Leiden University
Medical Center

Disease modification in Lupus Nephritis

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LEIDEN UNIVERSITY MEDICAL CENTER (NETHERLANDS)

Center of Expertise for
Lupus- Vasculitis- and Complement-mediated
Systemic autoimmune diseases

Disclosures

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Learning objectives

1. Discuss the novel concept of disease modification for lupus nephritis

    - modify the natural disease course

    - target the pathophysiological immune dysregulation

2. Translate disease modification to combination therapy for lupus nephritis

3. Define the ‘Future Kidney Health’ for lupus nephritis

The Spectrum of Remission in Lupus Nephritis

Clinical Remission

Absence of symptoms and signs that impact patient experience

Normalization of disease activity parameters

Renal Remission

Normalization of urinary findings (proteinuria <0.5-0.75g/24h)

Stable or improved GFR

Inactive urinary sediment

Histopathological Remission

Resolution of active inflammatory lesions on biopsy

Decreased or stable chronicity indices

Immunological Remission

Normalization of serological markers

Anti-dsDNA antibodies, complement levels

Absence of immunological activity

The paradox of ‘True Remission’ in a Chronic Autoimmune Disease

Most strictly: **True Remission Approaches Cure**

i.e. a complete absence of disease with permanent restoration of normal function

By definition: **Chronicity Makes Cure Fundamentally Unattainable**

as is the case for autoimmune conditions like lupus nephritis

Thus: **To pursue a destination of True Remission, one must defy the framework of chronicity itself**

→Chronicity requires to modify disease course = ‘Disease Modification’

‘Disease Modification’ is Not New

Rheumatological disorders	
General rheumatological disorders	• “Disease modification is the improvement of symptoms (disease process) in conjunction with the change of the disease course (disease outcome)”[1]
Rheumatoid arthritis	• “A DMARD is defined as a medicine that interferes with signs and symptoms of rheumatoid arthritis, improves physical function, and inhibits progression of joint damage”[2] • **EULAR:** “The concept of ‘disease modification’ comprises a combination of relief of signs and symptoms; improvement or normalization of physical function, quality of life and social and work capacity; and most characteristically the inhibition of occurrence of progression of structural damage to cartilage and bone”[3] • **ACR:** “Agents that apparently alter the course and progression of rheumatoid arthritis, as opposed to more rapidly acting substances that suppress inflammation and decrease pain, but do not prevent cartilage or bone erosion or progressive disability”[4]
Systemic sclerosis	• “Ideal DMT should halt the progression of the disease and hopefully induce remission, and preferably also reverse some of the major organ complications… It is reasonable to expect a DMT to stabilize organ function without any further worsening of other domains”[5]

van Vollenhoven R, et al. *Lupus Sci Med.* 2022;9(1)

Disease Modification changed the clinical practice on Rheumatoid Arthritis

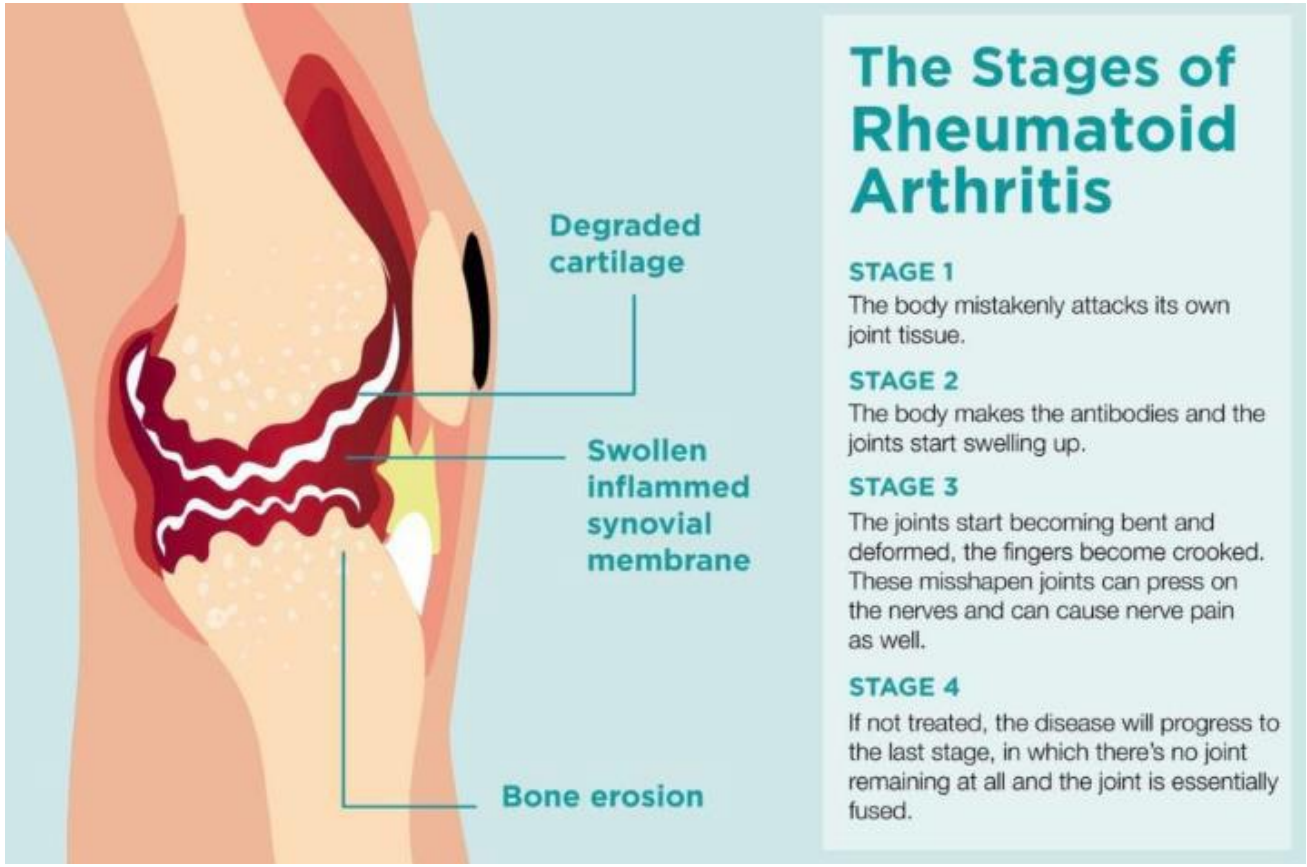
Cortico-steroids

Non-Steroidal Anti-Inflammatory Drugs

Disease Modifying Anti-Rheumatic Drugs

Biological DMARDs

Targeted synthetic DMARDs



Disease Modification is new to Nephrology

Neurodegenerative disorders

- General neurodegenerative disorders
- Alzheimer's disease
- Epilepsy
- Multiple sclerosis
- Parkinson's disease

Respiratory diseases

- COPD
- Emphysema

Nephrology ???

Disease modification is a sustained improvement in disease state following therapeutic intervention that persists when therapy is discontinued

van Vollenhoven R, et al. *Lupus Sci Med.* 2022;9(1)

Disease modification is also new for LN

EULAR Recommendations for SLE with Kidney Involvement (2025)

Diagnosis/Targets

- **Kidney biopsy**

  Indispensable for diagnosis; repeat in case of uncertainty regarding response to treatment

- **Target - Prevention of**

  - Chronic kidney disease
  - Flares

- **Milestones**

  - **Kidney function:** Preservation or improvement by 3 months
  - **Proteinuria:**
    * Reduction by 25% at 3 mo
    * Reduction by 50% by 6 mo
    * UPCR < 700 mg/g by 12 mo

Immune treatment

- **Early combination therapy**

  HCQ and glucocorticoids **with** immunosuppressive **and** CNI **or** biologic

- **Glucocorticoids**

  - Start with pulses
  - Continue with 0.3-0.7 mg/kg/day prednisone
  - Taper to ≤ 5 mg/day by 4-6 months and withdraw, when possible

- **Immunosuppressives**

  - MPAA, low-dose IV-CY

- **CNI**

  - Voclosporin or TAC

- **Biologics**

  Belimumab, Obinutuzumab

Non-immune treatment

- **Kidney protection**

  - Low salt (less than 5 g/day)
  - Control blood pressure (RAAS blockade 1st choice)
  - SGLT2-inhibitors (in stable disease, if residual proteinuria after 12 mo)

- **Dyslipidaemia**

- **Vaccinations**

  Influenza, COVID-19, HZV, S. pneumoniae

- **Bone health**

Severe or Refractory

- **RPGN**

  - Consider high-dose IV-CY plus pulse IV-MP

- **Refractory**

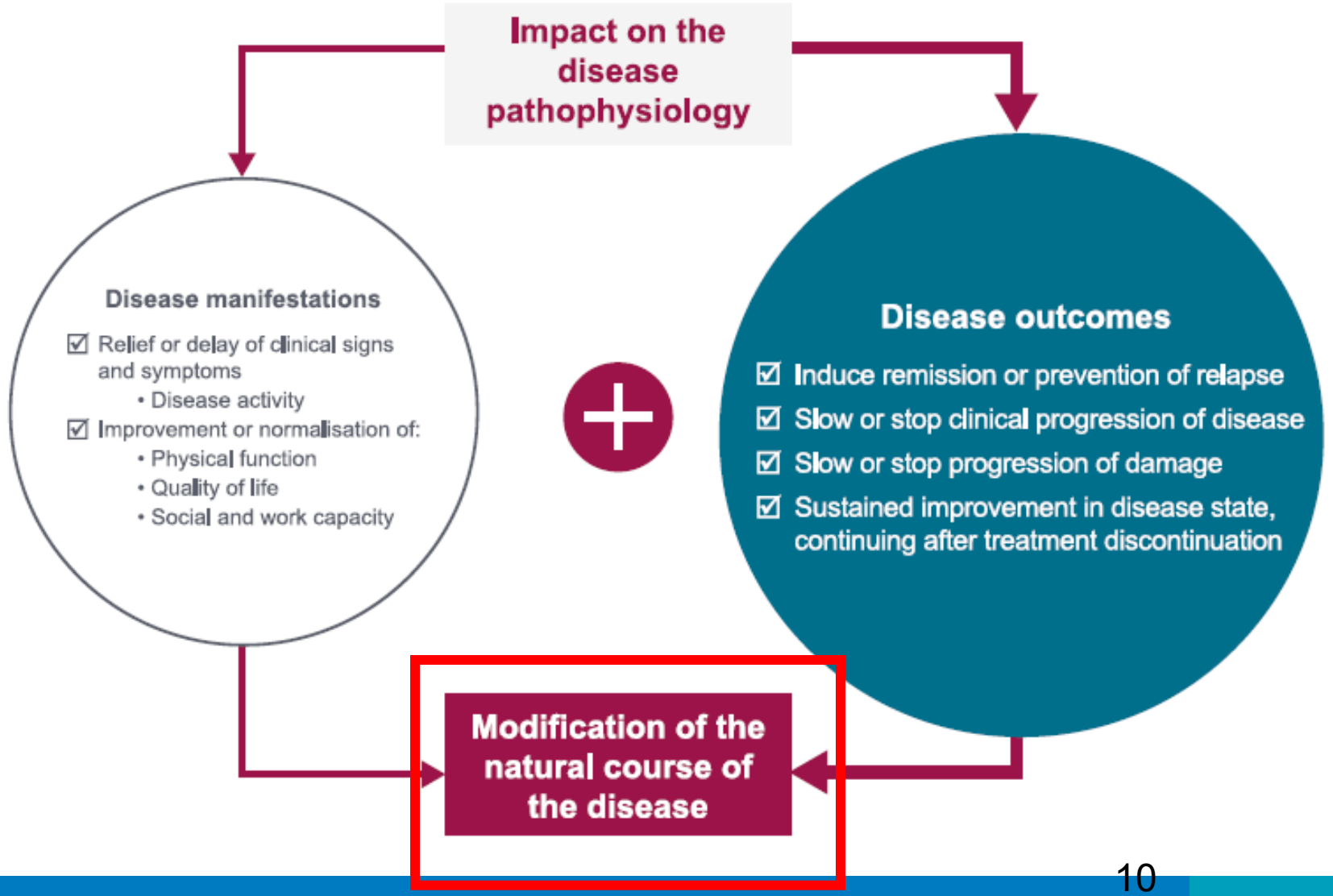
  - Assess patient adherence first
  - Combination of IV-CY with B cell depletion
  - Addition of a CNI if heavy proteinuria
  - Experimental therapies in the context of clinical trials

- **Thrombotic microangiopathy**

  - Plasma exchange
  - Complement inhibitors
  - Anti-vWf (caplacizumab)

Fanouriakis A, et al. Ann Rheum Dis. 2025:S0003-4967(25)04412-7.

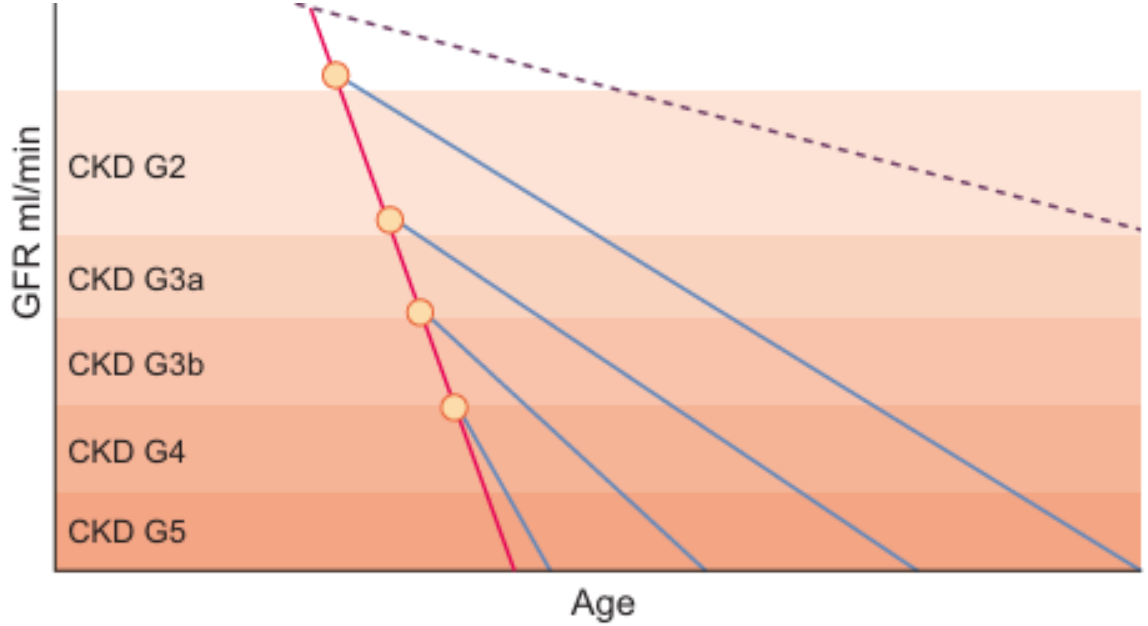
General Components in the Definition of Disease Modification



van Vollenhoven R, et al. *Lupus Sci Med.* 2022;9(1)

Determining Disease Modification for Lupus Nephritis: The *Non-immune* Part

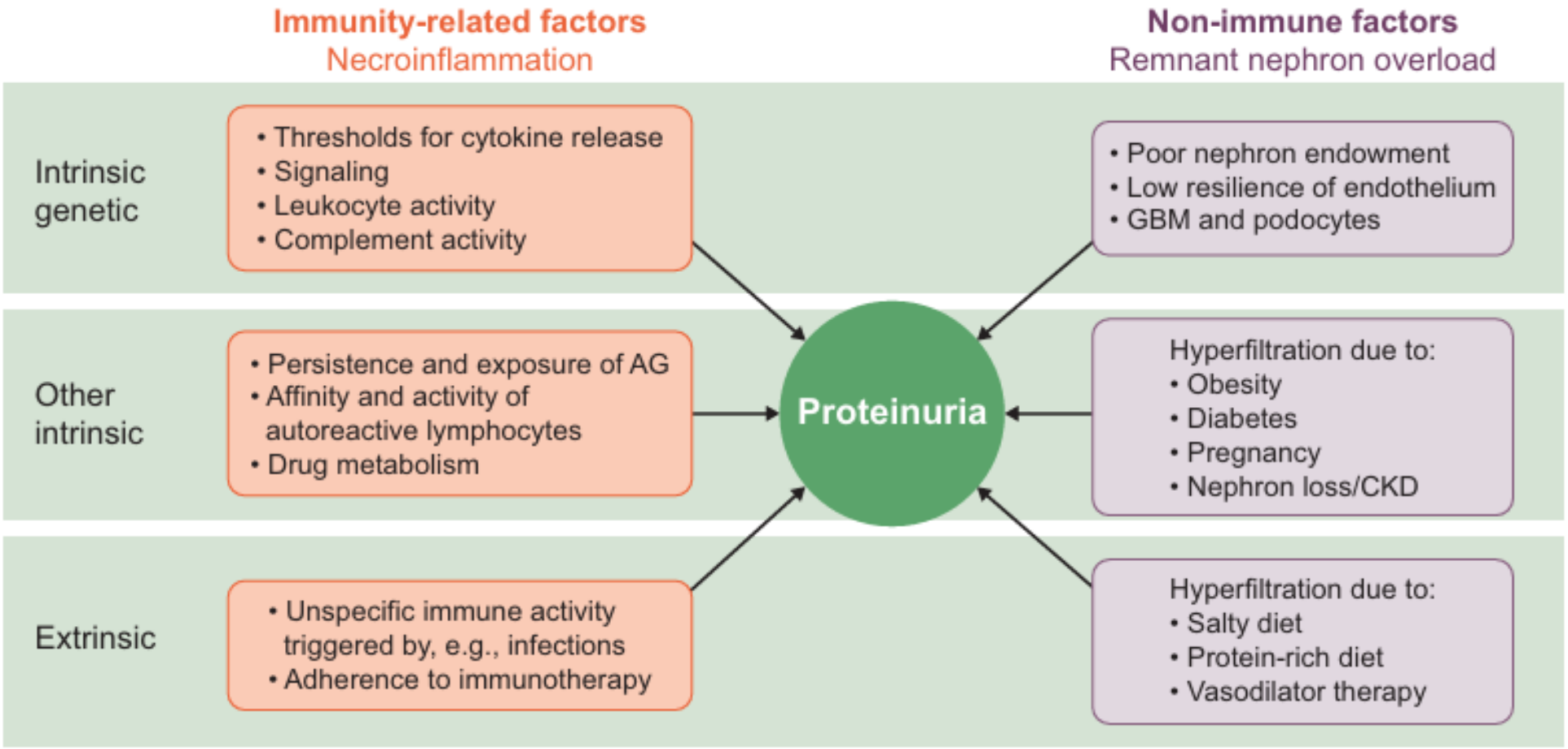
- Disease modification in CKD is easily defined: preventing or delaying end-stage kidney disease



- …however ultra-long follow-up necessary to determine a delay in ESKD
  - Well-defined and validated surrogate markers for ESKD in CKD:
    - eGFR slope over at least 3 years1
    - 30% eGFR decline
    - 40% eGFR decline
    - NOT proteinuria

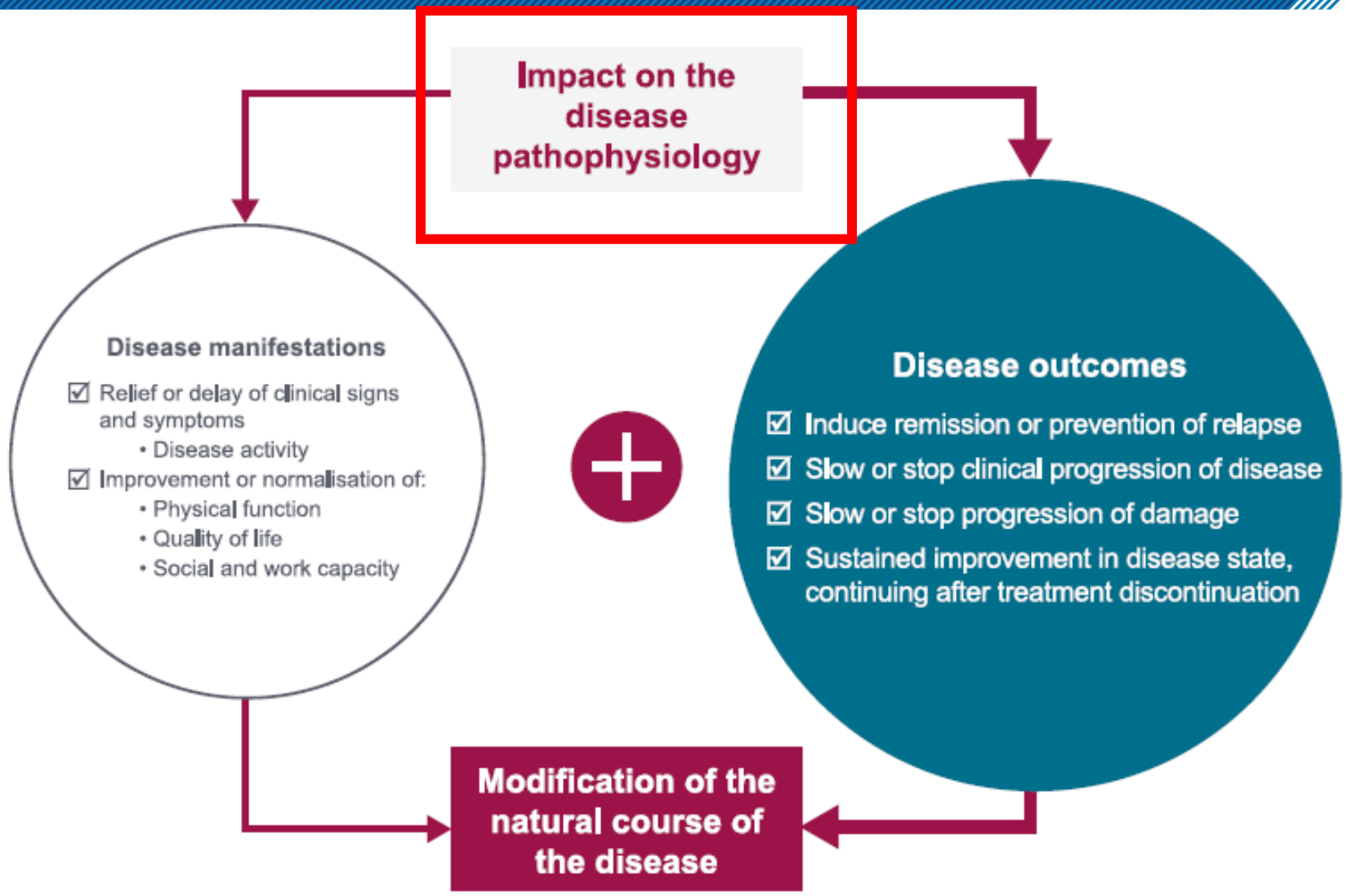
Inker LA, et al. *J Am Soc Nephrol.* 2019;30(9):1735-45.

Determining Disease Modification for Lupus Nephritis: The *Non-immune* Part



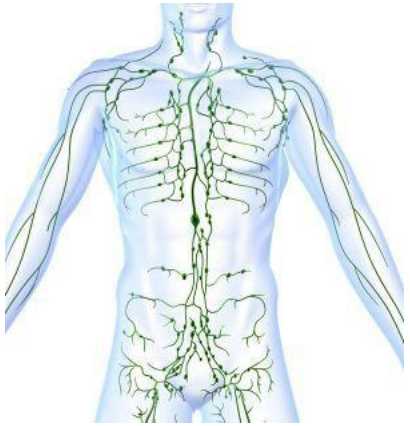
Anders HJ, et al. *Nephrol Dial Transplant.* 2023;38(3):551-61.

General Components in the Definition of Disease Modification

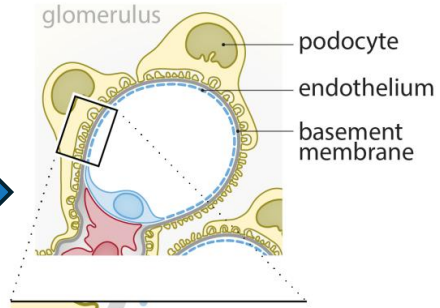


van Vollenhoven R, et al. *Lupus Sci Med.* 2022;9(1)

Determining Disease Modification for Lupus Nephritis: The *Immune* Part



Systemic Auto-Immunity



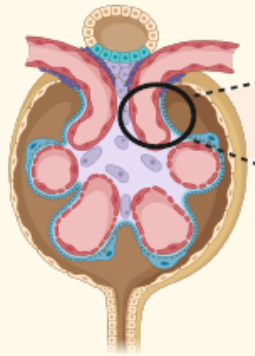
Glomerulonephritis

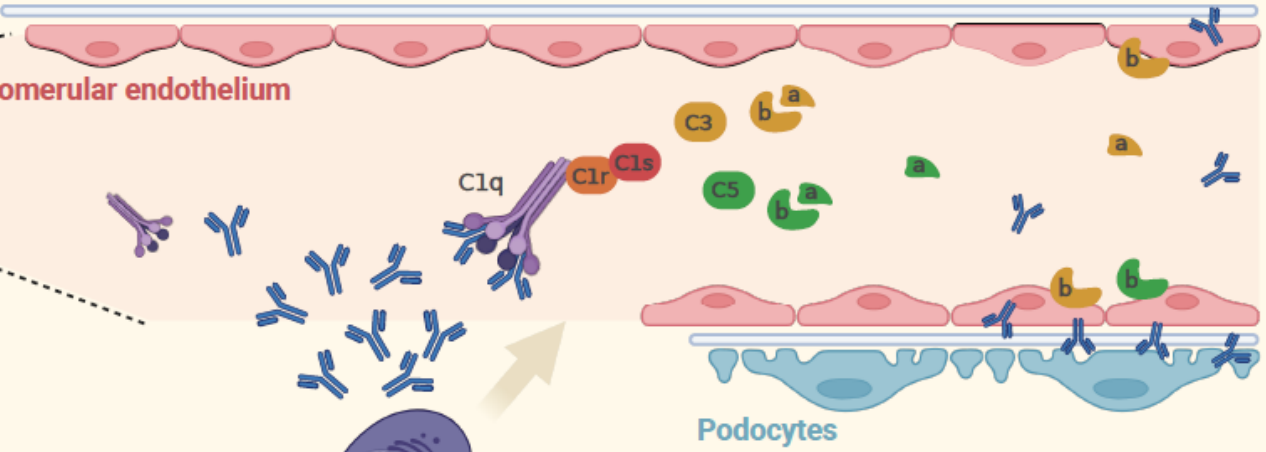
Renal Autoimmune Disease

Systemic Lupus Erythematosus	Immune Complexes + Complement	Lupus Nephritis
ANCA Associated Vasculitis	Neutrophils + Complement	Renal small-vessel vasculitis
Complement-Mediated Diseases	Complement	Membranoproliferative GN

Pathofysiology of SLE and LN

BAFF: B-cell activating factor
IFN: Interferon
NET: Neutrophil extracellular trap
pDC: plasmacytoid dendritic cell
TLR: Toll-like receptor

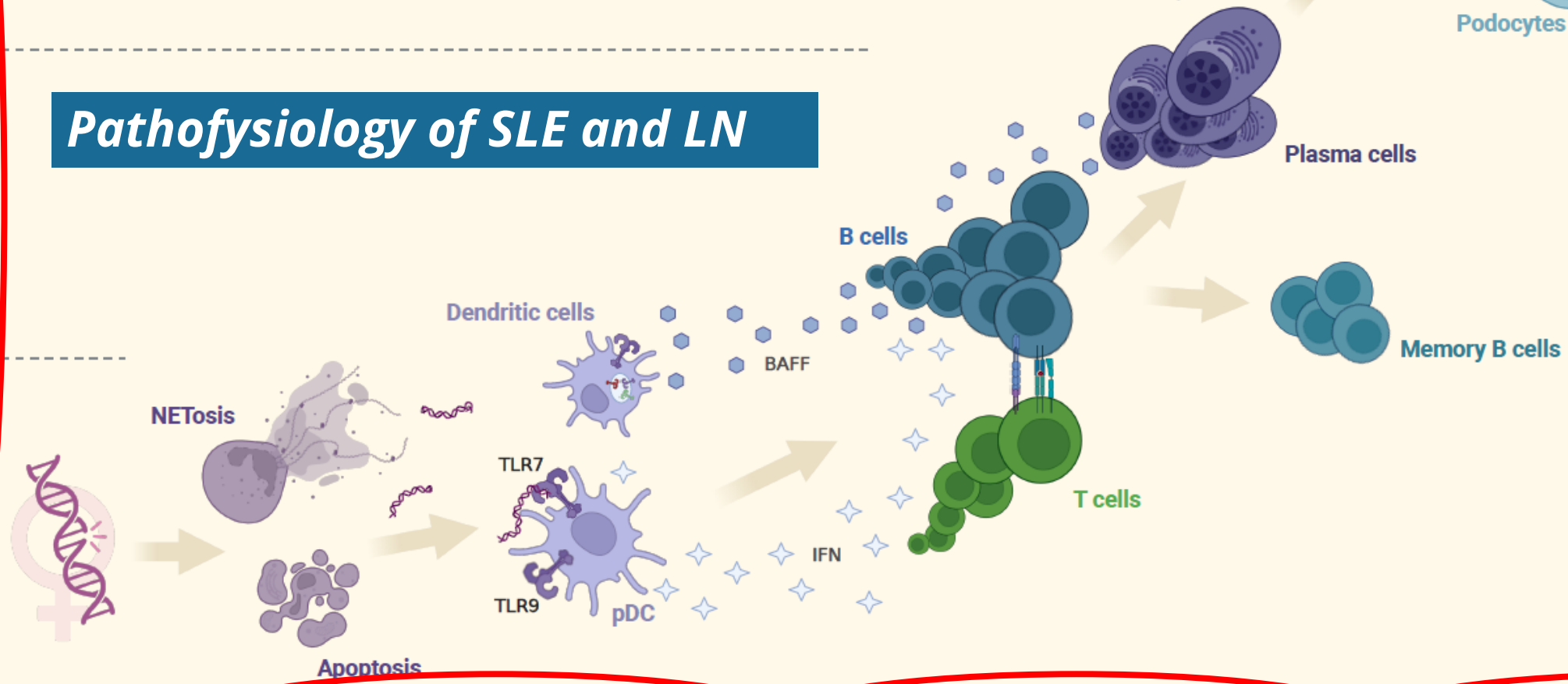




Inflammation

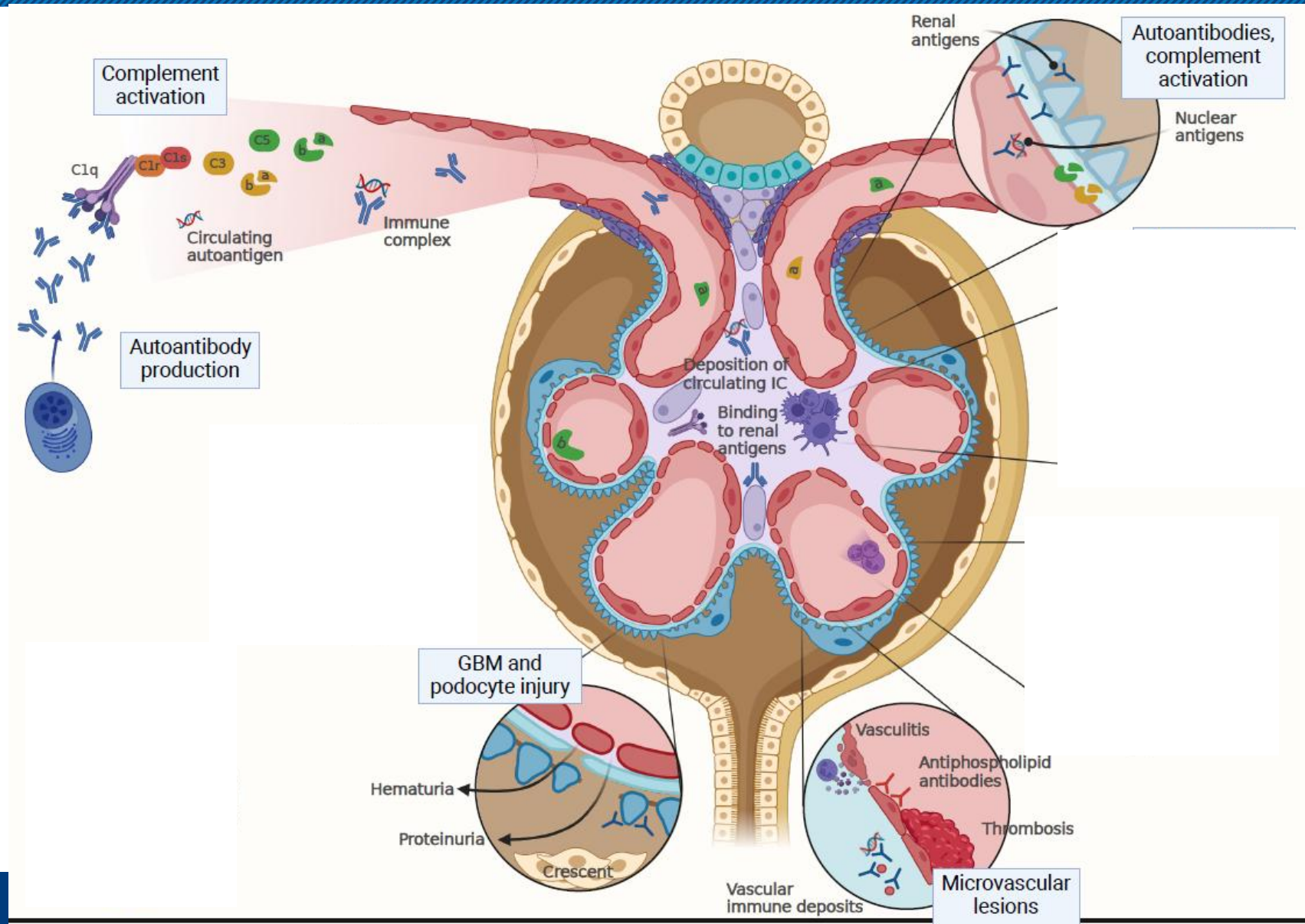
Autoimmunity

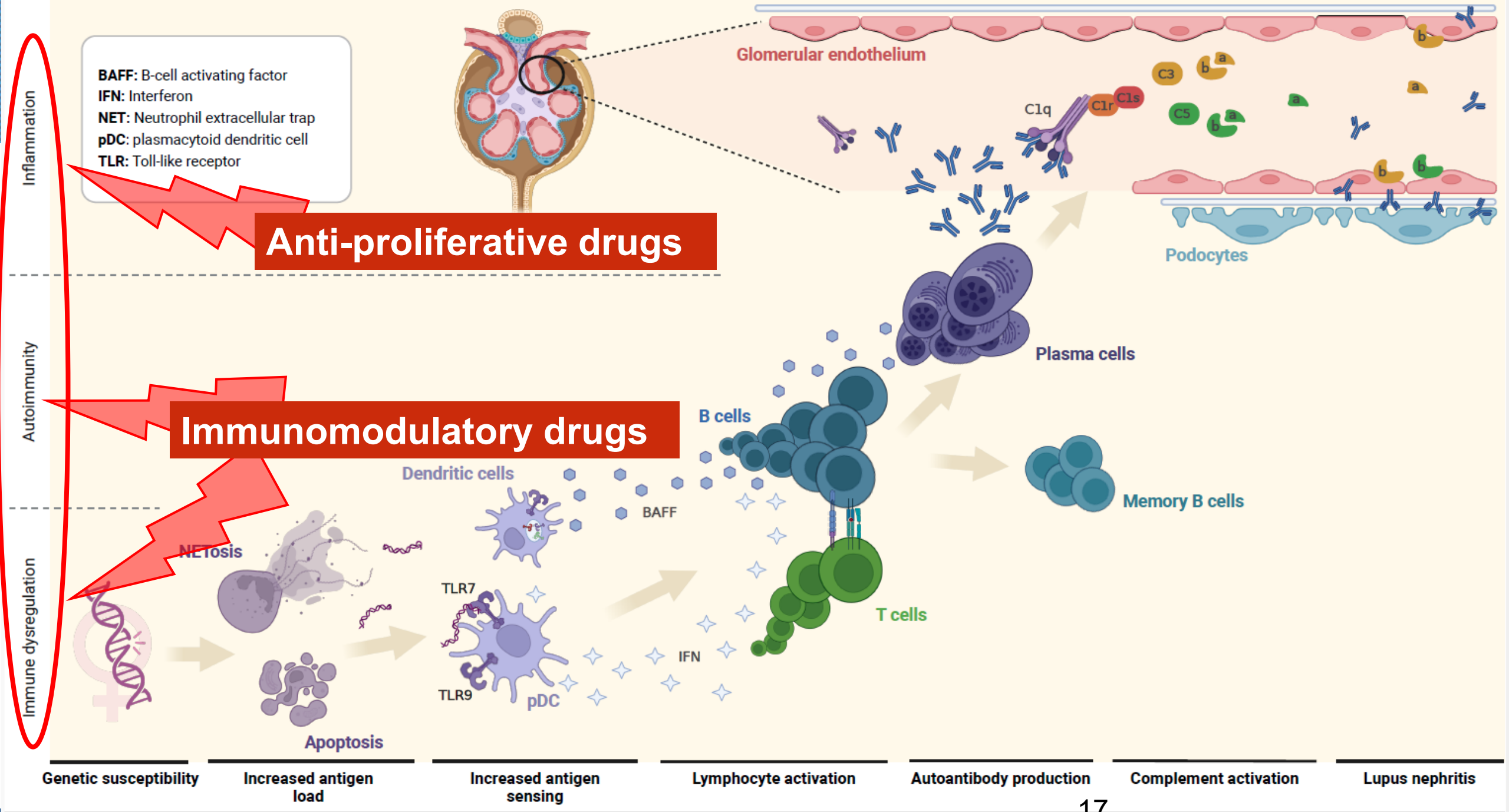
Immune dysregulation



Genetic susceptibility | Increased antigen load | Increased antigen sensing | Lymphocyte activation | Autoantibody production | Complement activation | Lupus nephritis

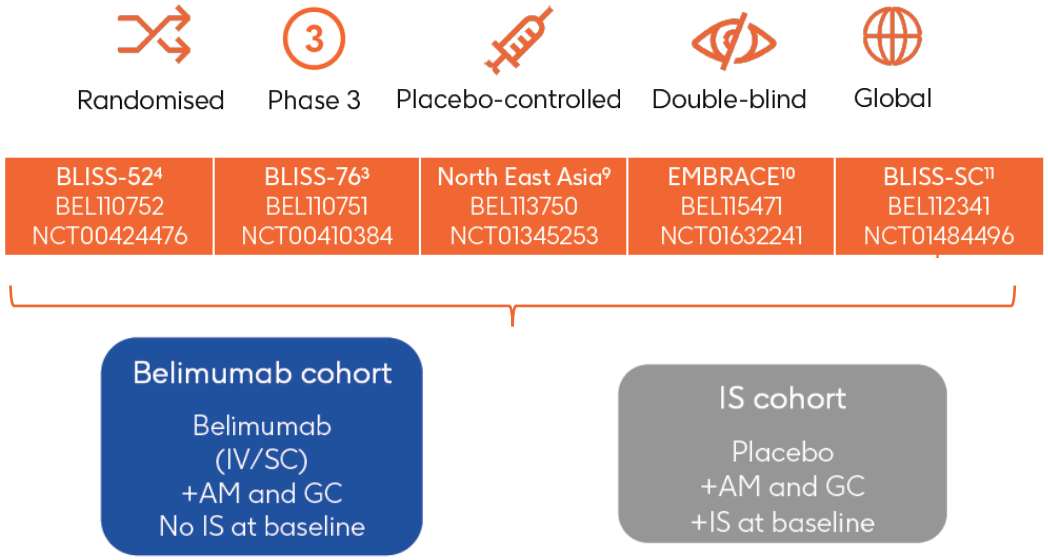
Autoimmunity in SLE: towards immune complex glomerulonephritis





Belimumab *prior to* standard IS in SLE

Figure 1: **Study design**



Inclusion criteria

≥18 years of age

SELENA-SLEDAI score:

- ≥6 (BLISS-52 and BLISS-76)
- ≥8 (North East Asia, EMBRACE and BLISS-SC)

Gatto M, et al. ACR 2025 poster.

Belimumab *prior to* standard IS in SLE

Figure 1: **Study design**

BLISS-52[4]	BLISS-76[3]	North East Asia[9]	EMBRACE[10]	BLISS-SC[11]
BEL110752	BEL110751	BEL113750	BEL115471	BEL112341
NCT00424476	NCT00410384	NCT01345253	NCT01632241	NCT01484496

Inclusion criteria

≥18 years of age

SELENA-SLEDAI score:

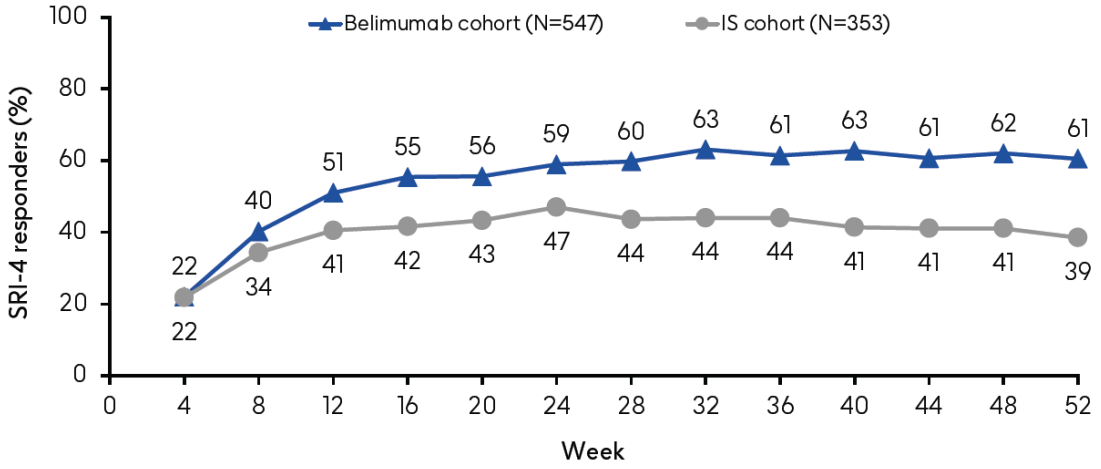
- ≥6 (BLISS-52 and BLISS-76)
- ≥8 (North East Asia, EMBRACE and BLISS-SC)

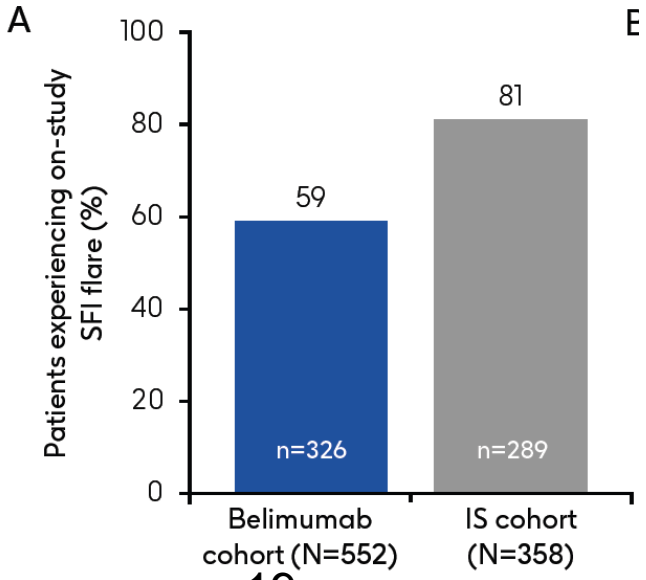
Belimumab cohort

Belimumab (IV/SC) +AM and GC No IS at baseline

IS cohort

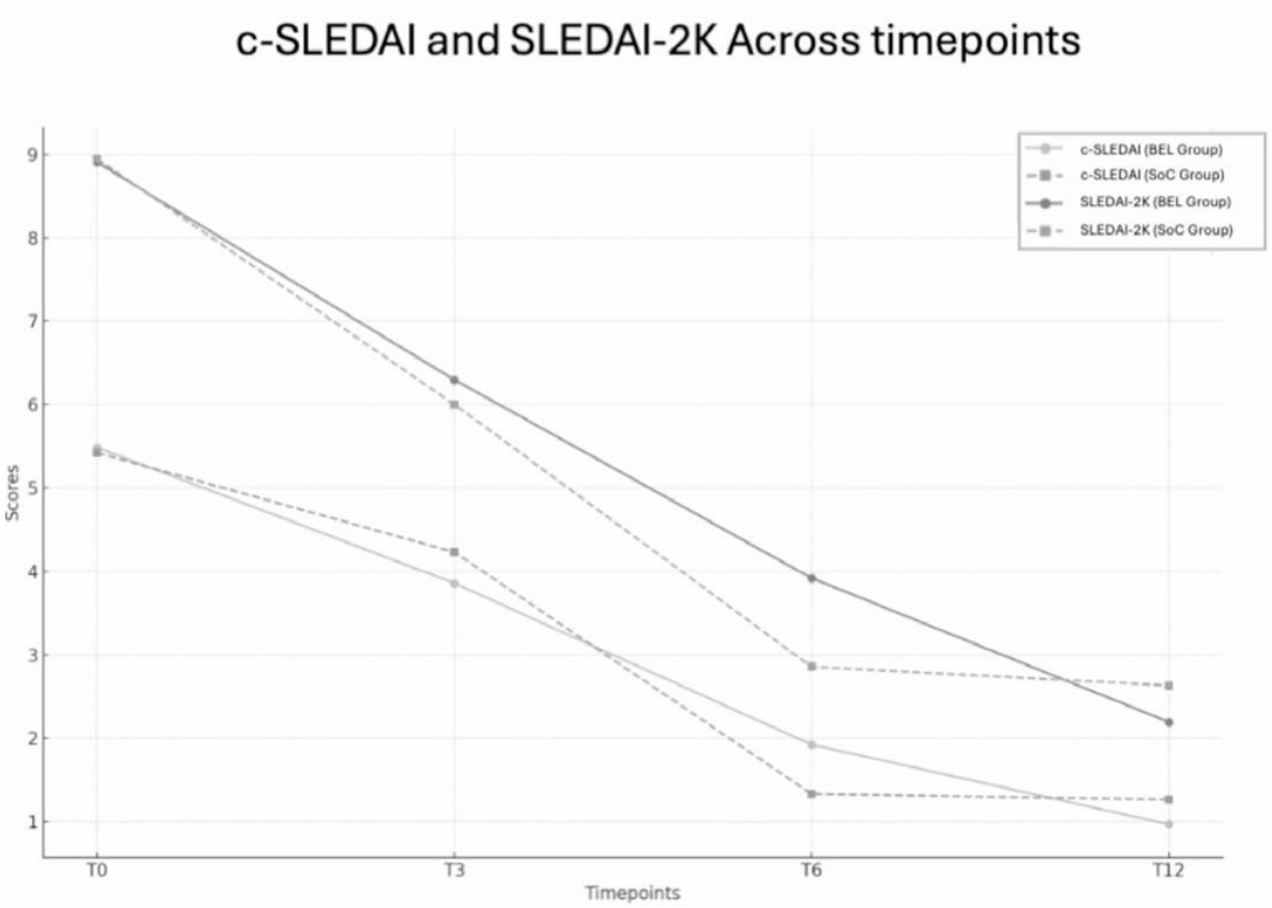
Placebo +AM and GC +IS at baseline

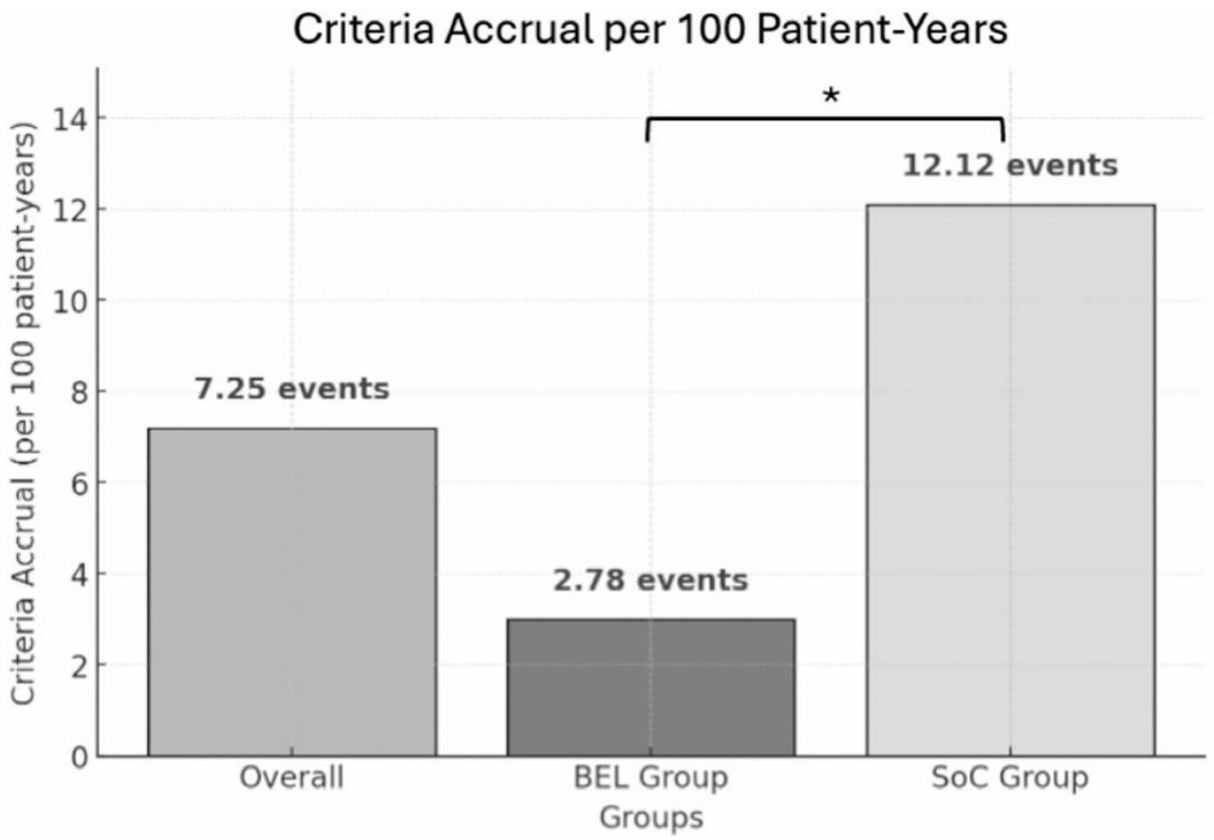




Gatto M, et al. ACR 2025 poster.

Administration of belimumab prior to standard immunosuppression





Gatto M, et al. Lupus Sci Med. 2025;12:e001662.

Disease-modifying anti-nephropathic drugs (DMANDs)

Proposed criteria for disease modification in immune-mediated GN and podocytopathies by the IWG of the ERA

Drugs targeting immunological activity of GN

1. **Minimizing disease activity**
   - i. Improvement in kidney biopsy features AND/OR
   - ii. Improvement in validated disease-specific biomarkers of active kidney inflammation AND/OR
   - iii. Improvement in validated clinical outcomes (such as time to remission or time to relapse of GN)
2. **Preventing kidney injury to structure and function**
   - i. Kidney failure AND/OR
   - ii. Validated surrogate markers of kidney failure (i.e., preventing a decline in eGFR of 40% or more)
3. **Reducing treatment-related toxicity**

Drugs targeting non-immune factors of CKD

1. **Preventing CKD-associated comorbidities**
   - i. Cardiovascular events of CKD AND/OR
   - ii. CKD- or inflammation-related comorbidities (e.g. CKD-MBD, metabolic acidemia, anemia, growth retardation in children OR chronic damage of major organs due to systemic inflammation)
2. **Preventing progressive kidney damage**
   - i. Kidney failure AND/OR
   - ii. Validated surrogate markers of kidney failure (i.e., preventing a decline in eGFR of 40% or more)
3. **Reducing treatment-related toxicity**

Teng YKO, et al. *Nephrol Dial Transplant.* 2025;40(6):1243-47.

Guideline Recommendations for Combination Therapy in LN

Triple Immunosuppressive Regimen		
Calcineurin Inhibitors + MPAA		**Belimumab + MPAA/CYC**
Tacrolimus + MPAA	**Voclosporin + MPAA**	
Tacrolimus (through level approx. 4-6 ng/ml) + reduced-dose MPAA (1-2g/d)	Voclosporin 23.7 mg b.i.d. + MPAA (2-3 g/d)	Belimumab (i.v. 10 mg/kg q2wk x 3 doses, then q4wk) + MPAA (2-3 g/d) or i.v. CYC (500 mg q2wk x 6 doses)
At least 6 months	Up to 36 months	Up to 2.5 years

Nordmann-Gomes A, et al. Lupus Sci Med. 2024;11(2) & Arthritis Rheumatol. 2025 Sep;77(9):1115-1135. doi: 10.1002/art.43212 & Fourniakis et al. Ann Rheum Dis 2025

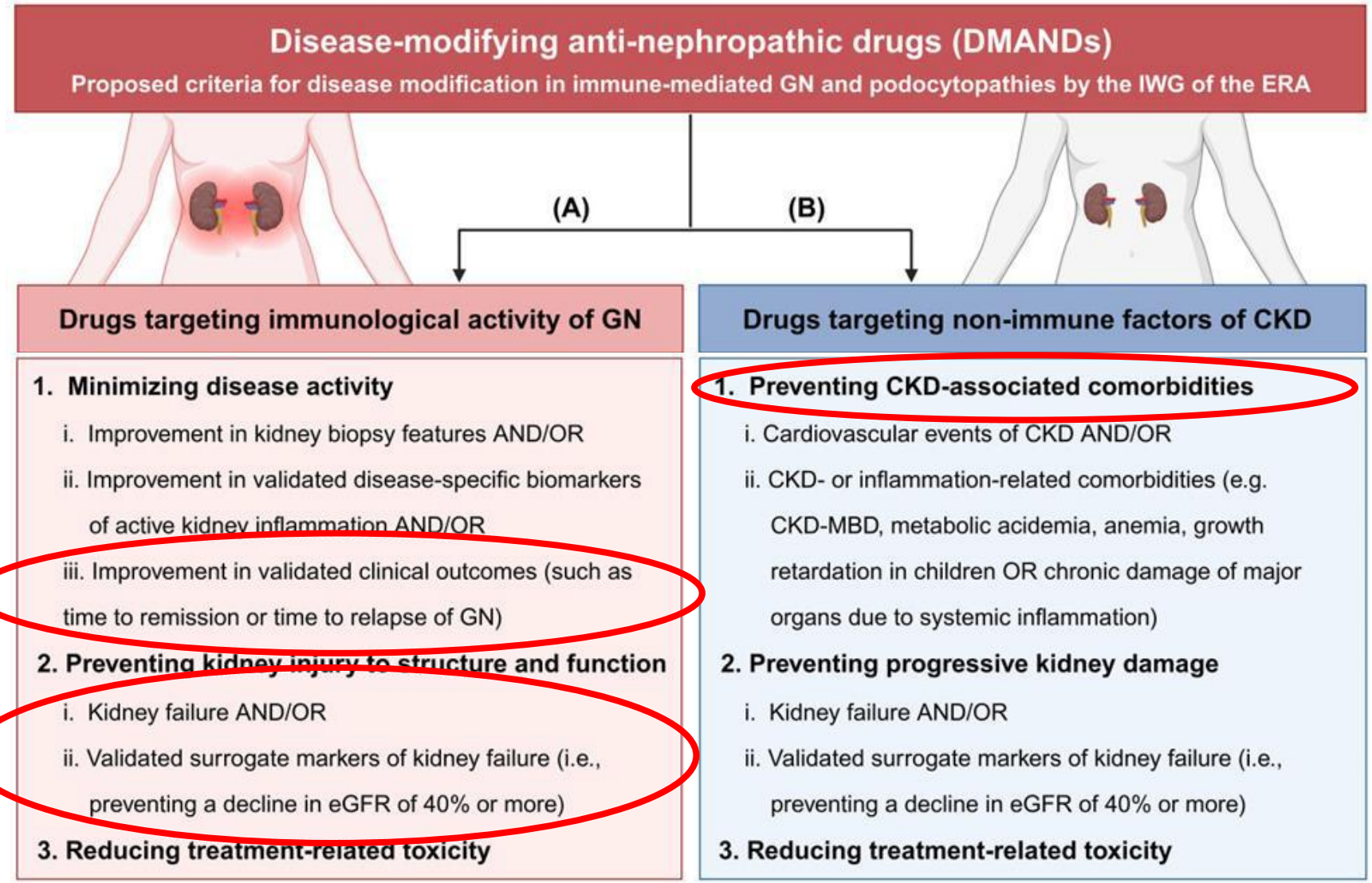
Disease Modification Criteria Across LN Trials

DM Criteria	BELIMUMAB: BLISS-LN	BELIMUMAB: BLISS-LN Posthoc	VOCLOSPORIN: AURORA-1	VOCLOSPORIN: AURORA-2
Histology - repeat biopsy	❌	❌	❌	❌
eGFR slope	❌	❌	✓ NS	✓ NS
≥30–40% eGFR decline	❌	❌	✓ NS	✓ NS
Hard renal events (ESKD/doubling creatinine)	✓ 👍	✓ 👍	❌	❌
CRR/Good renal outcome with eGFR constraint	✓ 👍	✓ 👍	✓ 👍	✓ NS
Minimised treatment toxicity	✓ 👍	✓ 👍	✓ 👍	✓ 👍

✓ = assessed ; ❌ = not assessed
👍 = significantly improved ; NS = not significantly different (or equal)

Furie R et al. NEJM 2020; Rovin BH et al. Kidney Int 2022; Rovin BH et al. Lancet 2021; Saxena A. et al. Ann Rheum Dis 2024

Important Next (small..) Steps



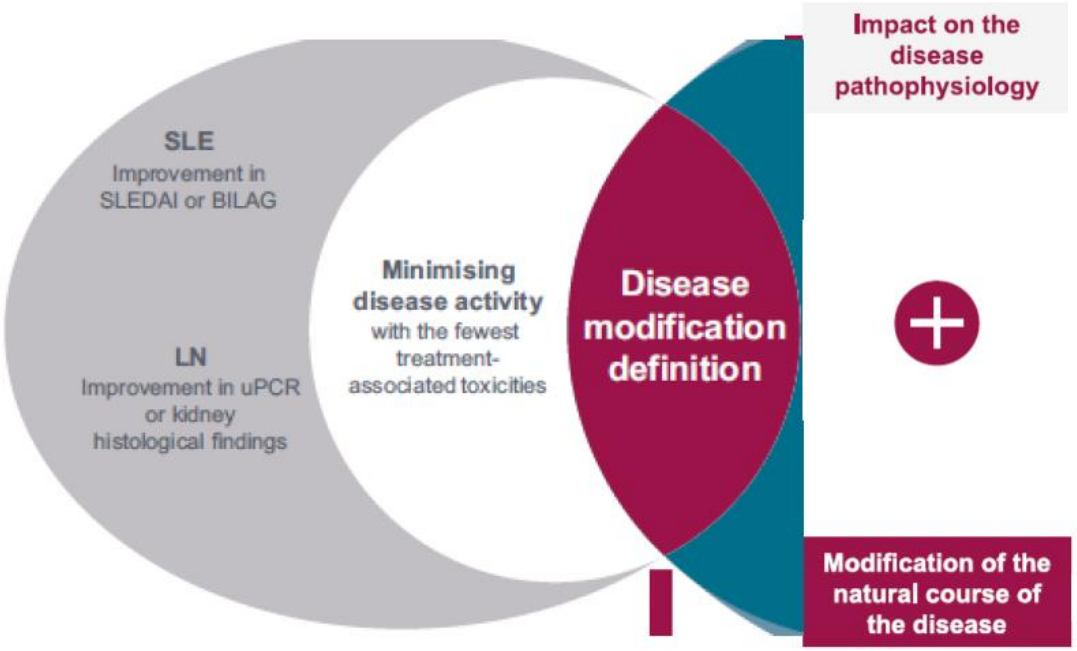
Unmet need for better (i.e. clinically relevant) trial endpoints

Unmet need for better (bio-) markers assessing immune-mediated AKI (uCD163, NETs)

Unmet need for improving long-term outcome in IMKDs .. and address them in trials!

Teng YKO, et al. *Nephrol Dial Transplant.* 2025;40(6):1243-47.

Aim for better defining & assessing Disease Modification for Lupus Nephritis



Immune part	Non-immune part
Diagnostic test: • Kidney biopsy • Urinary sediment • Auto-antibody seroconversion • Complement • NET autoantigen load • Immune-related urinary biomarkers (sCD163) • Proteinuria; Albuminuria	**Diagnostic test:** • Kidney biopsy • eGFR slope over 3 yrs • 30/40% ΔeGFR • CKD urinary biomarkers (DKK3) • Proteinuria ; Albuminuria

☑ Induce remission or prevention of relapse

☑ Slow or stop clinical progression of disease

van Vollenhoven R, et al. *Lupus Sci Med.* 2022;9(1)

Take Home Messages

<u>Disease modification in LN targets the chronicity – *in addition to activity* – of the disease:</u>

- DMANDs = disease-modifying anti-nephropathic drugs:
  - Drugs that modify immunological activity
  - Drugs that modify CKD progression

- Pathophysiology-based treatment strategies:
  - Target inflammation → non-targeted, anti-proliferative immunosuppression
  - Target auto-immunity & immune dysregulation → targeted, immunomodulatory immunosuppression
  - Target CKD progression

- **<u>Disease modification is the next step but also merely *a first step*</u>**

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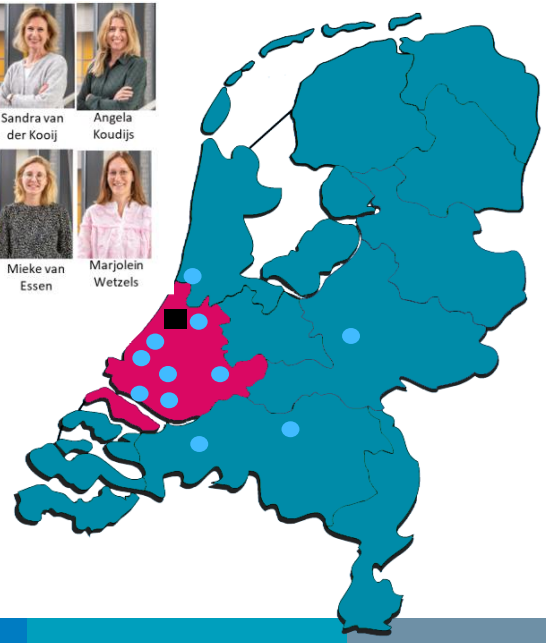

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