ERKNet
The European Rare Kidney Disease Reference Network

era edta
WGIKD working group
Working Group on Inherited Kidney Disorders

european society for paediatric nephrology

WELCOME TO

ERKNet/ESPN and Era-EDTA Educational Webinar on Nephrology & Rare Kidney Diseases

Date: 02 March 2021

Topic: Lupus nephritis in adults

Speaker: Hans Joachim Anders

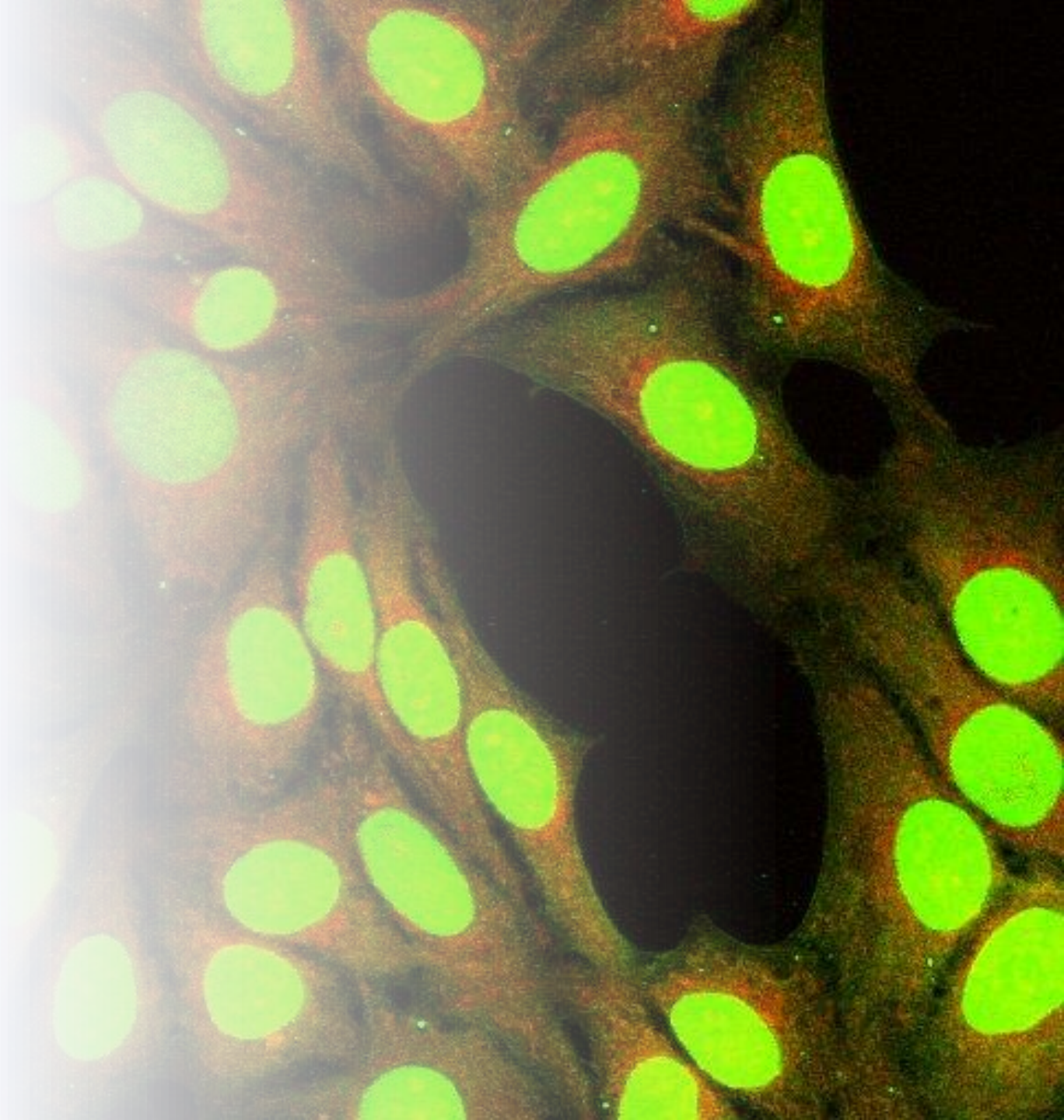
Moderator: Marina Vivarelli

Lupus Nephritis in Adults

Hans-Joachim Anders
LMU Munich

hjanders@med.uni-muenchen.de
@hjanders_hans

ERKNet/ESPN Webinar
02. March 2021



Disclosures

Research funding:	Deutsche Forschungsgemeinschaft, Volkswagen Foundation
Consultancy fees:	GSK, Novartis, Janssen, Kezar

Outline

Pathogenesis

Diagnosis

Treatment goals and patient education

Treatment of first episode and how to assess treatment response

Long-term management

Outline

Pathogenesis

Diagnosis

Treatment goals and patient education

Treatment of first episode and how to assess treatment response

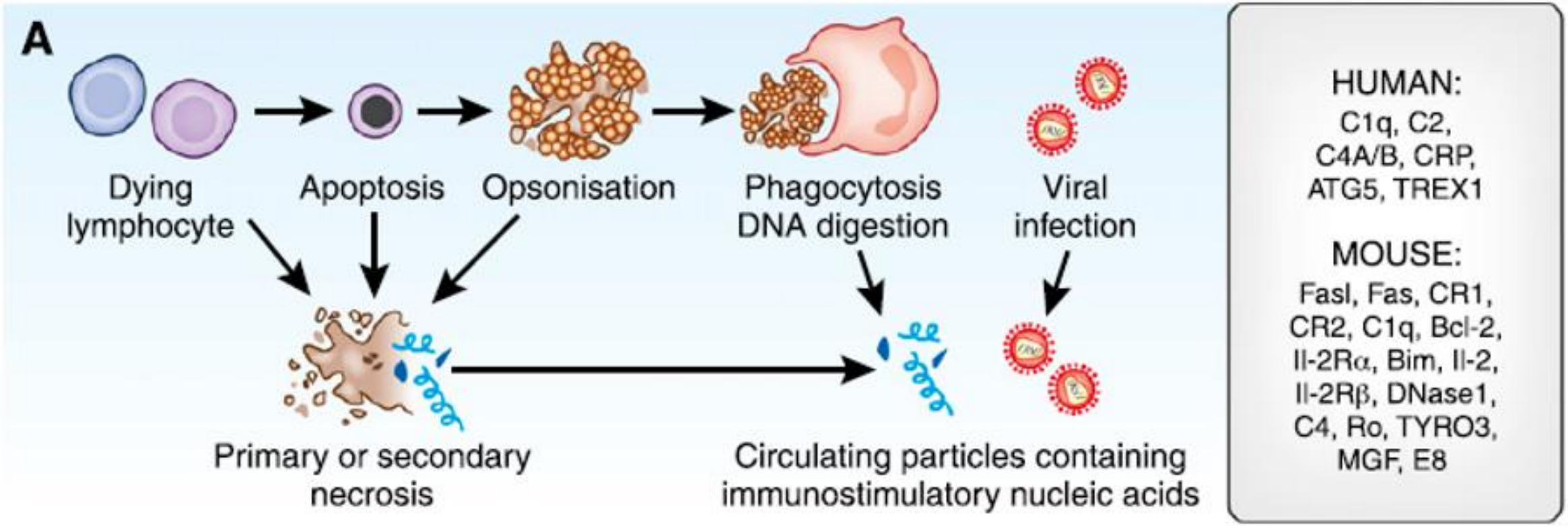
Long-term management

Question

Which statement on the pathogenesis of SLE is correct

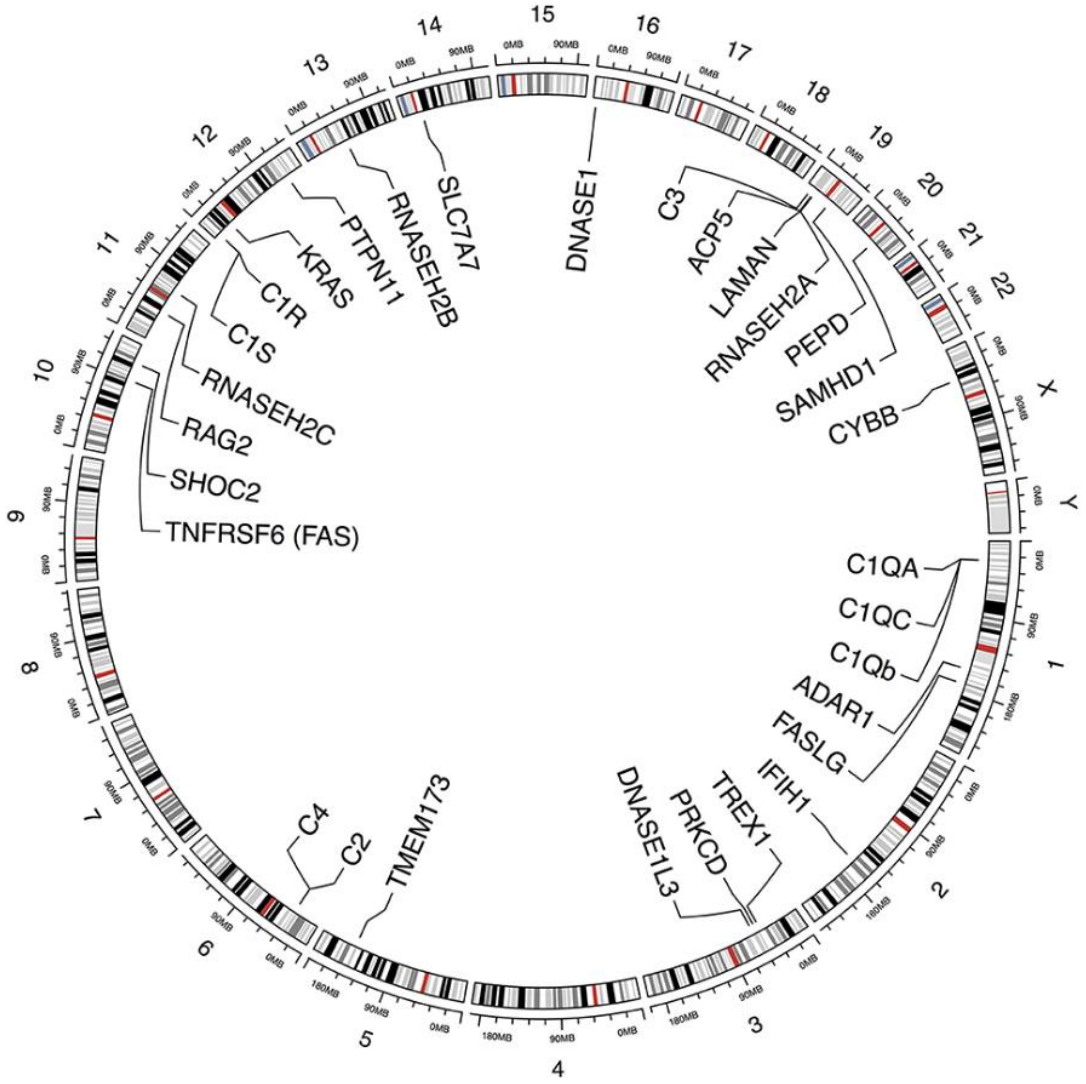
1. The pathogenesis of SLE is still unknown
2. SLE is a monogenic disease
3. SLE is a polygenic disease
4. SLE is an environmentally triggered disease
5. SLE is a multifactorial syndrome

Pathogenesis



Lech&Anders. The pathogenesis of lupus nephritis. J Am Soc Nephrol 2013

Pathogenesis



IFNopathies

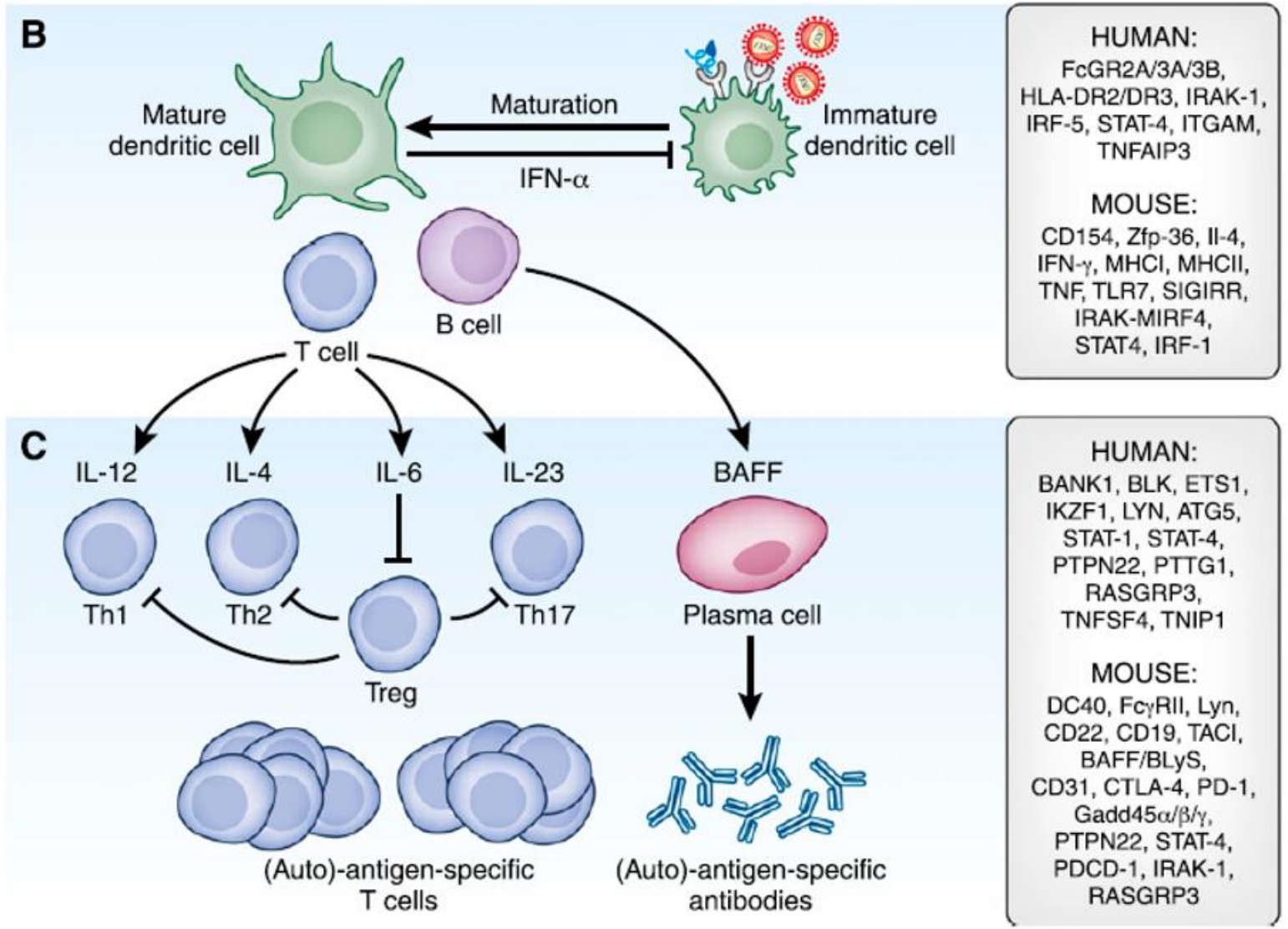
Complementopathies

DNAse/RNAse-deficiencies

Autoimmune LymphoProliferative Syndrome (ALPS), …

Alperin, *et al.* Frontiers Immunol 2018

Pathogenesis



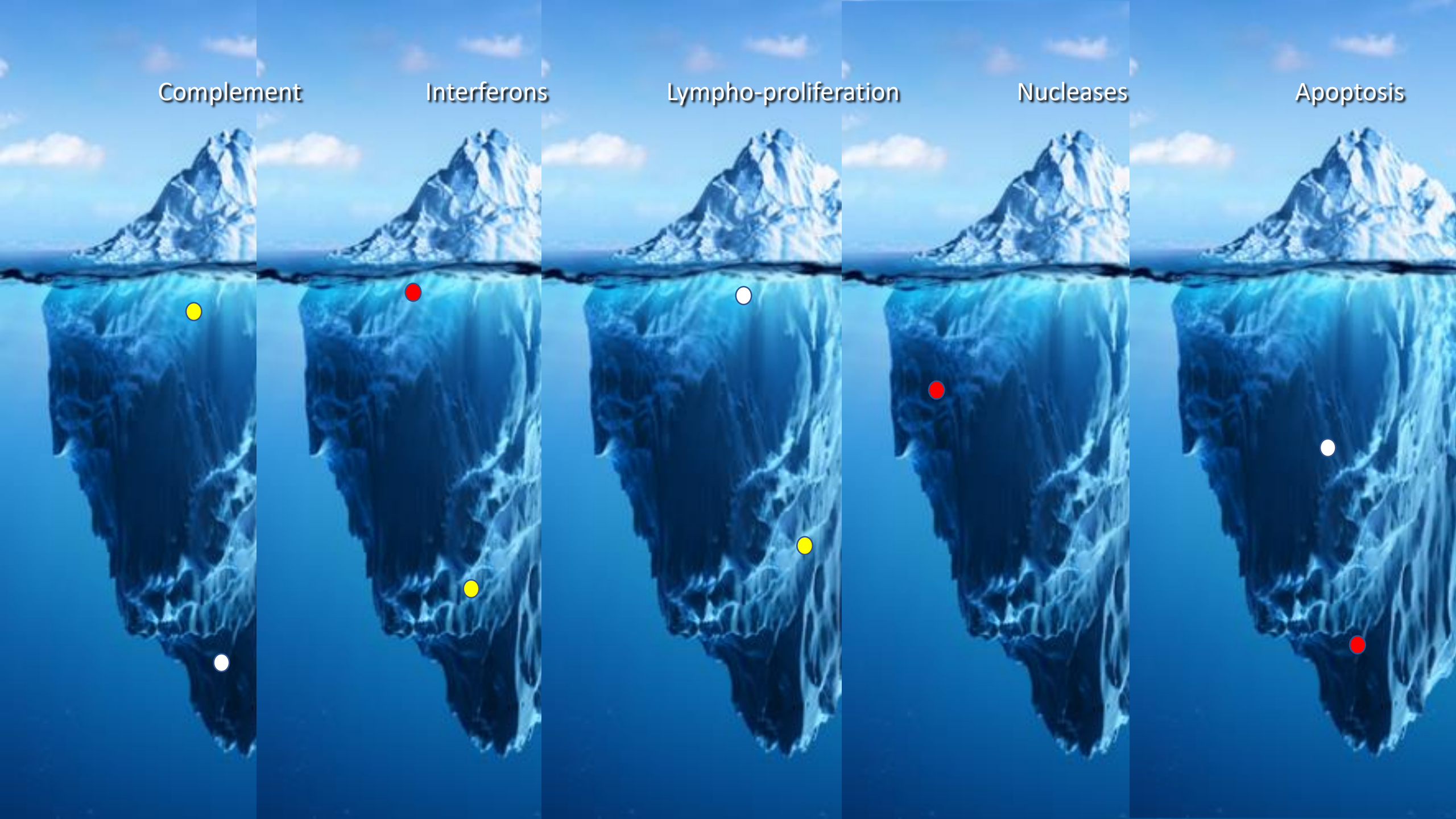
HUMAN:
FcGR2A/3A/3B, HLA-DR2/DR3, IRAK-1, IRF-5, STAT-4, ITGAM, TNFAIP3

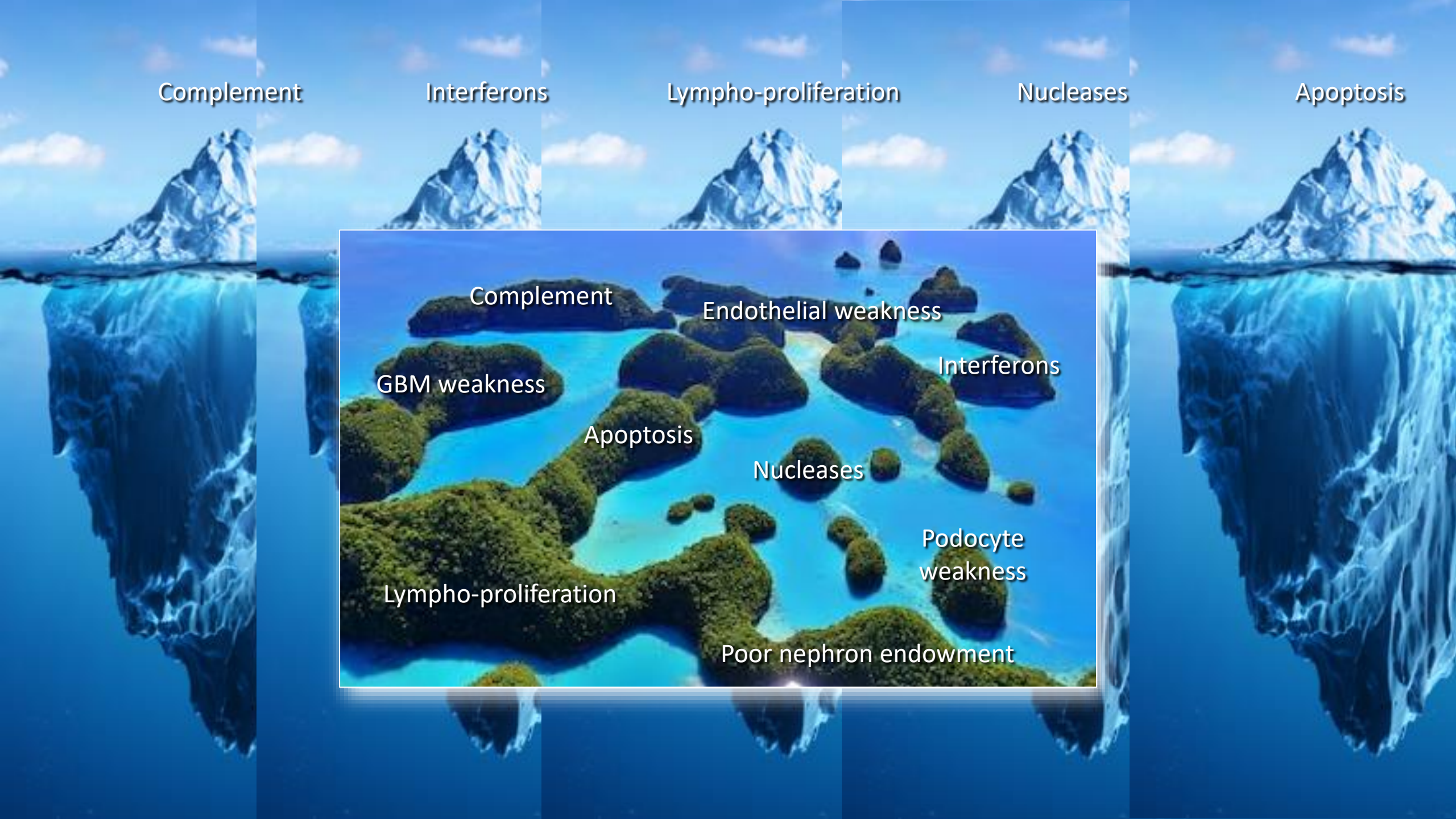
MOUSE:
CD154, Zfp-36, Il-4, IFN-γ, MHCI, MHCII, TNF, TLR7, SIGIRR, IRAK-MIRF4, STAT4, IRF-1

HUMAN:
BANK1, BLK, ETS1, IKZF1, LYN, ATG5, STAT-1, STAT-4, PTPN22, PTTG1, RASGRP3, TNFSF4, TNIP1

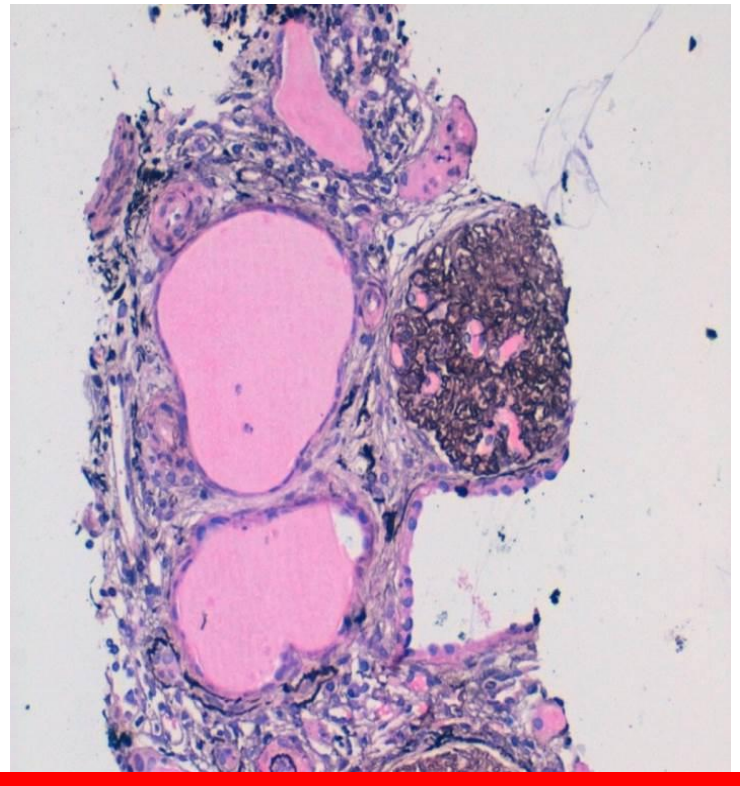
MOUSE:
DC40, FcγRII, Lyn, CD22, CD19, TACI, BAFF/BLyS, CD31, CTLA-4, PD-1, Gadd45α/β/γ, PTPN22, STAT-4, PDCD-1, IRAK-1, RASGRP3

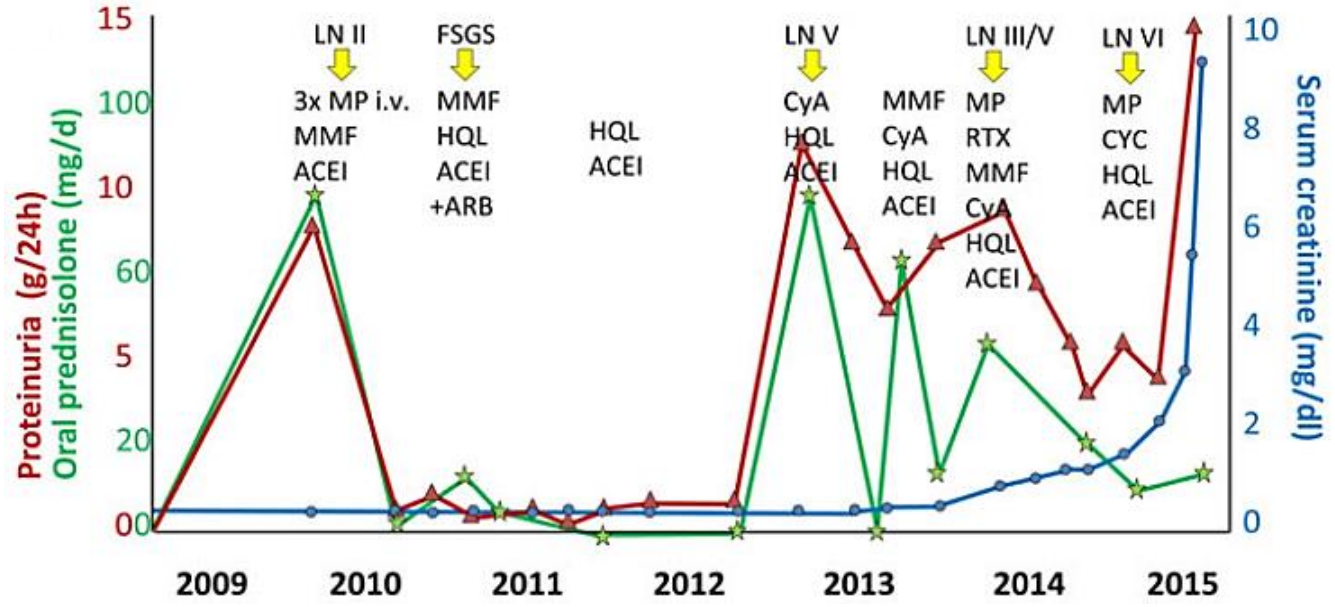
Lech&Anders. The pathogenesis of lupus nephritis. J Am Soc Nephrol 2013

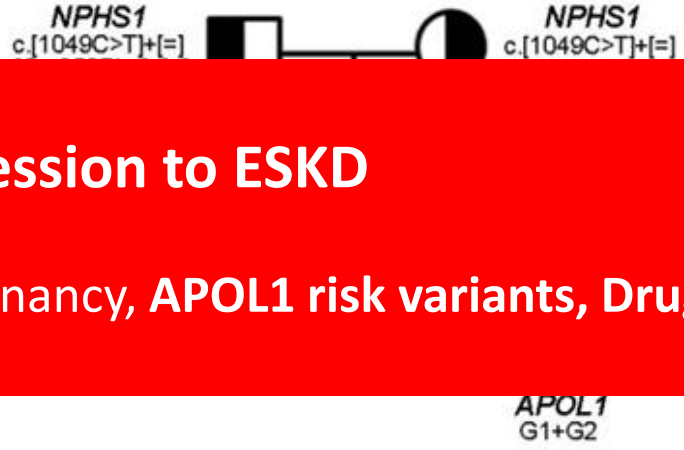

Complement
Interferons
Lympho-proliferation
Nucleases
Apoptosis


Complement
Interferons
Lympho-proliferation
Nucleases
Apoptosis
Complement
Endothelial weakness
Interferons
GBM weakness
Apoptosis
Nucleases
Podocyte weakness
Lympho-proliferation
Poor nephron endowment

Pathogenesis







CKD progression to ESKD

Partial-/no response, **obesity,** diabetes, pregnancy, **APOL1 risk variants, Drug non-adherance**

Romagnani, Anders, *et al.* NDT 2016

Outline

Pathogenesis

Diagnosis

Treatment goals and patient education

Treatment of first episode and how to assess treatment response

Long-term management

Diagnosis

2019 EULAR/ACR Classification criteria for SLE

ANA+ (1:80) plus >9 points

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis in at least two joints or tenderness in at least two joints, and at least 30 min of morning stiffness	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria >0.5g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG >40 GPL or anti-β2GP1 IgG >40 units or lupus anticoagulant	2
Complement proteins domain	
Low C3 or low C4	3
Low C3 and low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Smith antibody	6

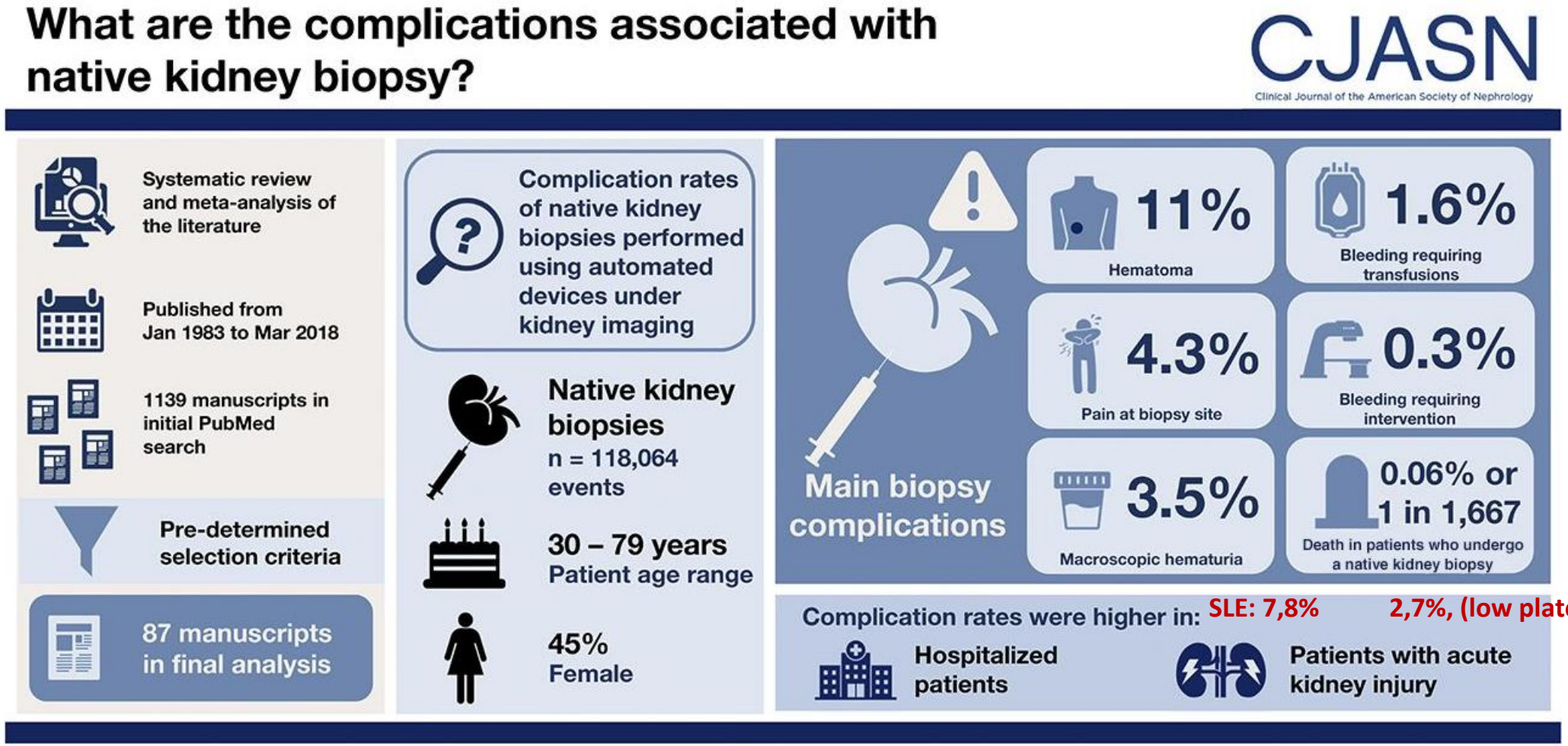
- Apply only if no other explanation
- May occur not simultaneously

- At least one clinical domain
- Per domain only highest score

Diagnosis

	Focal	Global
Activity low		
	Class I, II, III - low AI	+ podocytopathy (MCD), class VI
Activity high		
	Class III - high AI	Class V

Diagnosis



SLE: 7,8% 2,7%, (low platelets)

Chen, et al. Lupus 2012

Outline

Pathogenesis

Diagnosis

Treatment goals and patient education

Treatment of first episode and how to assess treatment response

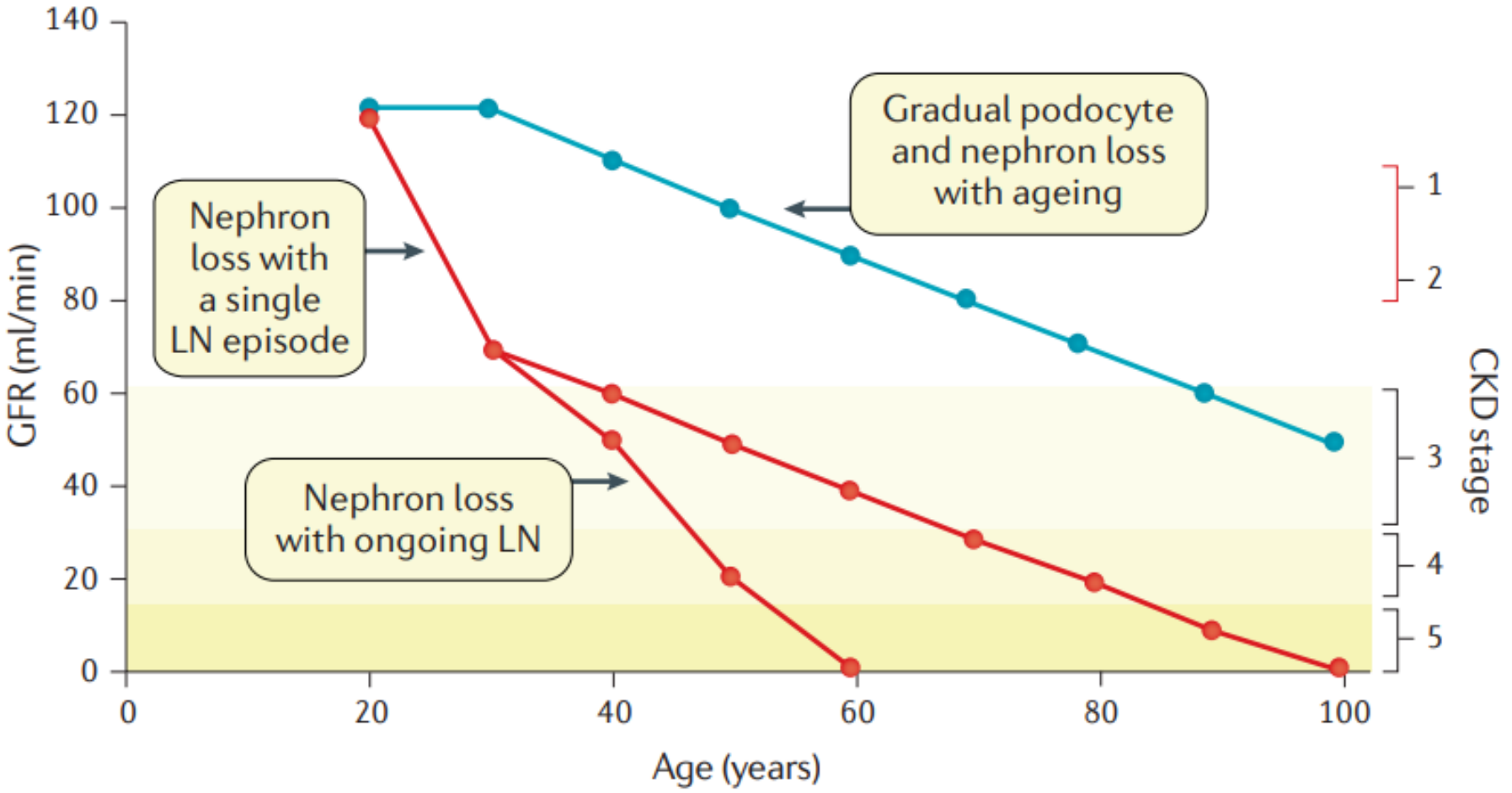
Long-term management

Question

Who should best treat a patient with lupus nephritis?

1. A nephrologist
2. A rheumatologist
3. An internist
4. A primary care physician
5. All of the above

Treatment goals and patient education



Anders, et al. Lupus nephritis. Nat Rev Dis Primers 2020; Jan 23.

Treatment goals and patient education

1. Mortality = Lifespan — Infections, CVD, BP
   - All pts with LN have CKD
   - CKD-AIDS with infections as first cause of mortality
   - CKD is the worst known CV risk factor (BP)
2. Organ failure = QOL — Kidney, Heart, Lungs, Bones
   - Kidney life span defined by nephron loss
   - First episode of LN = irreversible loss of 20-40% nephron = 20-40y kidney life span
   - Further SLE-related nephron loss must absolutely be avoided
3. Pregnancy outcomes — Mother, Child
   - Pregnancy is a challenge even for healthy kidneys
   - LN-related nephron loss diminishes renal reserve
   - CKD increases risk for fetal and maternal complications
4. Symptoms unrelated to organ failure and mortality = QOL — Skin, Joints, Fatigue

Pathogenesis (genetics, guilt, transmissibility), value of alternative medicine, normal life with lupus,
Family planning, vaccines, COVID19, drug adherance, sun exposure, tropical travels, social assistance, early retirement

Give patients a book about lupus to read.

Outline

Pathogenesis

Diagnosis

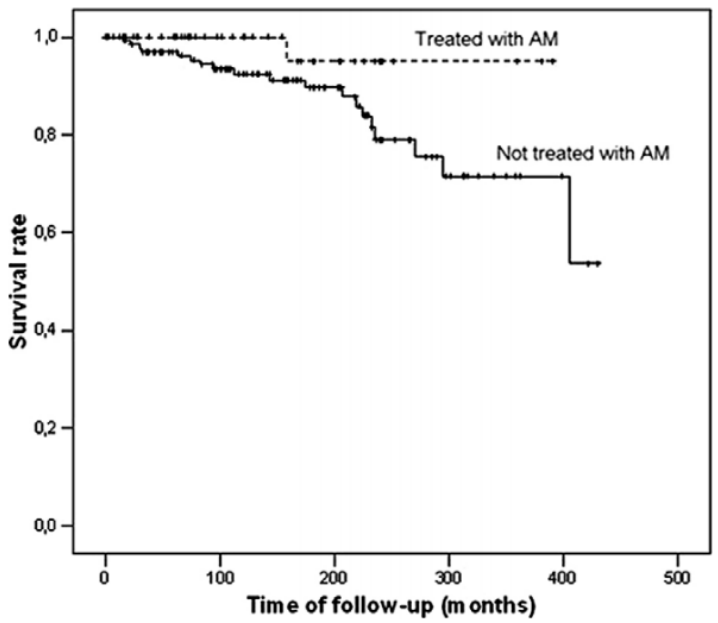
Treatment goals and patient education

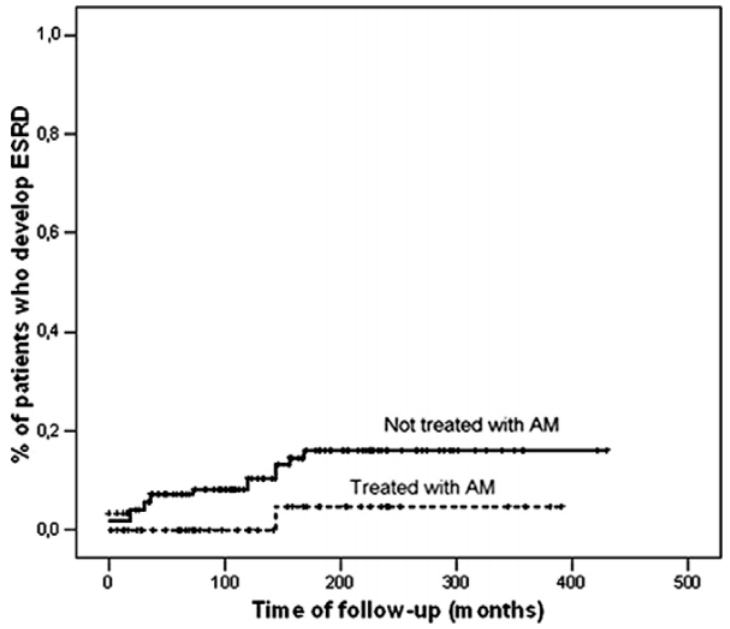
Treatment of first episode and how to assess treatment response

Long-term management

Treatment of first episode

HCQ: Fundament of SLE therapy also relevant for LN





Siso, et al. Lupus 2008

Other fundamentals:

Minimize sodium intake

Oral contraception no problem (APAS: minipill + second method)

Drug – App

Vaccinations (no life vaccines)

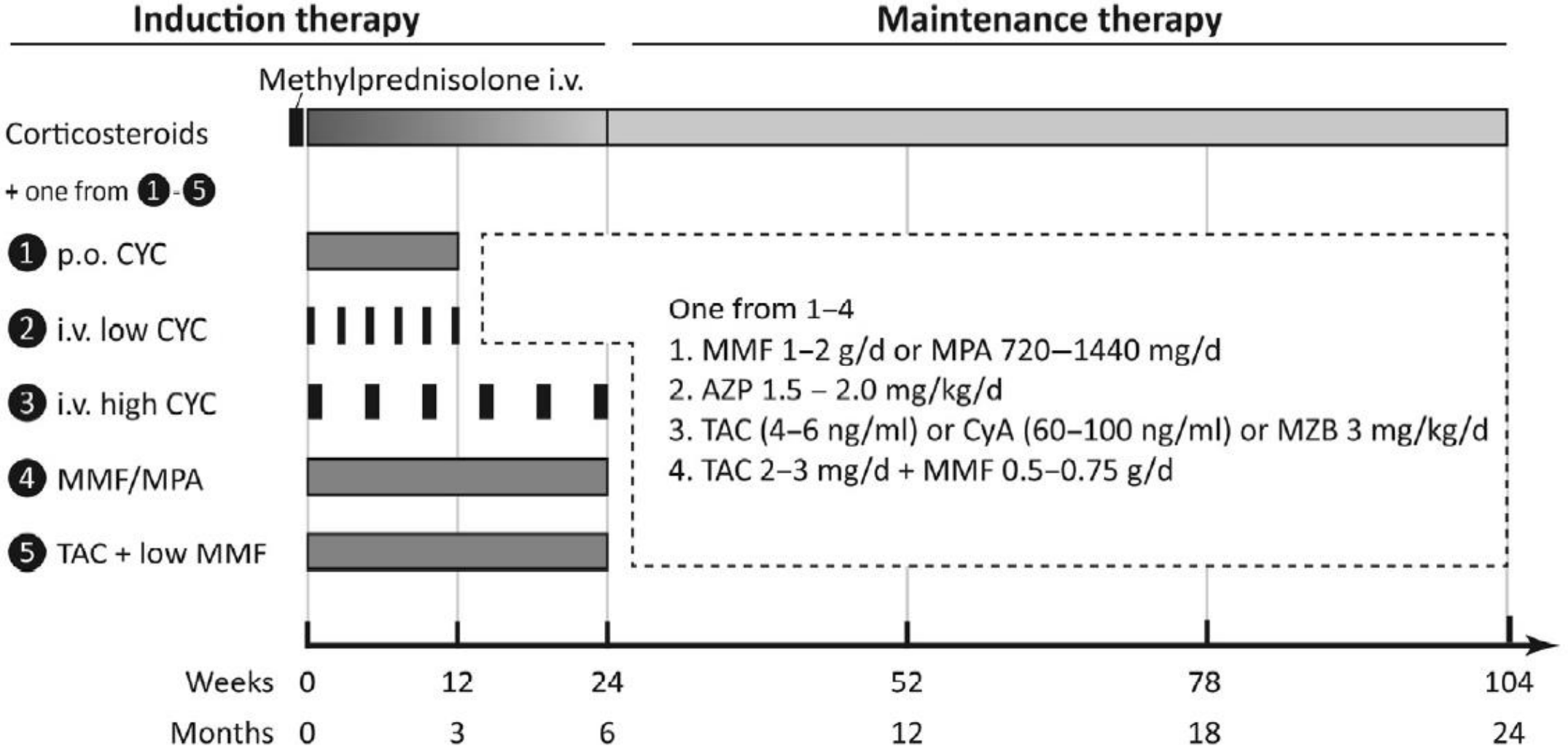
CV risk factor control

BMI <25

Sun protection

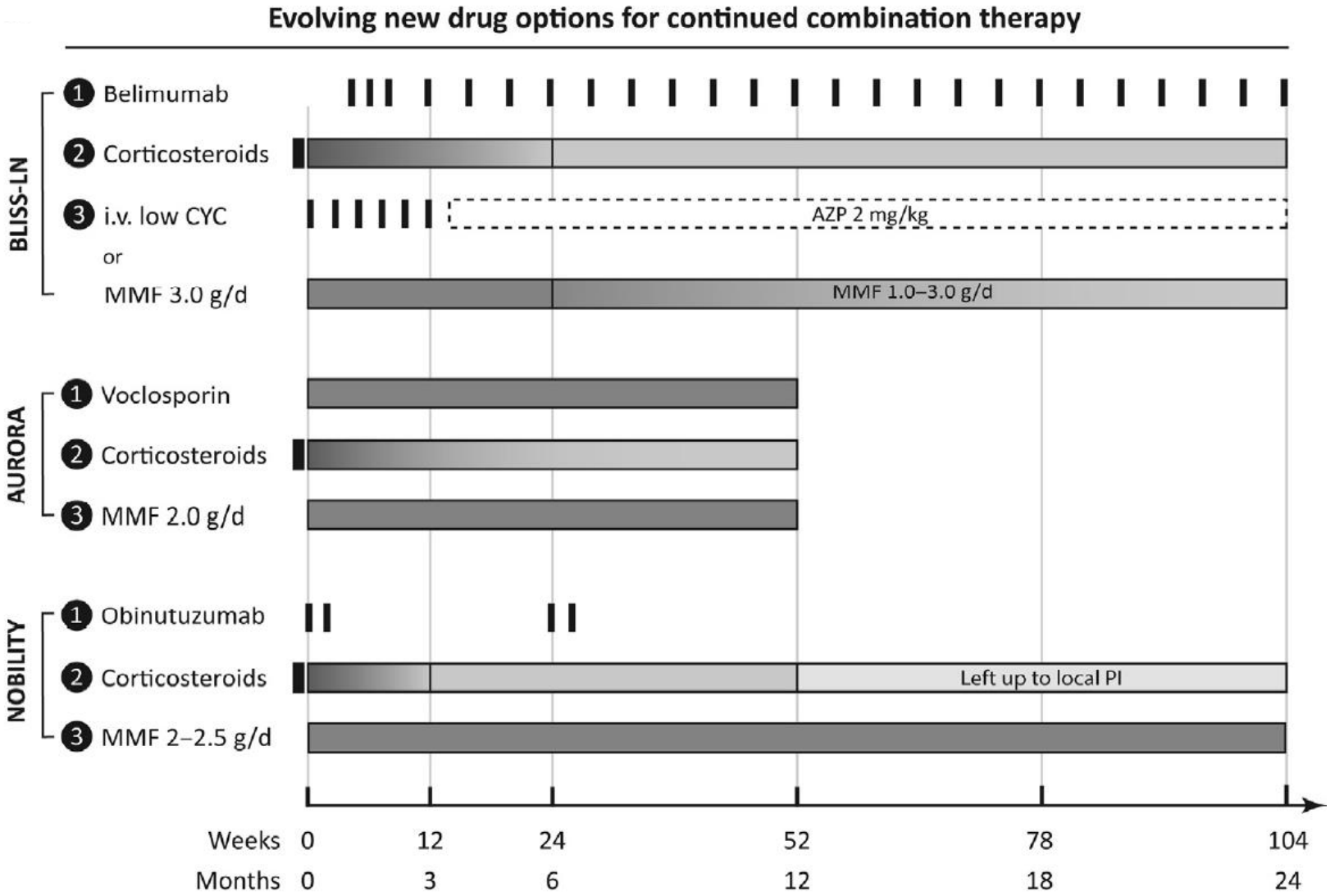
Vitamin D, calcium, if lactovegan

Treatment of first episode



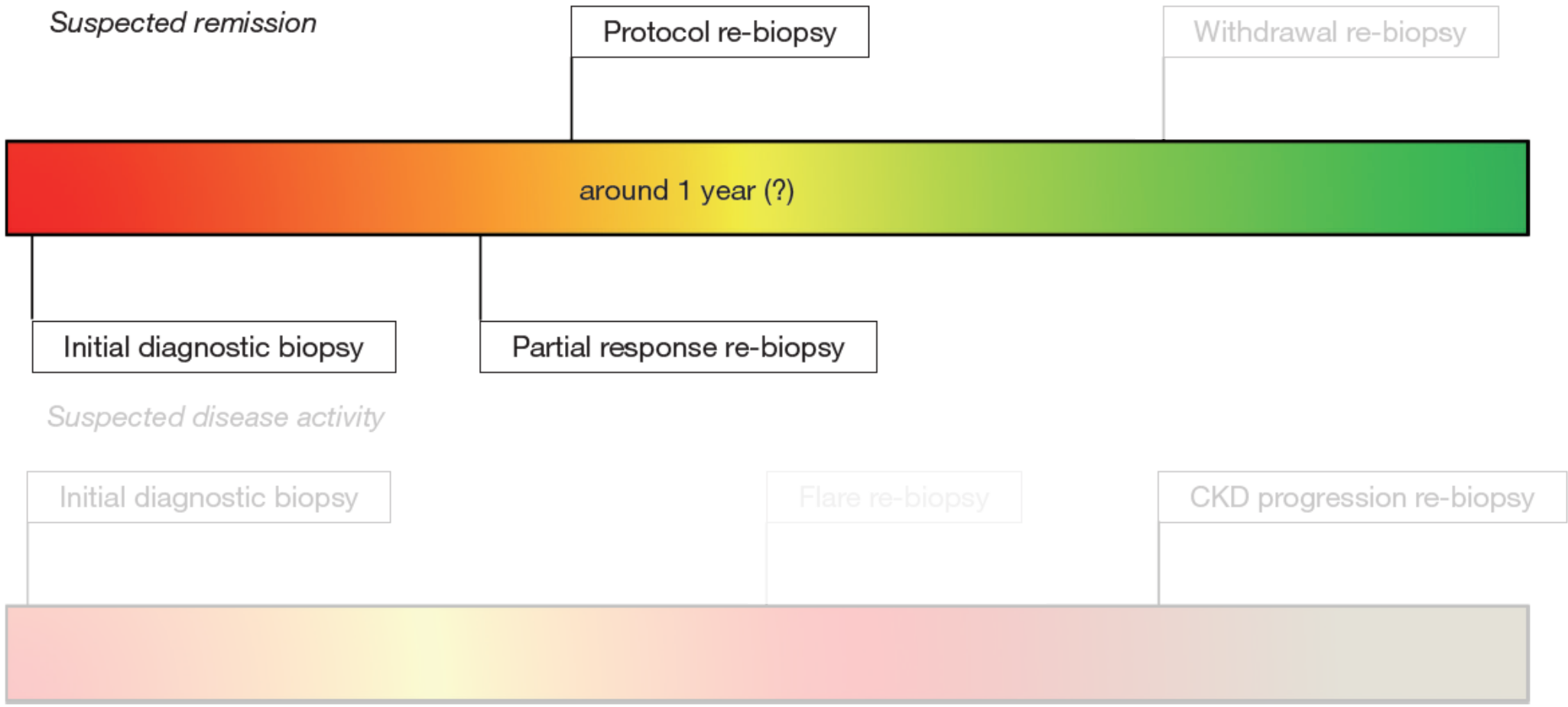
Anders, et al. Kidney Int 2021

Treatment of first episode



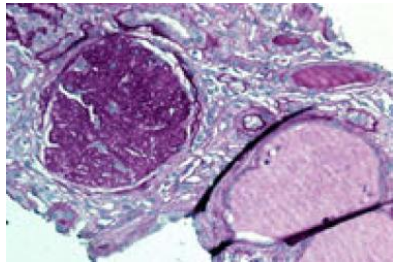
Anders, et al. Kidney Int 2021

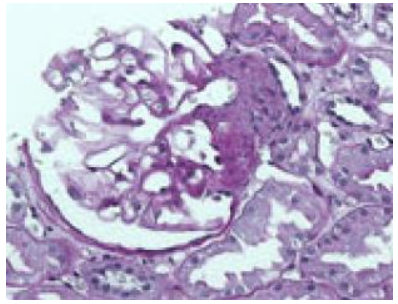
How to assess treatment response

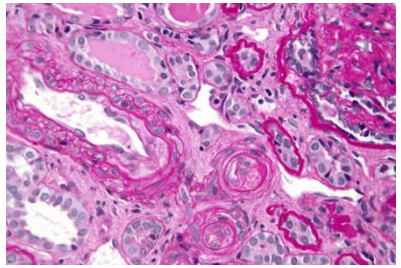


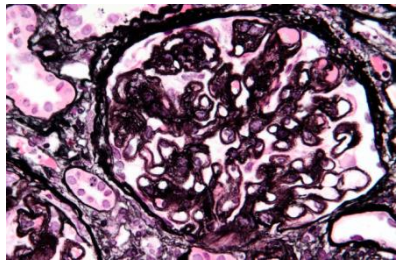
Anders HJ. Ann Transl Med. 2018

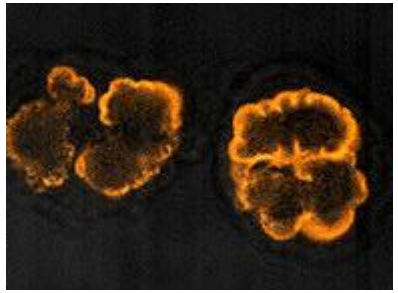
How to assess treatment response







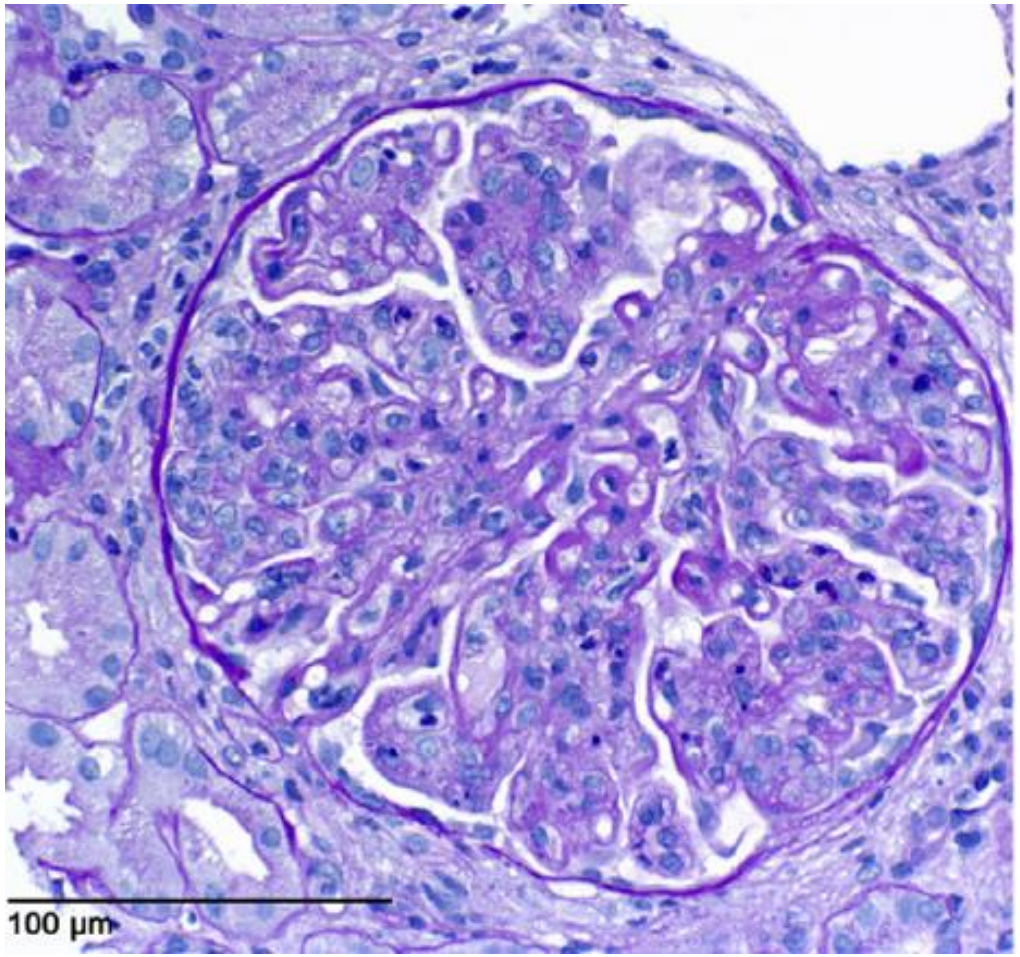


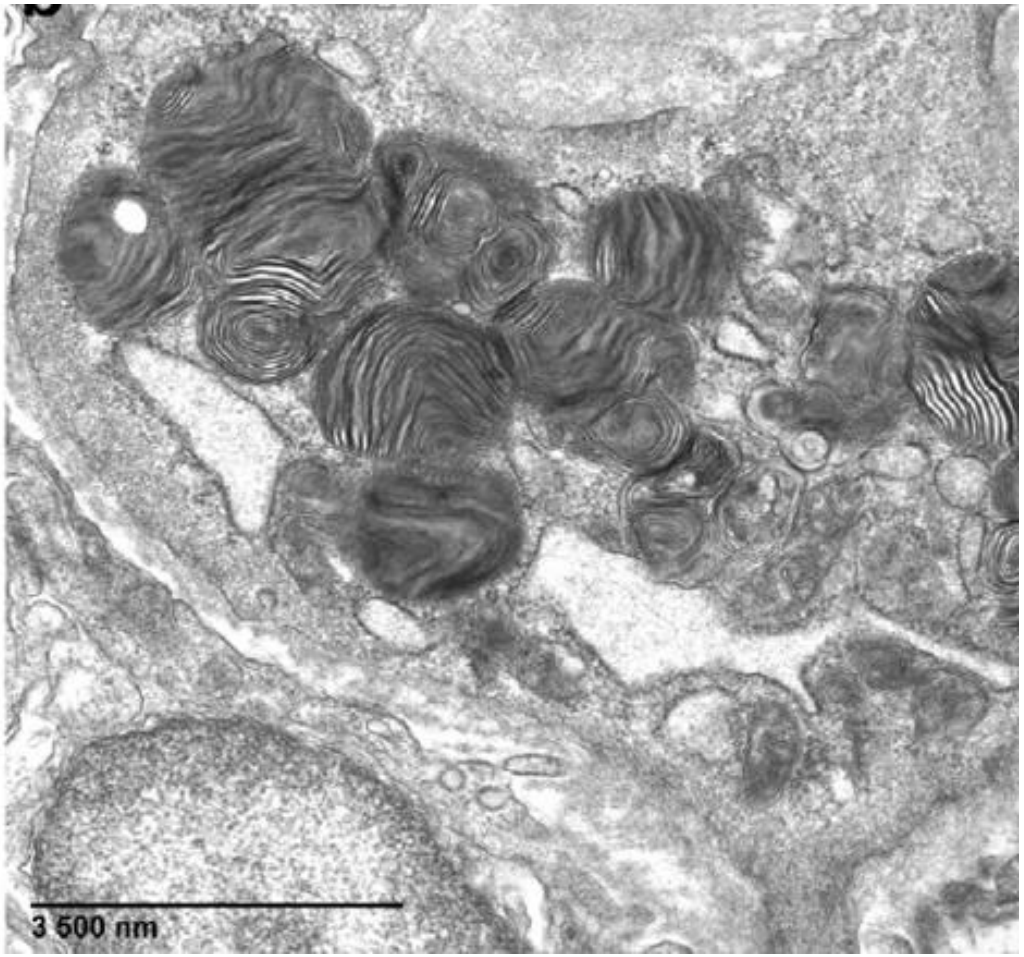


- Homozygous nephrin mutation = unrelated podocytopathy
- APOL1 G1/G2 = APOL1 podocytopathy
- C3 glomerulopathy = genetic or sec. acquired?
- C3 TMA = genetic or sec. acquired?
- incident ANCA vasculitis = sec. acquired?

How to assess treatment response

HCQ-induced podocytopathy but also true Fabry disease as comorbidity described

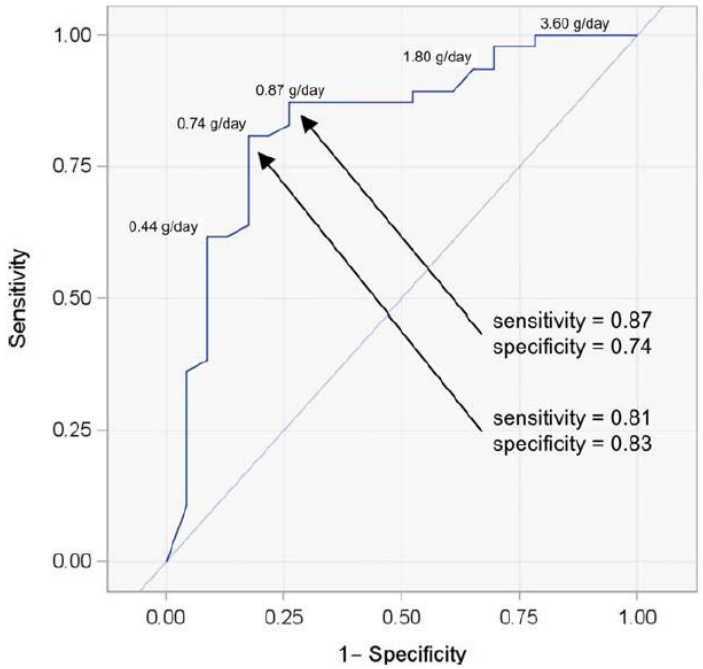




Kidney International (2017) **92,** 271–272

How to assess treatment response

Clinical response



Dall`Era, et al. Arthritis&Rheum 2015

Immunopathology response

How much SLE activity persists?

How much irreversible damage occured (subclinical CKD)?

Signs of remnant nephron hyperfiltration (Glomerulomegaly, podocytopathy)

Evidence of renal comorbidity?
Drug toxicity?

Gain for management

How much immunosuppression?

Kidney prognosis, risk stratification,

Maximize RAS inhibition (SGLT2i?)

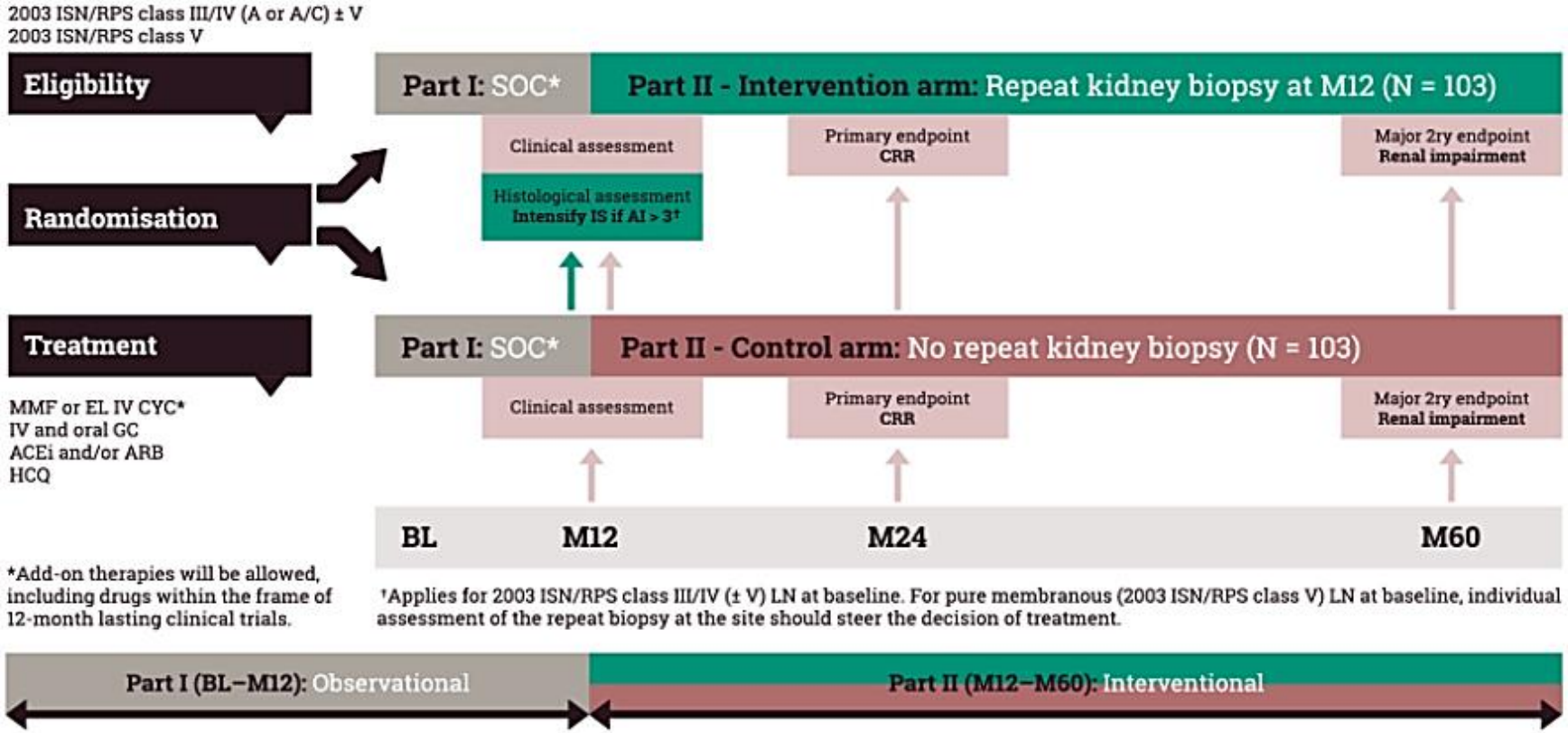
Specific interventions

How to assess treatment response

Lupus Nephritis Trials Network
www.lupusnephritis.org

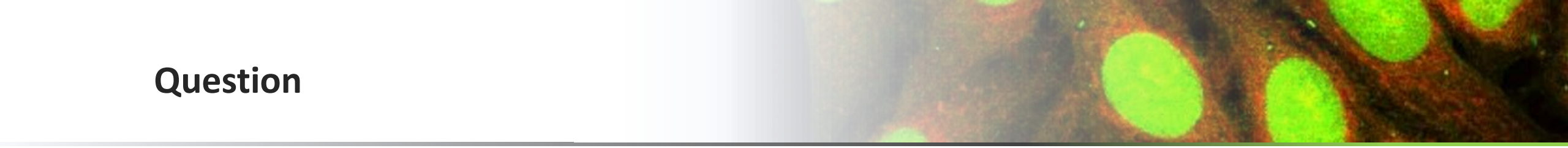
ReBioLup

Per-protocol repeat kidney biopsy in incident cases of lupus nephritis



http://rebiolup.com/

Question



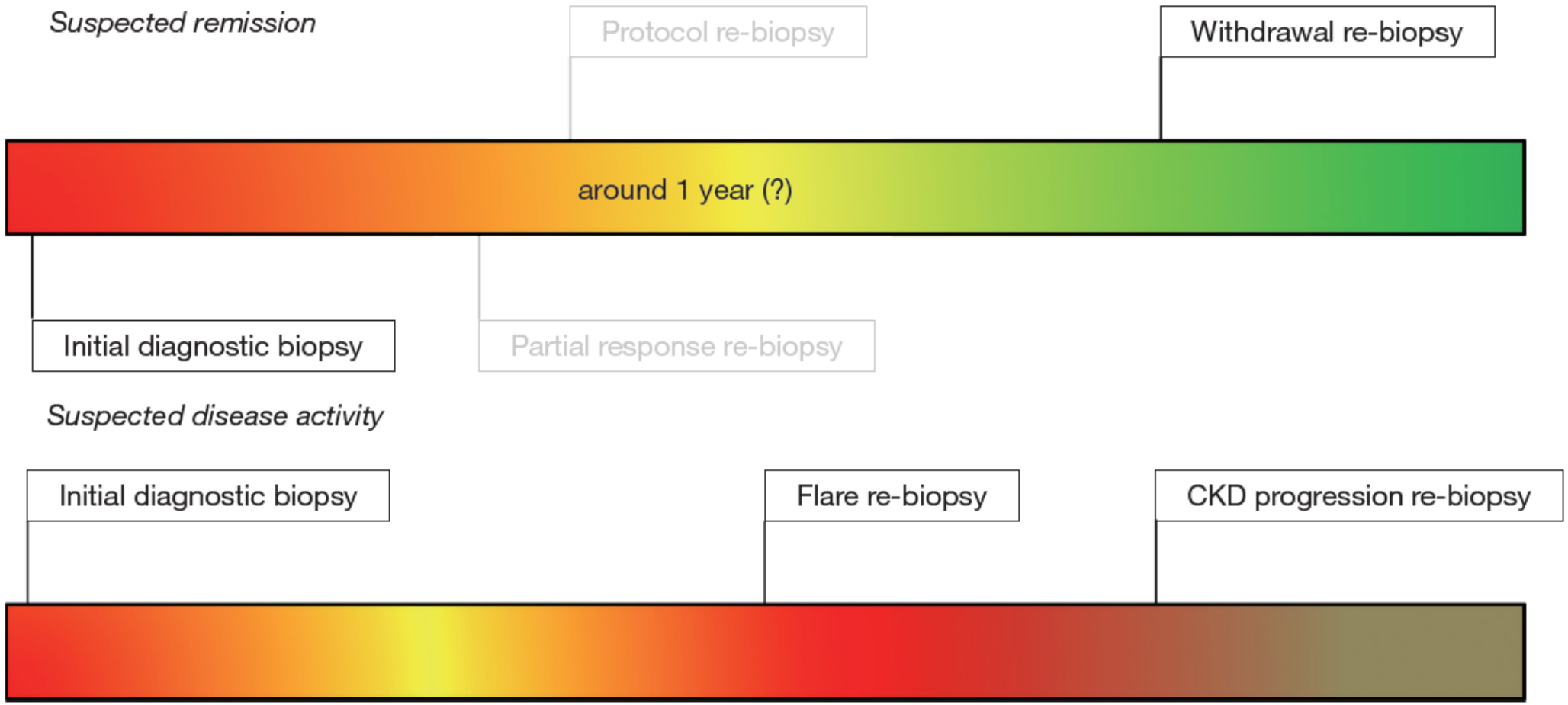
- Pathogenesis
- Diagnosis
- Treatment goals and patient education
- Treatment of first episode and how to assess treatment response
- Long-term management

Outline

For how many years immunosuppressants are needed after the first LN episode?

1. 1 year
2. 3 years
3. 5 years
4. Life-long
5. Depends from whether you and pt are more afraid of the SLE or of the drugs.

Repeat biopsy?



Anders HJ. Ann Transl Med. 2018

Long-term management - nephritic flares

Distribution of the ISN/RPS classes at the first and repeat renal biopsies in 686 well-documented published cases of patients with repeat biopsy performed only on clinical indications.

	Reference biopsy					
Repeat biopsy	**I**	**II**	**III**	**IV**	**V**	**VI**
I	2	3	0	1	0	0
II	1	15	8	40	2	0
III	0	13	26	25	4	0
IV	0	29	34	158	13	0
V	1	11	9	37	62	1
VI	0	1	1	15	1	2
Mixed II+V	0	0	0	2	1	0
Mixed III+V	0	6	7	21	19	0
Mixed IV+V	0	3	2	11	9	1

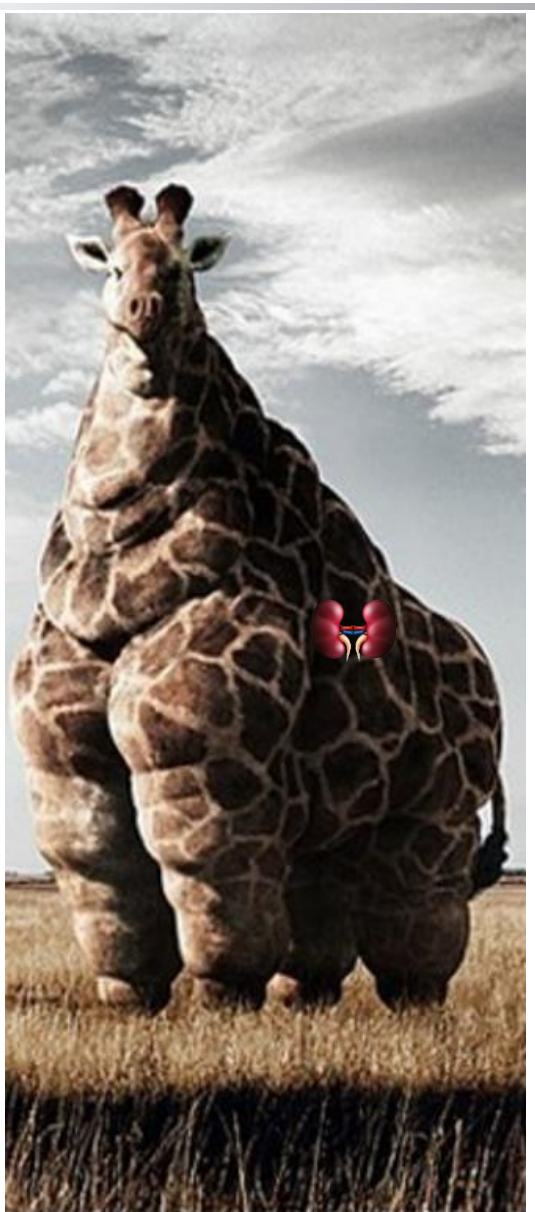
9,2%

11,4%

79,0%

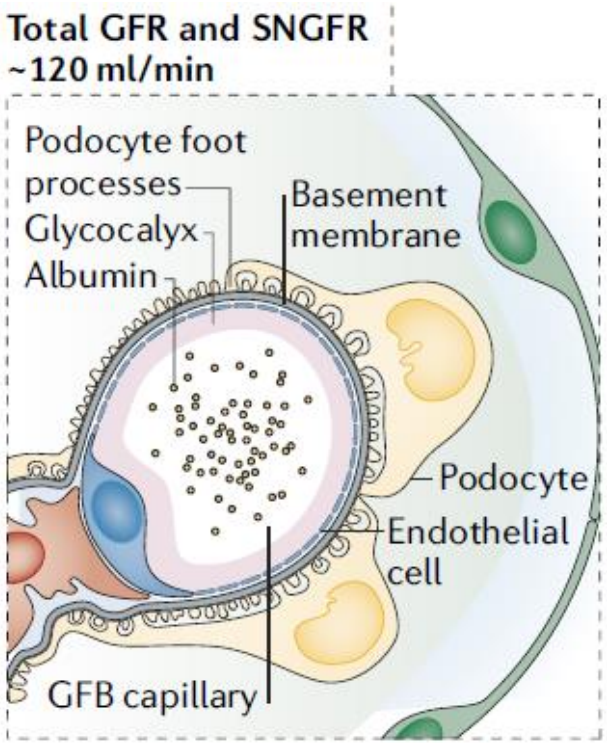
Narvaez, et al. Medicine 2017

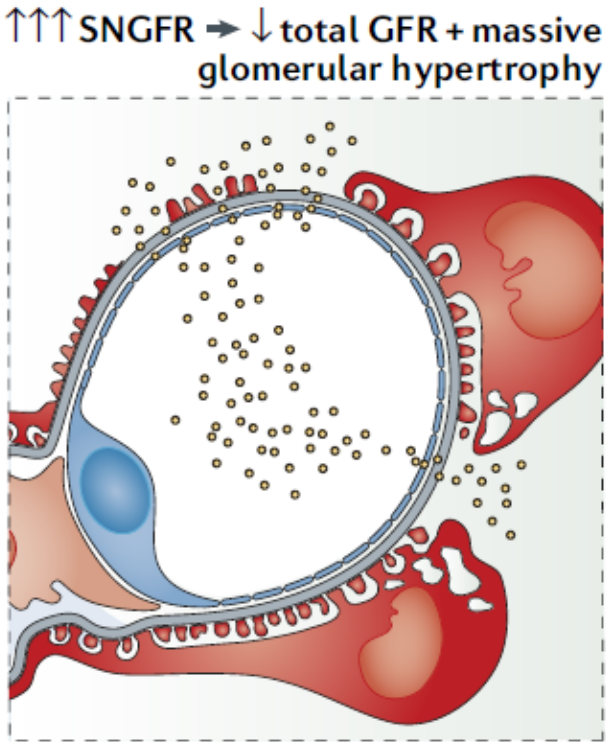
Long-term management – proteinuric flares



Obesity and/or diabetes affect the kidney like a permanent pregnancy!

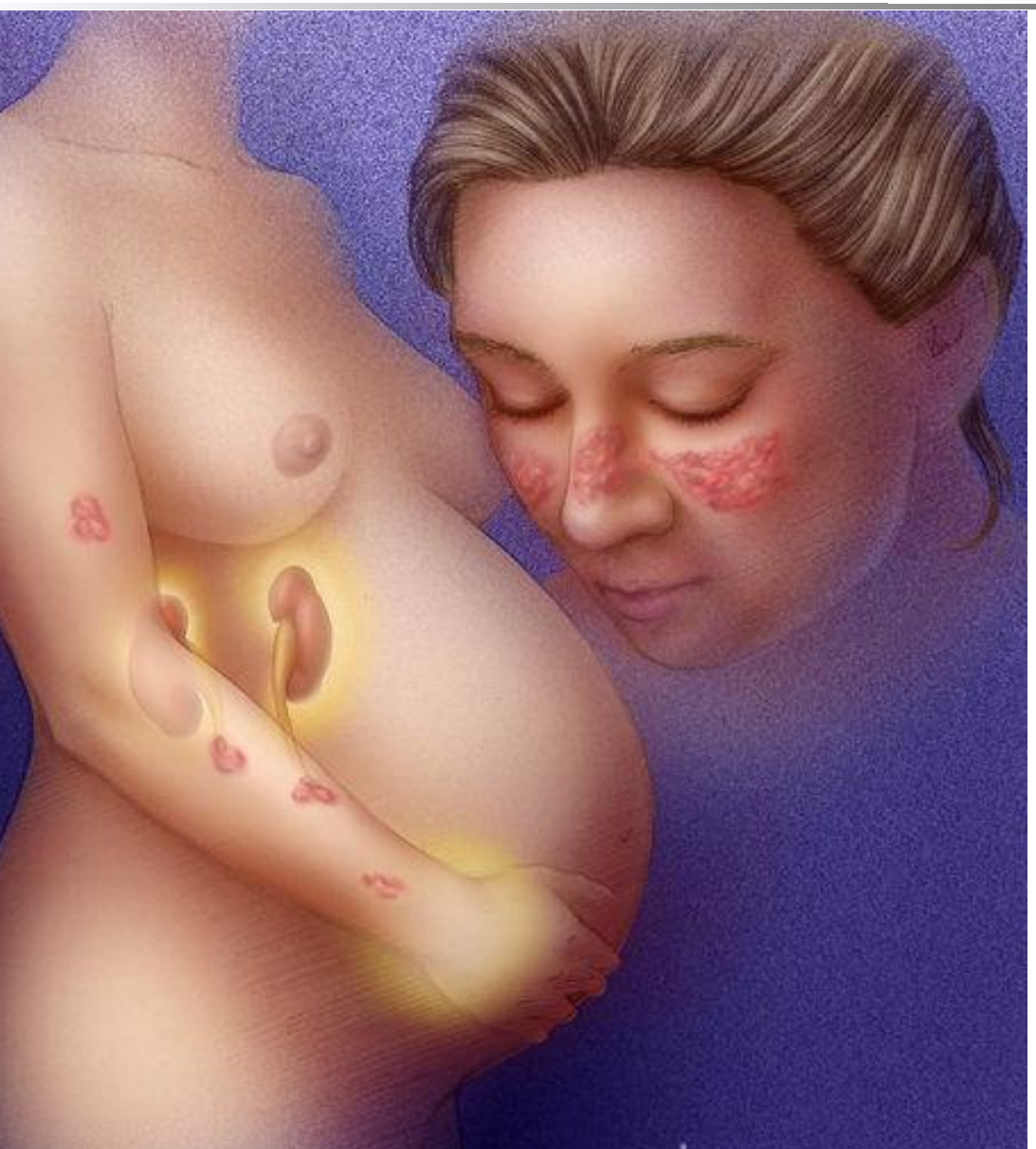
= persistent hemodynamic overload to the remnant nephrons of a LN kidney
= single nephron hyperfiltration = podocyte stress and loss
= proteinuria, sec. FSGS, CKD progression

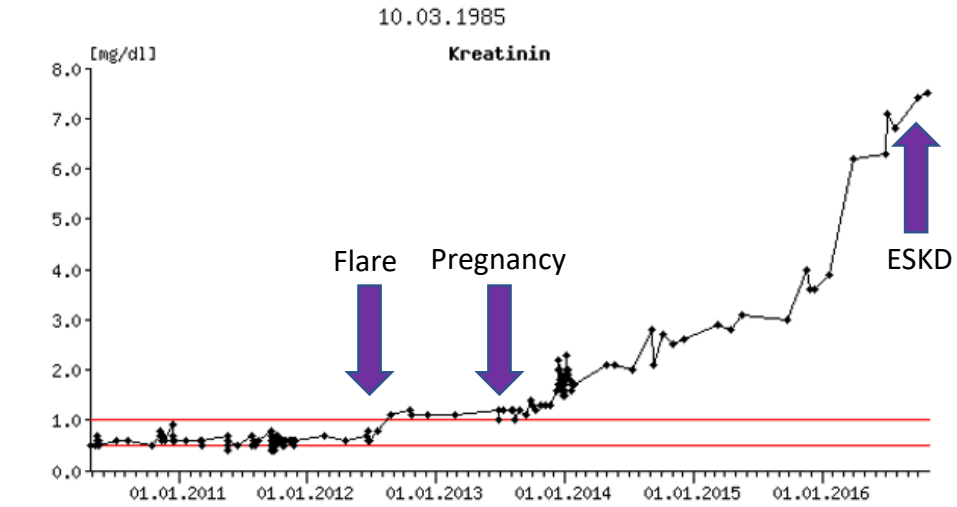


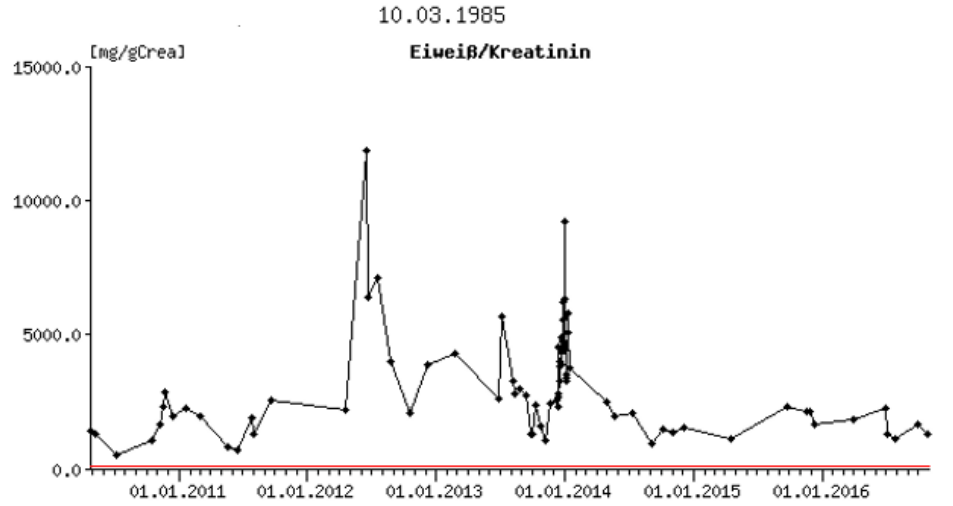


Anders HJ, et al. Nat Rev Nephrol 2018

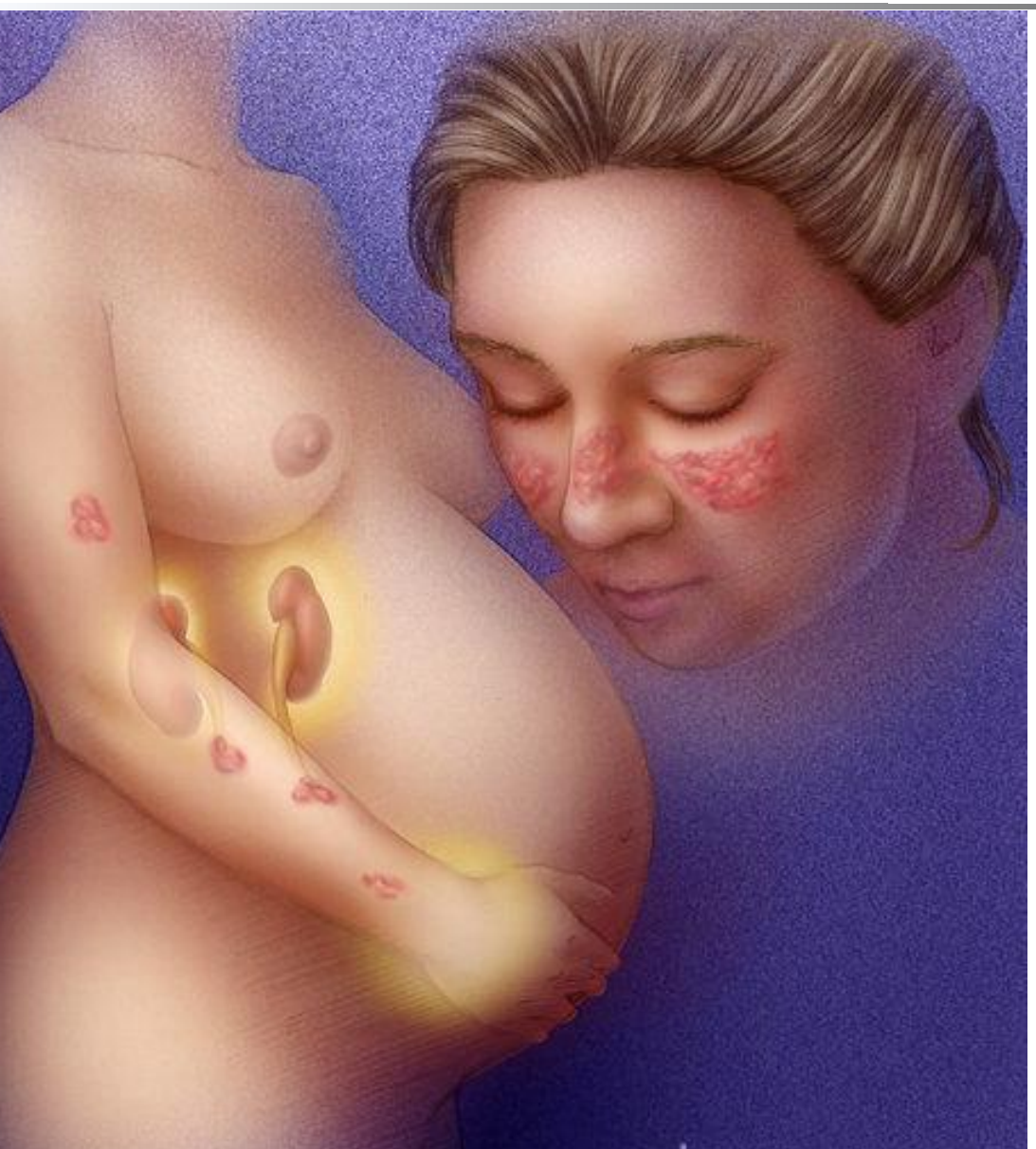
Long-term management – pregnancy







Long-term management – pregnancy



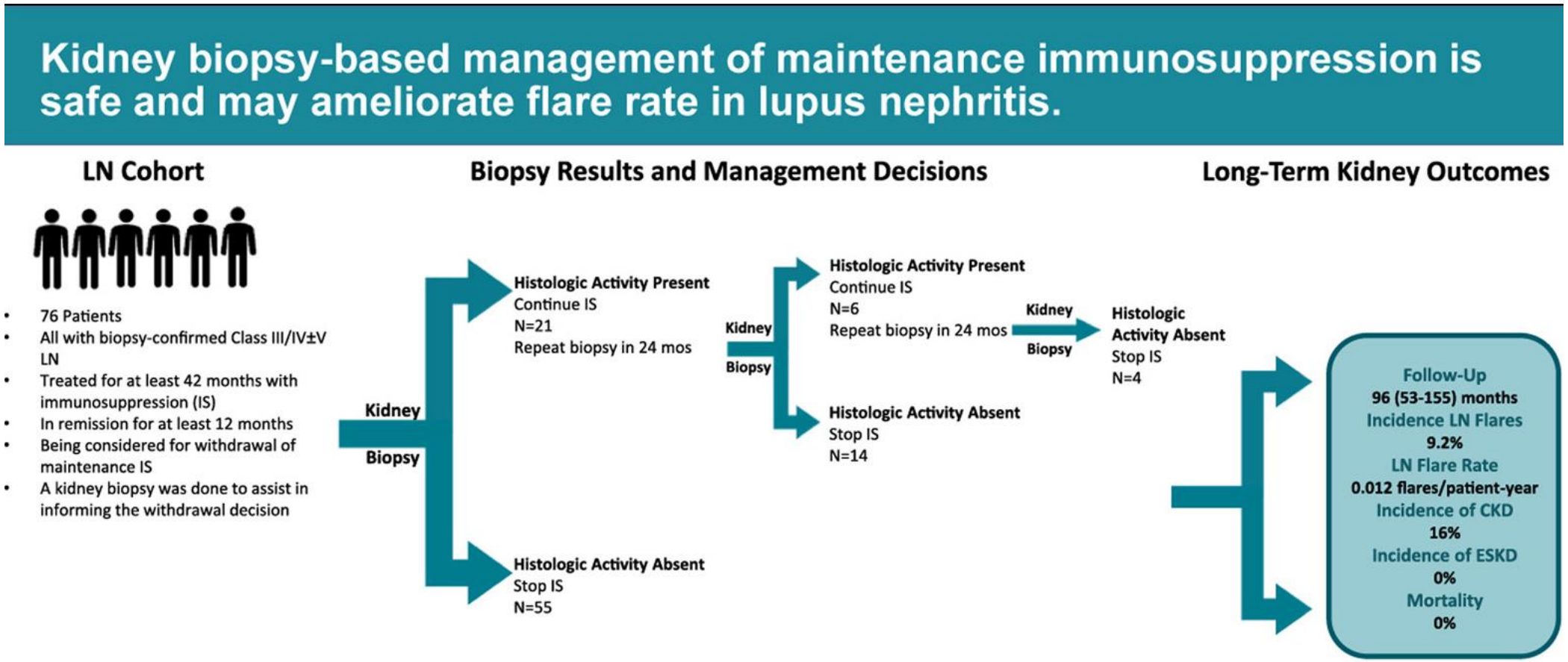
Planned pregnancy:
- 1y CR or PR with RASi: check for proteinuria without RASi
  Cave UPCR >1, any elevated SCr, counsel about kidney life span
  Consider biopsy beforehand
- Test for SS(A) and APA to identify specific SLE-related risks
  keep HCQ, switch to AZA
- Identify SLE experienced gyno, advise for hospital delivery

Unplanned pregnancy: review drug list, counsel about teratogenicity

- APA: aspirine and heparin
- New HTN:
  - new SLE symptoms, low C, unchanged UA at trimester
    = SLE flare
  - no SLE symptoms, unchanged C, increased UA, 3rd trim.
    = preeclampsia

Long-term management – stopping treatment

Kidney biopsy-based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis.



CONCLUSION:

Kidney biopsies done during maintenance therapy may help in deciding whether to continue or withdraw immunosuppression

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Malvar et al, 2018

Summary

- Pathogenesis
- Diagnosis
- Treatment goals and patient education
- Treatment of first episode and how to assess treatment response
- Long-term management