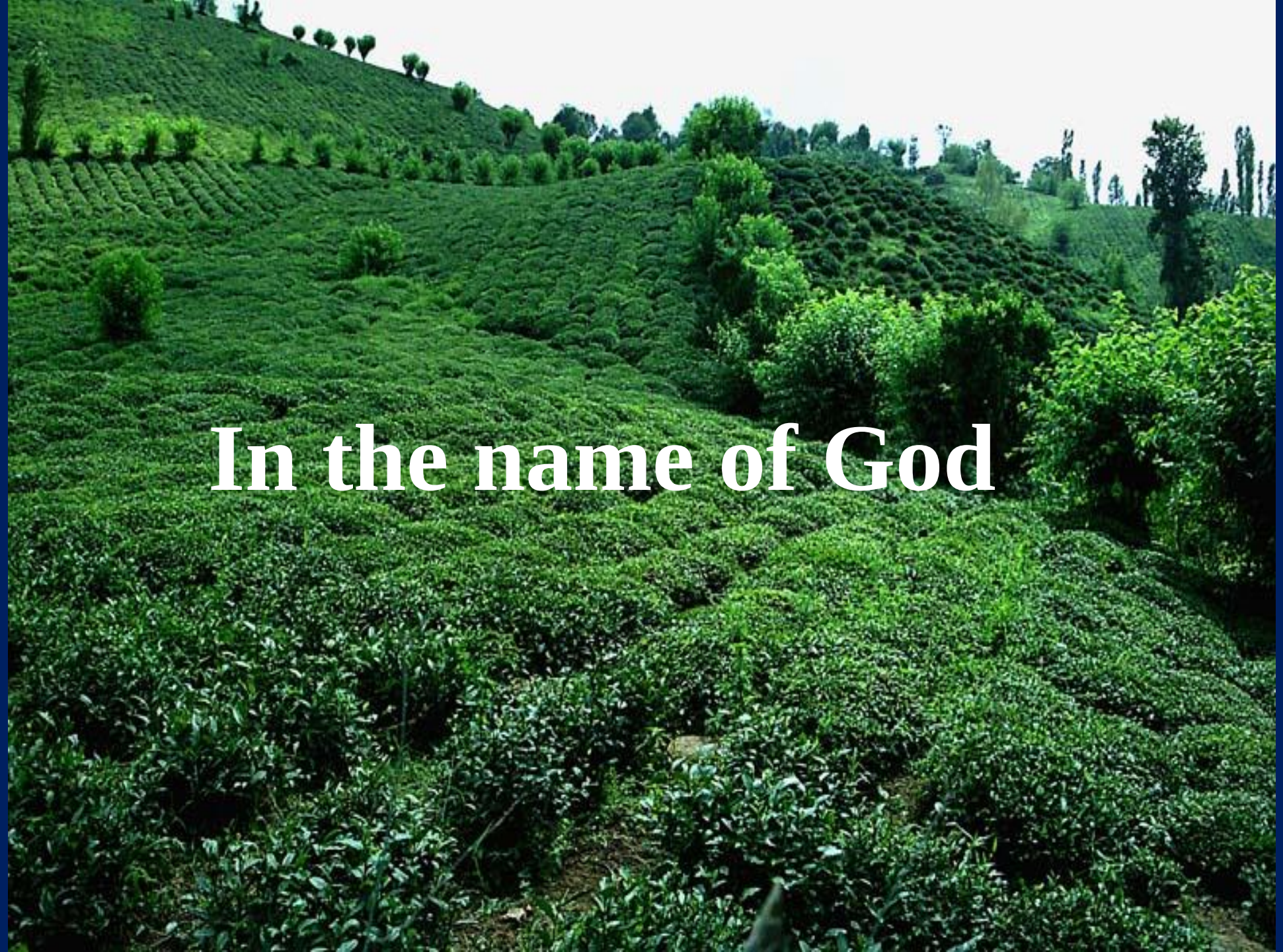

In the name of God

Update on the treatment of lupus nephritis

Asghar Haji Abbasi MD

Guilan University for Medical Sciences

Jan 18 2024

Introduction

- **Lupus nephritis occurs in up to 50% of patients with SLE.**

Compared to the general population:

- **Mortality risk is increased six- to nine-fold in patients with LN and 14 - 26-fold in patients with SLE with renal damage.**

- **Improved disease management to slow or stop progression to ESRD is essential .**

- **Despite numerous advances in the treatment of active LN , CRR rates remain low.**

Arthritis & Rheumatology Vol. 76, No. 1, January 2024, pp 59–67

Renal responses

Rates of complete response at 1–2 years with SoC therapy in recent clinical trials are consistently low, in the range of 20%–30% .

Fanouriakis A, et al. Ann Rheum Dis 2024;83:15–29.

Nearly 10% of patients with LN develop end-stage renal disease after long-term treatment, and the prognosis is relatively poor.

Front. Immunol. .2023.1232244

Looking for a New Vision

- **Despite aggressive treatment, approximately 60% of patients with LN do not have CR , and these patients have poor long-term outcomes.**
- **Furthermore, 27 to 66% of patients with lupus nephritis that is in remission have subsequent flares.**
- **Thus, safer therapies that reduce kidney inflammation, prevent flares, and preserve kidney function are needed.**

N Engl J Med 2020;383:1117-28

Four pillars in the management of SLE

- (1) need for early diagnosis
- (2) vigilant monitoring for new organ involvement, mainly LN, especially during the first years of the disease, but also thereafter.
- (3) pursuing a treatment target
- (4) the importance of patient adherence to treatment.

Fanouriakis A, et al. Ann Rheum Dis 2023;0:1–15

Treatment target

- This target should ideally be remission, as defined by the recent Definition Of Remission In SLE (DORIS) criteria.
- Alternatively, a state of low disease activity, such as the Lupus Low Disease Activity state (LLDAS).
- Both remission and LLDAS have been extensively validated and proven to reduce the risk for damage and other adverse outcomes in patients with SLE .

Fanouriakis A, et al. Ann Rheum Dis 2023;0:1–15

Definitions of renal outcomes: CR, PR, non-response and relapse.

Outcome	Definition
CR	Proteinuria ≤0.5 g/24 h or uPCR ≤0.5 g/g Inactive urinary sediment (≤5 RBC/hpf) Serum albumin ≥3.5 g/dL Normal eGFR or ≤10% inferior to baseline values
PR	Proteinuria reduction ≥50% with values between 0.6 and 3.5 g/24-h or uPCR 0.6–3.5 g/g Hematuria reduction (≤10 RBC/hpf) Serum albumin ≥3 g/dL Normal eGFR or ≤25% inferior to baseline values
Non-response	Absence of CR or PR
Relapse	Recurrence or significant increase in hematuria (>15 RBC/hpf) with dysmorphic RBC and/or RBC casts Sustained proteinuria increase: – ≥1 g/24-h or ≥1 g/g in patients with CR – ≥50% in patients with PR eGFR reduction ≥25% not attributable to other causes

Clinical Kidney Journal, 2023, vol. 16, no. 9, 1384–1402

General management

- **HCQ treatment is recommended as the background therapy for all patients with SLE without contraindications to this drug .**
- **In the large, international, multicenter, longitudinal SLICC cohort, using serum HCQ levels, authors found a 7.3% rate of severe nonadherence.**
- **Severe nonadherence to hydroxychloroquine was independently associated with the risk of an SLE flare, early damage, and mortality.**
- **This study suggests the benefits of testing for detecting severe nonadherence .**

Arthritis & Rheumatology Vol. 75, No. 12, December 2023, pp 2195–2206

Glucocorticoids in SLE

- **Next to HCQ , GCs are mainstay treatment of SLE, especially during acute exacerbations.**

- **Their potent anti-inflammatory and immunosuppressive effects through genomic and non-genomic pathways.**

- **Rapid IS effects are achieved through the non-genomic pathway, which is activated at levels >100 mg prednisone-equivalent/day .**

Best Practice & Research Clinical Rheumatology 2023

Strategies for the minimization of GC exposure in SLE

- **The genomic pathway is nearly completely saturated at doses >30 mg prednisone.**
- **Thus, the traditionally used 1 mg/kg regimen does not seem to confer additional therapeutic benefit, while it significantly increases the risk of harms.**
- **In any case, avoid doses over 30 mg/d and decrease rapidly to ≤5 mg/d.**
- **Patients with life and/or organ-threatening manifestations typically require high or very high initial doses.**
- **In this setting, pulses of intravenous MP are often administered.**

Best Practice & Research Clinical Rheumatology 2023

Efficacy and safety of immunosuppressive agents for adults with lupus nephritis

(a systematic review and network meta-analysis)

- **This study found that TAC plus MMF plus GC provided the best therapeutic effect in terms of the total remission rate, and SLEDAI.**

  (total remission included complete and partial remission)

- **TAC plus GC was associated with the highest total remission rate, and complete remission among the regimens of single-agent immunosuppressive plus GC.**

- **The VOC plus MMF plus GC regimen showed the best effect in terms of the complete remission rate.**

Front. Immunol. .2023.1232244

Comparison of the Effectiveness and Safety of MMF and CYC in LN: Evidence from a Real-World Study

- **Although both MMF and intravenous CYC have been widely used in patients with LN for years based on their similar efficacy shown in RCTs, there is little real-world data so far.**

- **This study suggested the effectiveness of MMF was at least equivalent to IV- CYC as an induction therapy for LN.**

- **MMF was associated with better tolerance compared to CYC, with less pneumonia, GI adverse reactions, and menstrual disturbance.**

Rheumatol Ther (2023) 10:1199–1213

Leflunomide versus AZA for maintenance therapy of LN

(a prospective, multicenter, randomised trial and long-term follow-up)

- **270 adult patients with biopsy-confirmed active LN from 7 Chinese Rheumatology Centers were enrolled.**
- **All patients received induction therapy with 6–9 months of IV- CYC plus GCs.**
- **Patients who achieved CR or PR were randomised to receive prednisone in combination with LEF or azathioprine as maintenance therapy for 36 months.**
- **In this study, the rate of kidney flare was 15.7% in the LEF group and 17.8% in the AZA group during the 36 months of follow-up**

Ann Rheum Dis. 2022 Nov; 81(11): 1549–1555

New drugs & extended indications for SLE

In the past several years, two new drugs have been developed for lupus treatment along with an extended indication for belimumab:

1) voclosporin, a calcineurin inhibitor, for the treatment of LN

2) belimumab for lupus nephritis

3) anifrolumab, the anti-type I interferon receptor medication, to treat non-renal SLE

A. Askanase, L. Khalili, W. Tang et al. Best Practice & Research Clinical Rheumatology 2023

Voclosporin

- **The pharmacokinetics of voclosporin suggest twice-daily dosing.**
- **The pharmacodynamics of voclosporin allow for a lower dose than that with cyclosporine.**
- **Low-dose voclosporin may be associated with less nephrotoxicity than cyclosporine and with less diabetes than tacrolimus.**
- **Voclosporin does not require therapeutic drug monitoring, does not affect MMF levels .**

Clinical Pharmacokinetics (2023) 62:693–703

Efficacy and safety of voclosporin versus placebo for LN (AURORA 1)

(a double-blind, randomised, multicenter, placebo-controlled, phase 3 trial)

Voclosporin in combination with MMF and low-dose steroids led to:

- **A clinically and statistically superior CRR rate versus MMF and low-dose steroids alone, with a comparable safety profile.**

- **This finding is an important advancement in the treatment of patients with active lupus nephritis.**

Lancet 2021; 397: 2070–80

Summary of complete and partial renal responses at weeks 24 and 52	Voclosporin group (n=179)	Placebo group (n=178)	OR or HR (95% CI)	p value
Primary endpoint*				
Complete renal response at 52 weeks	73 (41%)	40 (23%)	OR 2·65 (1·64–4·27)	<0·0001
Secondary endpoints				
Complete renal response at 24 weeks	58 (32%)	35 (20%)	OR 2·23 (1·34–3·72)	0·002
Partial renal response at 24 weeks	126 (70%)	89 (50%)	OR 2·43 (1·56–3·79)	<0·001
Partial renal response at 52 weeks	125 (70%)	92 (52%)	OR 2·26 (1·45–3·51)	<0·001
Time to UPCR ≤0·5 mg/mg, days	169 (141–214)	372 (295–NC)	HR 2·02 (1·51–2·70)	<0·001
Time to 50% reduction in UPCR, days	29 (29–32)	63 (57–87)	HR 2·05 (1·62–2·60)	<0·001

Data are n (%) or median (95% CI), unless otherwise specified. OR=odds ratio. HR=hazard ratio. UPCR=urine protein creatinine ratio. NC=non-calculable. *The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, mycophenolate mofetil use at baseline, and region.

Lancet 2021

Safety and Efficacy of Long-Term Voclosporin Treatment for Lupus Nephritis in the Phase 3 AURORA 2 Clinical Trial

- **AURORA 2 evaluated the long-term safety, tolerability, and efficacy of voclosporin compared to placebo in patients with LN receiving an additional two years.**
- **A total of 216 patients enrolled in AURORA 2.**
- **Treatment was well tolerated with 86.1% completing the study .**
- **AEs occurred in 86% and 80% of patients in the VOC and control groups, respectively, with an AE profile similar to that seen in AURORA 1, albeit with reduced frequency.**
- **Data demonstrate the safety and efficacy of long-term voclosporin treatment over three years of follow-up in patients with LN.**

Arthritis & Rheumatology 2023, pp 1–9

Two Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis (BLISS-LN trial)

- **In a phase 3, multinational, multicenter, randomized, double-blind, placebo controlled, 104-week trial conducted at 107 sites in 21 countries.**

- **They assigned adults with biopsy-proven, active LN in a 1:1 ratio to receive IV belimumab (at a dose of 10 mg /kg) or matching placebo, in addition to standard therapy.**

In this trial involving patients with active lupus nephritis:

- **More patients who received BEL plus standard therapy had a primary efficacy renal response than those who received standard therapy alone.**

N Engl J Med 2020;383:1117-28

Effect of BEL on kidney-related outcomes in patients with LN

(post hoc subgroup analyses of the phase 3 BLISS-LN trial)

- **BEL plus standard therapy improved kidney outcomes compared with placebo plus standard therapy, regardless of whether patients had newly diagnosed or relapsed LN.**

- **Compared with placebo plus standard therapy, BEL plus standard therapy improved kidney outcomes irrespective of GC pulse administration during induction.**

- **These data support the use of belimumab in clinical practice for all patients with LN, whether newly diagnosed or relapsed.**

Nephrology Dialysis Transplantation, Volume 38, Issue 12, December 2023

Safety of BEL in adult patients with SLE: Results of a large integrated analysis of controlled clinical trial data

- **Wallace et al. performed a pooled posthoc analysis of 52-week safety data from one phase 2 and five phase 3 belimumab trials in adult patients with SLE, including 4170 patients.**

- **The overall incidence of AEs was similar in the placebo and belimumab groups, except for a slightly higher proportion of post-infusion/injection systemic reactions in the belimumab group (10.2% vs. 8.1%).**

- **A similar proportion of patients experienced AEs and serious adverse events (SAEs) considered related to the study drug.**

Clinical and Experimental Rheumatology 2023

Time to onset of clinical response to anifrolumab in patients with SLE

(pooled data from the phase III TULIP-1 and TULIP-2 trials)

- **Anifrolumab is approved in several countries for the treatment of patients with moderate-to-severe SLE receiving standard therapy, based on results of the phase III TULIP-1 and TULIP-2.**

- **Anifrolumab treatment was associated with sustained improvements in overall SLE disease activity and skin responses versus placebo from Week 8.**

- **It likely led to greater glucocorticoid reductions in the anifrolumab versus placebo groups from Week 20.**

- **These findings provide insights to physicians and patients on when to expect potential clinical responses following anifrolumab treatment.**

Lupus Sci Med. 2023; 10(1): e000761.

Anifrolumab in lupus nephritis: results from second-year extension of a randomised phase II trial

- **The primary outcome of the first year of the phase II TULIP-LN randomised, placebo-controlled trial suggested that an intensified regimen (IR) of anifrolumab has potential to be a novel treatment option for patients with active LN.**

- **This 2-year analysis of the placebo-controlled TULIP-LN study shows acceptable long-term safety and tolerability of anifrolumab.**

- **Treatment with anifrolumab using an IR dosing regimen added to standard of care with MMF and GCs, improved renal and non-renal disease outcomes in patients with active class III or IV LN.**

Jayne D, et al. Lupus Science & Medicine 2023;10:e000910

Anifrolumab in lupus nephritis: results from second-year extension of a randomised phase II trial

- **The primary outcome of the first year of the phase II TULIP-LN randomised, placebo-controlled trial suggested that an intensified regimen (IR) of anifrolumab has potential to be a novel treatment option for patients with active LN.**

These results support investigation of the anifrolumab IR dosing regimen in patients with active class III or IV LN in the ongoing phase III IRIS study.

- **Treatment with anifrolumab using an IR dosing regimen added to standard of care with mycophenolate mofetil and glucocorticoids, improved renal and non-renal disease outcomes in patients with active class III or IV LN.**

Jayne D, et al. Lupus Science & Medicine 2023;10:e000910

Management of Lupus Nephritis

New Treatments and Updated Guidelines

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

Antonis Fanouriakis ,[1] Myrto Kostopoulou ,[1] Jeanette Andersen,[2] Martin Aringer ,[3] Laurent Arnaud ,[4] Sang-Cheol Bae ,[5] John Boletis,[6] Ian N Bruce,[7] Ricard Cervera,[8] Andrea Doria ,[9] Thomas Dörner ,[10] Richard A Furie ,[11] Dafna D Gladman ,[12] Frederic A Houssiau ,[13] Luís Sousa Inês ,[14] David Jayne ,[15] Marios Kouloumas,[16] László Kovács,[17] Chi Chiu Mok ,[18] Eric F Morand ,[19] Gabriella Moroni,[20] Marta Mosca,[21] Johanna Mucke ,[22] Chetan B Mukhtyar ,[23] György Nagy ,[24,25,26] Sandra Navarra,[27] Ioannis Parodis ,[28,29,30] José M Pego-Reigosa,[31] Michelle Petri ,[32] Bernardo A Pons-Estel,[33] Matthias Schneider,[22] Josef S Smolen,[34] Elisabet Svenungsson ,[28,29] Yoshiya Tanaka ,[35] Maria G Tektonidou ,[36] YK Onno Teng ,[37] Angela Tincani ,[38] Edward M Vital ,[39] Ronald F van Vollenhoven ,[40] Chris Wincup ,[41] George Bertsias ,[42] Dimitrios T Boumpas [1,43,44]

Fanouriakis A, et al. Ann Rheum Dis 2024;83:15–29.

VOL 105 | ISSUE 1S | JANUARY 2024

kidney INTERNATIONAL

KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis

Clinical Kidney Journal, 2023, vol. 16, no. 9, 1384–1402

https:/doi.org/10.1093/ckj/sfad055
Advance Access Publication Date: 22 March 2023
CKJ Review

CKJ REVIEW

Diagnosis and treatment of lupus nephritis: a summary of the Consensus Document of the Spanish Group for the Study of Glomerular Diseases (GLOSEN)

Jorge E. Rojas-Rivera [1,2,*], Clara García-Carro [3,*], Ana I. Ávila[4], Mar Espino[5], Mario Espinosa[6], Gema Fernández-Juárez[7], Xavier Fulladosa[8], Marian Goicoechea[9], Manuel Macía[10], Enrique Morales[5,11,12], Luis F. Quintana [13,14] and Manuel Praga[11,12]

Shifting the SLE management paradigm
(challenges and implications)

Newly published European guidelines for the management of SLE and lupus nephritis:

- **Specifically recommending early and aggressive use of new medications, signal that the old paradigm of SLE management is shifting.**

- **Although it presents challenges, this shift is welcome — and is likely to have far-reaching implications .**

Nature reviews rheumatology 2024

Old paradigm

Approach

- Delayed diagnosis
- Frequent, long-term use of high-dose glucocorticoids
- Late and step-wise use of conventional immunosuppressants
- No biologic drugs
- No combination therapy
- One-size-fits-all treatment without clear disease classifications

Outcomes

- Flares and high disease activity
- Organ damage
- Short-term and long-term adverse effects
- Poor quality of life

Access

- Disparities within and between countries

Nature reviews rheumatology 2024

Nature reviews rheumatology 2024

Paradigm in flux

Approach

- Early screening for disease activity
- Prioritization of glucocorticoid tapering and stopping
- Early and simultaneous use of conventional immunosuppressants and/or biologic drugs
- Combination therapy for lupus nephritis
- Recognized need for individualization of treatment based on disease characteristics

Outcomes

- Aim to achieve low disease activity or remission
- Less organ damage
- Less-extensive adverse effects of glucocorticoids and conventional immunosuppressants
- Unknown long-term effects of biologic drugs
- Improved quality of life

Access

- Disparities in the use of glucocorticoids and conventional immunosuppressants between countries
- Disparities in the use of new biologic drugs within and between countries

Nature reviews rheumatology 2024

Future 'ideal' paradigm

Approach

- Disease prediction and prevention before diagnosis
- Exceptional, short-term, low-dose use of glucocorticoids
- Early and aggressive use of conventional immunosuppressants and multiple biologic drugs as proven combination therapies
- Individualization and tailoring of therapy based on biology and biomarkers
- Evidence-based use of adjunctive therapies

It might provide biomarkers to facilitate the development of stratified treatment recommendations and SLE precision medicine.

Nature Reviews Rheumatology | Volume 19 | June 2023 | 331–342

EULAR Recommendations for the management of patients with SLE—2023 update

- **Patients with active proliferative LN should receive low-dose (EuroLupus) IV -CYC or MMF and glucocorticoids .**

(pulses of intravenous methylprednisolone followed by lower oral doses)

Combination therapy with:

- **Belimumab (either with cyclophosphamide or mycophenolate)**
- **or CNIs (especially voclosporin or tacrolimus) , with mycophenolate, should be considered.**

Fanouriakis A, et al. Ann Rheum Dis 2024;83:15–29.

EULAR Recommendations for the management of patients with SLE—2023 update

- **Following renal response, treatment of LN should continue for at least 3 years .**

- **Patients initially treated with mycophenolate alone or in combination with belimumab or a calcineurin inhibitor should remain on these drugs .**

- **AZA or MMF should replace cyclophosphamide for those initially treated with cyclophosphamide alone or in combination with belimumab.**

Fanouriakis A, et al. Ann Rheum Dis 2024;83:15–29.

EULAR Recommendations for the management of patients with SLE—2023 update

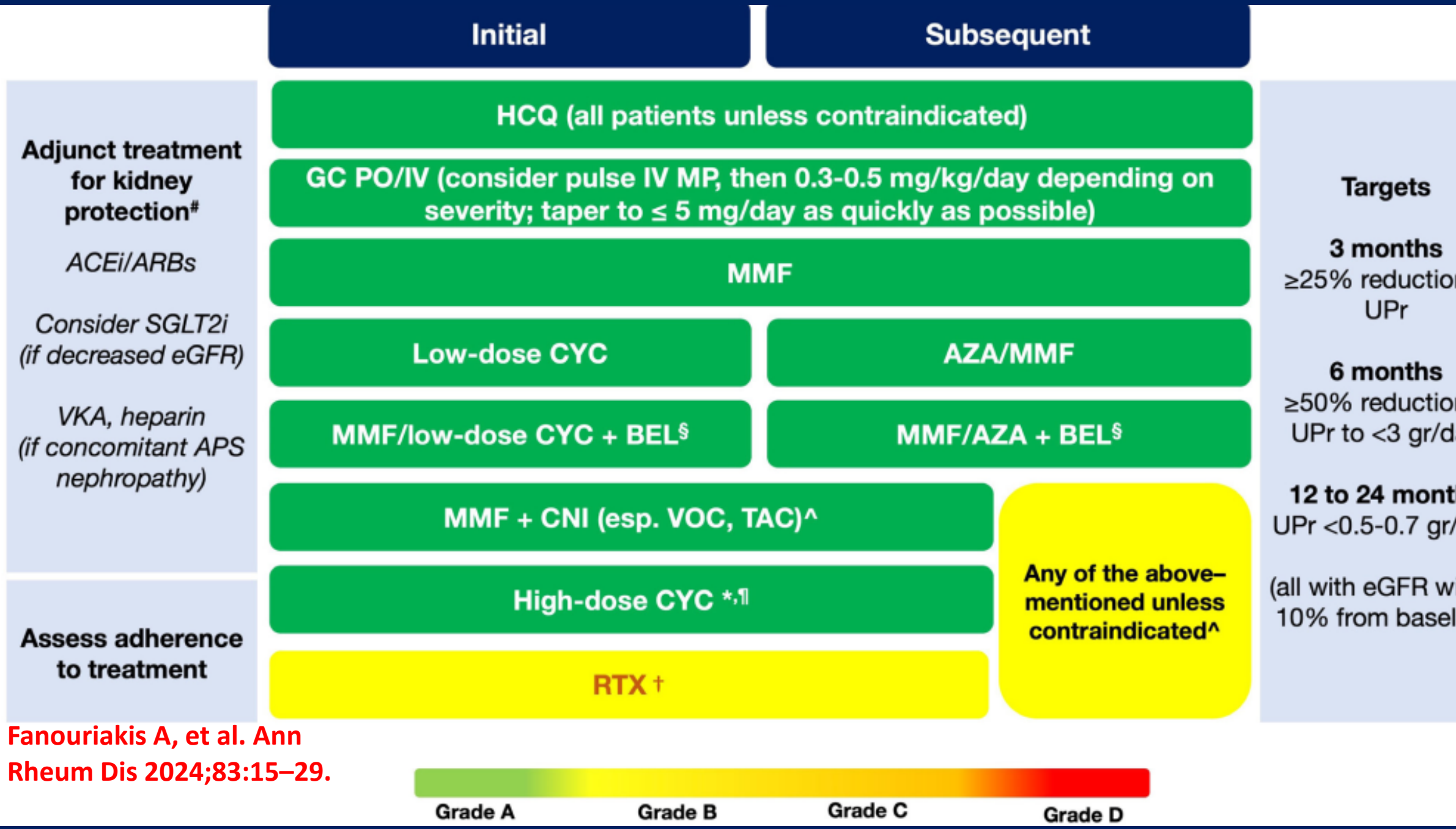
In patients at high-risk for renal failure:

(defined as reduced GFR, histological presence of cellular crescents or fibrinoid necrosis, or severe interstitial inflammation):

↓

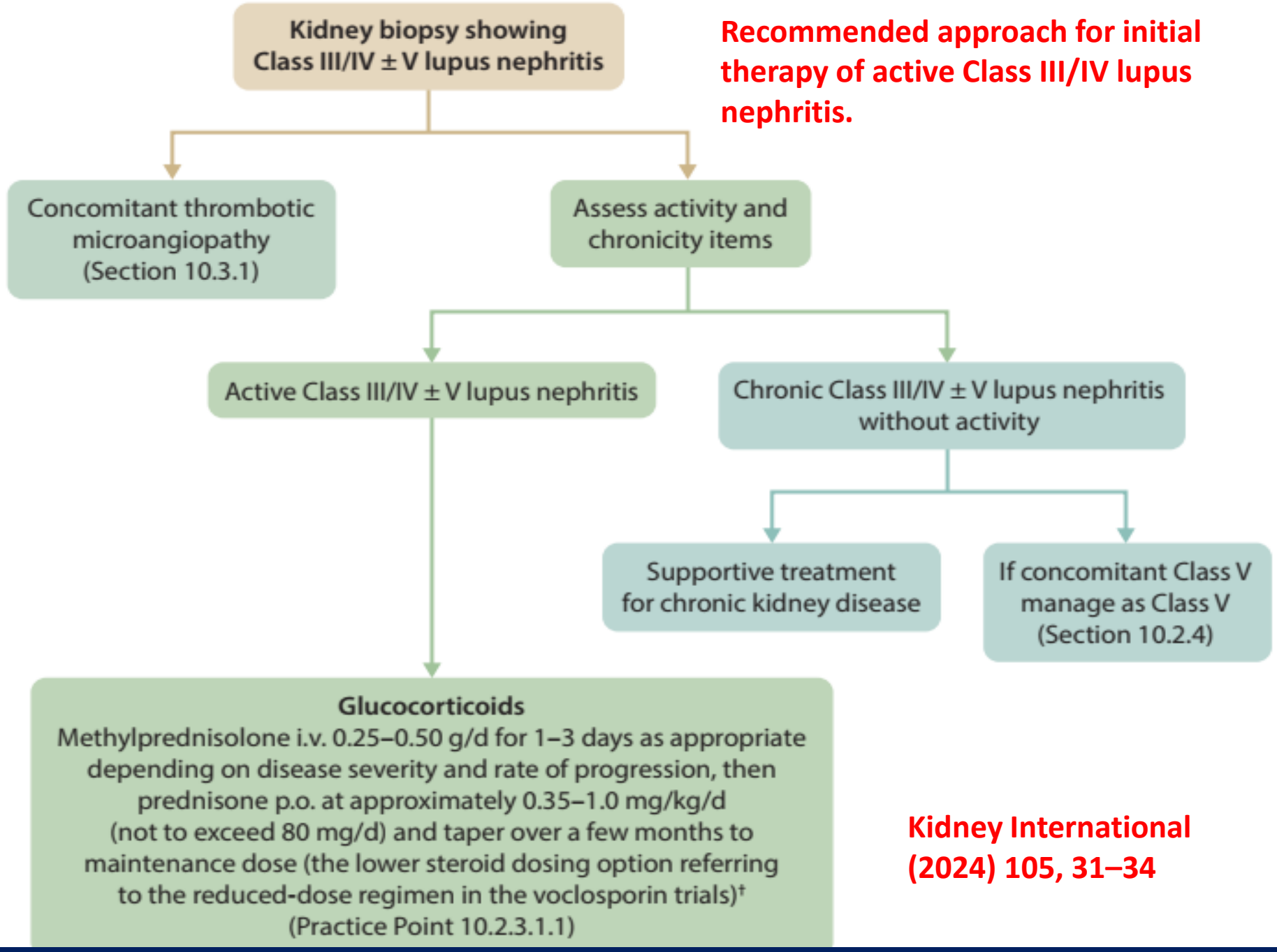
High-dose (NIH regimen) intravenous CYC in combination with pulse IV methylprednisolone, can be considered.

Fanouriakis A, et al. Ann Rheum Dis 2024;83:15–29.



Fanouriakis A, et al. Ann Rheum Dis 2024;83:15–29.

Recommended approach for initial therapy of active Class III/IV lupus nephritis.



Kidney International (2024) 105, 31–34

Glucocorticoids
Methylprednisolone i.v. 0.25–0.50 g/d for 1–3 days as appropriate depending on disease severity and rate of progression, then prednisone p.o. at approximately 0.35–1.0 mg/kg/d (not to exceed 80 mg/d) and taper over a few months to maintenance dose (the lower steroid dosing option referring to the reduced-dose regimen in the voclosporin trials)† (Practice Point 10.2.3.1.1)

and one of the following options

CNI + MPAA
Voclosporin 23.7 mg b.i.d. and MPAA in patients with eGFR >45 ml/min per 1.73 m^2

Tacrolimus (trough level approximately 5.5 ng/ml [6.8 nmol/l], data mainly from Chinese patients) and reduced-dose MPAA in patients with SCr <3.0 mg/dl (265 μmol/l) as initial and maintenance therapy

Consider cyclosporine when voclosporin and tacrolimus are not available

(Practice Point 10.2.3.1.4)

CNI duration up to 3 years‡

Mycophenolic acid analogs (MPAA) for at least 6 months
MMF p.o. 1.0–1.5 g b.i.d. or mycophenolic acid sodium 0.72–1.08 g b.i.d. (Practice Point 10.2.3.1.3)

Cyclophosphamide for up to 6 months
i.v. 500 mg q2wk × 6 or 0.5–1.0 g/m^2 monthly × 6; or p.o. 1.0-1.5 mg/kg/d for 3 months (Practice Point 10.2.3.1.2)§

Belimumab + MPAA or reduced-dose cyclophosphamide
Belimumab (i.v., 10 mg/kg q2wk for 3 doses then q4wk) and MPAA or i.v. cyclophosphamide 500 mg q2wk × 6 (Practice Point 10.2.3.1.5)

Belimumab duration up to 2.5 years

Recommended approach for initial therapy of active Class III/IV lupus nephritis.

Kidney International (2024) 105, 31–34

Initial therapy of active Class III/IV lupus nephritis (Practice points)

- IV cyclophosphamide can be used as the initial therapy for active Class III and Class IV LN in patients who may have difficulty adhering to an oral regimen.

- 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 CYC exposure.

Initial therapy with an immunosuppressive regimen that includes a CNI may be preferred in patients with:

- Nephrotic range proteinuria likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPAA or are unfit for or will not use CYC .

Kidney International (2024) 105 (Suppl 1S), S1–S69

Initial therapy of active Class III/IV lupus nephritis (Practice points)

A triple IS regimen of BEL with GCs and either MPAA or reduced-dose CYC may be preferred in patients with:

- **Repeated kidney flares or at high-risk for progression to kidney failure .**

- **Other therapies, such as AZA or LEF combined with glucocorticoids, may be considered in lieu of the recommended initial drugs for proliferative LN.**

- **Situations of patient intolerance, lack of availability, and/or excessive cost of standard drugs, but these alternatives may be associated with inferior efficacy.**

Kidney International (2024) 105 (Suppl 1S), S1–S69

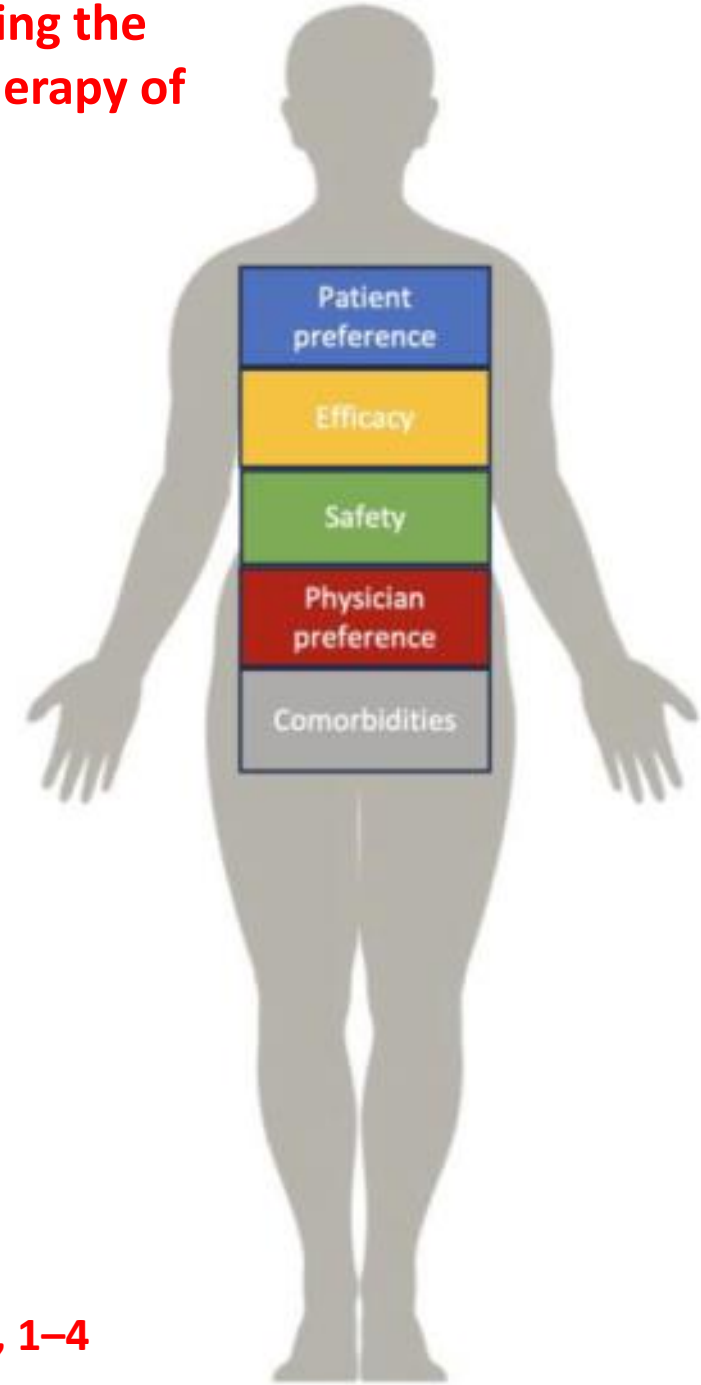
Specific considerations when evaluating the optimal currently approved add-on therapy of a patient with active LN class III–V

eGFR < 45 ml/min/1.73 m²
Belimumab (limited experience)

Proteinuria < 3 g/d
Belimumab or Voclosporin

Adherence
Belimumab (preferred option)

Background therapy
Use of cyclophosphamide (only tested with belimumab)



eGFR ≥ 45 ml/min/1.73 m²
Belimumab or Voclosporin

Proteinuria ≥ 3 g/d
Voclosporin (preferred option)

Patient preference
Oral medication (VCS; pill burden) versus i.v./s.c. administration (BEL)

Rigorous glucocorticoid tapering
Voclosporin (preferred option)

Extra-renal disease activity
Belimumab (preferred option)

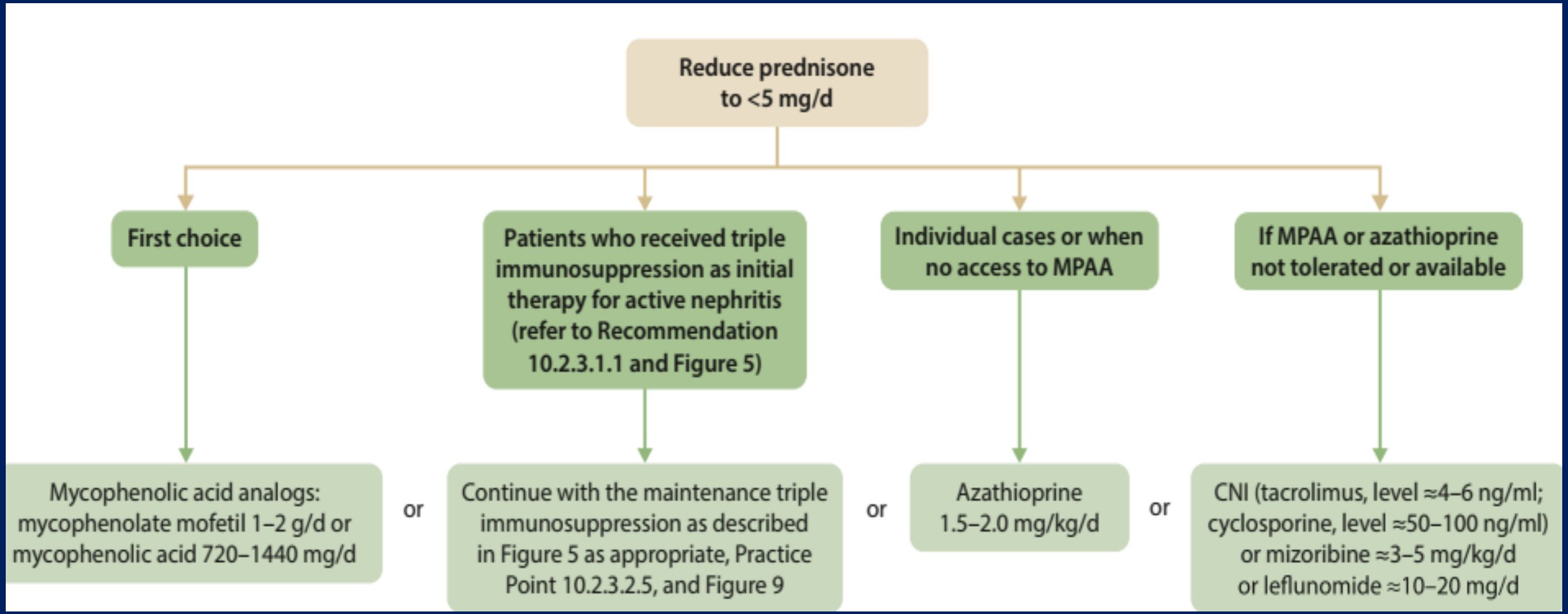
Nephrol Dial Transplant, 2023, 0, 1–4

Early predictors of renal outcome in patients with proliferative lupus nephritis: a 36-month cohort study

- **Proteinuria ≥2 g/day at 3 months after starting induction was identified as a robust predictor of failure to achieve CRR in proliferative LN.**
- **This can be used as a red flag for considering early rescue induction treatment in clinical practice to, ultimately, avoid progression to chronic kidney disease .**
- **After attaining CRR, patients with age ≤25 years at LN diagnosis and those with positive anti-RNP present higher risk of renal flare.**
- **This may be associated with the higher incidence of LN or lower therapeutic compliance in younger ages.**

Rheumatology (Oxford) Nov 2021

Recommended options of maintenance therapy for Class III and Class IV lupus nephritis



Kidney International (2024) 105 (Suppl 1S), S1–S69

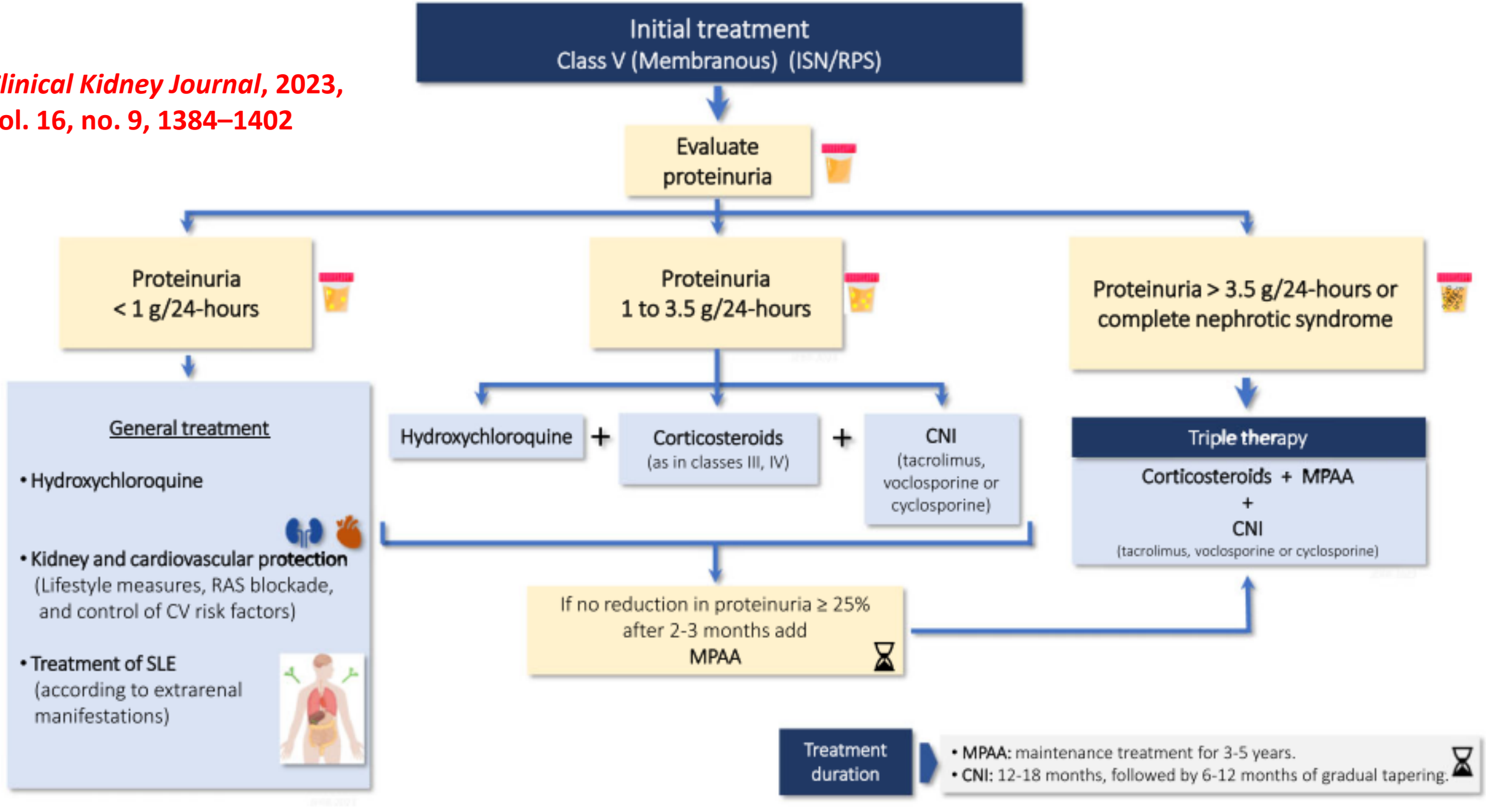
Low-dose GC should be withdrawn or continued in SLE ?

(A systematic review and meta-analysis on risk of flare and damage accrual)

- **GCs should be the first drug, when possible, to be withdrawn during the maintenance period .**
- **But there are no specific guidelines advising GC withdrawal protocols, which vary in clinical practice.**
- **GC discontinuation leads to a slightly increased risk of global flare but not major flare.**
- **GC withdrawal was associated with a borderline reduction of risk in organ damage accrual.**

Rheumatology (Oxford) December 2021

Clinical Kidney Journal, 2023, vol. 16, no. 9, 1384–1402



Glucocorticoids in treatment of Class V - LN

It is important to remember that Class V lupus nephritis is a *non-inflammatory* subtype of lupus nephritis.

Thus, even lower doses of glucocorticoids should be used.

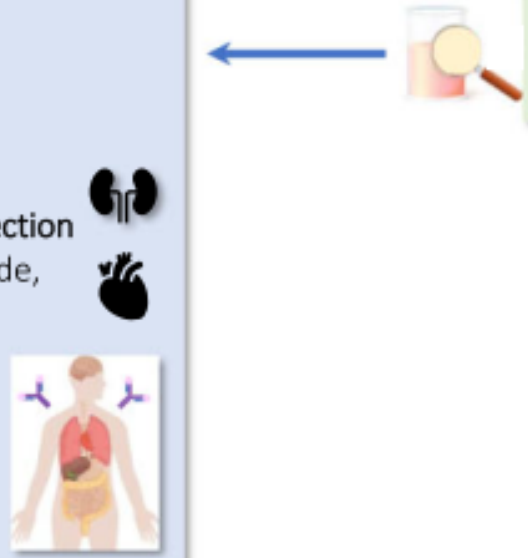
A starting dose of oral prednisone in the range of 20 mg/d may suffice.

John H. Stone, A Clinician's Pearls & Myths in Rheumatology , Second Edition 2023

Class I (ISN/RPS)

General treatment

- Hydroxychloroquine
- Kidney and cardiovascular protection (Lifestyle measures, RAS blockade, and control of CV risk factors)
- Treatment of SLE (according to extrarrenal manifestations)



Class II (ISN/RPS)

Monitoring of proteinuria and urinary sediment

Proteinuria < 1g/24-hours and normal urinary sediment

Proteinuria ≥ 1g/24-hours and/or glomerular hematuria despite RAS blockade

Re-evaluate kidney biopsy or consider to perform a new one to discard changes in histological class

If class II is confirmed

Add
Corticosteroids + MPAA
for at least 6-12 months, with progressive tapering for another 6 months
+
General treatment

Clinical Kidney Journal, 2023, vol. 16, no. 9, 1384–1402

CKD progression in LN

- Loss of nephron mass occurs with every episode of active LN, putting patients on track toward progressive loss of kidney function, and even kidney failure.

Management of patients with LN must include not only IS for acute treatment of active LN, but also measures to slow or stop CKD progression.

- This section is currently limited to blood pressure control, renin-angiotensin-aldosterone system blockade, flare prevention, and nephrotoxin avoidance.

- It is likely to expand in the future as data on LN and sodium-glucose cotransporter-2 inhibitors or other new agents such as endothelin-A receptor blockers become available.

Kidney International (2024) 105, 31–34

TRANSLATIONAL SCIENCE

SGLT2 inhibitors alleviated podocyte damage in lupus nephritis by decreasing inflammation and enhancing autophagy

Xin-yu Zhao,[1,2] Shuang-shuang Li,[1,2,3,4] Ying-xin He,[1,2,3,4] Li-jie Yan,[1,2,3,4] Fu Lv,[1,2] Qi-meng Liang,[1,2] Yu-hui Gan,[1,2,3,4] Li-pei Han ,[1,2] Hong-de Xu,[2,4] Yong-chun Li,[2,4] Yuan-yuan Qi [1,2,5]

In addition to immunosuppressive therapies to improve immunological disorders, authors are optimistic that SGLT2 inhibitors with strong renoprotective and cardioprotective effects will offer significant therapeutic benefits to patients with LN.

Sodium-glucose cotransporter-2 inhibitors (SGLT2)

Ann Rheum Dis 2023;82:1328–1340. doi:10.1136/ard-2023-224242

Management of patients who show unsatisfactory response to initial therapy for active LN

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

Kidney International (2024) 105 (Suppl 1S), S1–S69

Definition of refractory lupus nephritis

Refractory LN is commonly defined as “no response to standard treatment according to EULAR/EDTA guidelines.

- **Failure to improve within 3–4 months**
- **Not achieving partial response after 6–12 months**
- **No complete response to SOC therapy after 2 years of treatment.**

Drugs (2023) 83:117–134

Targeted therapies for Lupus nephritis

Joint Bone Spine 90 (2023) 105523

Contents lists available at ScienceDirect

Joint Bone Spine

journal homepage: www.elsevier.com

Review

New biologics and targeted therapies in systemic lupus: From new molecular targets to new indications. A systematic review

Renaud Felten[a], Marc Scherlinger[a], Philippe Mertz[a], François Chasset[b], Laurent Arnaud[a,*]

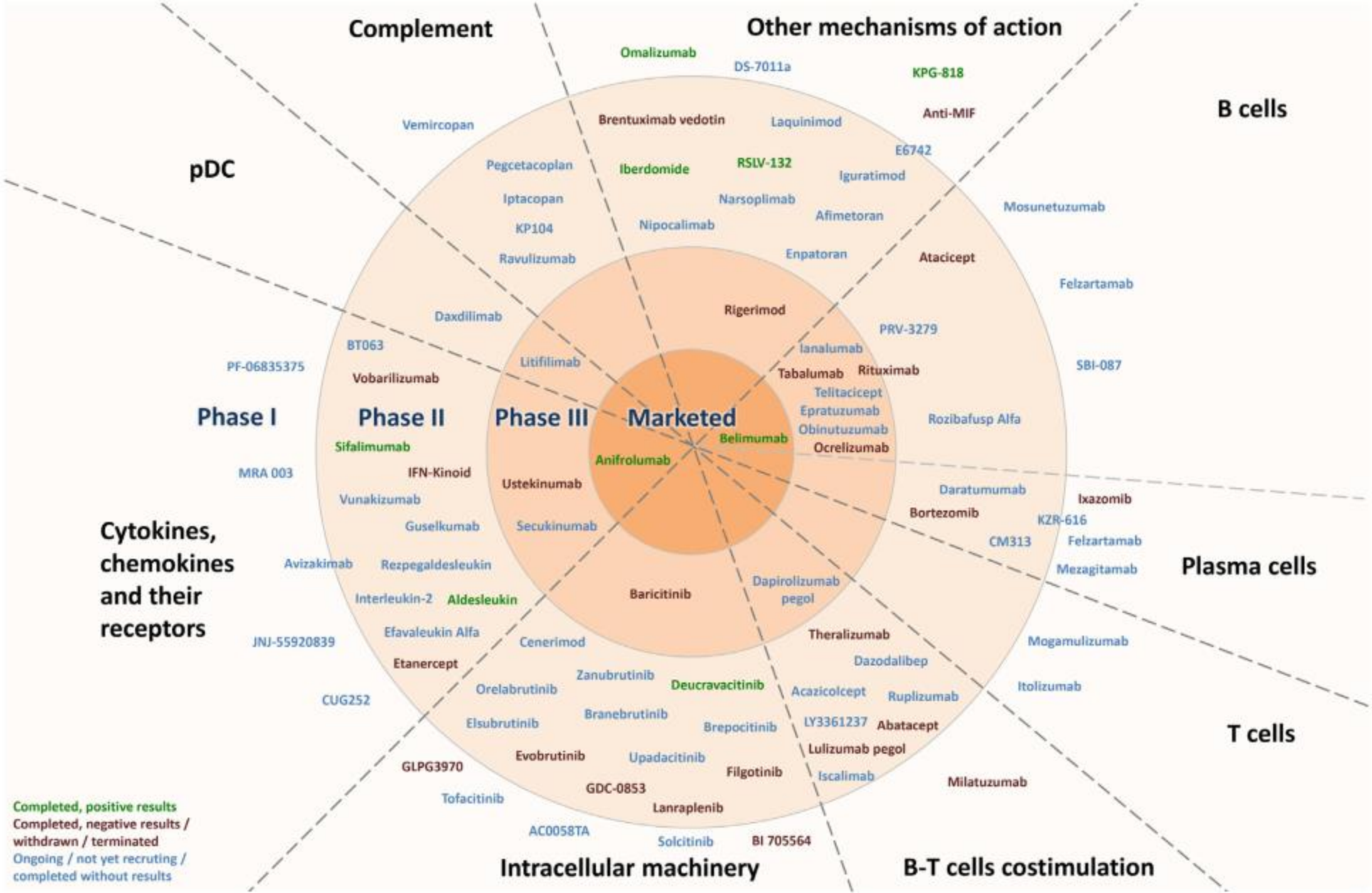
[a] *Service de rhumatologie, hôpitaux universitaires de Strasbourg, université de Strasbourg, centre national de référence RESO-Lupus, 67000 Strasbourg, France*

[b] *Sorbonne université, faculté de médecine Sorbonne université, AP–HP, service de dermatologie et allergologie, hôpital Tenon, 75020 Paris, France*

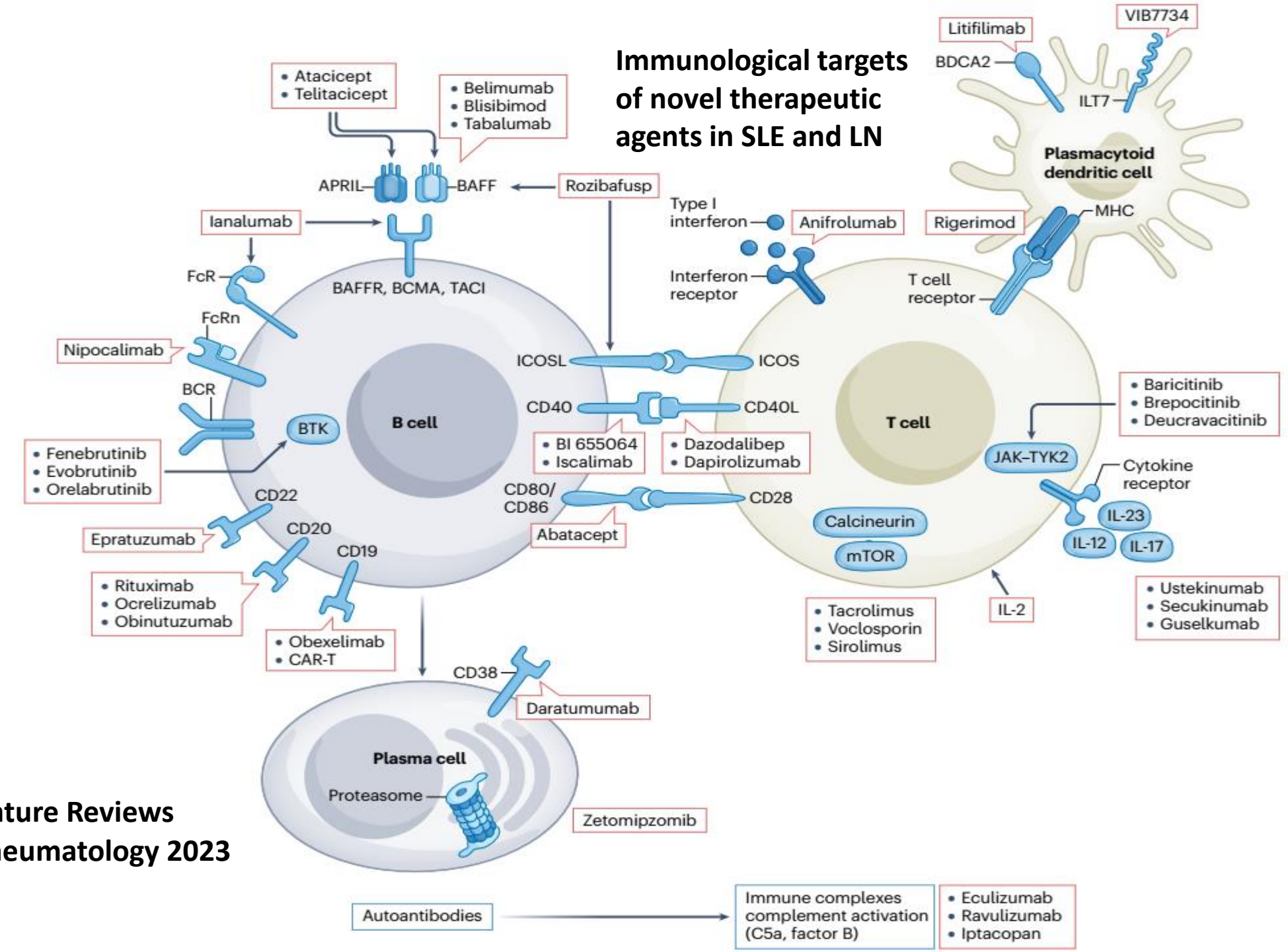
Targeted therapies according to their mechanisms of action, phases of development and status

R. Felten, M. Scherlinger, P. Mertz et al.

Joint Bone Spine 90 (2023) 105523



Immunological targets of novel therapeutic agents in SLE and LN



Nature Reviews Rheumatology 2023

B Cell Suppressing/Depleting Therapies

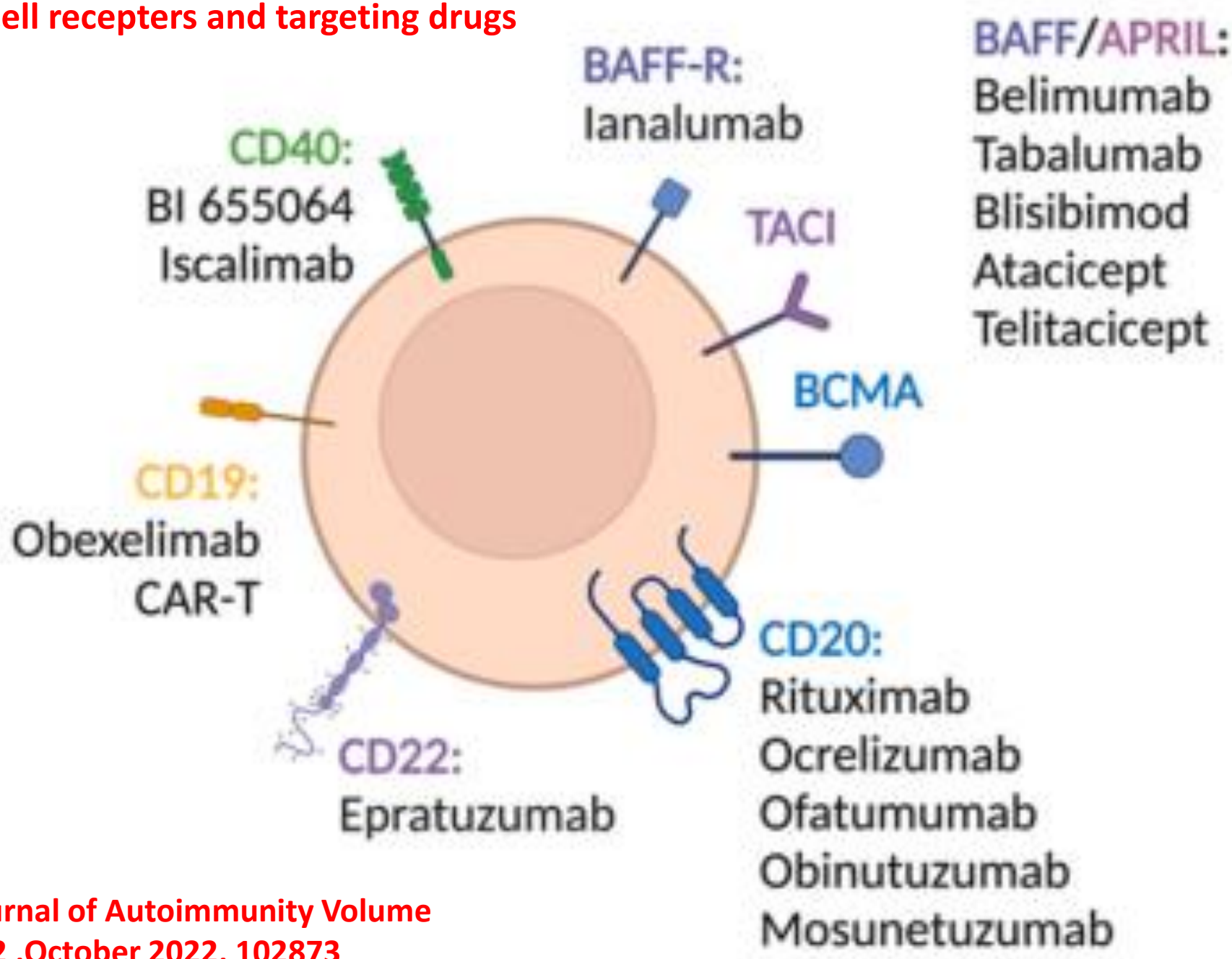
- **B cells have a central role in the pathogenesis of LN and are the most investigated axis for drug therapy.**

Approaches include:

- **B-cell depletion (ie, rituximab, obinutuzumab, ofatumumab, and ocrelizumab)**
- **Anti-B-cell activation (ie, belimumab, obexelimab, atacicept, blisibimod, and ianalumab)**
- **Co-stimulatory blockade (ie, iscalimab, abatacept, ruplizumab, and dapirolizumab pegol)**
- **Anti-plasma cell therapy (ie, bortezomib, daratumumab, and ixazomib).**

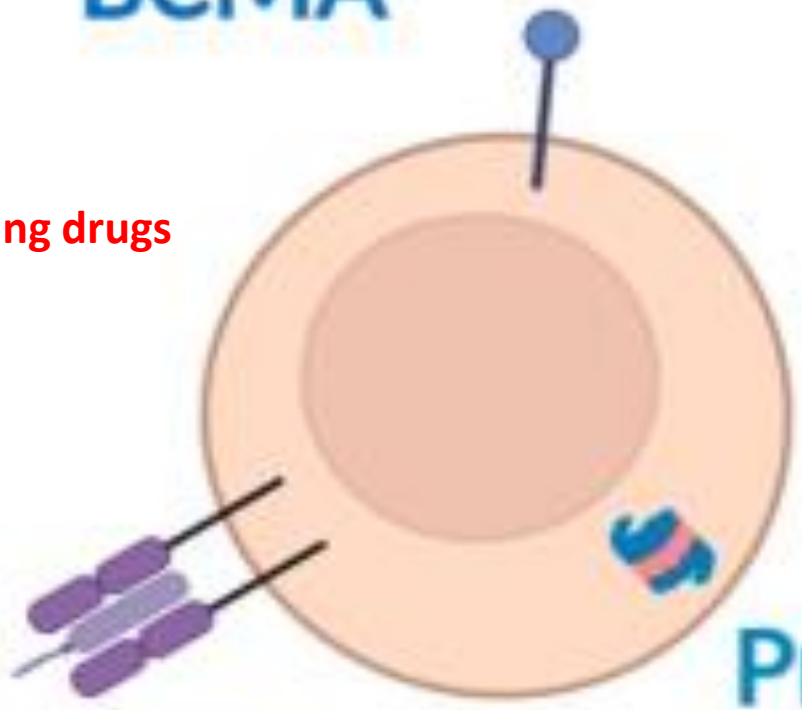
Kidney Med. 5(8):100688. Published online June 14, 2023

B cell recepters and targeting drugs



Journal of Autoimmunity Volume
132 ,October 2022, 102873

Plasma cell targeting drugs



CD38:
Daratumumab

Proteasome:
Bortezomib
Zetomipzomib

Journal of Autoimmunity Volume 132 ,October 2022, 102873

B cell targeting in SLE

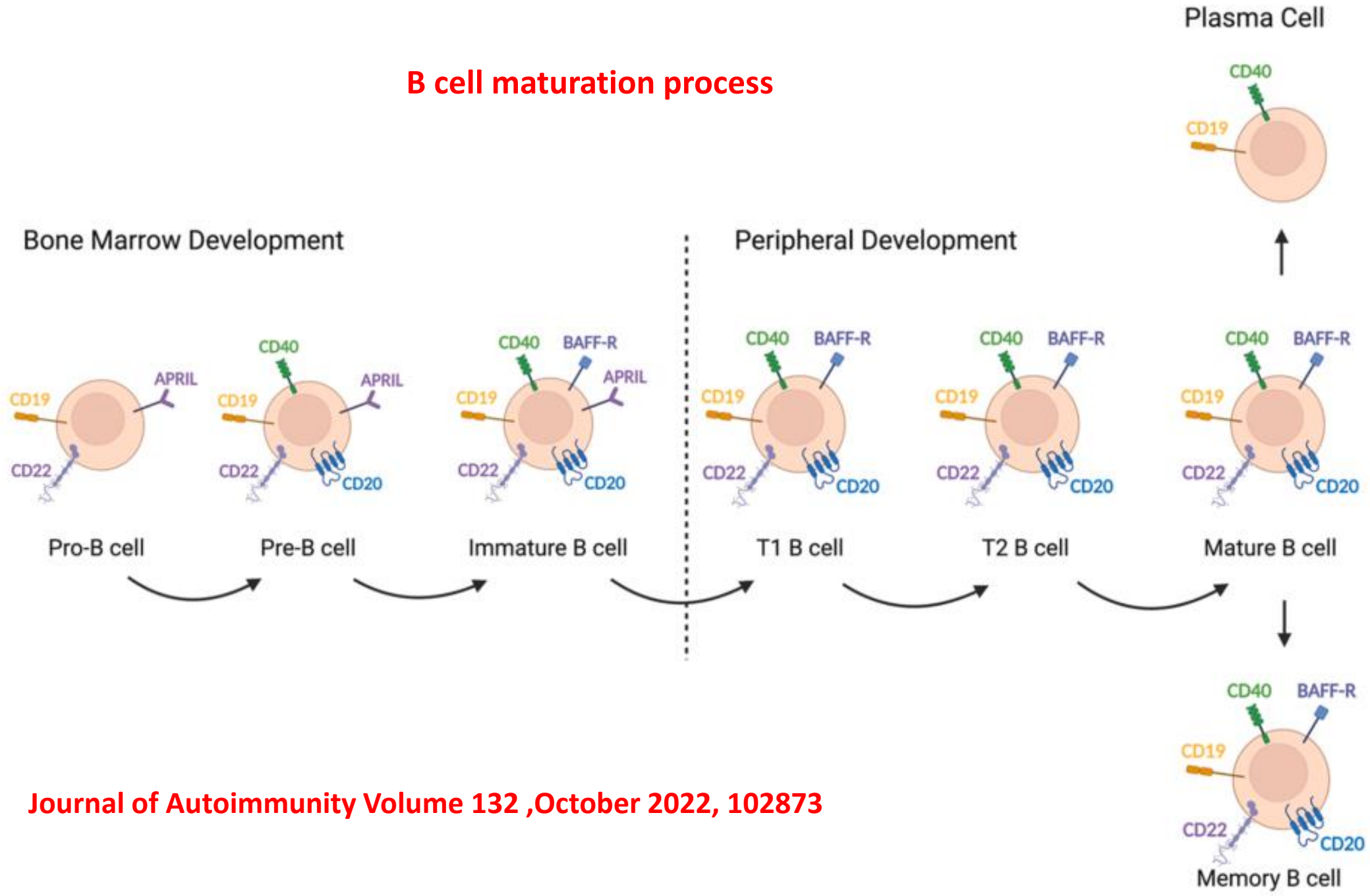
- Unexpectedly, B cell depletion by administration of the monoclonal anti-CD20 antibody RTX did not show significant effects in preventing or delaying relapses in patients with extra-renal SLE (EXPLORER trial) and in LN (LUNAR trial).

- While the reasons for these negative trial outcomes may be heterogeneous (patient selection, glucocorticoid effects), **it is important to consider that rituximab does not completely deplete B cells from the body.**

- Biopsy studies have shown large numbers of B cells residing in the lymph nodes, tonsils, bone marrow and synovium in patients receiving RTX despite good B cell depletion in the circulation .

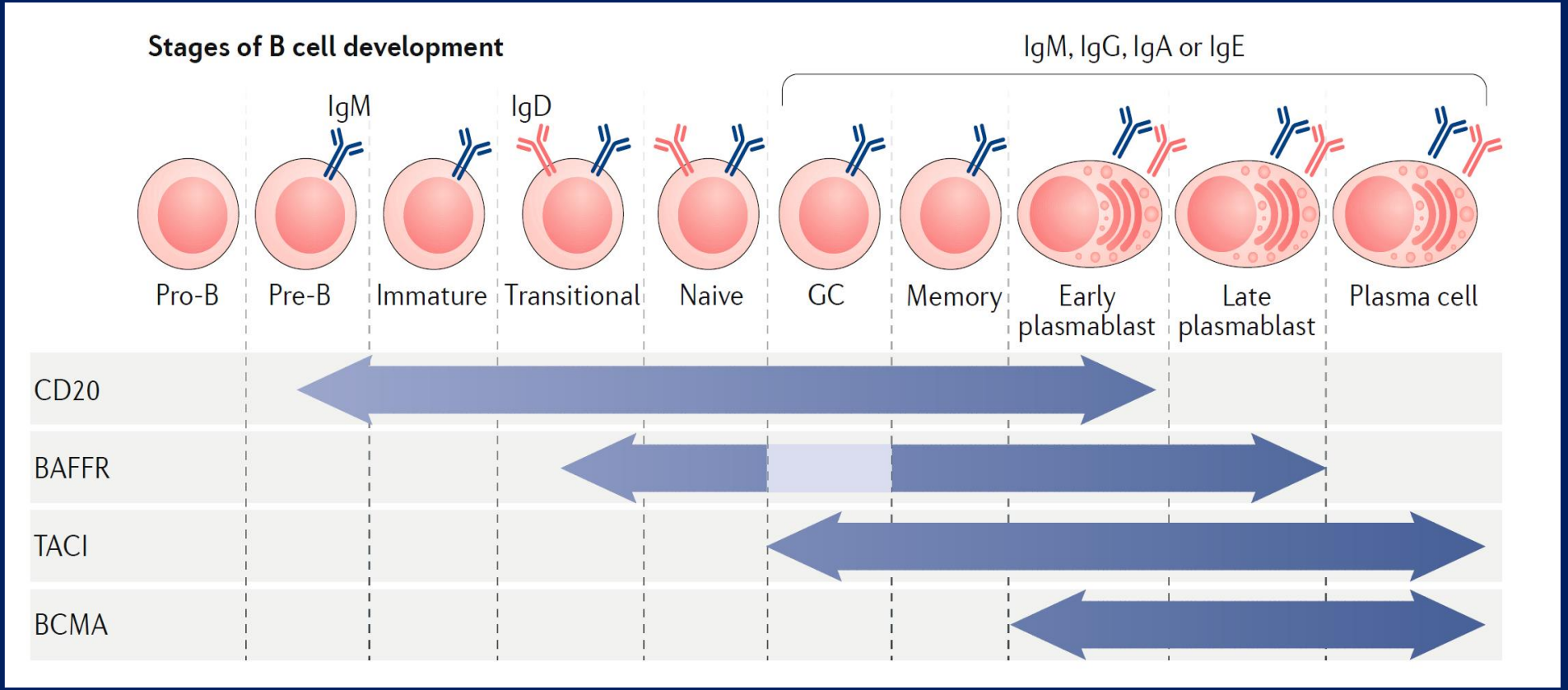
Arthritis & Rheumatology Dec 2023

B cell maturation process



Journal of Autoimmunity Volume 132 ,October 2022, 102873

Stages of B cell development and expression of cell surface receptors



Nat Rev Rheumatol 14, 580–591 (2018).

WORLD ACADEMY OF SCIENCES JOURNAL 3: 48, 2021

Rituximab therapy for lupus nephritis: A meta-analysis

LEI SHEN[1*], XIANGYING LIU[2*], CI SUN[3], GUOYUAN LU[1], LING ZHOU[1] and JIANZHONG LI[1]

[1]Department of Nephrology, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215006; [2]Department of Nephrology, Suzhou Ninth People's Hospital, Suzhou, Jiangsu 215299; [3]Department of Nephrology, The Second Affiliated Hospital of Soochow University (The General Hospital of Nuclear Industry, The Sino-France Friendship Hospital), Suzhou, Jiangsu 215004, P.R. China

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REVIEW ARTICLE

Clin Invest Med • Vol 43, no 2, June 2020

Zijie Yuan, MM[1]
Qifang Xie, MM[2]
Xiaochuan Wu, MD[3]
Boyu Tan, MM[4]
Xianhua Zhang, MM[1]

Rituximab treatment for lupus nephritis: A systematic review

Modern Rheumatology, **33**, 2023, 145–153
DOI: https://doi.org/10.1093/mr/roac007
Advance access publication date: 15 February 2022
Original Article

OXFORD

Rituximab in the real-world treatment of lupus nephritis: A retrospective cohort study in Japan

Yoshiya Tanaka[a,*], Shingo Nakayamada[a], Kunihiro Yamaoka[b], Koichiro Ohmura[c] and Shinsuke Yasuda[d]

[a]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
[b]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan
[c]Department of Rheumatology, Kobe City Medical Center General Hospital, Hyogo, Japan
[d]Department of Rheumatology, Tokyo Medical and Dental University, Tokyo, Japan

*Correspondence: Yoshiya Tanaka; tanaka@med.uoeh-u.ac.jp; The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahata-nishi, Kitakyushu 807-8555, Japan.

WORLD ACADEMY OF SCIENCES JOURNAL 3: 48, 2021

Rituximab therapy for lupus nephritis: A meta-analysis

Remission rate of RTX in the treatment of LN was a significantly higher than that of CYC and MMF group, Additionally, rituximab exhibited good safety.

REVIEW ARTICLE

Clin Invest Med • Vol 43, no 2, June 2020

Zijie Yuan, MM[1]
Qifang Xie, MM[2]
Xiaochuan Wu, MD[3]
Boyu Tan, MM[4]
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Rituximab treatment for lupus nephritis: A systematic review

Rituximab is effective for the treatment of Japanese patients with LN refractory to conventional therapy

Rituximab in the real-world treatment of lupus nephritis: A retrospective cohort study in Japan

Yoshiya Tanaka[a,*], **Shingo Nakayamada**[a], **Kunihiro Yamaoka**[b], **Koichiro Ohmura**[c] and **Shinsuke Yasuda**[d]

[a]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan
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[c]Department of Rheumatology, Kobe City Medical Center General Hospital, Hyogo, Japan
[d]Department of Rheumatology, Tokyo Medical and Dental University, Tokyo, Japan

*Correspondence: Yoshiya Tanaka; tanaka@med.uoeh-u.ac.jp; The First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, 1-1 Iseigaoka, Yahata-nishi, Kitakyushu 807-8555, Japan.

B cell targeting in SLE

- **Newer B cell targeting antibodies directed against CD20, such as ocrelizumab and obinutuzumab, which induce more robust B cell depletion.**
- **In active LN, overall renal response rates with ocrelizumab were numerically but not statistically significantly higher than placebo .**
- **while obinutuzumab showed significant clinical effects and steroid-sparing activity in patients with renal SLE.**

Arthritis & Rheumatology Dec 2023

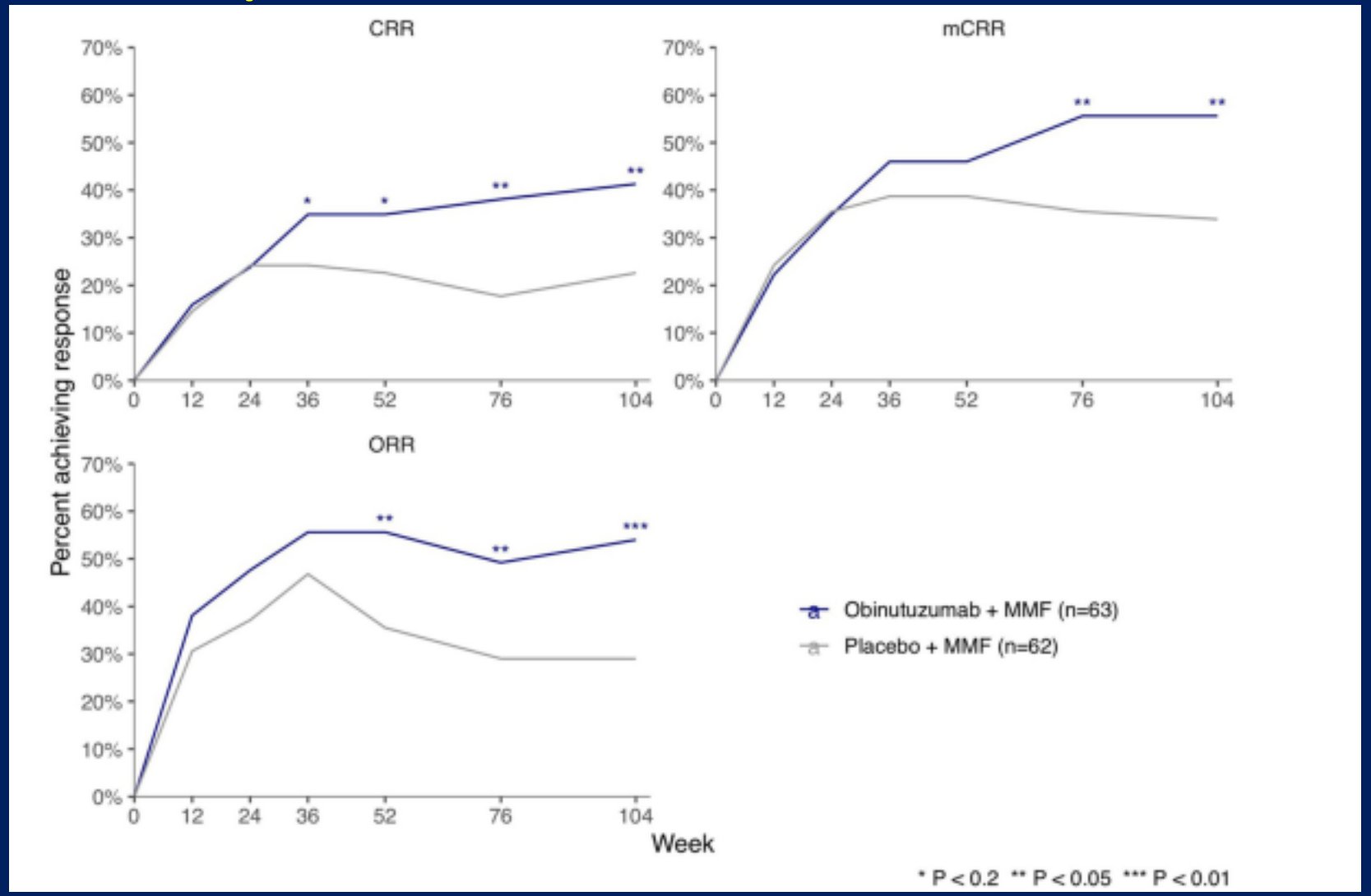
B-cell depletion with obinutuzumab for the treatment of proliferative LN

- **In this RCT , phase 2 trial (NOBILITY), obinutuzumab was superior to placebo for the achievement of complete and overall renal responses at week 52 when added to MMF and corticosteroids.**
- **Improved renal responses with obinutuzumab compared with placebo continued through week 104.**
- **Obinutuzumab resulted in rapid and potent depletion of peripheral B cells without an increase in the incidence of serious adverse events, serious infections or death compared with placebo.**
- **NOBILITY showed that obinutuzumab on a background of standard-of-care therapies improved renal responses through 104 weeks without increasing the frequency of serious adverse events.**
- **Based on the results from this study, the use of obinutuzumab in proliferative lupus nephritis is being further evaluated in a global phase 3 study.**

Furie RA, et al. Ann Rheum Dis 2022;81:100–107.

B-cell depletion with obinutuzumab for the treatment of proliferative LN

Renal responses over time.
CRR, complete renal response; mCRR, modified CRR; ORR, overall renal response.



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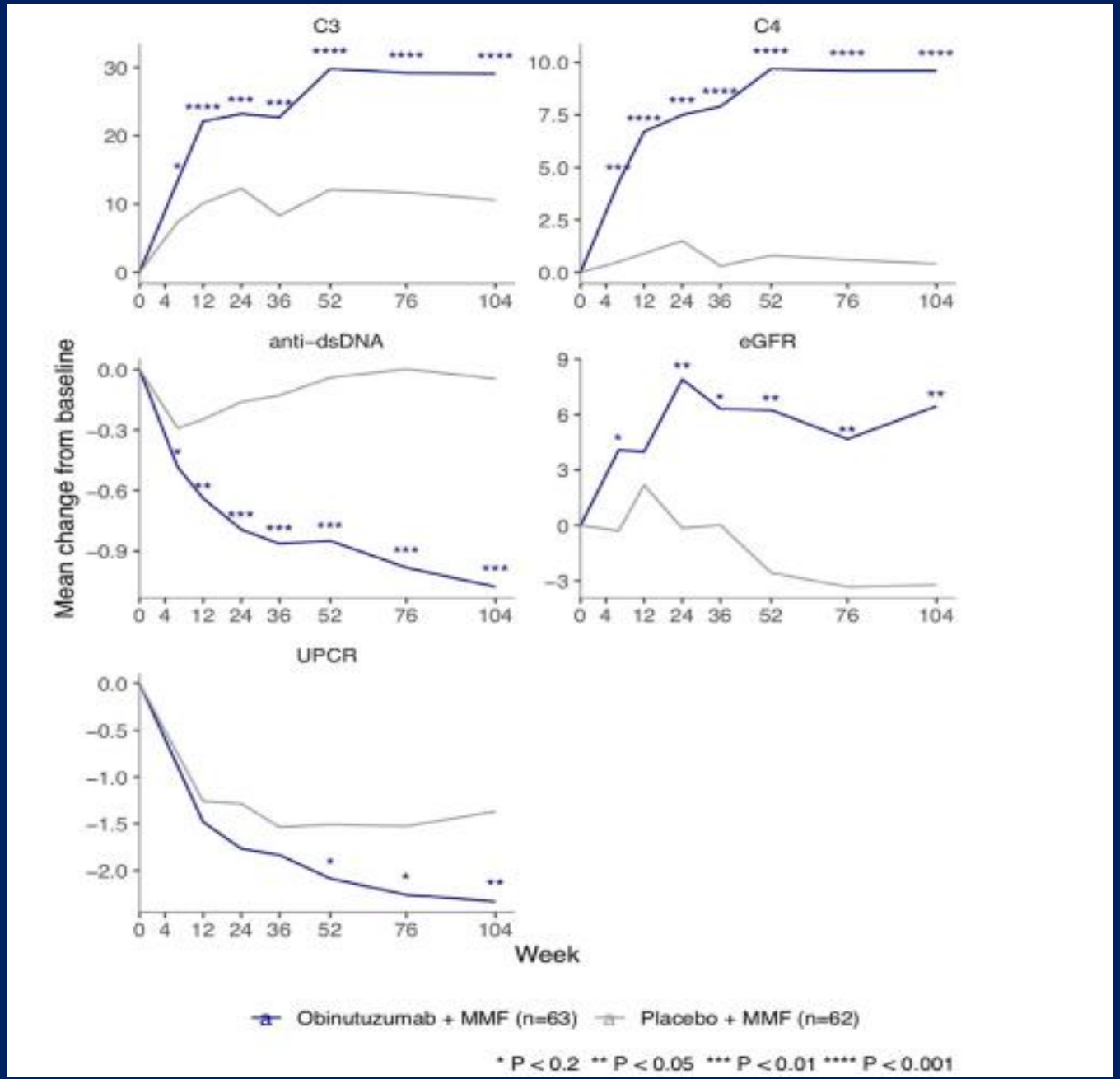
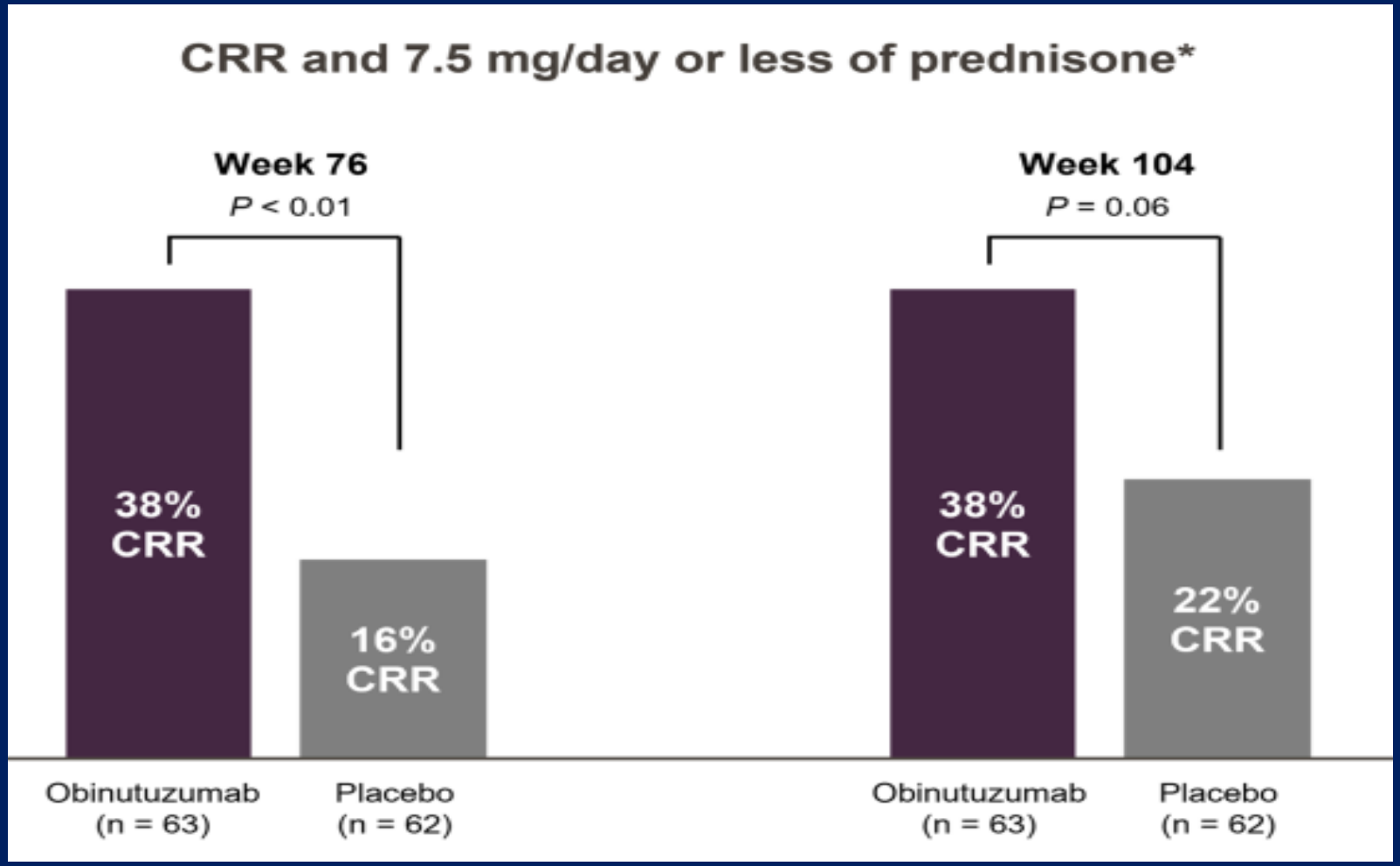


Change from baseline in laboratory parameters

Furie RA, et al. Ann Rheum Dis 2022;81:100–107.

Kidney Outcomes and Preservation of Kidney Function With Obinutuzumab in Patients With LN: A Post Hoc Analysis of the NOBILITY Trial

Arthritis & Rheumatology 2023



Obinutuzumab, in combination with SOC therapy, is the first CD20-targeted biologic to show efficacy and safety in lupus nephritis compared with SOC therapy alone in a randomized study.

Phase II Randomized Trial of RTX Plus CYC Followed by Belimumab for the Treatment of LN

In a multicenter, randomized, open-label clinical trial, 43 patients with recurrent or refractory LN were treated with:

- **RTX, CYC, and GC followed by weekly BEL infusions until week 48 (RCB group), or treated with RTX and CYC but no BEL infusions .**
- **Patients were followed up until week 96.**

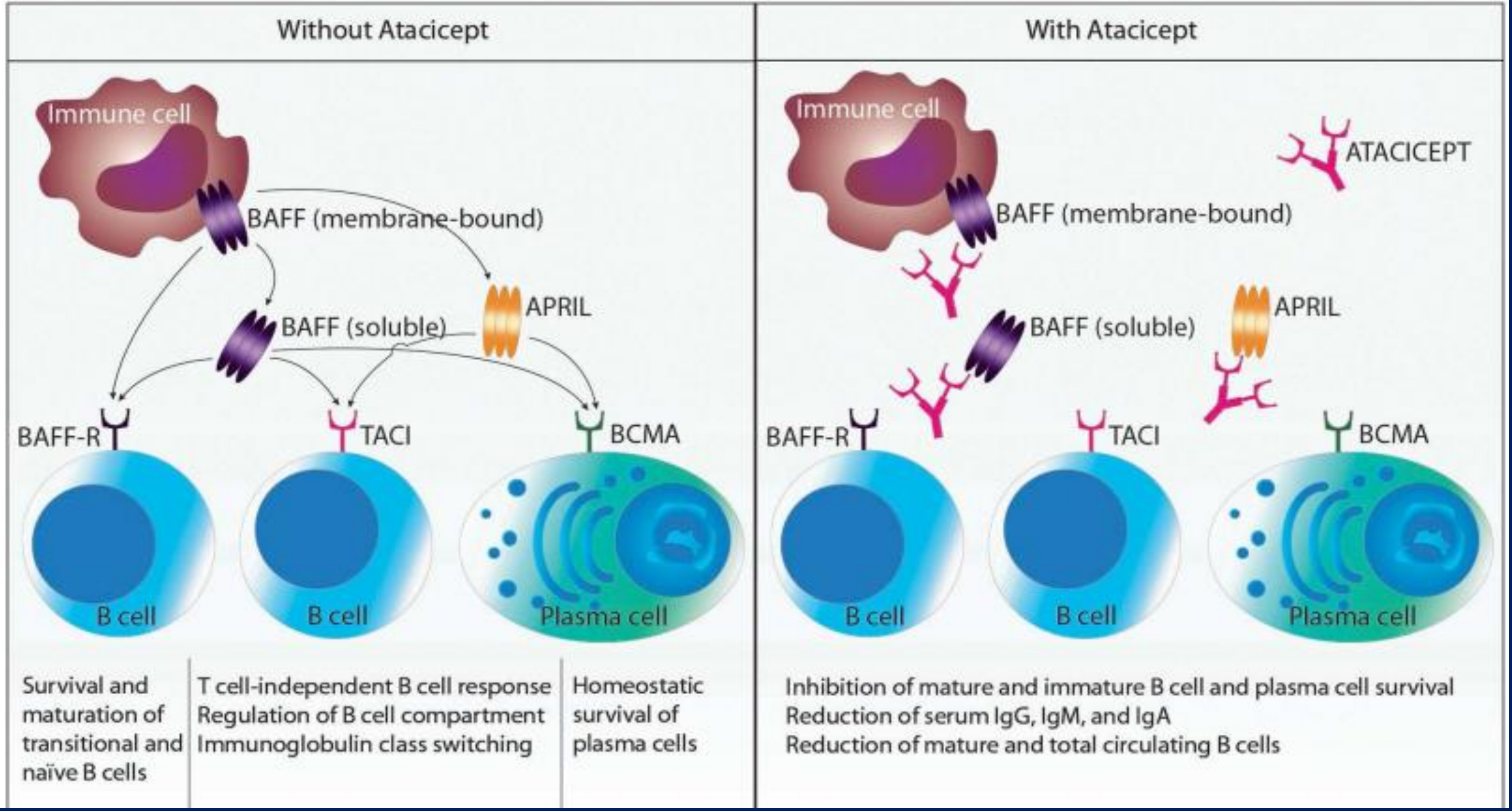
- **Percentages of total and autoreactive B cell subsets in the patients' peripheral blood were analyzed by flow cytometry.**

Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 121–131

Phase II Randomized Trial of RTX Plus CYC Followed by Belimumab for the Treatment of LN

- **The addition of belimumab to a treatment regimen with rituximab and CYC was safe in patients with refractory LN.**
- **This regimen diminished maturation of transitional to naive B cells during B cell reconstitution, and enhanced the negative selection of autoreactive B cells.**
- **Clinical efficacy was not improved with rituximab and CYC in combination with belimumab when compared to a therapeutic strategy of B cell depletion alone in patients with LN.**
- **The CALIBRATE trial is an important step in understanding the mechanisms of action of combination therapy with rituximab and belimumab for the treatment of LN in SLE.**

Arthritis & Rheumatology Vol. 73, No. 1, January 2021, pp 121–131



Front. Immunol. 11:433. doi: 10.3389/fimmu.2020.00433

Systematic Review of Safety and Efficacy of Atacicept in Treating Immune-Mediated Disorders

- Atacicept is a fully human recombinant fusion protein consisting of the Fc region of human IgG1 and the binding portion of transmembrane activator and CAML interactor, which is able to bind the cytokines BAFF and APRIL.
- Atacicept acts as a “decoy receptor” for BAFF and APRIL by binding soluble APRIL, soluble BAFF and membrane-bound BAFF .
- Thus, atacicept interferes with the interaction of these cytokines with their cognate receptors TACI, B-cell maturation antigen (BCMA) and BAFF-R.
- To sum up, atacicept failed to show a superior effect on disease activity in comparison to placebo in patients suffering from MS, optic neuritis, RA or SLE.

Front. Immunol. 11:433. doi: 10.3389/fimmu.2020.00433

Telitacicept

- Telitacicept is a novel fusion protein that binds to the extracellular BLyS/APRIL-binding portion of the TACI receptor and Fc fragment of human IgG_1, thereby inhibiting both BLyS and APRIL.
- Patients in the telitacicept group exhibited a greater SLE Responder Index 4 (SRI-4) frequency at week 48 as a measure of improved disease.
- Telitacicept has now been approved by the National Medical Products Administration (MNPA) for the treatment of patients with SLE in China.
- The Phase II clinical trial of telitacicept in the United States is ongoing.

J. Clin. Med. 2023, 12, 6268

Daratumumab monotherapy for refractory LN

A case series of six patients (one male and five females) with a median age of 41.3 years (range, 20–61 years) with refractory LN

- These treated with intravenous daratumumab, an anti-CD38 monoclonal antibody (weekly for 8 weeks, followed by eight biweekly infusions and up to eight monthly infusions).
- One patient did not show any improvement after 6 months of therapy, and daratumumab was discontinued. **In five patients, the mean disease activity, as assessed by the SLEDAI 2000 index, decreased from 10.8 before treatment to 3.6 at 12 months after treatment.**
- Mean proteinuria (5.6 g per 24 h to 0.8 g per 24 h) and mean serum creatinine (2.3 mg dl−1 to 1.5 mg dl−1) also decreased after 12 months.
- **These data suggest that daratumumab monotherapy warrants further exploration as a potential treatment for refractory LN.**

Nature Medicine | Volume 29 | August 2023 | 2041–2047

chimeric antigen receptor (CAR) T cell therapy

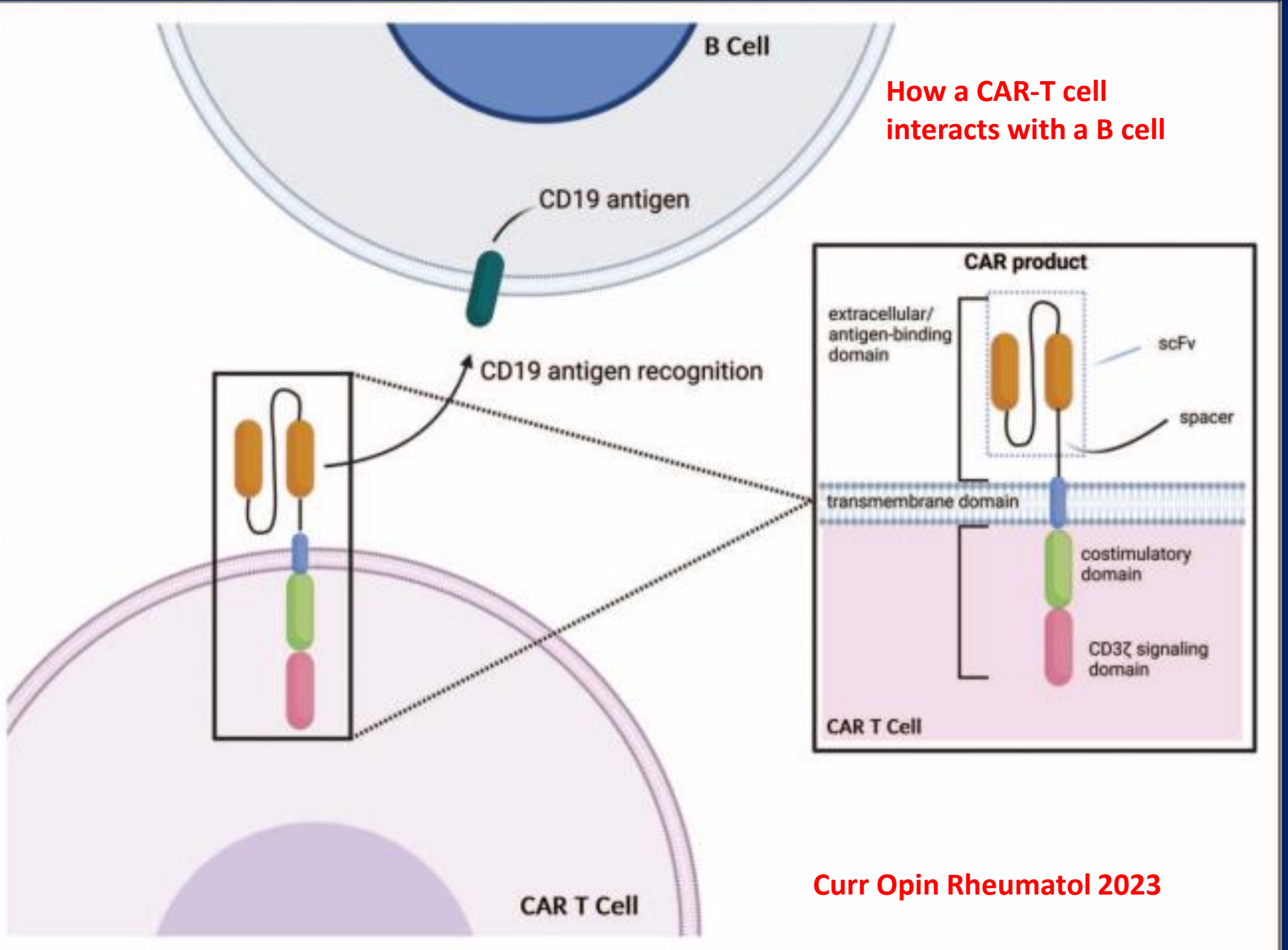
- With the rise of CAR T therapies, autoimmunity researchers have now embraced the B cell-killing potential of this modality.
- As with rituximab, CAR T therapies were first developed to kill blood cancer cells.
- To make these therapies, T cells are collected from a patient's blood and engineered in a lab to express a CAR that binds to a B cell marker, such as CD19.
- When these bespoke cells are re-infused into patients, they seek out and destroy their quarry — killing B cells in tissues that are out of reach to rituximab

Nature reviews drug discovery Volume 22 | November 2023 | 859–861 | 861

Chimeric Antigen Receptor (CAR) T cell therapy

- **CD19 CAR-T therapy has shown clinical and serological improvement in humans with rheumatic diseases such as systemic lupus erythematosus.**
- **CD19 CAR-T therapy effectively eliminated all autoantibody-producing cells.**
- **Dual-targeting of CD19 and B-cell maturation antigen (BCMA) targets both B-cells and plasma cells, thus eliminating all the sources of autoantibodies.**
- **Challenges include assessing the long-term safety, efficacy, expense, and durability of the treatment response.**

Curr Opin Rheumatol 2023



How a CAR-T cell interacts with a B cell

Curr Opin Rheumatol 2023

Iguratimod

- Iguratimod (IGU) is a methane sulfonanilide chemically composed of (N-[7-[(*methanesulfonyle*) *amino*]–4-oxo-6-phenoxy-4H-1-benzopyran-3-yl]-formamide).
- It was found to have an inhibitory effect on the expression of IL1 and IL-6 in monocytes, and selectively inhibited COX–2 activity .
- Further investigations have revealed that IGU down-regulated NF-κB activation.
- Moreover, IGU significantly inhibited the expression of MMP-1 and MMP-3 in RA synovial fibroblasts.
- These data indicate that IGU is a new DMARD for the treatment of RA.

The Lancet Regional Health - Western Pacific 10 (2021) 100128

Efficacy and safety of Iguratimod as an add-on therapy for refractory LN (A preliminary investigational study)

- **They enrolled 26 eligible participants.**
- **11/26 patients had CKD stage 2/3 at the baseline.**
- **The IS combined with IGU included MMF , tacrolimus, and cyclosporine A.**
- **80.7% of patients had baseline steroids less than 0.5mg/kg daily and there was no steroids escalation during the IGU treatment.**
- **With a median follow-up of 52 weeks (range: 23-116 weeks), the CRR rate at the last visit was 50% (13/26) .**

Front. Immunol.2023.1062919

Low-dose interleukin-2 therapy: a promising targeted therapeutic approach for SLE

- **Interleukin (IL)-2 plays an essential role in the generation, function and homeostasis of the T_{regs} and is reduced in SLE**
- **Two recent RCT phase 2 have consistently demonstrated that low-dose IL-2 therapy in SLE is very well tolerated.**
- **In these studies they didn't have any signals for augmented immunosuppression.**
- **It is capable of selectively recovering and expanding a functionally competent Treg population.**

Curr Opin Rheumatol 2023, 35:98–106

Low-dose interleukin-2 therapy: a promising targeted therapeutic approach for SLE

- **Its favorable safety profile also renders low-dose IL-2 therapy an ideal candidate for combination with other immunotherapeutic including biologics.**

- **Low-dose IL-2 could provide synergistic and complementary immunomodulatory effects without increasing the risk for infections.**

- **Several randomized clinical trials using either native IL-2 or IL-2 muteins in diverse inflammatory and autoimmune diseases are currently ongoing including one phase 3 trial in SLE in China.**

Curr Opin Rheumatol 2023, 35:98–106

Does baricitinib reduce disease activity in patients with SLE?

(A systematic review and meta-analysis of randomized controlled trials)

- ***In this meta-analysis, baricitinib 2 mg did not show any clinical benefit.***
- ***In contrast, baricitinib 4 mg significantly reduced SLE activity in terms of SRI-4 response at week 24.***
- ***However, this did not reach statistical significance at week 52.***
- ***Further studies are required to investigate the long-term efficacy of baricitinib 4 mg in patients with SLE.***

Clinical Rheumatology 2023

JAKinibs in SLE
(Deucravacitinib)

Deucravacitinib is the first compound that targets the pseudokinase domain of a JAK, namely TYK2, and therefore represents a highly selective, allosteric TYK2 inhibitor that can inhibit IL-12, IL-23 and IFN signaling.

In a phase II randomised, double-blind, placebo-controlled trial, safety and efficacy of deucravacitinib was shown in patients with active SLE with a higher response rate for the SLE Responder Index 4 at week 32 with an acceptable safety profile.

Bonelli M, et al. Ann Rheum Dis 2023;0:1–22

Refractory or resistant lupus nephritis

- **Patients who do not respond to rituximab or extended CYC therapy could benefit from newer anti-CD20 (obinutuzumab) or anti-plasma cell (bortezomib, daratumumab) therapies .**

- **Cellular therapy with CAR-T cells could be an alternative for patients with LN refractory to several approaches.**

- **Ideally, LN patient refractory to several lines of treatment should be included in ongoing clinical trials evaluating new therapies.**

Clinical Kidney Journal, 2023, vol. 16, no. 9, 1384–1402

Conclusion

- **LN outcomes have improved over recent decades, but there is a great need for safer and more effective therapies.**
- **As seen in other glomerular diseases, lower doses of GCs may be as efficacious and safer than higher-dose steroids.**
- **A minimum of 3 years for most patients is now a widely accepted .**
- **Recent trials show that the addition of BEL or VOC to induction therapy may lead to improved kidney outcomes, but cost remains a major issue.**

Thank you for your attention