Lupus Nephritis ‘New Vision’

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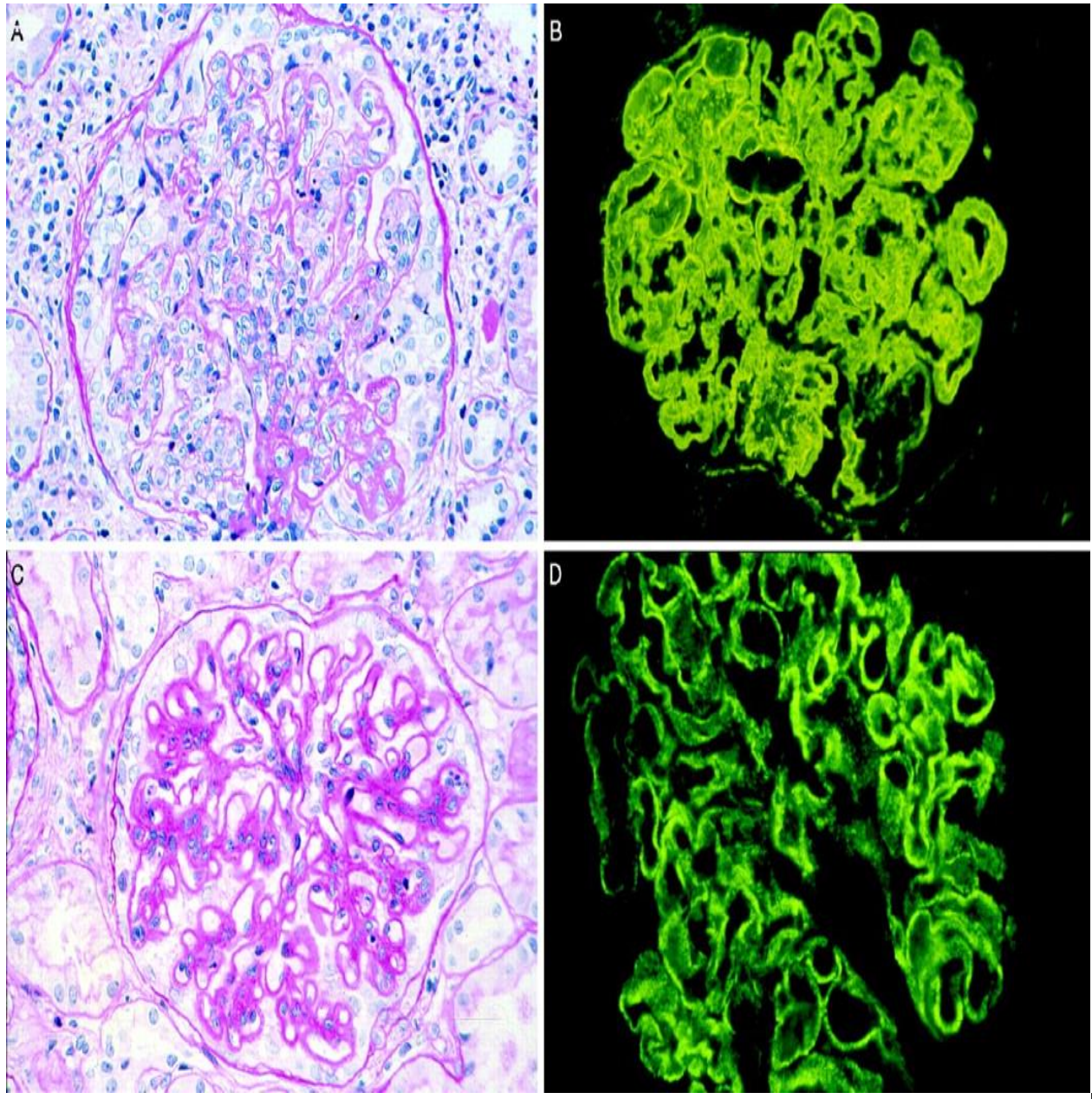


In the next 30 minutes……

- Case presentation
- Burden of lupus nephritis
- Types of lupus nephritis
- Management of LN
- New concepts in treatment
- How long to continue maintenance TTT
- Take home messages

Case Presentation

- Eman 26 years old single female with no habits of medical importance and with no family history of autoimmune diseases;
- **2018,** there was polyarthritis of hands, feet and elbow joints, negative RF and ACCP…….> seronegative RA and received treatment for which she partially responded
- **2019,** malar rash, puffy eyelids, lower limb edema, palpitation and dyspnea
- CBC normocytic normochromic anaemia (Hb 9), ANA 1/640, consumed C3 and C4, UPCR 6 mg/g, positive comb's test, negative assay for APS and echocardiography showed pericardial effusion

SLE with lupus nephritis, serositis and auto-immune haemolytic anaemia

Case Presentation

- Eman refused to do renal biopsy
- Induction of remission by methylprednisolone 3 gms followed by cyclophosphamide 750 mg/m2 for six months …… Hydroxycholoquine 400 mg/d and Glucocorticoids 0.5 mg/d
- **Maintenance therapy;** Glucocorticoids, Hydroxycholoquine, Mycophenolate mofetil 2….3 gm/d combined later on by cyclosporin 200-300 mg/d, Asprin and TTT for hperlipidaemia
- Poor response of proteinurea UPCR 4 mglg

Patient was convinced to do renal biopsy

Age :	24	**Sex :**	F
Code :	K20B162	**Date:**	29/02/2020

Diagnosis:

Renal Biopsy;
Light Microscopic and Immunoperoxidase Findings are Compatible with:
- Membranous Glomerulonephritis with Secondary Focal Segmental Glomerulosclerosis. For Antiphospholipase Type 2 Receptor Evaluation (aPLA2R)
- Additional Features: Focal Global Glomerulosclerosis (25%)

Gross: One core of needle biopsy, grayish brown in color. Totally processed.

Stains: H&E, Masson trichrome, PAS and Congo red stains.

Light Microscopy: Examination of serial sections prepared from the biopsy received revealed renal cortical tissue.
Eighteen (18) glomeruli were seen, in all serial sections examined, out of which 5 were globally sclerosed. The tufts showed mildly thickened capillary basement membranes. Most of the glomeruli showed segmental tuft sclerosis with focal overlying epithelial cell hyperplasia. Three (3) glomeruli showed periglomerular fibrosis.
Tubules showed mild injury.
Interstitium showed focal minimal lymphocytic infiltrate.
Arteries and arterioles were unremarkable.

Congo red: Examination of congo red stained sections viewed under polarized light revealed no amyloid deposits.

Immunohistochemistry: Serial sections on charged slides were treated for anti IgA, IgG and C3 antibodies. Examination revealed
IgA: Negative IgG: diffuse deposits along GBM (+2)
IgM: Negative C3: diffuse deposits along GBM (+2)

Electron Microscopy: No tissue for electron microscopy was provided.

Case Presentation

- Rituximab was started…..1gm/dose wk 0 1nd 2 then wk 26
- **Maintenance therapy;** Glucocorticoids, Mycophenolate mofetil , Mycophenolate mofetil combined with cyclosporin
- UPCR 3-4 mglg ……1.6 mglg …….. 0.6 mglg
- Mycophenolate mofetil 3g/d …..2 gm/d, Cyclosprine 300 mg/d…. 100 mg/d, Mycophenolate mofetil 200 mg/d, Glucocorticoids 7.5 mg/d

- Burden of lupus nephritis

- Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown cause involving a loss of immune tolerance of endogenous nuclear material, which leads to systemic autoimmunity that can lead to damage to various tissues and organs

- Lupus nephritis (LN) is not only a form of glomerulonephritis and constitutes one of the most severe organ manifestations of SLE

- Most patients with SLE develop LN within 5 years of SLE diagnosis, although in some cases, LN is the presenting manifestation that results in the diagnosis of SLE

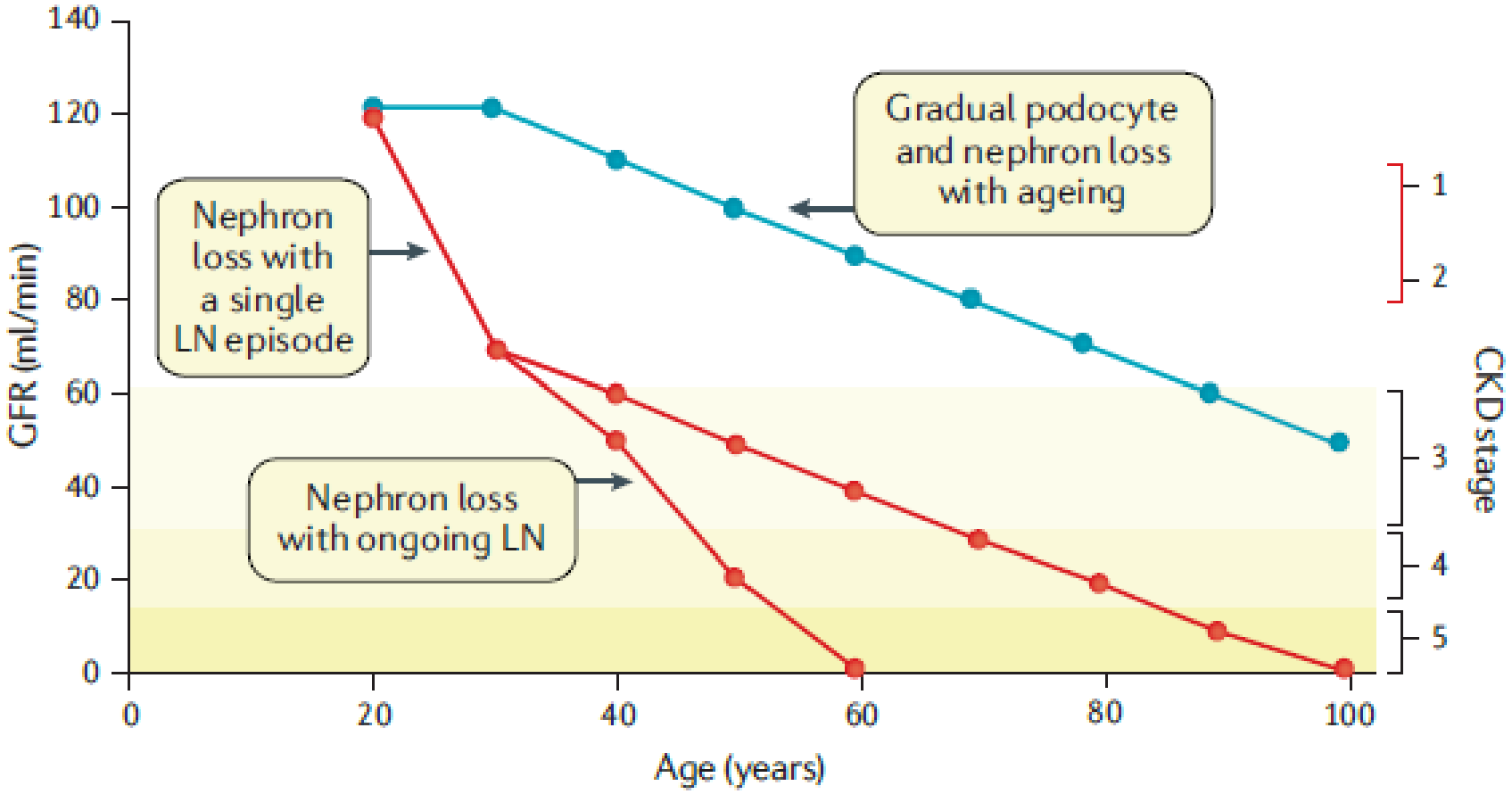
- Till 2020, there was no approved therapies for LN and unapproved SOC therapies are only partially effective despite high rates of toxicity

Lupus nephritis imposes a huge burden

Anders etal., Nature Reviews.2020

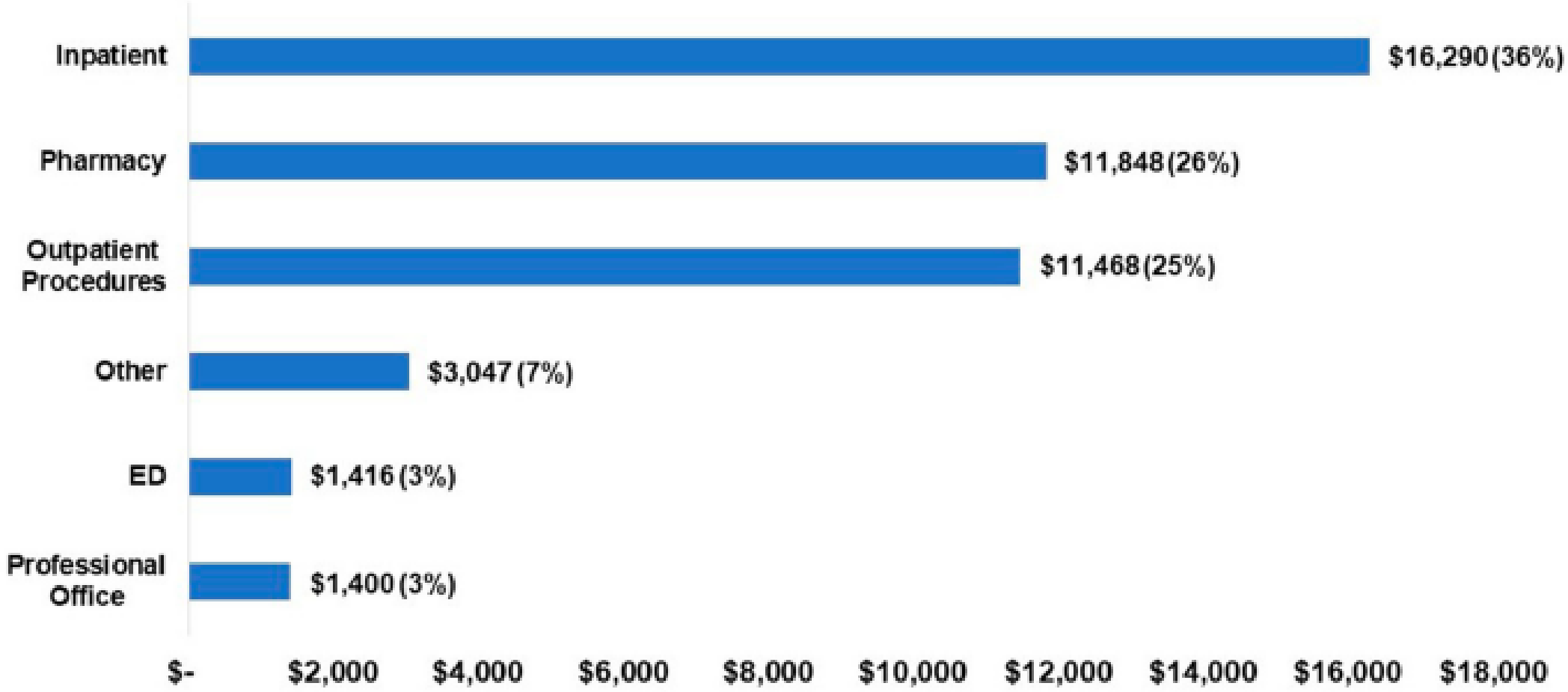
O

- LN and … survival … s' life, kidney … atment
- The res… significa… tions are also … r successful treatme…

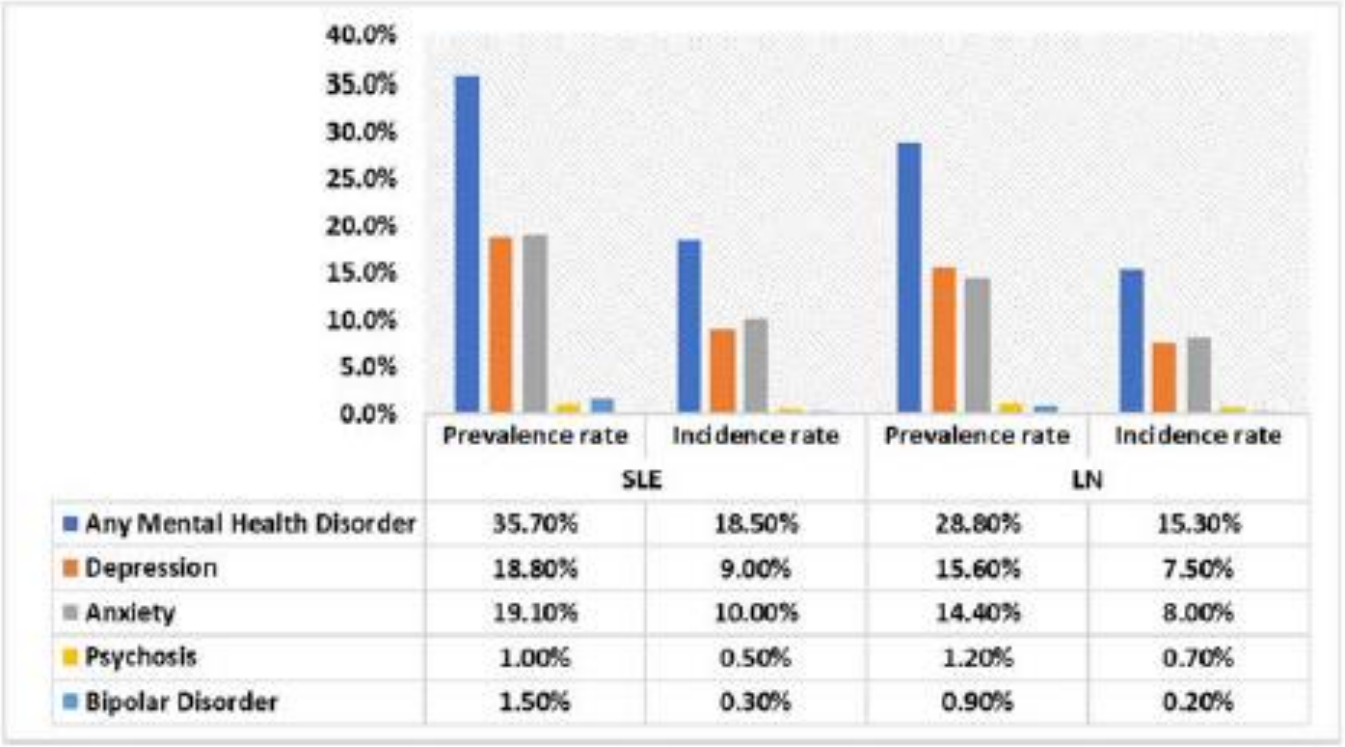


Among those who satisfy the ACR-11 definition of renal disease within 1 year of SLE diagnosis, the risk of renal failure within 20 years is 20%

Anders etal., Nature Reviews.2020



Open Access Rheumatology: Research and Reviews 2020:12 117–124



	SLE		LN	
	Prevalence rate	Incidence rate	Prevalence rate	Incidence rate
Any Mental Health Disorder	35.70%	18.50%	28.80%	15.30%
Depression	18.80%	9.00%	15.60%	7.50%
Anxiety	19.10%	10.00%	14.40%	8.00%
Psychosis	1.00%	0.50%	1.20%	0.70%
Bipolar Disorder	1.50%	0.30%	0.90%	0.20%

Strategic Organization, Compound Development Team, Horsham, United States of America

Conclusion: This real-world study shows that MH comorbidities have a high incidence and prevalence rate in SLE and LN patients. Health care costs and utilization for SLE and LN patients with MH comorbidities were significantly higher than patients without MH comorbidities. This study highlights not just the high prevalence of MH comorbidity but its large contribution to SLE healthcare costs.

- Types of lupus nephritis

Pathophysiology

✓ These autoantibodies form pathogenic immune complexes intravascularly, which are deposited in glomeruli

Autoimmunity plays a major role in the pathogenesis of lupus nephritis with production of autoantibodies directed against nuclear elements:

✓ Alternatively, autoantibodies may bind to antigens already located in the glomerular basement membrane, forming immune complexes in situ

•Some anti-dsDNA antibodies cross-react with the glomerular basement membrane

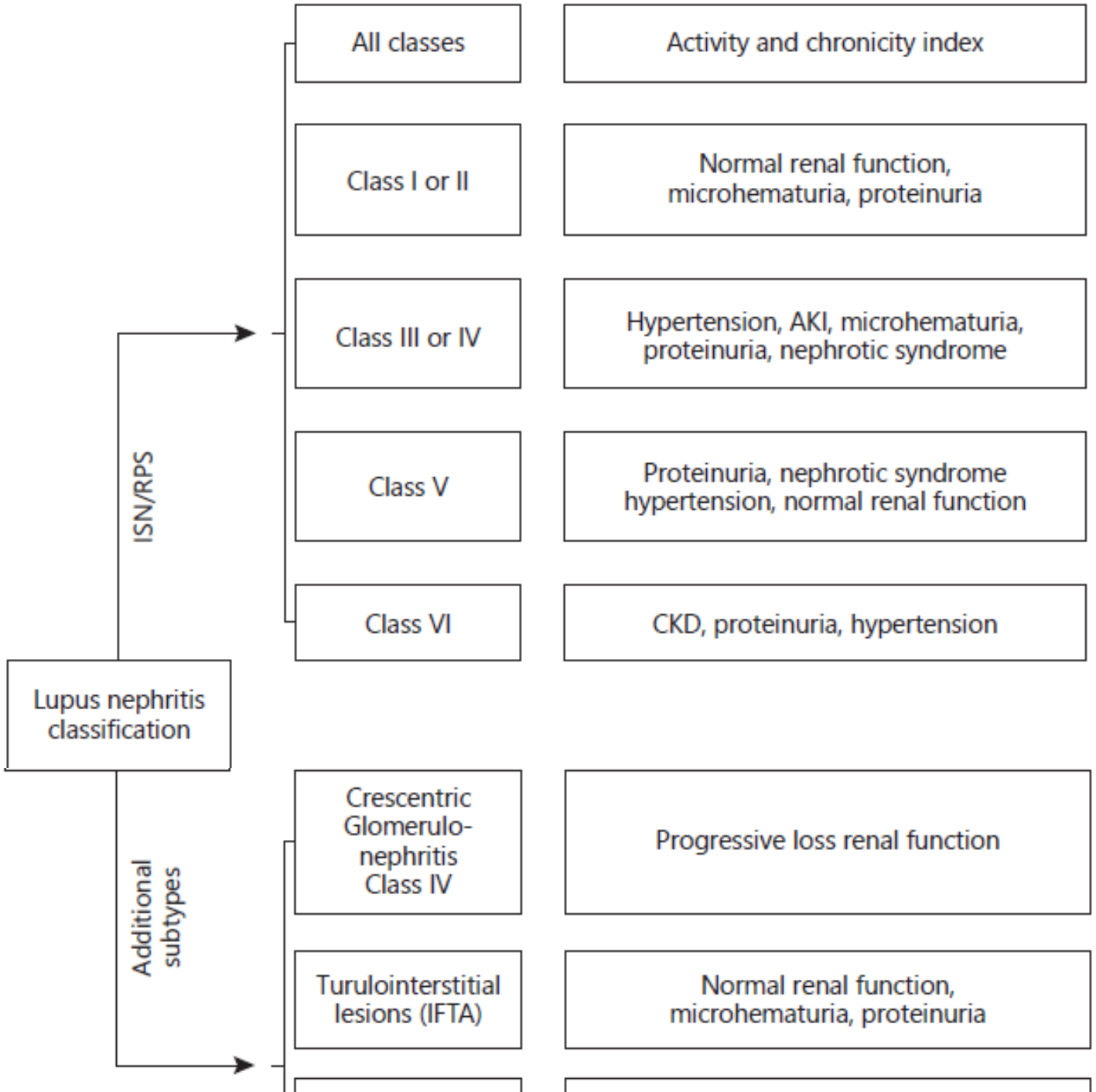
✓ Immune complexes promote an inflammatory response by activating complement and attracting inflammatory cells, including lymphocytes, macrophages, and neutrophils

•Cationic autoantibodies have a higher affinity for the anionic glomerular basement membrane

•Autoantibodies of certain isotypes (immunoglobulin IgG_1 and IgG_3) readily activate complement

✓ In more severe forms of lupus nephritis, proliferation of endothelial, mesangial, and epithelial cells and the production of matrix proteins lead to fibrosis

Davidson A, Berthier C, Kretzler M. Pathogenetic mechanisms in lupus nephritis. Wallace DJ, Hahn BH, eds. *Dubois' Lupus Erythematosus and Related Syndromes*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2013. 237-55



Morales E et al., Nephron 2021;145:1–13

- Management of LN
- New concepts in treatment

Recommendation/statement	LoE/GoR	LoA, mean (SD)
1. Investigation of the patient with suspected LN		
1.1 Kidney biopsy should be considered when there is evidence of kidney involvement, especially in the presence of persistent proteinuria ≥0.5 g/24 hours (or UPCR ≥500 mg/g in morning first void urine),	2b/B	9.84 (0.54)
and/or an unexplained decrease in GFR.	2b/C	
1.2 Kidney biopsy remains indispensable and its diagnostic and prognostic value cannot be substituted by other clinical or laboratory variables.	2b/B	9.96 (0.20)
2. Pathological assessment of kidney biopsy		
2.1 The use of the International Society of Nephrology/Renal Pathology SocietyISN/RPS 2003 classification system is recommended,	2a/B	9.56 (0.94)
with additional assessment of activity and chronicity indices,	1b/A	
as well as of thrombotic and vascular lesions associated with aPL/syndrome.	2b/C	
Antonis Fanouriakis, Myrto Kostopoulou, Kim Cheema, Hans-Joachim Anders,		
3. Indications for immunosuppressive treatment		
3.1 Immunosuppressive agents, administered in combination with glucocorticoids, are recommended in class III_A or $III_{A/C}$ (±V) and IV_A or $IV_{A/C}$ (±V) nephritis.	1a/A	9.96 (0.20)
3.2 In pure class V nephritis, glucocorticoids and immunosuppression are recommended in cases of nephrotic-range proteinuria,	2b/B	9.04 (1.80)
or when UPCR exceeds 1000 mg/g despite the optimal use of renin–angiotensin–aldosterone system blockers.	5/D	
Maria Trachana, Ronald F van Vollenhoven, Alexandre E Voskuyl,		
Goals of treatment		
4.1 Treatment aims for optimisation (preservation or improvement) of kidney function, accompanied by a reduction in proteinuria of at least 25% by 3 months,	2b/D	
50% by 6 months,	2a/B	9.60 (0.63)
and a UPCR target below 500–700 mg/g by 12 months (*complete clinical response*).	2a/B	
4.2 Patients with nephrotic-range proteinuria at baseline may require an additional 6–12 months to reach *complete clinical response*; in such cases, prompt switches of therapy are not necessary if proteinuria is improving.	2a/C	9.68 (0.68)

4.7 In pure class V nephritis, MMF (target dose 2 to 3 g/day; or MPA at equivalent dose),

in combination with pulse intravenous methylprednisolone (total dose 500–2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by 3 months)

is recommended as initial treatment due to best efficacy/toxicity ratio.

4.8 Alternative options for class V nephritis include intravenous CY,

or CNIs (especially TAC) in monotherapy

or in combination with MMF/MPA, particularly in patients with nephrotic-range proteinuria.

Subsequent treatment for Class III/IV(±V) LN – 2020

2019 update of the joint EULAR and ERE-EDTA recommendations for the management of lupus nephritis.

dose 500-2.500mg

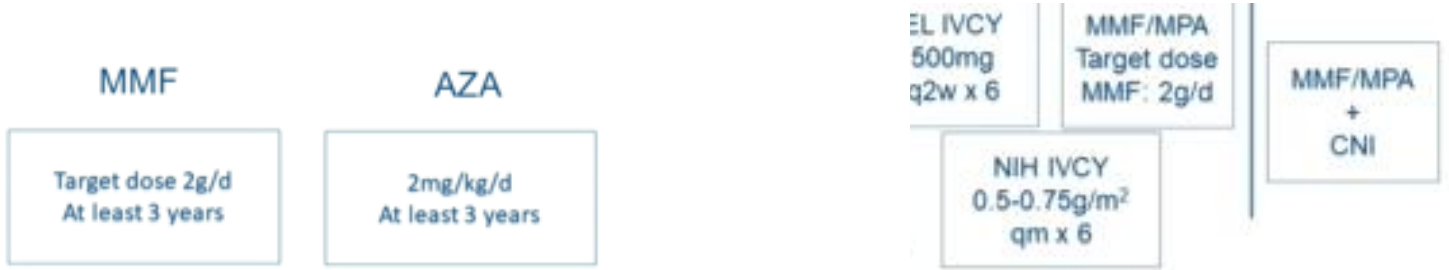
prednisolone

Non-responding/refractory disease

4.13 In case of failure to achieve the treatment goals, thorough evaluation of the possible causes is recommended, including assessment of adherence to treatment and therapeutic drug monitoring.

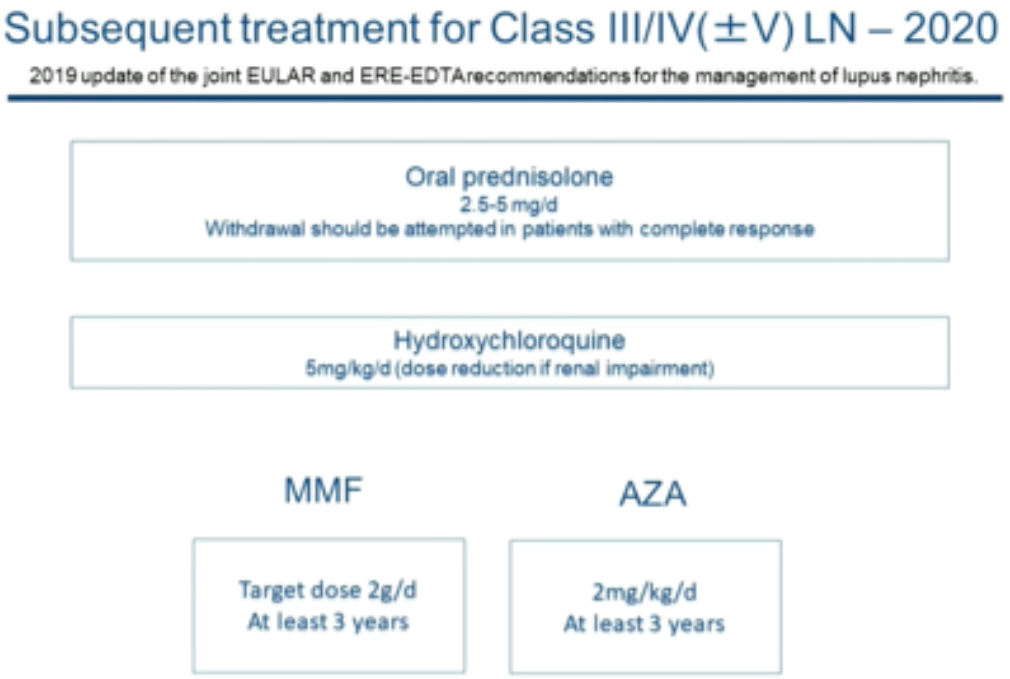
4.14 For active non-responding/refractory disease, treatment may be switched to one of the alternative initial therapies mentioned above,

or RTX (1000 mg on days 0 and 14) may be given.

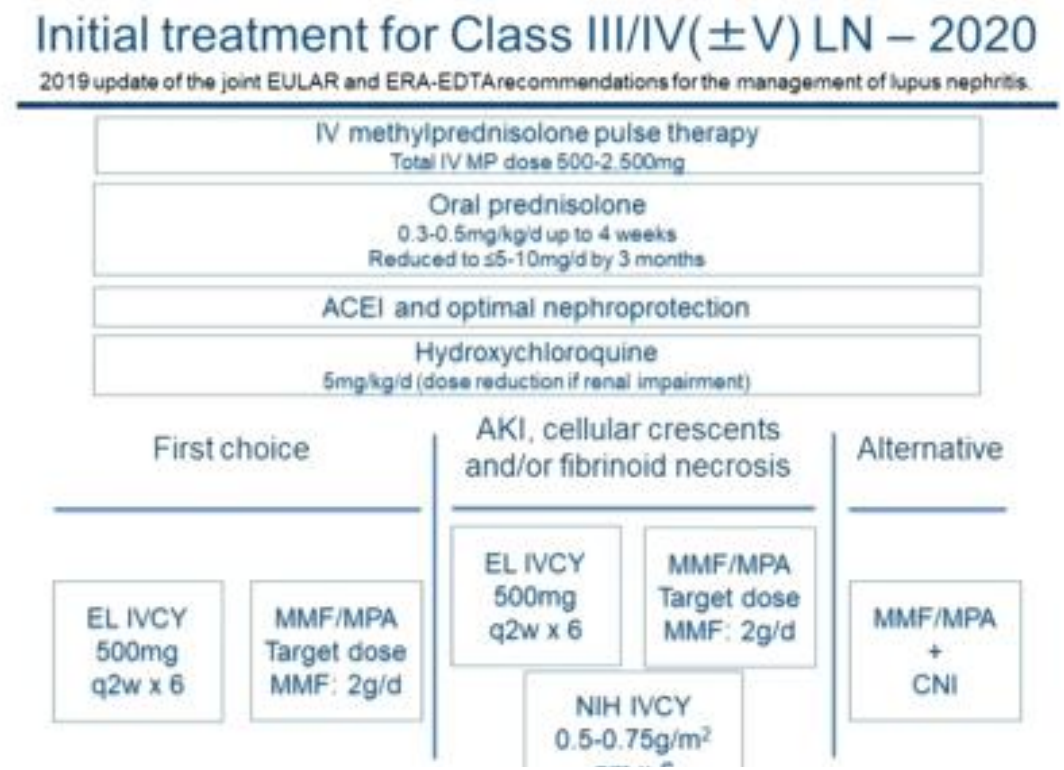


Fanouriakis A. *et al*. Ann Rheum Dis 2020; 79: 713

Sequential Therapy



Fanouriakis A. *et al*. Ann Rheum Dis 2020; 79: 713



- 20-30% complete clinical renal response at 6-12M
- 20-25% relapses at 3-5Y
- 5-20% ESKD at 10Y
- CKD

How to improve the outcome of lupus nephritis?

Treat-To-Target Approach →

Combination therapy

Clinical Target

Clinical and epidemiological research
Extended report

The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide

F A Houssiau [1], C Vasconcelos [2], D D'Cruz [3], G D Sebastiani [4], E de Ramon Garrido [5], M G Danieli [6], D Abramovicz [7], D Blockmans [8], A Cauli [9], H Diamantopoulos [10], M Galeazzi [11], A Gül [12], Y Levy [13], P Petera [14], P Popovic [15], P Petrovic [16], R A Sinico [17], R Cattaneo [18], J Font [19], G Depresseux [1], J-P Cosyns [20], R Cervera [19]

Correspondence to Professor F A Houssiau, Rheumatology Department, Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Avenue Hippocrate, 10, B-1200 Bruxelles, Belgi

- Early proteinuria decrease predicts good long term renal outcome
- Cut off level of proteinuria that best predicts serum creatinine ≤ 1mg/dl is at least 0.7 gm/d

Clinical and epidemiological research
EXTENDED REPORT
OPEN ACCESS

Long-term follow-up of the *MAINTAIN* Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis

Farah Tamirou,[1] David D'Cruz,[2] Shirish Sangle,[2] Philippe Remy,[3] Carlos Vasconcelos,[4] Christoph Fehm,[5] Maria del Mar Ayala Gutiérrez,[6] Inge-Magrethe Gilboe,[7] Maria Tektonidou,[8] Daniel Blockmans,[9] Isabelle Ravelingien,[10] Véronique le Guern,[11] Geneviève Depresseux,[1] Loïc Guillevin,[11] Ricard Cervera,[12] Frédéric A Houssiau,[1] and the *MAINTAIN* Nephritis Trial Group

- **CRR** = UPCR < 0.5, Serum creatinine ≤ upper limit of normal, Serum creatinine ≤ 115% of baseline value, <10 RBC/hpf *Without RBC casts*
- **PRR** = UPCR ≥ 50% reduction to <1 (to <3 if baseline ≥3), Serum creatinine ≤ 115% of baseline value RBC ≤50% above baseline or <10 RBC/hpf

Pathological Target

Immunological Target

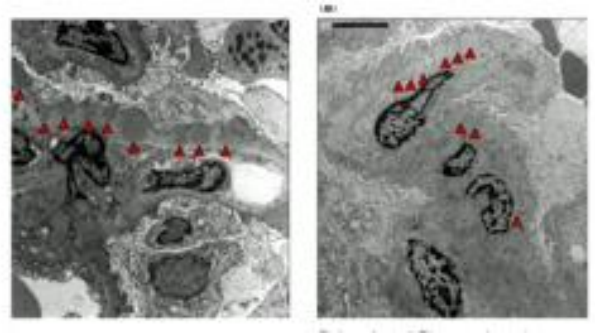
Renal Biopsy

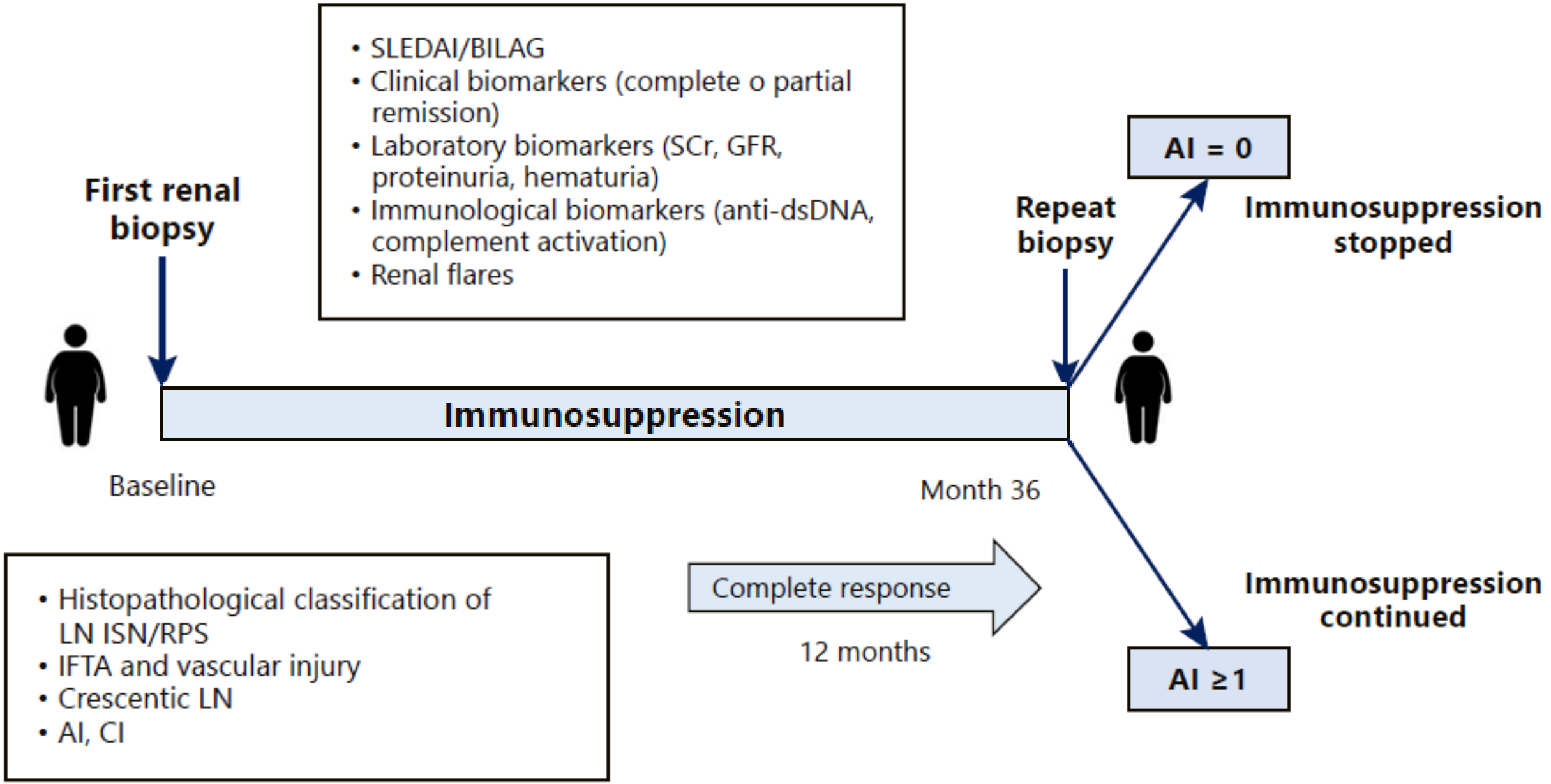
Challenging

To identify patients who did not reach the clinical (proteinric) target and may develop poor long-term outcome and for whom the change in therapy may be appropriate

Pre-protocol repeat renal biopsy

Resorption of immune complexes by electron microscopic studies at tissue levels




• SLEDAI/BILAG
• Clinical biomarkers (complete o partial remission)
• Laboratory biomarkers (SCr, GFR, proteinuria, hematuria)
• Immunological biomarkers (anti-dsDNA, complement activation)
• Renal flares
First renal biopsy
AI = 0
Repeat biopsy
Immunosuppression stopped
Immunosuppression
Baseline
Month 36
• Histopathological classification of LN ISN/RPS
• IFTA and vascular injury
• Crescentic LN
• AI, CI
Complete response
12 months
Immunosuppression continued
AI ≥1

How to improve the outcome of lupus nephritis?

Treat-To-Target Approach

Combination therapy 

Belimumab

mAb to B cell–activating factor
(BAFF)

December 2020 FDA approved BENLYSTA (belimumab) for the treatment of adult patients with active lupus nephritis who are receiving standard therapy

In the phase III BLISS-LN study, 448 patients with active proliferative lupus nephritis, more patients who received belimumab plus standard therapy had a primary efficacy renal response than those who received standard therapy alone

	PERR (%)	CRR (%)
PBO (n=223)	32.3	19.7
BLM (n=223)	43.0	30.0
OR (95% CI)	1.55 (1.0, 2.32)	1.74 (1.11, 2, 74)
P value	0.031	0.017

(PERR):primary efficacy renal response CRR: complete renal remission

Belimumab 10 mg/kg, days 1 (baseline), 15, and 29 and every 28 days, in conjunction with SoC

Furei et al., N Engl J Med 2020;383:1117-28

Voclosporin: Calcineurin inhibitor

January 2021 FDA approved Voclosporin (LUPKYNIS), in combination with an existing immunosuppressive therapy regimen, for treatment of adult patients with lupus nephritis.

AURORA Phase 3 study and the AURA-LV Phase 2 study. Over the course of 52 weeks, patients receiving voclosporin had vastly improved outcomes when taken in combination with standard-of-care therapy (SoC), mycophenolate mofetil (MMF), and low dose steroids

The phase 3 study demonstrated that voclosporin was twice as effective at achieving a complete renal response at wk 24 than the SoC group

voclosporin 23.7 mg twice a day in conjunction with SoC and a MMF target dose of 2g daily

Rovin et al., Lancet 2021; 397: 2070-2080

	Belimumab	Voclosporin
Better Safety		
Nephrotoxicity	✓	
Infection	✓	
Cardiovascular/Metabolic	✓	
Malignancy	✓	
Neurologic	✓	
Drug-Drug Interactions	✓	
Pregnancy	Tacrolimus	
Adherence	✓	

✓ Shows better safety (safety) or potential better adherence (adherence)

Obinutuzumab: Anti-CD20 mAb

- Obinutuzumab is a humanized Type II anti-CD20 approved for combination treatment of CLL and follicular lymphoma[1]

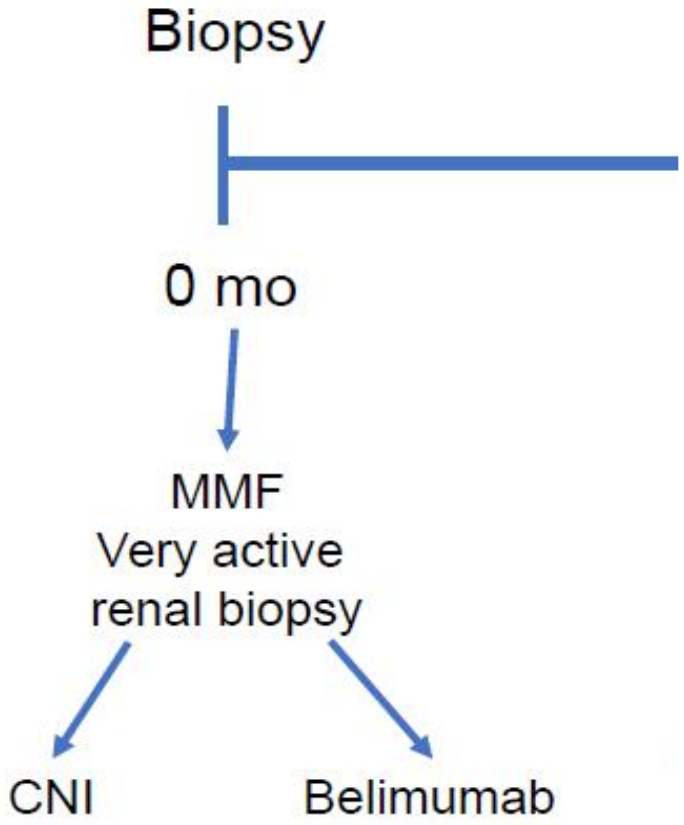
- Enhanced B-cell depletion vs. rituximab and ofatumumab:
  - **Glycoengineering**: Up to 100x antibody-dependent cytotoxicity[2,3]
  - **Type II binding conformation**: Greater direct cell death, reduced internalization, lower complement-dependent cytotoxicity[2,3]

- Greater B-cell depletion than rituximab in tissue[3] and SLE patient samples[4]

- It is used in LN based on the results of Nobility trial where it induced CRR in 35% of patients and overall renal remission(CRR-PRR) in 56% at a dose 1000 mg (0…2 wks….then 24 ..26 wks)

1. Obinutuzumab USPI. Obinutuzumab is not approved for the treatment of lupus nephritis; 2. Herter *Mol Cancer Ther* 2013; 3. Mossner *Blood* 2010;
4. Reddy *Rheumatology* (Oxford) 2017; 5. Goede *N Engl J Med* 2014; 6. Marcus *N Engl J Med* 2017

New Paradigm



- How long to continue maintenance TTT

- ✓ As most of renal flares occur within 5-6 years from initiation of treatment, EULAR/ERA-EDTA recommends maintenance therapy to be continued at least for 3-5 years after achieving complete clinical response. Start by corticosteroids and bear in mind that anti-malarial should be continued for a long time

- ✓ Goals of maintenance therapy should be thought of when considering treatment withdrawal. These include preventing relapse, maintain long-term organ health and reducing treatment-related toxicity

- ✓ It is possible to withdraw maintenance in some patients, BUT there is risk of flare of LN after withdrawal

- Take home messages

Take Home Messages

- ✓ Lupus nephritis (LN) is not only a form of glomerulonephritis and constitutes one of the most severe organ manifestations of SLE
- ✓ Despite increased knowledge and improved treatment options, LN remains a substantial cause of morbidity and death among patients with SLE
- ✓ Conventional immunosuppressive treatments are not uniformly effective, and even in patients who respond, a good percentage may relapse
- ✓ Clearly, early and accurate diagnosis of LN and prompt initiation of therapy are of vital importance to prevent disease progression
- ✓ Treat-to-target to avoid nephron lose, Pre-protocol renal biopsy may be part of this approach, switch from sequential to combination therapy and always co-work with a nephrologist

Working together: Who benefits

The rheumatologist

- When to do renal biopsy in lupus patients? What are poor prognostic predictors?
- When and for how long CNI? How to follow up?
- Role of pre-protocol Renal Biopsy?
- When to dialyze patients with LN?
- When to do renal transplant in patients with LN?
- How to treat lupus flares post-transplant

The nephrologist

- Approach in patients with TMA LN?
- Indications of Rituximab in SLE?
- Extra-renal lupus

The patient

Good control of lupus nephritis in the context of Systemic lupus Erythematosus with better preservation of renal function

Thank you

Samah El-Bakry