refers to Chapter 5 of the KDIGO Guideline on Glomerular Diseases.

Although optimal duration is not known, maintenance with low-dose glucocorticoid plus an additional agent such as mycophenolic acid analogs (MPAA), azathioprine, or a CNI is suggested, especially in patients with a history of relapse

Results from a secondary analysis and an open-label extension study of 28 weeks showed that the efficacy advantage was maintained, and patients treated with the belimumab-containing triple immunosuppressive regimen had lower rates of adverse kidney outcomes.



Belimumab: in patients with repeated kidney flares or at high risk for progression to kidney failure due to severe chronic kidney disease.

The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should be ‡36 months

Figure 5 | Recommended approach for initial therapy of active Class III/IV lupus nephritis. Caution is warranted when calcineurin inhibitors (CNI) are used in patients with significantly

Cyclophosphamide dosing regimens, combined with glucocorticoids, in initial treatment for active Class III/IV LN

	High-dose intravenous cyclophosphamide (NIH regimen)	Low-dose intravenous cyclophosphamide (Euro-Lupus regimen)	Oral cyclophosphamide
Cyclophosphamide	i.v. 0.5–1 g/m^2 monthly for 6 months	i.v. 500 mg every 2 weeks for 3 months	p.o. 1.0–1.5 mg/kg/d (max 150 mg/d) for 2–6 months
Comments	Efficacy data included patients of different races/ethnicities	Efficacy data mainly in Caucasian patients, with some data from patients of African or Caribbean descent, Hispanic descent, Indian patients, and other Asian countries	Efficacy data included patients of different races/ethnicities

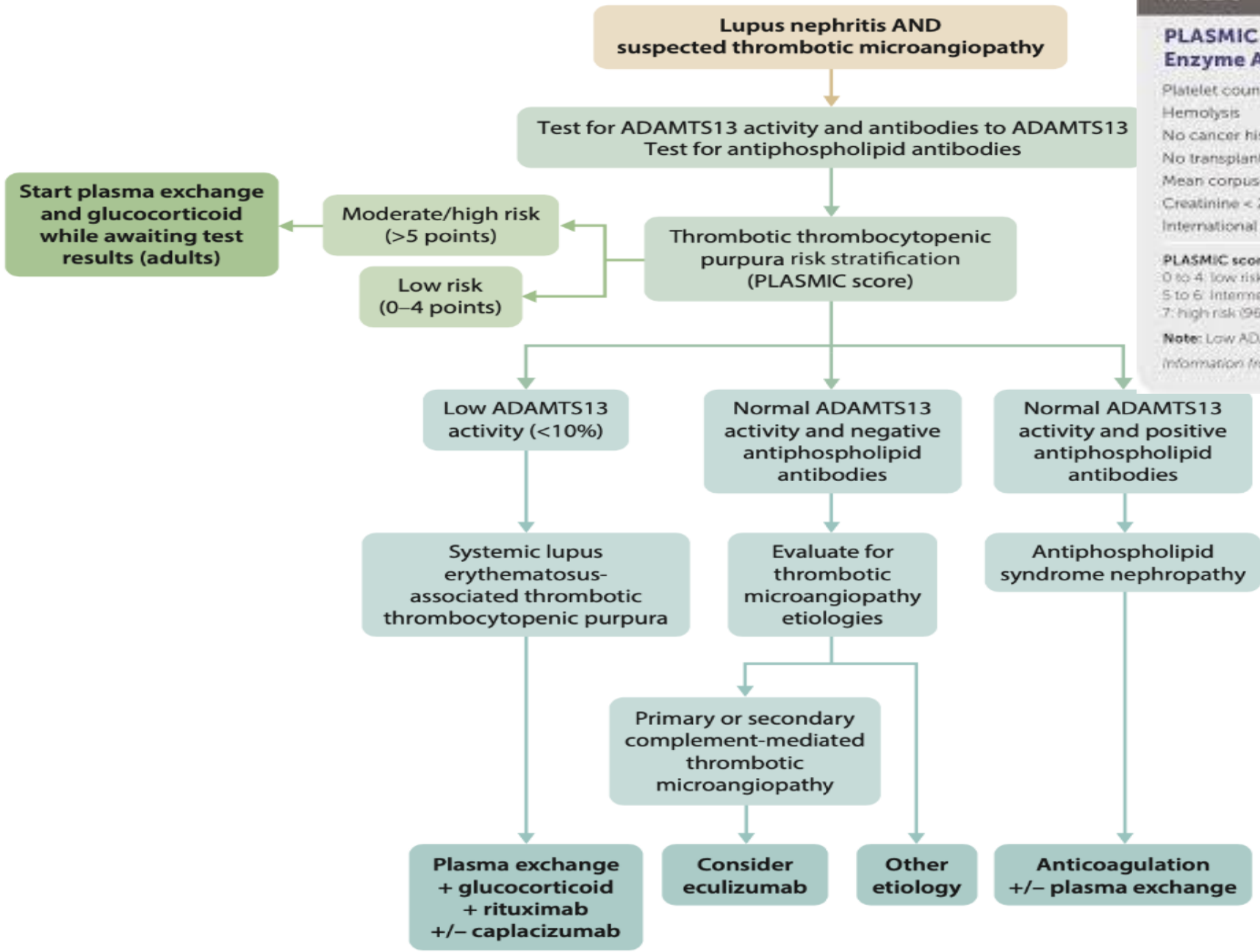


TABLE 5

PLASMIC Score for Predicting ADAMTS13 Enzyme Activity

Platelet count < 30 × 10^3 per μL (30 × 10^9 per L)
Hemolysis
No cancer history
No transplantation history
Mean corpuscular volume < 90 μm^3 (90 fL)
Creatinine < 2.0 mg per dL (177 μmol per L)
International normalized ratio < 1.5

PLASMIC score (one point per item present)
0 to 4: low risk (4.3%)
5 to 6: intermediate risk (56.8%)
7: high risk (96.2%)

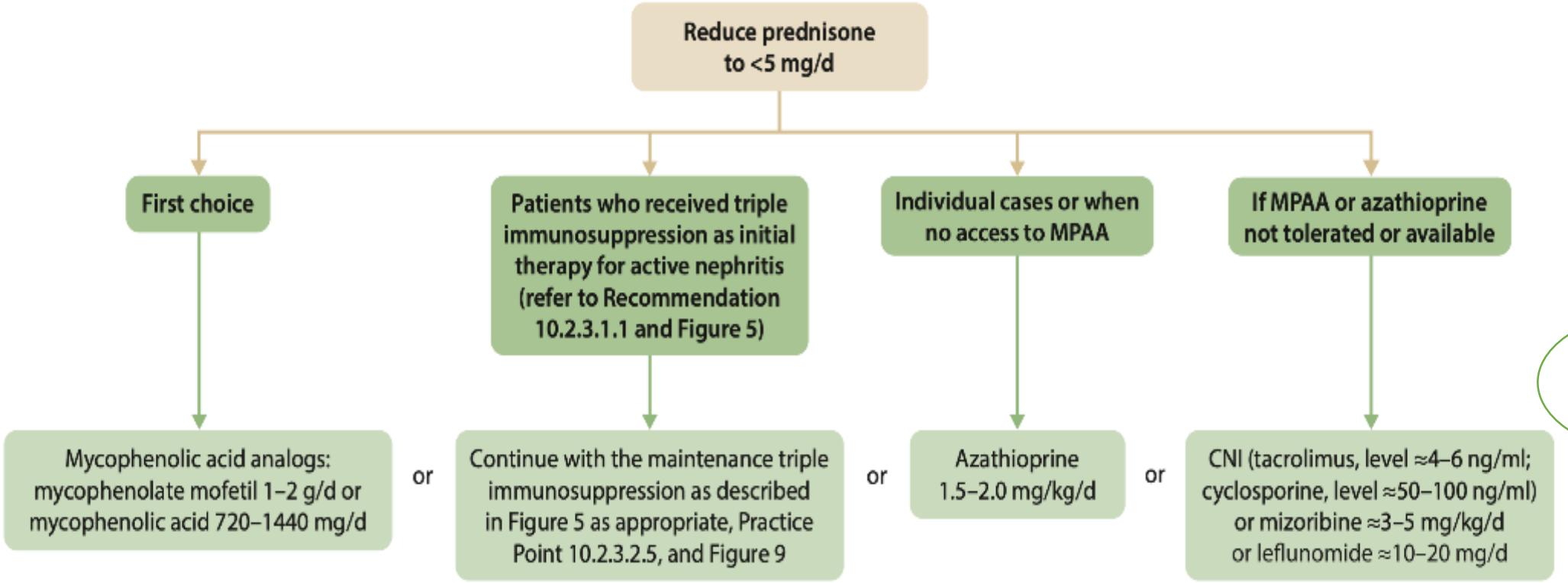
Note: Low ADAMTS13 enzyme activity is defined as ≤ 10%.

Information from reference 10.

Figure 13 | Management of patients with lupus nephritis and thrombotic microangiopathy (TMA). Bendapudi PK, Hurwitz S, Fry A, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. *Lancet Haematol*. 2017;4:e157–e164.[1] ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13;

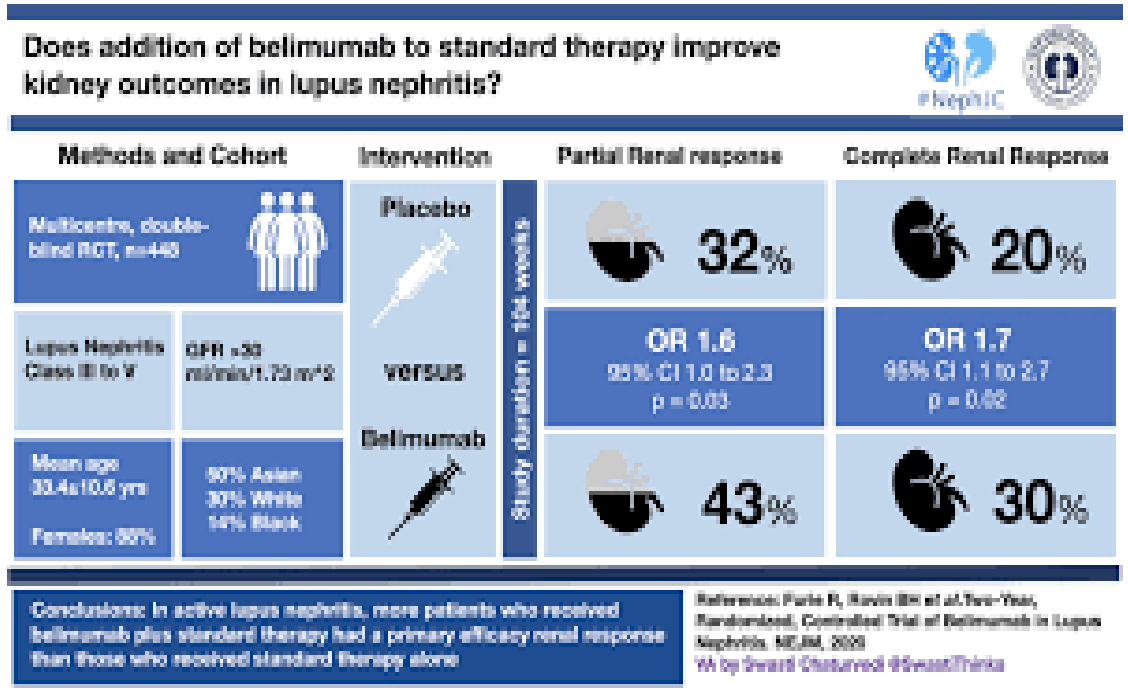
Practice Point 10.2.3.1.3: An MPAA-based regimen is the preferred initial therapy of proliferative LN for patients at high risk of infertility, such as patients who have a moderate-to-high prior cyclophosphamide exposure.

Practice Point 10.2.3.2.2: Glucocorticoids should be tapered to the lowest possible dose during maintenance, except when glucocorticoids are required for extrarenal lupus manifestations; discontinuation of glucocorticoids can be considered after patients have maintained a complete clinical renal response for ‡12 months.



Mizoribine Mostly in Japanese

Figure 8 | Recommended options of maintenance therapy for Class III and Class IV lupus nephritis. The target ranges of calcineurin inhibitors (CNIs) have been based on the transplant literature. The Kidney Disease: Improving Global Outcomes (KDIGO) Work Group acknowledges that targets for glomerular diseases are not known. Most clinicians check these levels to verify adherence and avoid CNI toxicity. At present, the most reasonable dosing of a CNI may be to titrate in the individual patient to obtain the desired effect on proteinuria, balancing dose escalation against serum creatinine level, reducing the dose if the serum creatinine level increases but does not plateau or increases to over 30% of baseline. If the serum creatinine level does not fall after dose reduction, the CNI should be discontinued. MPAA, mycophenolic acid analogs.


Does addition of belimumab to standard therapy improve kidney outcomes in lupus nephritis?
#NephIC
Methods and Cohort
Intervention
Partial Renal response
Complete Renal Response
Multicentre, double-blind RCT, n=448
Lupus Nephritis Class III to V
GFR ≥30 ml/min/1.73 m^2
Mean age 32.4±10.6 yrs
Females: 89%
50% Asian
30% White
14% Black
Placebo
versus
Belimumab
Study duration = 104 weeks
32%
20%
OR 1.6
95% CI 1.0 to 2.3
p = 0.03
OR 1.7
95% CI 1.1 to 2.7
p = 0.02
43%
30%
Conclusions: In active lupus nephritis, more patients who received belimumab plus standard therapy had a primary efficacy renal response than those who received standard therapy alone
Reference: Furie R, Rovin BH et al.Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. NEJM, 2020
Vk by Swasti Chaturvedi #SwastiThinks

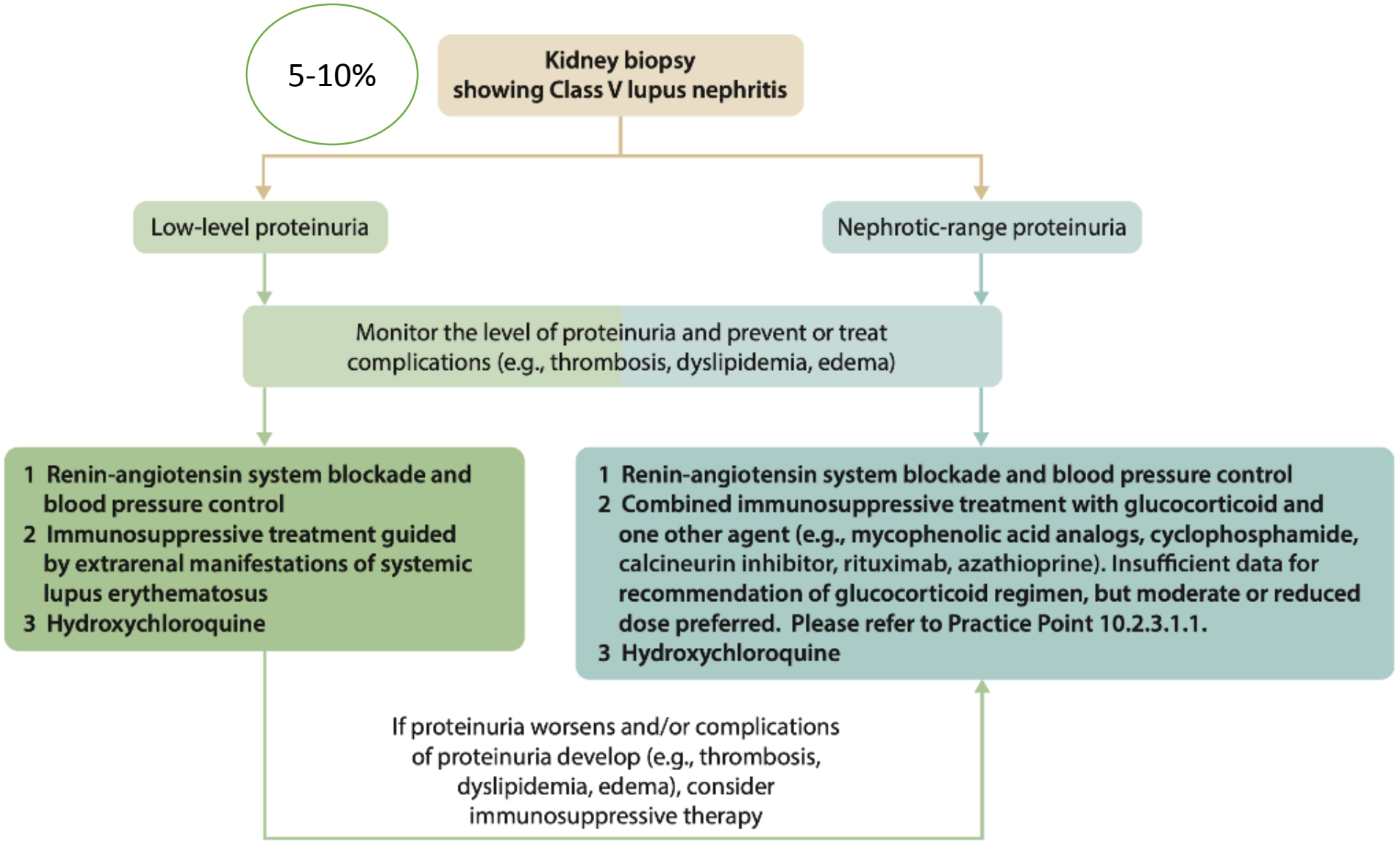


Figure 10 | Management of patients with pure Class V lupus nephritis.

The 2025 ACR guidelines of LN

- Conditional recommendation for a triple immunosuppressive regimen in patients with active Class III & IV lupus nephritis: Triple therapy for Class III/IV lupus nephritis includes glucocorticoid, and one of three immunosuppressive combination regimens: mycophenolate plus belimumab, mycophenolate plus calcineurin inhibitor therapy, or low dose cyclophosphamide plus belimumab.
- Conditional recommendation for treatment with a specific “triple therapy” as the most desirable therapy for pure Class V lupus nephritis with proteinuria greater than 1 g/g: Triple therapy for Class V lupus nephritis includes glucocorticoid, mycophenolate, and calcineurin inhibitor therapy.
- Conditional recommendation for a lower dose glucocorticoid regimen (after initial intravenous pulse therapy) to minimize toxicity, starting at 0.5 mg/kg/day prednisone (maximum of 40 mg daily) with taper to a prednisone goal of less than or equal to 5 mg/day by six months of treatment.

Criteria	Definition
Complete response*	• Reduction in proteinuria <0.5 g/g (50 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy, but could take more than 12 mo
Primary efficacy renal response	• PCR ≤0.7 g/g (70 mg/mmol) • eGFR that was no worse than 20% below the pre-flare value or ≥60 ml/min per 1.73 m^2 • No use of rescue therapy for treatment failure
Partial response	• Reduction in proteinuria by at least 50% and to <3 g/g (300 mg/mmol) measured as the PCR from a 24-h urine collection • Stabilization or improvement in kidney function (±10%–15% of baseline) • Within 6–12 mo of starting therapy
No kidney response	• Failure to achieve a partial or complete response within 6–12 mo of starting therapy

Management of patients who show unsatisfactory response to initial therapy for active lupus nephritis.

1	Verify adherence to treatment
2	Ensure adequate dosing of immunosuppressive medications by measuring plasma drug levels if applicable or available (check mycophenolic acid level if on mycophenolic acid analogs/check infusion records if on cyclophosphamide)
3	Repeat biopsy if concern for chronicity or other diagnosis (e.g., thrombotic microangiopathy)
4	Consider switching to an alternative recommended treatment regimen when there is persistent active disease
5	Consider the following in patients refractory to first-line treatment regimens: • Addition of rituximab or other biologic therapies • Extended course of i.v. pulse cyclophosphamide • Enrollment in clinical trials if eligible

Biologic agents in LN

Pharmacology
. 2022 Nov 3;108(1):17–26.

Comparative Efficacy and Safety of Biological Agents in the Treatment of Lupus Nephritis: A Network Meta-Analysis

Young Ho Lee [1,*], Gwan Gyu Song [1]

Background

To date, no studies have described randomized controlled trials (RCTs) evaluating the effectiveness and safety of various biological agents used in induction therapy for lupus nephritis.

Objectives

We designed this study to assess the relative efficacy and safety of some of these biological agents in patients with lupus nephritis.

Method

We collected data from RCTs that examined the efficacy and safety of any biological agents for lupus nephritis and then used these data to complete a Bayesian network meta-analysis to combine the direct and indirect evidence from these studies.

Results

We identified nine RCTs evaluating rituximab, abatacept, belimumab, anifrolumab, obinutuzumab, ocrelizumab, and low-dose interleukin-2 (IL-2) across 1,480 patients. Low-dose IL-2, obinutuzumab, rituximab, and belimumab achieved complete remission in a significant proportion of respondents when compared with that in the control. Ranking probability based on the surface under the cumulative ranking curve (SUCRA) indicated that low-dose IL-2 had the highest probability of achieving complete remission, followed by obinutuzumab, rituximab, belimumab, anifrolumab, abatacept, ocrelizumab, and the control. The risk of serious adverse events (SAE) tended to be lower for low-dose IL-2, rituximab, belimumab, and obinutuzumab than for the control. SUCRA-based ranking indicated that IL-2 had the highest probability of being safe, followed by rituximab, belimumab, obinutuzumab, anifrolumab, abatacept, and ocrelizumab.

Conclusions

Low-dose IL-2 was the most effective induction treatment for patients with lupus nephritis and had the lowest potential for SAE. Higher complete remission rates and a more favorable safety profile suggest that low-dose IL-2, obinutuzumab, rituximab, and belimumab may be superior to the current control as treatments for lupus nephritis.

Low-dose Interleukin-2 Therapy in Systemic Lupus Erythematosus: a double-blind, randomised, placebo-controlled, phase IIb trial

Xia Zhang[1], Ruiling Feng[1], Zhanguo Li[2] and Jing He[1], [1]Peking University People's Hospital, Beijing, China (People's Republic), [2]Peking Univeristy People's Hospital, Beijing, China (People's Republic)

Date of first publication: October 13, 2025

- **Background/Purpose:** Low-dose Interleukin-2 (Ld-IL2) has shown therapeutic effect in autoimmune diseases, particularly systemic lupus erythematosus (SLE). Various doses from 0.33 to 3.0 million units of IL-2 have been used widely in clinics. As far, the optimal dose in SLE treatment has not been evaluated, which leads to uncertainty of efficacy and causes difficulty of dose decision in practice.
- **Methods:** In this multicenter, randomized, double-blind, Phase IIb trial, 152 active SLE patients were randomized (1:1:1:1) to receive subcutaneous IL2 (0.2, 0.5, or 1.0 million IU) or placebo every other day for 12 weeks, then weekly for further 12 weeks.
- **Results:**
- At week 12, significantly higher SRI-4 response rates were demonstrated in IL2 1M IU (69.7%), 0.5M IU (64.7%), and 0.2M IU (42.9%) than in placebo (23.5%). Notably, these significant differences proceeded until the end of treatment period at week 24 ($p < 0.001$). Secondary outcomes revealed SLE patients achieving LLDAS at doses of 1M IU, 0.5M, and 0.2M (51.5%, 37.1%, and 28.5% respectively) at week 24. In the 1M IU Ld-IL2 group, significant reductions were observed in PGA scores, anti-dsDNA antibody, and prednisone dosages, accompanied by remarkable increases in serum C3 and C4 levels. Infection rates were lower in IL2 groups compared to placebo. Ld-IL2 drives expansion of Tregs and rebalance of Tregs/Teff ratio.
- **Conclusion:** Ld-IL2 demonstrates efficacy for patients with SLE in a dose-dependent manner, associated with expansion of Tregs and rebalance of Tregs/Teff ratio.

Rituximab

- RTX is recommended as 1st line therapy in patients with very active disease, severe hemolytic anemia, or thrombocytopenia with risk of death or organ damage, severe kidney disease (presence of glomerular crescents and/or renal failure), or with severe CNS disease.
- RTX is recommended as 2nd line therapy in patients with persistently active disease for at least one year with flares and particularly in patients with very active disease, hemolytic anemia or thrombocytopenia, severe kidney disease, or moderate or severe CNS disease.

- *Duxbury B, Combescure C, Chizzolini C. Rituximab in systemic lupus erythematosus: An updated systematic review and meta-analysis. Lupus (2013) 22(14):1489–503.*
- *Alshaiki F, Obaid E, Almuallim A, Taha R, El-Haddad H, Almoallim H. Outcomes of rituximab therapy in refractory lupus: A meta-analysis. Eur J Rheumatol (2018) 5(2):118–26. doi: 10.5152/eurjrheum.2018.17096*
- *Zhong Z, Li H, Zhong H, Zhou T. Clinical efficacy and safety of rituximab in lupus nephritis. Drug Des Devel Ther (2019) 13:845–56.*

- The clinical efficacy of rituximab in treating SLE demonstrates considerable variability, probably attributable to the following factors: elevated levels of BAFF (B-cell activating factor), B-cell reconstitution and the disease-specific high degree of heterogeneity in lupus. B-cell reconstitution after the infusion of rituximab is associated with increased BAFF levels. Elevated BAFF promote autoreactive B-cell proliferation.
- Additionally, SLE is a highly heterogeneous disease with various pathogenic mechanisms
- To overcome these challenges, potential strategies include combination therapy and sequential treatment. The potential of combining anti-B cell and anti-BAFF therapies should be further explored. Besides, in terms of sequential treatment, clinical studies of belimumab administration followed by RTX or RTX administration followed by belimumab are currently under investigation.

- 84. Shipa, M, Embleton-Thirsk, A, Parvaz, M, Santos, LR, Muller, P, Chowdhury, K, et al. Effectiveness of Belimumab after rituximab in systemic lupus erythematosus: a randomized controlled trial. *Ann Intern Med*. (2021) 174:1647–57

B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo- controlled trial

Ann Rheum Dis
2022;81:100–107

ABSTRACT

Objective Randomised trials of type I anti-CD20 antibodies rituximab and ocrelizumab failed to show benefit in proliferative lupus nephritis (LN). We compared obinutuzumab, a humanised type II anti-CD20 monoclonal antibody that induces potent B-cell depletion, with placebo for the treatment of LN in combination with standard therapies.

Methods Patients with LN receiving mycophenolate and corticosteroids were randomised to obinutuzumab 1000 mg or placebo on day 1 and weeks 2, 24 and 26, and followed through week 104. The primary endpoint was complete renal response (CRR) at week 52. Exploratory analyses through week 104 were conducted. The prespecified alpha level was 0.2.

Results A total of 125 patients were randomised and received blinded infusions. Achievement of CRR was greater with obinutuzumab at week 52 (primary endpoint, 22 (35%) vs 14 (23%) with placebo; percentage difference, 12% (95% CI −3.4% to 28%), p=0.115) and at week 104 (26 (41%) vs 14 (23%); percentage difference, 19% (95% CI 2.7% to 35%), p=0.026). Improvements in other renal response measures, serologies, estimated glomerular filtration rate and proteinuria were greater with obinutuzumab. Obinutuzumab was not associated with increases in serious adverse events, serious infections or deaths. Non-serious infusion-related reactions occurred more frequently with obinutuzumab.

Conclusions Improved renal responses through week 104 were observed in patients with LN who received obinutuzumab plus standard therapies compared with standard therapies alone. Obinutuzumab was well tolerated and no new safety signals were identified.

Trial registration number NCT02550652

ORIGINAL ARTICLE

Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

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ABSTRACT

BACKGROUND

Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, provided significantly better renal responses than placebo in a phase 2 trial involving patients with lupus nephritis receiving standard therapy.

METHODS

In a phase 3, randomized, controlled trial, we assigned adults with biopsy-proven active lupus nephritis in a 1:1 ratio to receive obinutuzumab in one of two dose schedules (1000 mg on day 1 and at weeks 2, 24, 26, and 52, with or without a dose at week 50) or placebo. All patients received standard therapy with mycophenolate mofetil, along with oral prednisone at a target dose of 7.5 mg per day by week 12 and 5 mg per day by week 24. The primary end point was a complete renal response at week 76, defined by a urinary protein-to-creatinine ratio of less than 0.5 (with protein and creatinine both measured in milligrams), an estimated glomerular filtration rate of at least 85% of the baseline value, and no intercurrent event (i.e., rescue therapy, treatment failure, death, or early trial withdrawal). Key secondary end points at week 76 included a complete renal response with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 and a urinary protein-to-creatinine ratio lower than 0.8 without an intercurrent event.

RESULTS

A total of 271 patients underwent randomization; 135 were assigned to the obinutuzumab group (combined dose schedules) and 136 to the placebo group. A complete renal response at week 76 was observed in 46.4% of the patients in the obinutuzumab group and 33.1% of those in the placebo group (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 2.0 to 24.8; P=0.02). A complete renal response at week 76 with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 was observed in more patients in the obinutuzumab group than in the placebo group (42.7% vs. 30.9%; adjusted difference, 11.9 percentage points; 95% CI, 0.6 to 23.2; P=0.04), and a urinary protein-to-creatinine ratio lower than 0.8 without an intercurrent event was more common with obinutuzumab than with placebo (55.5% vs. 41.9%; adjusted difference, 13.7 percentage points; 95% CI, 2.0 to 25.4; P=0.02). No unexpected safety signals were identified. More serious adverse events, mainly infections and events related to coronavirus disease 2019, occurred with obinutuzumab than with placebo.

CONCLUSIONS

Among adults with active lupus nephritis, obinutuzumab plus standard therapy was more efficacious than standard therapy alone in providing a complete renal response. (Funded by F. Hoffmann–La Roche; REGENCY ClinicalTrials.gov number, NCT04221477.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Furie can be contacted at rfurie@northwell.edu or at the Division of Rheumatology, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra–Northwell, 865 Northern Blvd., Suite 302, Great Neck, NY 11021.

*A list of investigators in the REGENCY trial is provided in the Supplementary Appendix, available at NEJM.org.

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Bortezomib (Velcade)

- Proteasome Inhibitor
- In patients with very active disease and RTX-experienced, bortezomib can be considered as 2nd line therapy. Bortezomib reduced disease activity in refractory SLE and LN and treated successfully one SLE patient with warm-type hemolytic anemia refractory to RTX . However, its safety profile requires the monitoring of adverse events, such as peripheral neuropathy and hypogammaglobulinemia .

- *Segarra A, Arredondo KV, Jaramillo J, Jatem E, Salcedo MT, Agraz I, et al. Efficacy and safety of bortezomib in refractory lupus nephritis: A single-center experience. Lupus (2020) 29(2):118–25.*

Eculizumab

- In patients with refractory lupus nephritis, eculizumab can be considered in multi-refractory cases.
- Eculizumab is a recombinant humanized monoclonal antibody (mAb) that binds to the complement component C5 and prevents its activation.
- A placebo-controlled, double-blind phase I RCT with 24 SLE patients failed to demonstrate the efficacy of eculizumab, according to laboratory and clinical parameters and SLEDAI scores (81). However, case reports described good results with eculizumab in the treatment of refractory LN (82, 83).
- In a review of SLE with renal involvement, irrespective of concomitant LN, all patients (n=6) showed a sustained improvement in renal function and normalization of complement parameters after treatment with eculizumab (median follow-up of 9 months) (80). This successful response was also observed in patients with refractory thrombotic microangiopathy associated with LN or SLE

81. *Furie R, Matis L, Rollins S, Mojcik C. A single dose, placebo controlled, double blind, phase I study of the humanized anti-C5 antibody h5G1.1 in patients with systemic lupus erythematosus. Arthritis Rheum (2004) 50:S35–S747*

82.Pickering MC, Ismajli M, Condon MB, McKenna N, Hall AE, Lightstone L, et al. Eculizumab as rescue therapy in severe resistant lupus nephritis. Rheumatology (2015) 54(12):2286–8

Other biologics

- RCTs have failed to demonstrate *abatacept* efficacy in the treatment of active LN (93, 94) or SLE (95), although some exploratory endpoints related to articular involvement showed good results.

- 93. *Group AT. Treatment of lupus nephritis with abatacept: The abatacept and cyclophosphamide combination efficacy and safety study. Arthritis Rheumatol (2014) 66(11):3096–104*

- A phase I RCT showed that 5 out of 12 patients treated with *dapirolizumab* (CD40 ligand inhibitors) achieved an SRI-4 response by week 12 (vs 1 out of 7 in the placebo group) (96). However, the phase IIb RCT in adults with moderately-to-severely active SLE failed to meet its primary endpoint at week 24, despite the improvement of other secondary endpoints and biomarkers (97). A phase III study is ongoing (NCT04294667).
- *Daratumumab*, a monoclonal antibody targeting CD38, induced substantial clinical responses in cases with life-threatening lupus, sustained afterward by maintenance therapy with belimumab (98, 99).

- 98. *Ostendorf L, Burns M, Durek P, Heinz GA, Heinrich F, Garantziotis P, et al. Targeting CD38 with daratumumab in refractory systemic lupus erythematosus. N Engl J Med (2020) 383(12):1149–55.*

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Trial of Anifrolumab in Active Systemic Lupus Erythematosus

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ABSTRACT

BACKGROUND

Anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1 investigated for the treatment of systemic lupus erythematosus (SLE), did not have a significant effect on the primary end point in a previous phase 3 trial. The current phase 3 trial used a secondary end point from that trial as the primary end point.

METHODS

We randomly assigned patients in a 1:1 ratio to receive intravenous anifrolumab (300 mg) or placebo every 4 weeks for 48 weeks. The primary end point of this trial was a response at week 52 defined with the use of the British Isles Lupus Assessment Group (BILAG)–based Composite Lupus Assessment (BICLA). A BICLA response requires reduction in any moderate-to-severe baseline disease activity and no worsening in any of nine organ systems in the BILAG index, no worsening on the Systemic Lupus Erythematosus Disease Activity Index, no increase of 0.3 points or more in the score on the Physician Global Assessment of disease activity (on a scale from 0 [no disease activity] to 3 [severe disease]), no discontinuation of the trial intervention, and no use of medications restricted by the protocol. Secondary end points included a BICLA response in patients with a high interferon gene signature at baseline; reductions in the glucocorticoid dose, in the severity of skin disease, and in counts of swollen and tender joints; and the annualized flare rate.

RESULTS

A total of 362 patients received the randomized intervention: 180 received anifrolumab and 182 received placebo. The percentage of patients who had a BICLA response was 47.8% in the anifrolumab group and 31.5% in the placebo group (difference, 16.3 percentage points; 95% confidence interval, 6.3 to 26.3; P=0.001). Among patients with a high interferon gene signature, the percentage with a response was 48.0% in the anifrolumab group and 30.7% in the placebo group; among patients with a low interferon gene signature, the percentage was 46.7% and 35.5%, respectively. Secondary end points with respect to the glucocorticoid dose and the severity of skin disease, but not counts of swollen and tender joints and the annualized flare rate, also showed a significant benefit with anifrolumab. Herpes zoster and bronchitis occurred in 7.2% and 12.2% of the patients, respectively, who received anifrolumab. There was one death from pneumonia in the anifrolumab group.

CONCLUSIONS

Monthly administration of anifrolumab resulted in a higher percentage of patients with a response (as defined by a composite end point) at week 52 than did placebo, in contrast to the findings of a similar phase 3 trial involving patients with SLE that had a different primary end point. The frequency of herpes zoster was higher with anifrolumab than with placebo. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT02446899.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Morand at the School of Clinical Sciences at Monash Health, Monash Medical Centre, 246 Clayton Rd., Clayton 3168, Melbourne, VIC, Australia, or at eric.morand@monash.edu.

*A list of investigators in the TULIP-2 trial is provided in the Supplementary Appendix, available at NEJM.org.

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- According to some reviews, *IVIG* can be considered in acute severe flares or refractory SLE, as well as in LN treatment . IVIG was also used successfully in the treatment of SLE-associated severe myelitis .
- A prospective, open-label, single-arm, phase I/IIa trial evaluated the safety, tolerability, and response of Treg to low-dose *interleukin-2* (IL-2) in patients with active and refractory SLE (103). Even though the responsiveness to IL-2 in Treg from SLE patients showed no impairment, the clinical response was transient and declined almost to baseline levels in between the cycles, suggesting that the cyclic treatment modality may be suboptimal.
- The use of anti-tumor necrosis factor (TNFα) in SLE is controversial, due to the risk of disease flare (14, 104). The short-term use of *infliximab* was successful in an open-label study with moderately active SLE patients (105). However, patients with lupus arthritis (n=5) maintained clinical response for less than 2 months after the last infusion. Long-term therapy was also associated with serious adverse events (SAEs) in two patients.

- 105. *Aringer M, Houssiau F, Gordon C, Graninger WB, Voll RE, Rath E, et al. Adverse events and efficacy of TNF-alpha blockade with infliximab in patients with systemic lupus erythematosus: Long-term follow-up of 13 patients. Rheumatology (2009) 48(11):1451–4.*

Recommendations for off-label biologic therapy of systemic lupus erythematosus.

First-line therapy

1. In pts with very active disease (i.e., SLEDAI>20 or BILAG 3A's)

RTX is recommended	2a	B	I
RTX-BEL may be used	2b	B	II

2. In pts with severe hemolytic anemia or severe thrombocytopenia (i.e., risk of death or organ damage)

RTX is recommended	4	C	I

3. **In pts with severe kidney disease** (stage IV, presence of glomerular crescents and/or renal failure [GFR < 60 ml/min/1.73 m^2])

RTX is recommended	2a	C	I
RTX-BEL may be used	2b	C	II

4. In pts with severe CNS disease

RTX is recommended	4	C	I
RTX-BEL may be used in recurrent cases	4	C	II

Second-line therapy Recommendations for off-label biologic therapy of systemic lupus erythematosus.

Second-line therapy			
5. In pts with persistently active disease for at least one year, with flares			
RTX is recommended in RTX-naïve cases	2a	C	I
baricitinib may be used in pts with predominant arthritis flares	1b	B	II
tocilizumab can be considered in pts with predominant arthritis flares	4	C	III
6. In pts with severe kidney disease,			
RTX is recommended in RTX-naïve cases	2a	C	I
RTX-BEL may be used in multi-refractory cases	4	C	II
secukinumab can be considered in multi-refractory cases	4	D	III
7. In pts with very active disease,			
RTX is recommended in RTX-naïve cases	2a	B	I
RTX-BEL may be used in RTX-naïve cases	2b	B	I
bortezomib can be considered in			

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Recommendations

EULAR recommendations for the management of systemic lupus erythematosus with kidney involvement: 2025 update

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ABSTRACT

Objectives: The objective of this study was to update the 2019 European Alliance of Associations for Rheumatology (EULAR)/ European Renal Association/European Dialysis Transplantation Association (ERA-EDTA) recommendations for the management of systemic lupus erythematosus (SLE) with kidney involvement, taking into consideration emerging evidence and recent developments in the field.

Methods: We recruited an international Task Force of experts and followed the EULAR standard operating procedures. We performed systematic literature research (period January 2019 to March 2024), followed by the modified Delphi method, to form questions, elicit expert opinions, and reach consensus. The new evidence was examined, taking into consideration previous updates.

Results: The Task Force agreed on 4 overarching principles and 13 recommendations, which were also evaluated for their feasibility and impact on clinical care. These concern the use of kidney biopsy for diagnosis; targets of therapy and treatment milestones; immunomodulatory therapy with antimalarials, glucocorticoids, immunosuppressives (mycophenolate, cyclophosphamide, and calcineurin inhibitors), and biologics (belimumab, obinutuzumab, and rituximab); nonimmune therapy (kidney protection, vaccinations, cardiovascular, and bone protection); family planning; and management of kidney failure. Guidance on single-agent or early combination immune therapy, glucocorticoid tapering and withdrawal, duration of immune therapy, and treatment of refractory disease is provided.

Conclusions: The updated EULAR recommendations provide evidence- and expert-based consensus on the management of SLE with kidney involvement, adjusted for severity, and taking into consideration long-term efficacy, safety, cost, and local availability of drugs.

EULAR recommendations for the management of patients with SLE and kidney involvement—2025 update

Recommendations		
1. Kidney biopsy is recommended in every patient with evidence of kidney involvement, especially in those with persistent proteinuria (≥0.5 g/24 h or urine protein-creatinine ratio [UPCR] ≥500 mg/g) (2b/B), glomerular haematuria (2b/C), and/or unexplained decrease in glomerular filtration rate (2b/C).	9.86 (0.44)	100
2. Treatment should aim for optimisation (preservation or improvement) of kidney function within 3 months, accompanied by a reduction in proteinuria of at least 25% by 3 months (2b/C), 50% by 6 months (2a/B), and a UPCR target <700 mg/g by 12 months (1b/B), and as low as possible afterwards.	9.83 (0.47)	100
3. For patients with active lupus nephritis, IV pulse methylprednisolone is recommended (2b/C), followed by oral glucocorticoids gradually tapered to ≤5 mg/d prednisone-equivalent by 4-6 mo (2b/C), and slowly withdrawn in patients with sustained complete renal response.	9.59 (0.68)	100
4. For patients with active lupus nephritis, especially those with poor prognostic factors, we recommend combination therapy of (a) mycophenolate or low-dose intravenous cyclophosphamide with belimumab (1b/A), (b) mycophenolate with a calcineurin inhibitor (voclosporin or tacrolimus) (1b/A), or (c) mycophenolate with obinutuzumab (1b/A). Alternative regimens include single-agent therapy with either mycophenolate (1a/A) or low-dose intravenous cyclophosphamide (1a/A).	9.59 (0.78)	96.5
5. In patients with rapidly progressive glomerulonephritis, a short course (6-7 monthly pulses) of high-dose intravenous cyclophosphamide can also be considered (1a/A).	8.97 (1.66)	93.1
6. Following renal response, treatment should continue for at least 3 years (2b/B); patients initially treated with mycophenolate alone (1a/A) or in combination with (1) belimumab (1b/A), (2) a calcineurin inhibitor (1b/A), or (3) obinutuzumab[a] should remain on these drugs; mycophenolate (1a/A) or azathioprine (1a/A) should replace cyclophosphamide for those initially treated with cyclophosphamide, alone or in combination with belimumab.	9.31 (1.14)	96.5
7. In patients with sustained complete renal response, gradual withdrawal of immunosuppressive and/or biologic therapy should be considered after 3 years of therapy following response, taking into consideration the risk for flare (2a/B).	9.31 (0.97)	93.1
8. For patients with persistently active or relapsing disease, switching among the aforementioned immunosuppressive (2b/B) and/or biologic drugs (2b/B) and referral to experts is recommended.	9.72 (0.59)	100

9. Repeat kidney biopsy should be considered, especially in cases of clinical uncertainty, to evaluate (1) response to treatment, (2) worsening of kidney-specific laboratory tests, or (3) contemplated withdrawal of immunosuppressive treatment (2b/B).	9.76 (0.58)
10. Nonimmune treatment with renin-angiotensin-aldosterone blockade (for patients with persistent proteinuria or arterial hypertension) (5/D), sodium glucose transporter 2 inhibitors (for stable patients with persistent proteinuria or estimated glomerular filtration rate <60 ml/min/m^2, or other risk factors for progressive chronic kidney disease) (5/D), statins (based on cardiovascular risk levels) (5/D), and/or bone protective agents (5/D) is recommended.	9.69 (0.71)
11. In patients with features of thrombotic microangiopathy (antiphospholipid syndrome nephropathy, thrombotic thrombocytopenic purpura-like, or complement-mediated hemolytic uremic syndrome), glucocorticoids (IV pulse methylprednisolone) (4/C), complement inhibitors (4/C), B-cell depleting agents (4/C), caplacizumab (4/C), plasma exchange (4/C), and/or anticoagulation (2b/C) should be considered.	9.52 (0.83)
12. In patients with inactive nephritis and adequately controlled extrarenal manifestations, pregnancy may be planned after preconception counselling, initiation of pregnancy-compatible medications, and regular multidisciplinary assessments (1b/A).	9.86 (0.35)
13. All methods of kidney replacement therapy can be used in patients with SLE; in those with clinically inactive extrarenal disease for at least 6 months, transplantation (including living donor and pre-emptive transplantation) should be considered (2b/C).	9.86 (0.52)

[a] Obinutuzumab was used for a maximum of 1 year (52 weeks) in the REGENCY trial; longer courses await further evaluation.
Levels of evidence according to the Oxford Evidence-based Medicine grading levels (https://www.cebm.net/wp-content/uploads/2014/06/
dence-2.1.pdf).

Treatment of LN relapse

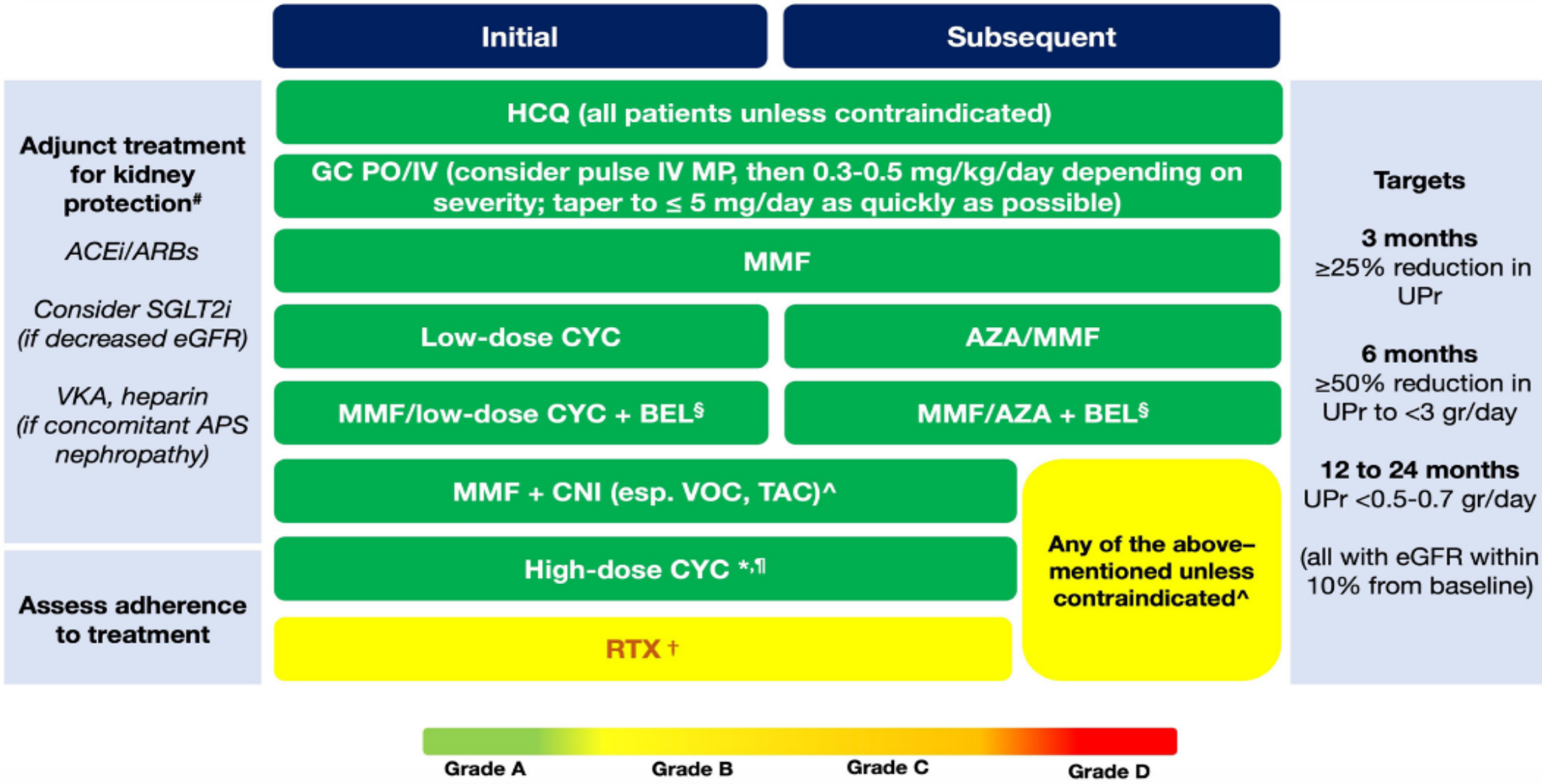
- Relapses of LN are common, and LN flare is an important predictor of poor long-term kidney survival.
- LN flare rates of 10%–50%
- Failure to achieve complete remission increases the risk of subsequent relapse.
- After a complete or partial remission has been achieved, LN relapse should be treated with the same initial therapy used to achieve the original response, or an alternative recommended therapy.

Cyclophosphamide: Ovarian failure has been associated with age (and oocyte reserve) and cumulative dose, with sustained amenorrhea occurring in up to 50% of patients aged >32 years with a cumulative exposure of 8 g/m2. The chance of future malignancy increases after a total exposure of 36 g

Monitoring

- Strong recommendations to quantify proteinuria at least every three months in patients with lupus nephritis who have not achieved complete renal response and every three to six months in patients with sustained complete renal response.

Treatment of Lupus Nephritis




Thank you