Thursday, 9th December
11:15 am – 12:00 pm
Congress Center Kursaal Interlaken Room A

"(How) can we reduce corticosteroid exposure in lupus nephritis?"

Chair: Prof. Dr. med. Uyen Huynh-Do, Bern
Speaker: PD Dr. med. Andreas Kistler, Frauenfeld

This symposium is supported by Otsuka Pharmaceutical (Switzerland) GmbH

Otsuka

Nephrology and Otsuka – creating the future together.

(How) can we reduce steroid exposure in lupus nephritis?

Andreas Kistler

Kantonsspital Frauenfeld

Case vignette: 29 y/o female patient

- Diagnosis of SLE 6 years back
- LN class V 3 years back (UPCR 0.5 – 1.0)
- Under HCQ, AZA and intermittent low / intermediate dose steroids for extrarenal manifestations (joints, skin, pleurisy)
- Successful pregnancy 1.5 years back
- Now rising proteinuria for 6 months (up to 3g/d), active sediment, slightly deteriorating renal function
- Biopsy: class IV and V LN with high activity and moderate chronicity
- You decide to switch to MMF 2 x 1.5g
- In addition...

Case vignette

Do you give IV methylprednisolone pulses?

a) No
b) Yes, 3 x 1000 mg
c) Yes, 3 x 500 mg
d) Yes, 3 x 250 mg
e) Yes, 1-2 x 1000 mg
f) Yes, 1-2 x 500 mg
g) Yes, 1-2 x 250 mg

Case vignette (patient weight 73 kg)

Which oral prednisone taper do you prescribe?

a) 70mg, taper to 5-10 mg by 6 months, following a scheme
b) 70mg, taper based on response (which parameters?)
c) 50mg, taper to 5 mg by 4-6 months, following a scheme
d) 50mg, taper based on response
e) 25mg, taper to 5 mg by 3 months, following a scheme
f) 25mg, taper based on response
g) no oral prednisone

Case vignette

Provided that the patient responds to treatment (proteinuria reduction, improvement of the sediment, GFR stabilisation, no extrarenal activity), how long do you keep low dose PDN?

a) Stop asap (before month 6)
b) Stop between month 6 and 12
c) Keep at 7.5 mg for ≥ 12 months in total
d) Keep at 5 mg for ≥ 12 months in total
e) Keep at 2.5 mg for ≥ 12 months in total
f) Stop if no serological activity (complement levels, dsDNA-Ab)

Case vignette

Same patient, but 10 years older with DM2 and osteoporosis. (How) do you try to minimise glucocorticoid exposure?

a) No IV pulses, use a low dose scheme (e.g. start at 25-30mg, rapid taper)

b) Use IV pulses to reduce the subsequent oral steroid dose

c) Use IV pulses and Rituximab 2x1g, avoid oral steroids

d) Use a calcineurin inhibitor (in addition to MMF) to minimize the steroid dose

e) Use belimumab (in addition to MMF) to minimize the steroid dose

How many patients with newly diagnosed / severely flaring lupus nephritis have you treated (induction therapy) in 2021 (personally)?

a) None
b) 1
c) 2
d) 3-5
e) 6-10
f) >10

Overview

An introduction to the pharmacological effects of glucocorticoids

Steroid use in lupus nephritis

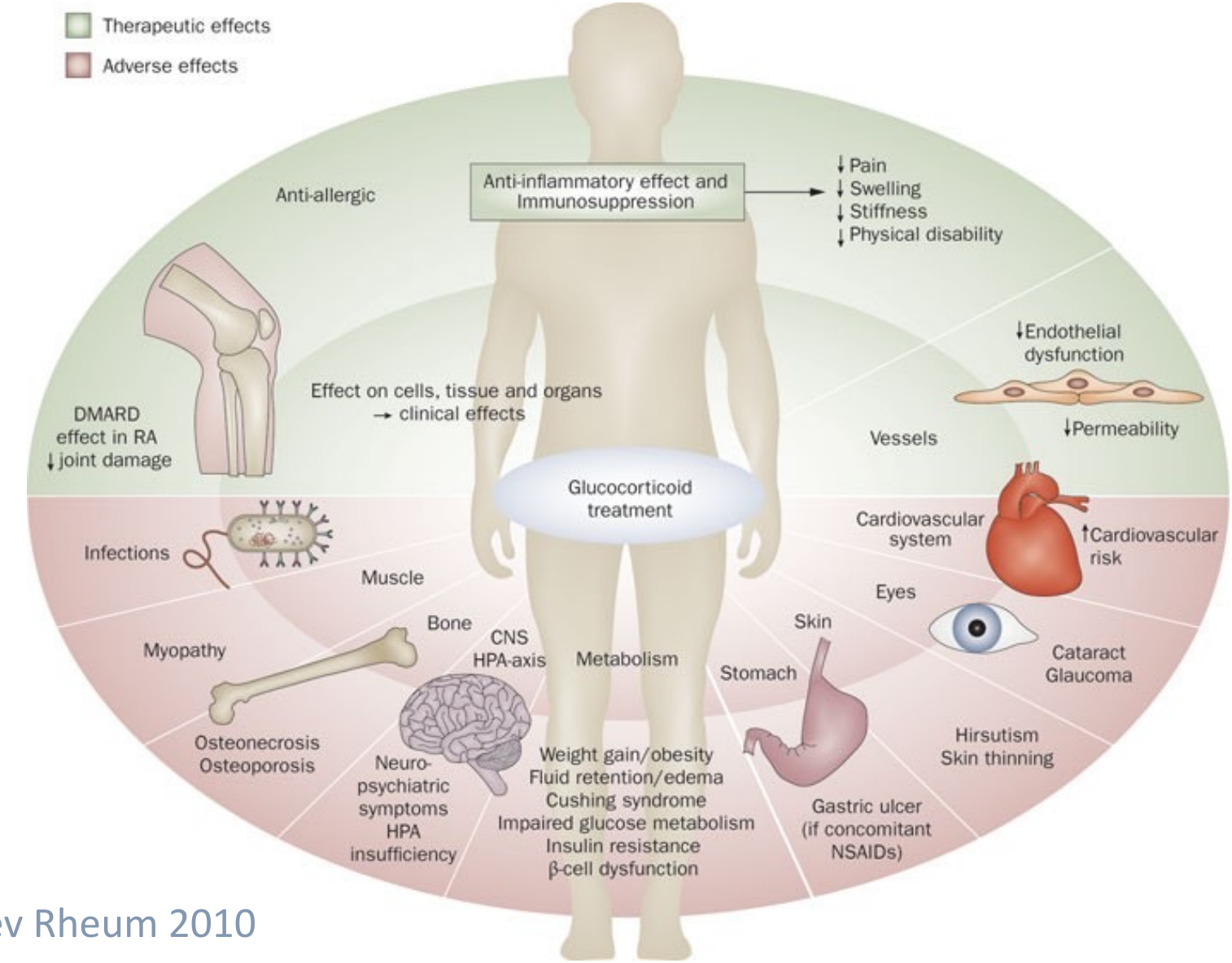
Why should we reduce steroid exposure? – *adverse effects of glucocorticoids*

(How) can we reduce steroid exposure in lupus nephritis?

Strategies for steroid-sparing:

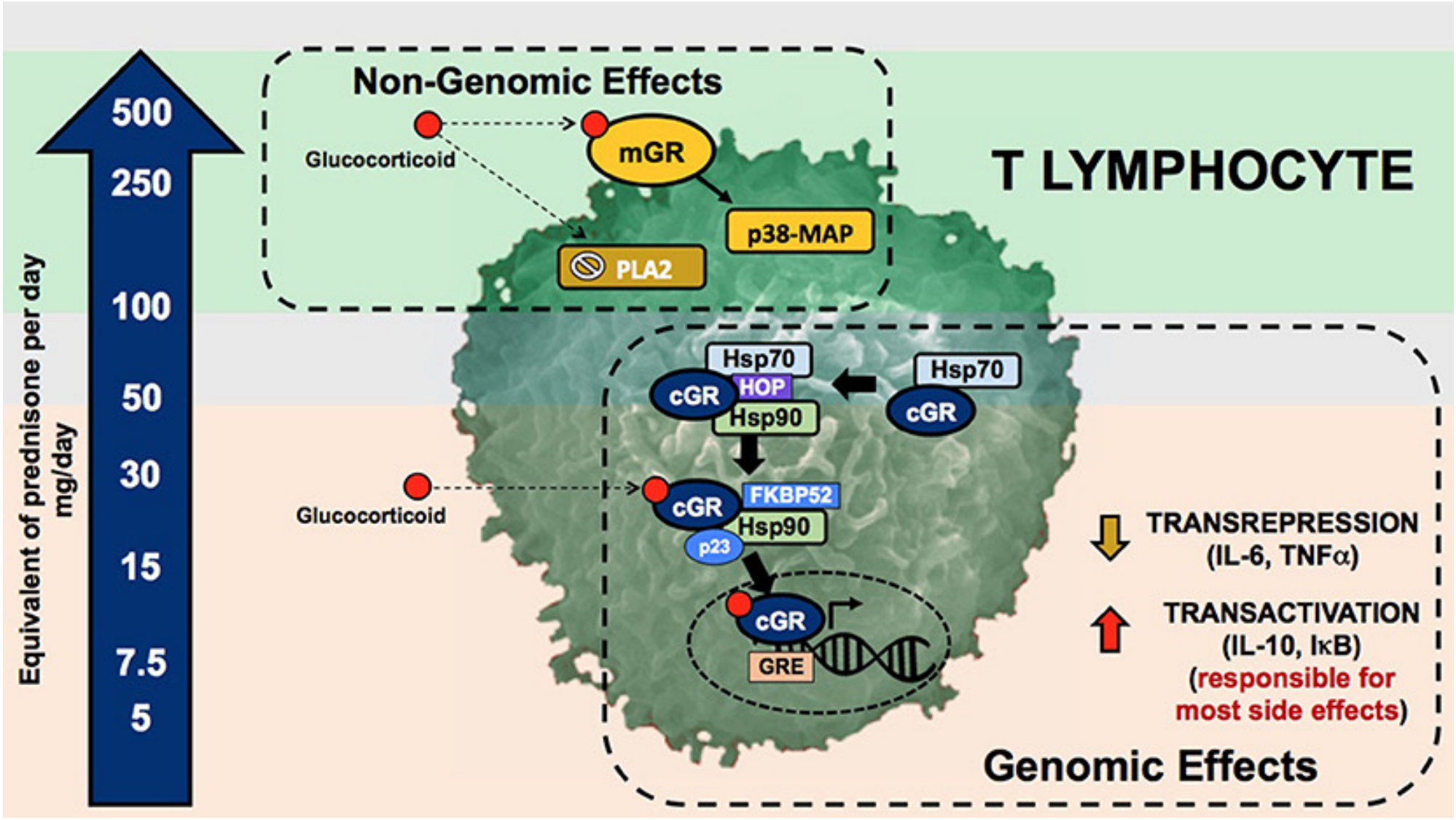
- ***Reduce***
- ***Replace***

Glucocorticoids: therapeutic and adverse effects



Hoes, Nat Rev Rheum 2010

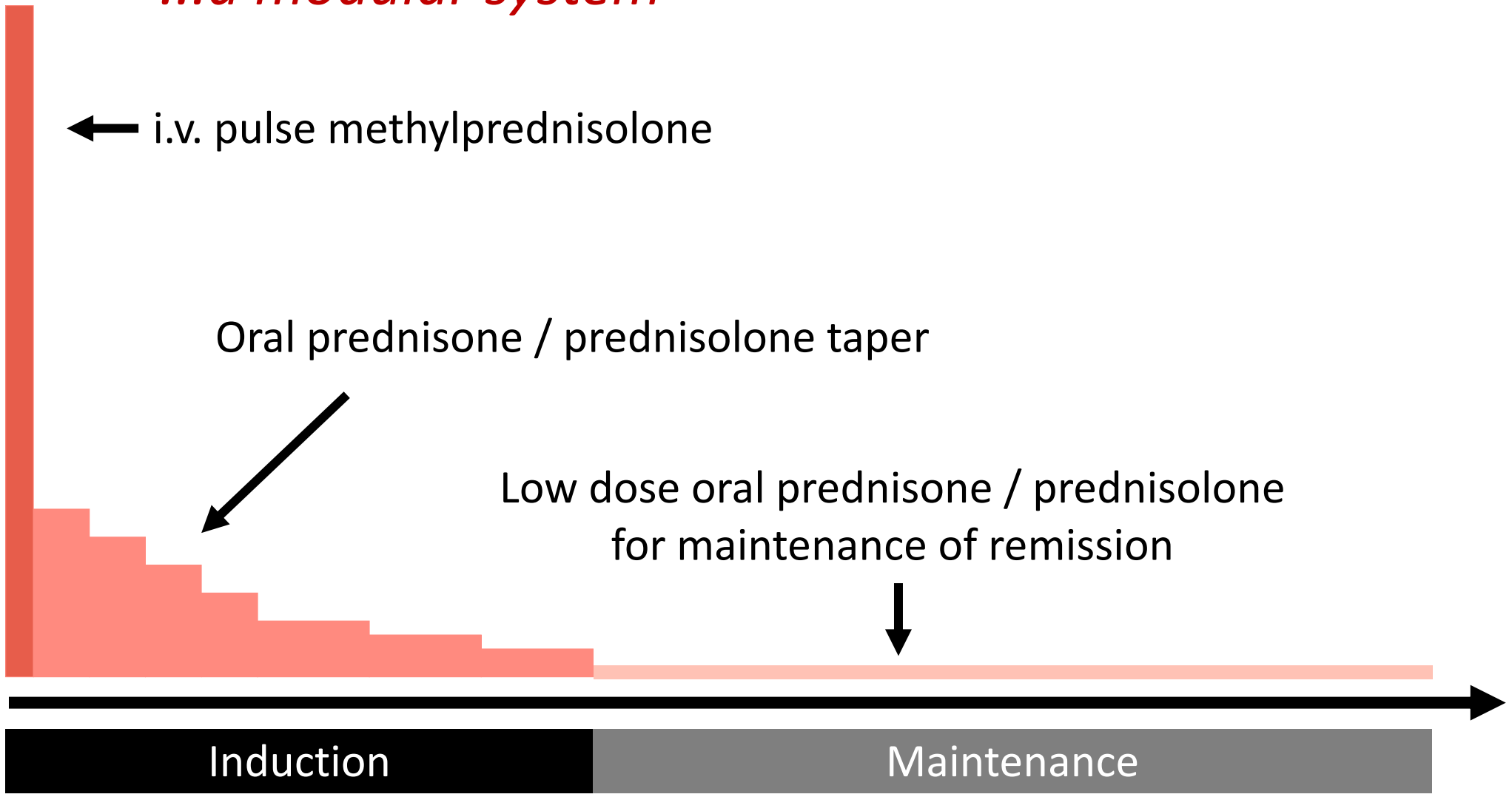
Glucocorticoids: mechanisms of action



Mejía-Vilet and Ayoub, Frontiers in Medicine 2021

Steroids in the treatment of Lupus nephritis

...a modular system



Steroid schemes and doses in various LN trials

TABLE 2 | Estimated cumulative glucocorticoid doses in a 24-week period for a 60 kg patient in different induction to remission schemes.

Regimen	Methylprednisolone total cumulative dose (g)	Oral prednisone total cumulative dose (g)	Oral prednisone average dose (mg/day)	Total GC dose (g)
Modified NIH, 2001 (76)	9.00	2.84	16.9	11.8
ELNT, 2002 (77)	2.25	3.12	18.5	5.37
ALMS, 2009 (85)	–	4.27	25.4	4.27
MYLUPUS, 2011 (80)	1.50	2.14	12.7	3.64
RITUXILUP, 2013 (86)	1.00	–	–	1.00
LupusCRUCES, 2014 (48)	1.50-3.00	1.30-1.50	8.0-9.0	2.80–4.50
Chinese multitarget, 2015 (81)	1.5	3.25	16.2	4.75
4+2 Rituximab, 2015 (87)	2.70	2.52	15.0	5.22
AURA-LV, 2019 (84)	1.00	1.33	7.9	2.33
BLISS-LN, 2020 (88)	0.50–3.00*	3.12–4.27	18.5–25.4	3.12–4.27
NOBILITY, 2020 (89)	0.75–3.00*	1.79–1.93	10.6–11.5	1.79–1.93

Methylprednisolone pulses elective at discretion of the investigator.

Mejía-Vilet and Ayoub, Frontiers in Medicine 2021

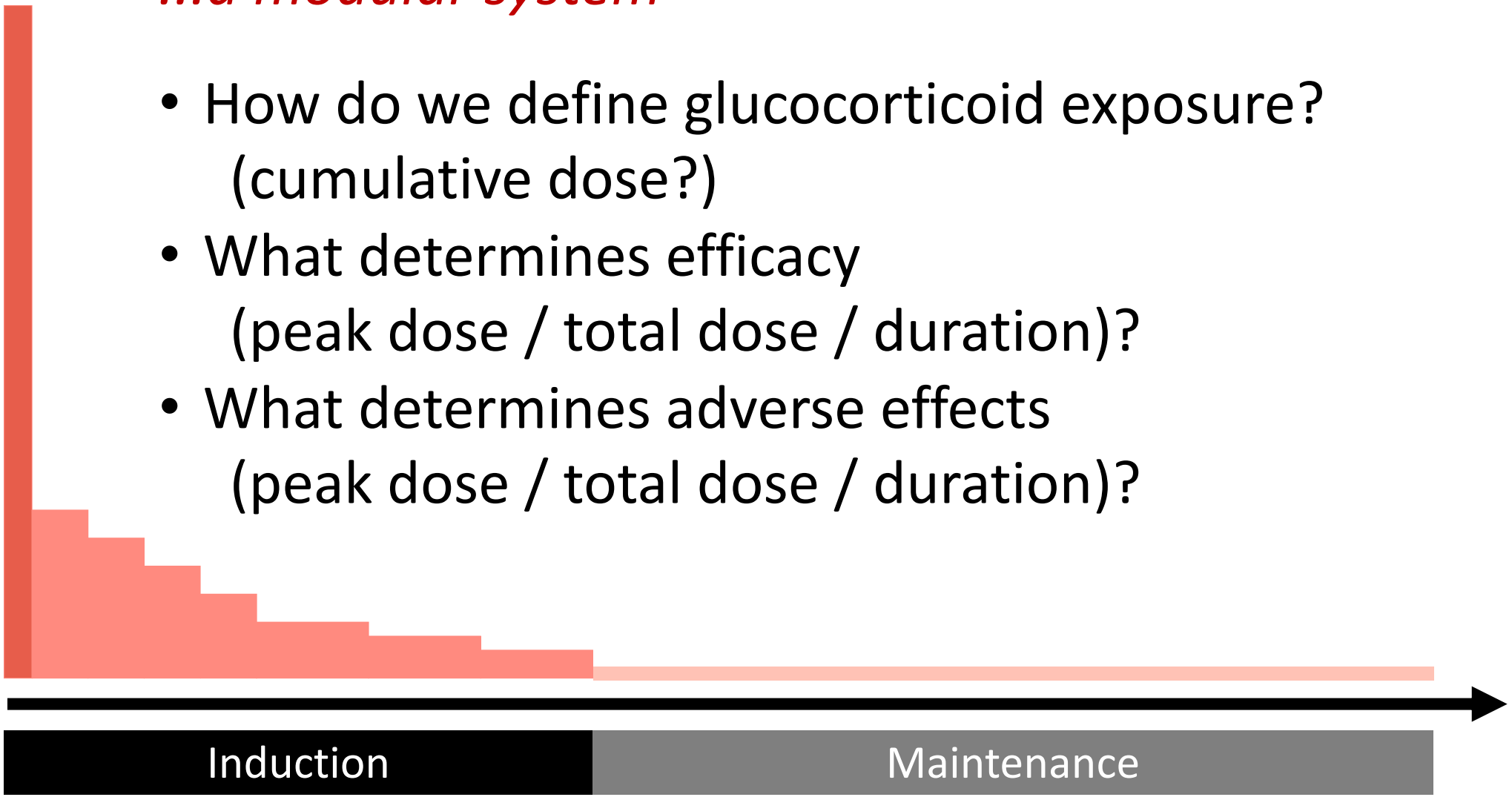
The heterogeneity of Lupus nephritis trial designs

Study	IS regimen	IV MPDN pulses	Oral GC (total dose in 6 m)	Study duration	Primary end point
ALMS induction	CYC NIH vs MMF 2 x 1.5 g	none	60mg/d Taper to 10mg/d at 24 weeks total ca. 4.3 g	6 m	UPCR < 3 or –50% SCr ± 25%
EUROLUPUS	CYC 0.5 g / 2w x 6, then AZA vs. CYC 0.5g /m^2 x 8, then AZA	3 x 0.75 g	0.5 (–1) mg/kg/d x 4 w Then taper by 2.5mg/d every 2 w, maintain 5 – 7.5 mg/d total ca. 3.2 g	41 m (median)	Treatment failure
LUNAR	MMF 2 x 1.5 g ± RTX 4 x 1 g	2 x 1 g	0.75 mg/kg/d Taper to ≤ 10mg/d by week 16	12 m	UPCR -50% and < 1 (if BL ≥ 1) or ≤ 3 (if BL >3) SCr ≤ 115% BL RBC ≤ 50% BL
BLISS-LN	CYC EUROLUPUS or MMF 2 x 1.5 g	Optional 1-3 x 0.5-1 g	0.5 – 1 mg/kg/d then taper	24 m	UPCR ≤ 0.7 eGFR ≥ 60 / ≥ 80% pre-flare No rescue therapy
AURORA	MMF 2 x 1 g	2 x 0.5 g	25 mg/d Taper to 2.5 mg/d at 16 weeks total ca. 1.2 g	12 m	UPCR ≤ 0.5 eGFR ≥ 60 / ≥ 80% BL No rescue therapy

Steroids in the treatment of Lupus nephritis

...a modular system

- How do we define glucocorticoid exposure?
  (cumulative dose?)
- What determines efficacy
  (peak dose / total dose / duration)?
- What determines adverse effects
  (peak dose / total dose / duration)?



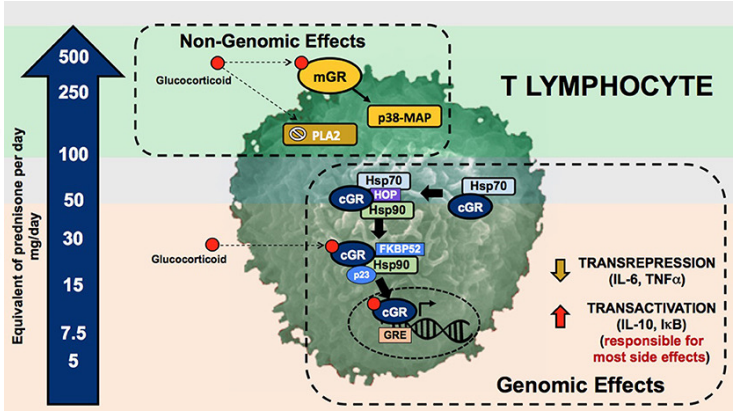
Is cumulative Steroid dose: a meaningful measure?

Lessons from endocrine orbitopathy (n=70)

Cumulative Dose: 4 g 4.5 g

	Oral prednisolone	Intravenous methylprednisolone	*P* value
Number of events	29	8	<0.001
Patients with events	18/35 (51%)	6/35 (17%)	0.005
Female with events	13/24 (54%)	4/25	0.007
Male with events	5/11 (45%)	2/10	0.361
Major events	2	0	
Weight gain (>3 kg)	9 (26%)	1	0.006
Gastrointestinal	6 (17%)	1	0.106
Sleeplessness	5 (14%)	2	0.428
Myalgias	3	0	
Hypertension	2	0	
Hirsutism	2	0	
Depression	1	0	
Palpitations	1	4	0.356

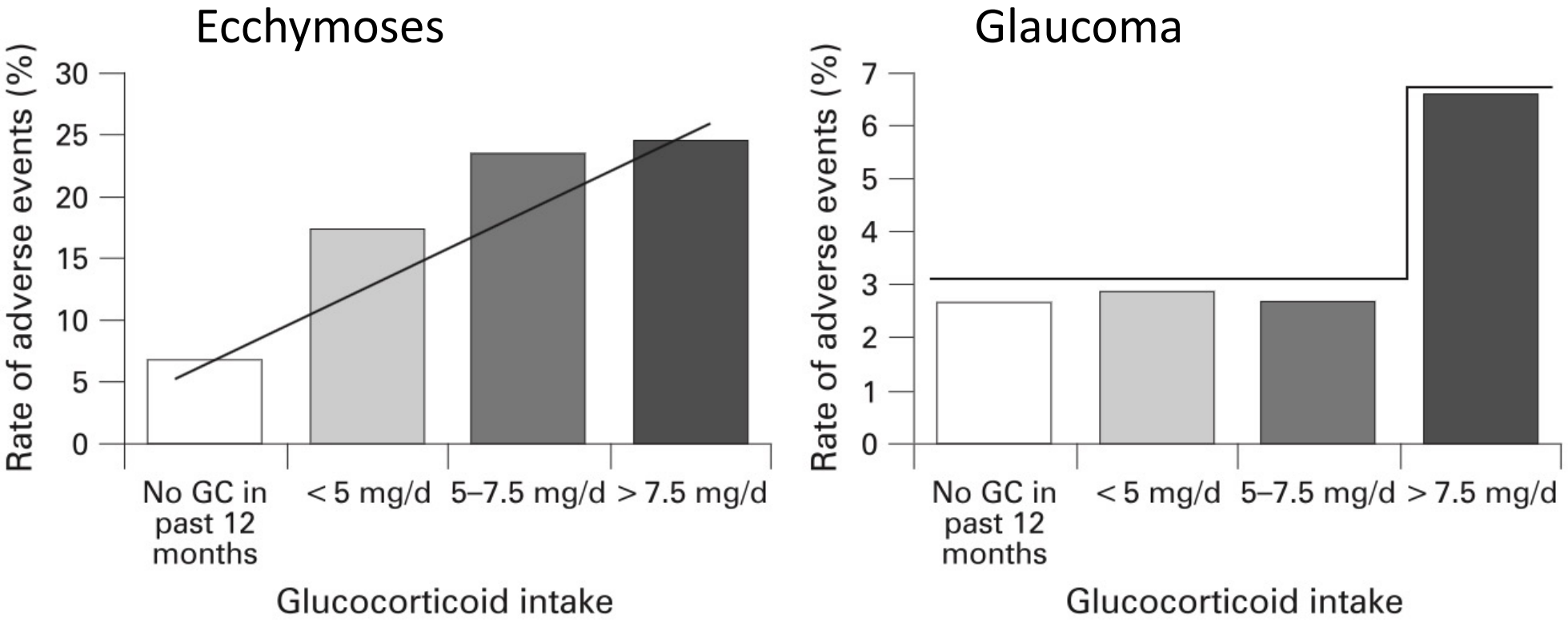
The exact test of Fisher (two-tailed) was performed.



Kahaly, J Clin Endocrinol Metab 2005

Dose-adverse-event-relation for glucocorticoids

Lessons from rheumatoid arthritis



Huscher, Ann Rheum Dis 2009

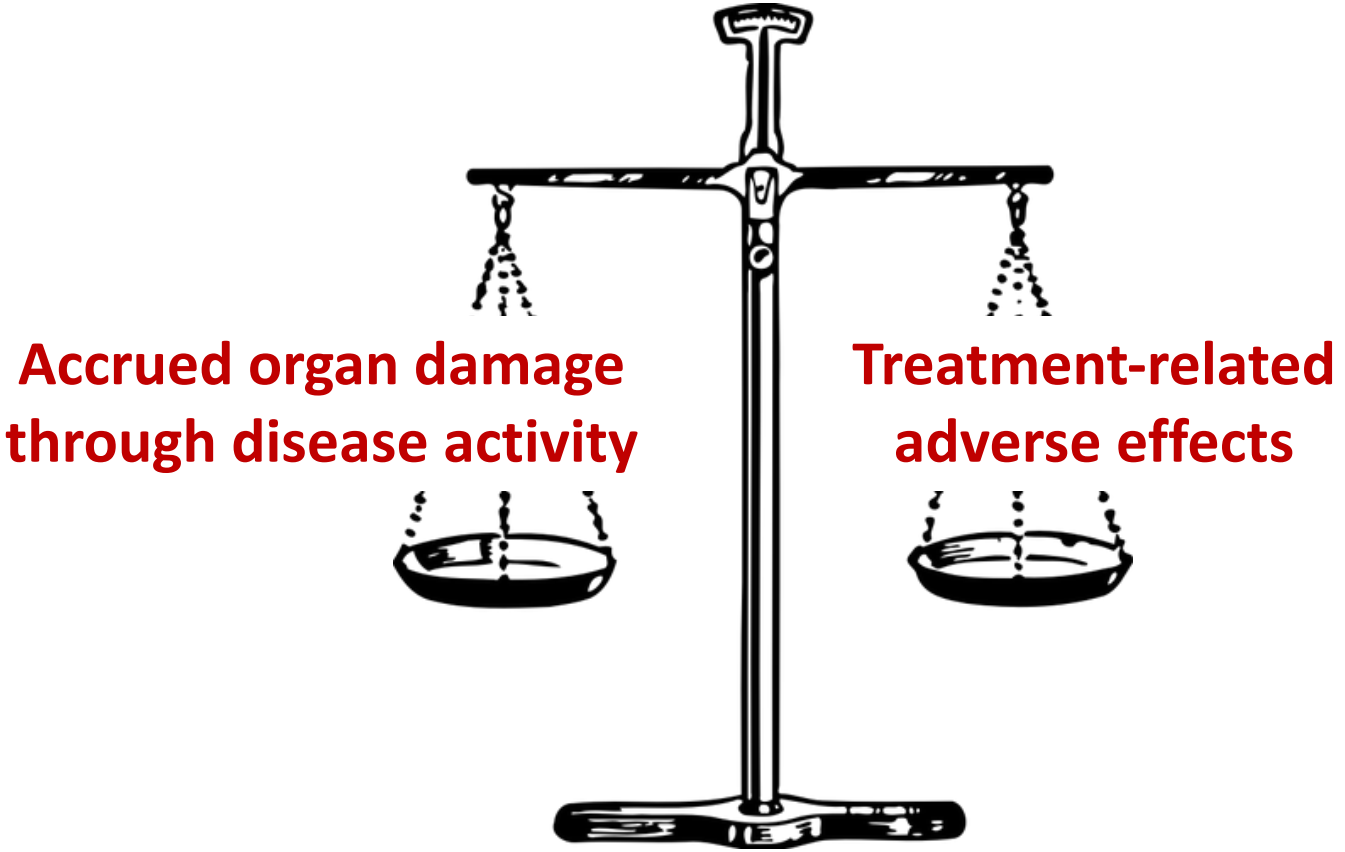
	No glucocorticoids in past 12 months	Patients with glucocorticoid intake for >6 months		
		<5 mg/day	5–7.5 mg/day	>7.5 mg/day
Patterns of adverse event rates (%) by dose of glucocorticoids				
"Linear" rising				
Cushingoid phenotype*	2.7	4.3	15.8	24.6
Ecchymosis*	6.8	17.4	23.5	24.6
Leg oedema*	9.5	11.6	20.2	26.2
Mycosis	4.5	5.8	6.6	8.2
Parchment-like skin*	3.2	10.1	15.8	21.3
Shortness of breath	9.5	10.1	12.6	16.4
Sleep disturbance*	20.7	33.3	37.2	44.3
Threshold at				
<5 mg/day				
Eye cataract	2.7	10.1	7.7	8.2
5–7.5 mg/day				
Epistaxis*	1.4	1.4	6.6	4.9
Weight gain*	9.5	8.7	22.4	21.3
>7.5 mg/day				
Depression, listlessness	12.6	10.1	13.7	19.7
Glaucoma	2.7	2.9	2.7	6.6
Increase in blood pressure	18.9	18.8	16.4	23.0

*The influence of the glucocorticoid dose on these adverse events was confirmed in a multivariate logistic regression model. OM, osteoporosis module.

Huscher, Ann Rheum Dis 2009

Accumulating organ damage in SLE

(How) can we differentiate damage through ongoing lupus activity vs. treatement-related adverse effects?



Accumulating organ damage in SLE

Hopkins Lupus Cohort
n = 2199
mean FU 6y

Table 2 Distribution of any and first organ damage and organ damage by organ system during follow-up

	Any organ damage N (%)	First organ damage N (%)
Any organ damage (total)	1428 (100.0)	826 (100.00)
Ocular damage	225 (15.76)	135 (16.34)
Cataract damage	196 (13.73)	116 (14.04)
Neuropsychiatric damage	191 (13.38)	128 (15.50)
Stroke	57 (3.99)	28 (3.39)
Renal damage	75 (5.25)	51 (6.17)
Pulmonary damage	165 (11.55)	94 (11.38)
Pulmonary fibrosis	90 (6.30)	48 (5.81)
Cardiovascular damage	128 (8.96)	55 (6.66)
Peripheral damage	46 (3.22)	21 (2.54)
Gastrointestinal damage	77 (5.39)	51 (6.17)
Musculoskeletal damage	290 (20.31)	168 (20.34)
Osteoporotic fracture damage	177 (12.39)	88 (10.65)
Skin damage	32 (2.24)	21 (2.54)
Gonadal failure damage	30 (2.10)	19 (2.30)
Diabetes damage	60 (4.20)	24 (2.91)
Malignancy damage	109 (7.63)	59 (7.14)

Al Sawah et al., Lupus Science & Medicine 2015;2:e000066

Predictors of organ damage in SLE

	Model 1		Model 2		Model 3	
Variable	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Age at cohort entry	1.032 (1.026 to 1.038)	<0.001	1.033 (1.027 to 1.039)	<0.001	1.032 (1.026 to 1.038)	<0.001
Sex (female vs male)	1.071 (0.833 to 1.377)	0.592	1.089 (0.847 to 1.400)	0.508	1.080 (0.840 to 1.388)	0.550
Race						
Black (vs White)	1.113 (0. 963 to 1.286)	0.149	1.109 (0.960 to 1.282)	0.161	1.132 (0.980 to 1.307)	0.091
Asian (vs White)	0.894 (0.541 to 1.476)	0.661	0. 897 (0.543 to 1.482)	0.672	0.908 (0.550 to 1.499)	0.705
Other (vs White)	0.879 (0.559 to 1.382)	0.576	0.870 (0.553 to 1.368)	0.545	0.882 (0.561 to 1.387)	0.587
Year of SLE diagnosis	0.992 (0.984 to 1.000)	0.044	0.991 (0.983 to 0.998)	0.018	0.989 (0.981 to 0.997)	0.005
SDI at cohort entry	1.064 (1.023 to 1.106)	0.002	1.064 (1.024 to 1.107)	0.002	1.064 (1.023 to 1.107)	0.002
SELENA-SLEDAI score during follow-up (≥6 vs <6)	1.398 (1.170 to 1.670)	<0.001	1.370 (1.146 to 1.638)	<0.001	1.374 (1.149 to 1.642)	<0.001
Immunosuppressant use during follow-up (yes vs no)	1.225 (1.046 to 1.434)	0.012	1.209 (1.032 to 1.417)	0.019	1.246 (1.068 to 1.455)	0.005
Antimalarial use during follow-up (yes vs no)	0.926 (0.801 to 1.071)	0.299	0.958 (0.827 to 1.109)	0.566	0.964 (0.832 to 1.116)	0.623
Mean prior prednisone dose, mg/day*						
(≥7.5 vs <7.5)	1.742 (1.489 to 2.039)	<0.001	NA		NA	
(≥7.5–<15 vs <7.5)	NA		1.537 (1.284 to 1.840)	<0.001	NA	
(≥15–<20 vs <7.5)	NA		1.799 (1.350 to 2.399)	<0.001	NA	<0.001
(≥20 vs <7.5)	NA		2.514 (1.977 to 3.196)	<0.001	NA	
1 mg/day	NA		NA		1.028 (1.022 to 1.035)	

Al Sawah et al., Lupus Science & Medicine 2015;2:e000066

Disease activity, steroid use and organ damage

Cataract:

	HR		
Mean prior prednisone dose during follow-up, mg/day			
≥7.5 vs <7.5	2.412	(1.778 to 3.273)	<0.001
SELENA-SLEDAI score			
≥6 vs <6	1.475	(1.008 to 2.157)	0.045

Osteoporotic fractures:

Mean prior prednisone dose during follow-up (mg/day)			
≥7.5 vs <7.5	2.161	(1.546 to 3.022)	<0.001
SELENA-SLEDAI score			
≥6 vs <6	1.055	(0.676 to 1.646	0.813

Cardiovascular damage:

Mean prior prednisone dose during follow-up, mg/day			
≥7.5 vs <7.5	1.544	(1.018 to 2.341)	0.041
SELENA-SLEDAI score			
≥6 vs <6	2.737	(1.780 to 4.209)	<0.001

Renal damage:

Mean prior prednisone dose during follow-up, mg/day			
≥7.5 vs <7.5	1.440	(0.863 to 2.403)	0.163
SELENA-SLEDAI score			
≥6 vs <6	4.079	(2.521 to 6.600)	<0.001

(How) can we reduce steroid exposure in lupus nephritis?

Strategies to minimize glucocorticoid exposure:

- Reduce the dose and duration of glucocorticoids
- Replace oral glococorticoids by IV pulses
- Replace glucocorticoids by alternative agents

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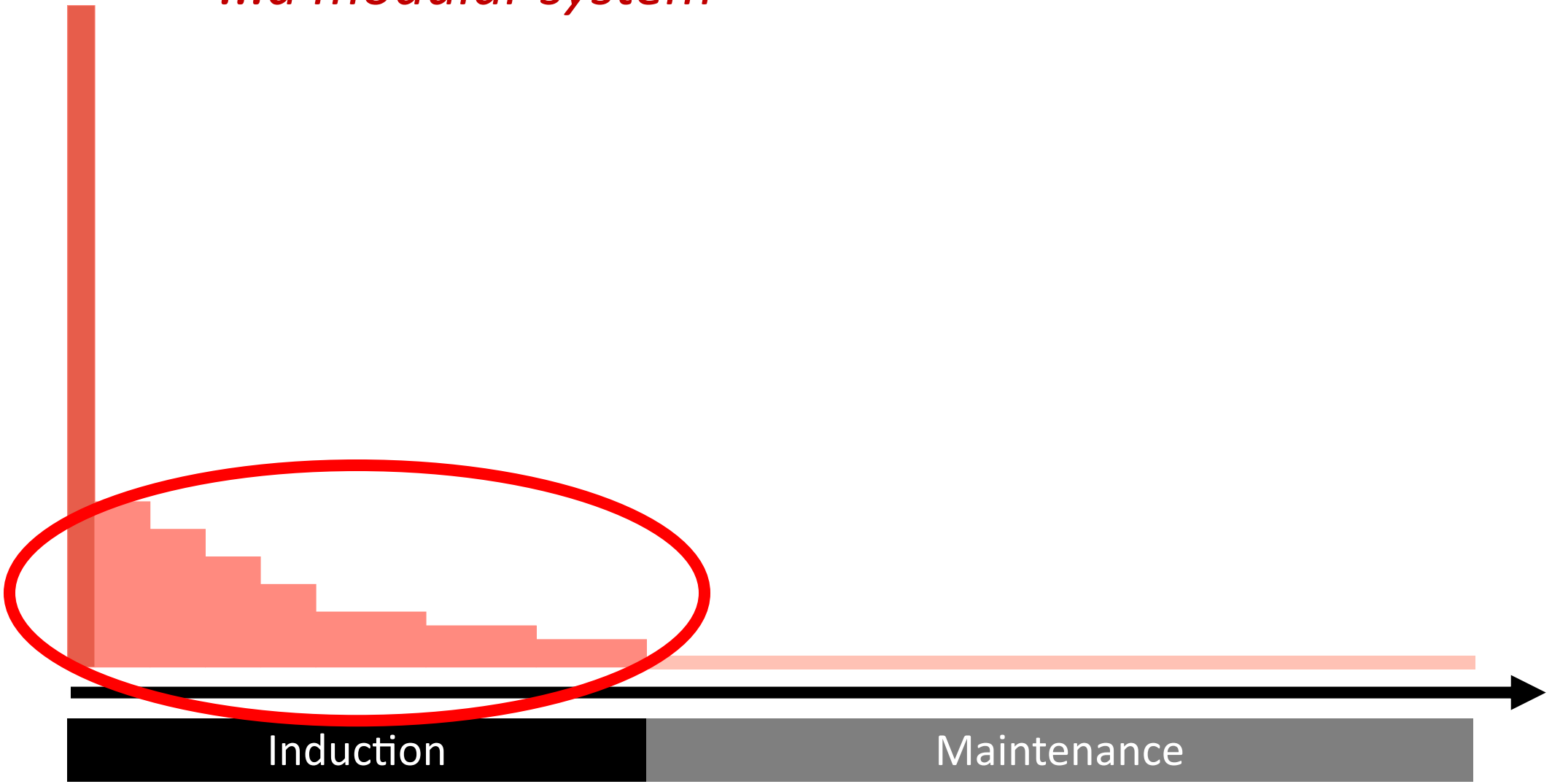
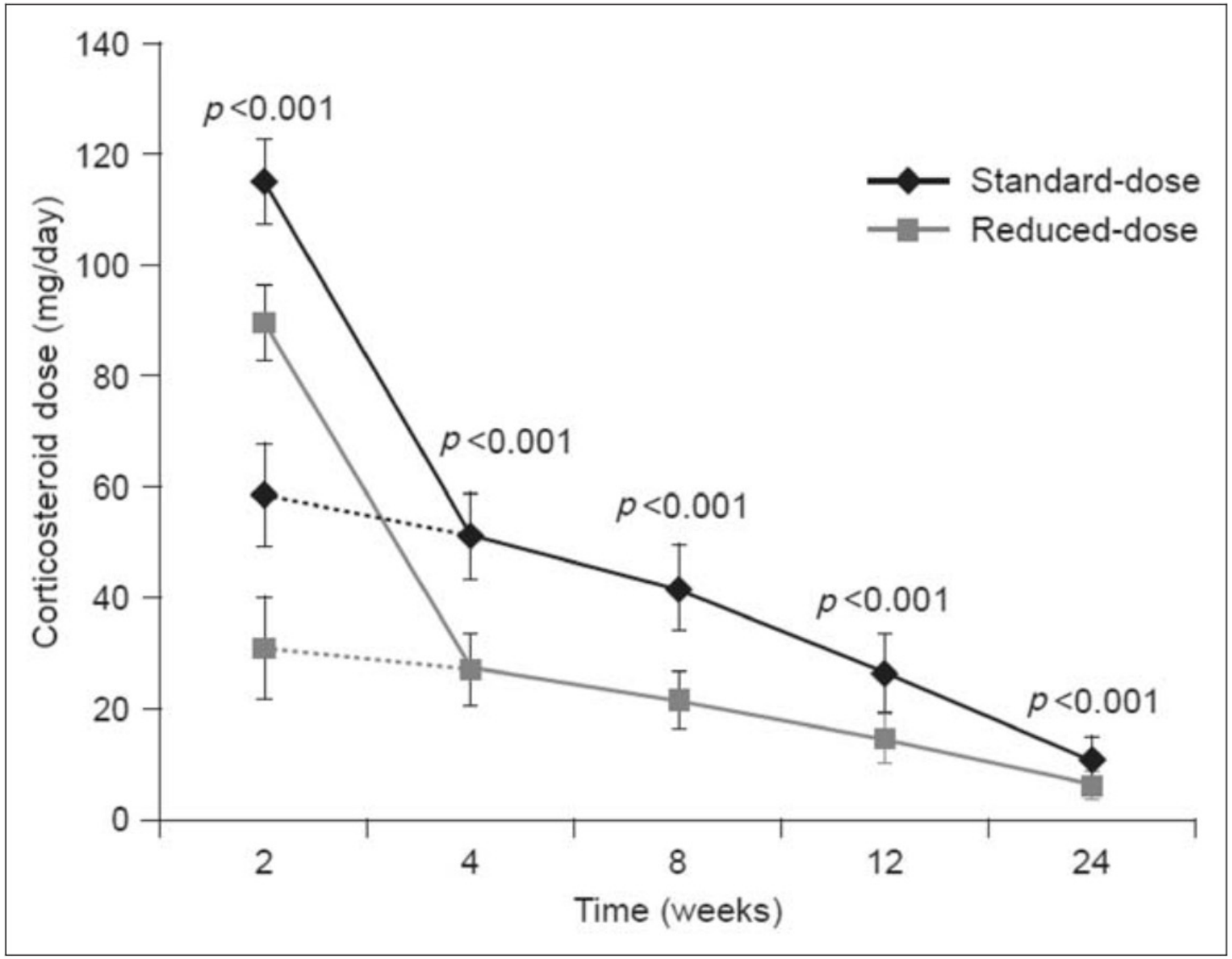
Steroids in the treatment of Lupus nephritis

...a modular system



MyLupus: MPA + standard vs. low-dose GC



n = 81

3 x 0.5g MPDN

1 mg/kg/d PDN, taper to 5-10 mg/d (weight adjusted) by week 24

vs.

0.5 mg/kg/d PDN, taper to 2.5-5 mg/d (weight adjusted) by week 24

My Lupus: Zeher et al., Lupus 2011;20:1484–1493

MyLupus: MPA + standard vs. low-dose GC

- The only RCT comparing standard vs low dose GC in LN
- open label, underpowered (non-inferiority not shown)

	All patients (n = 81)	*Standard- dose steroids (n = 42)*	*Reduced-dose steroids (n = 39)*
Complete response			
Week 12	14 (17.3%)	9 (21.4%)	5 (12.8%)
Week 24	16 (19.8%)	8 (19.0%)	8 (20.5%)
Partial response			
Week 12	27 (33.3%)	16 (38.1%)	11 (28.2%)
Week 24	34 (42.0%)	20 (47.6%)	14 (35.9%)

My Lupus: Zeher et al., Lupus 2011;20:1484–1493

Steroids in the treatment of Lupus nephritis

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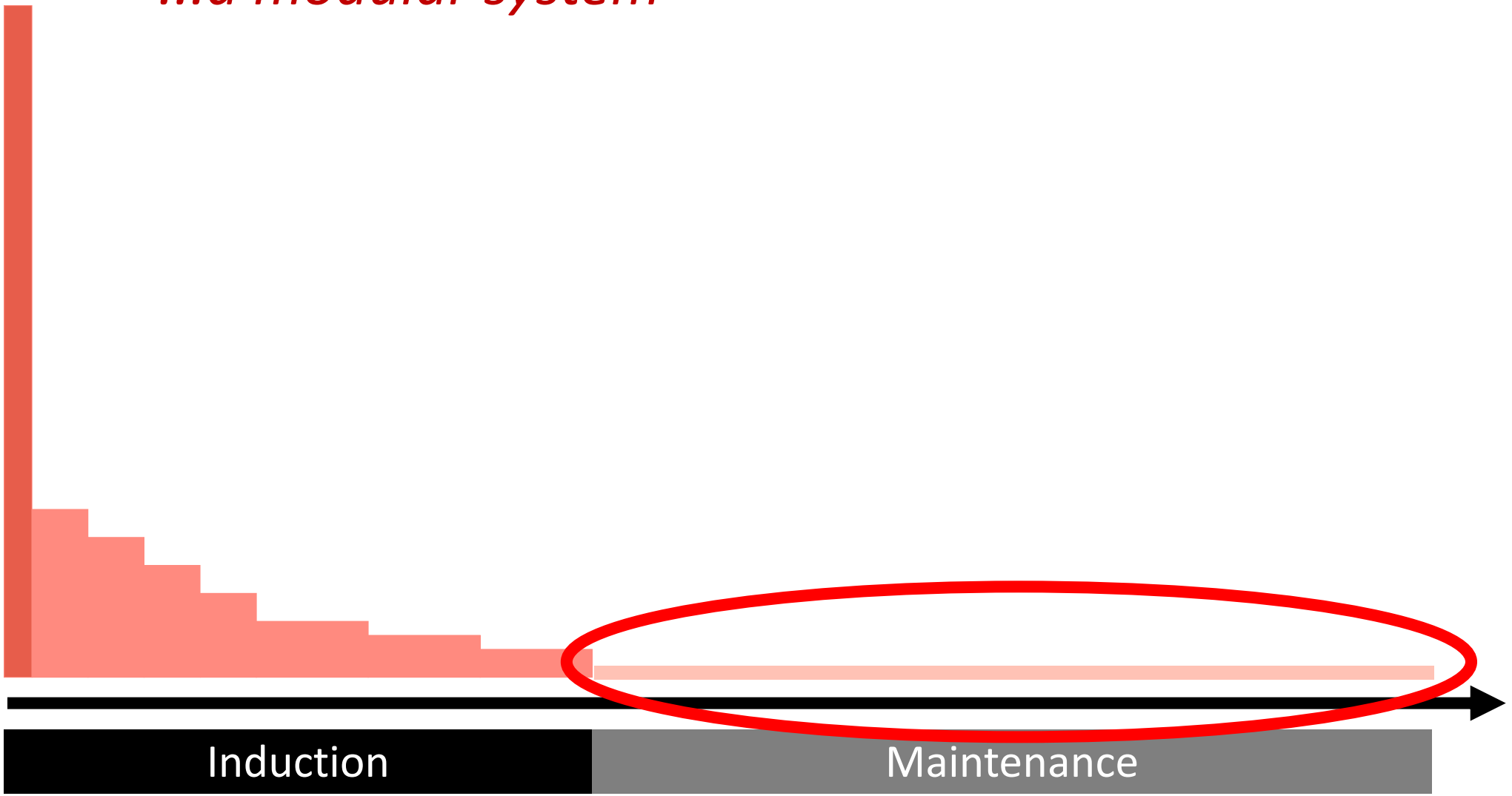


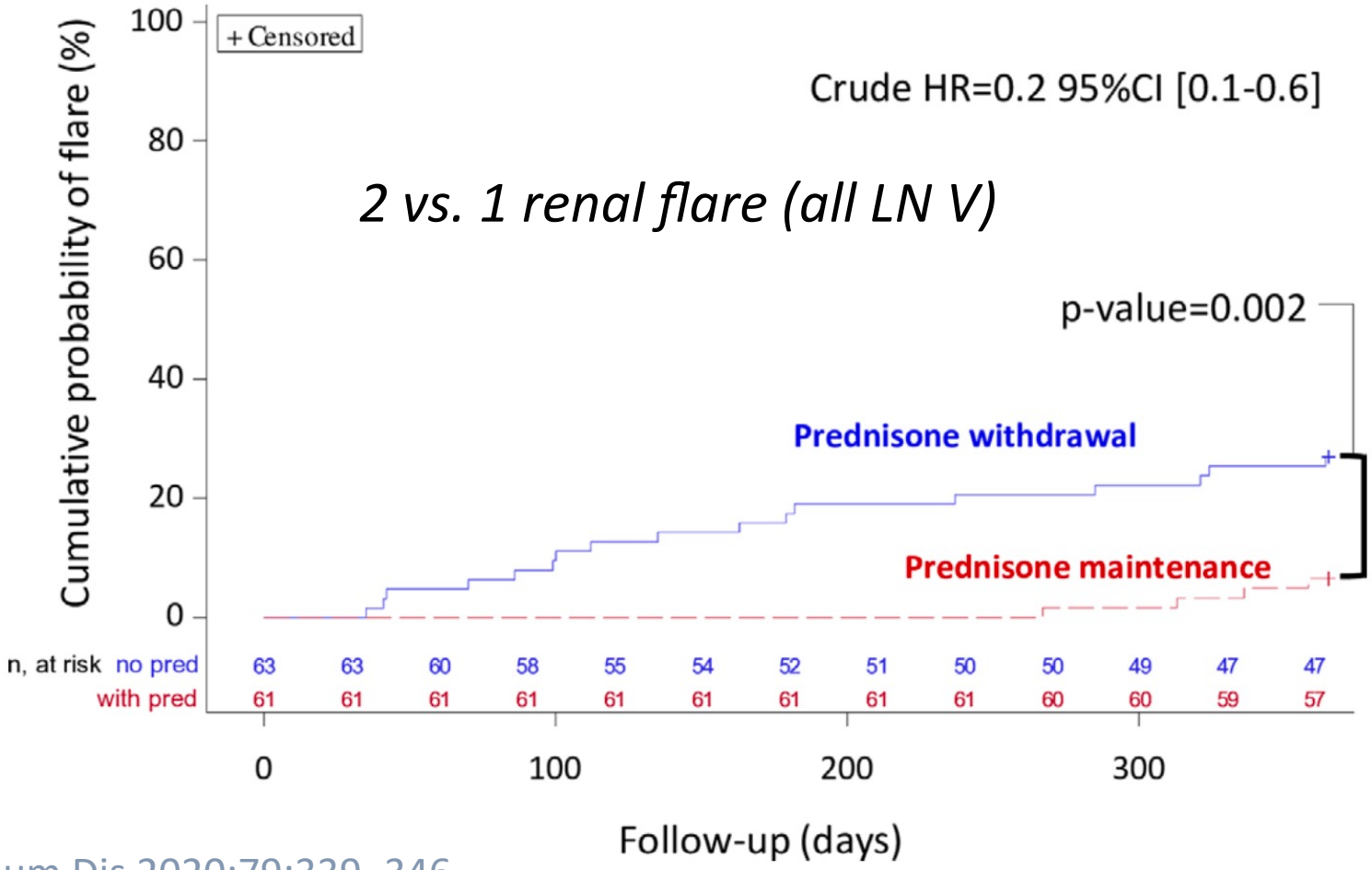
CORTICOLUP:
Low dose PDN for maintenane of remission

Design / baseline:

- Open-label RCT
- 124 patients
- No active disease
- 5 mg/d PDN
- Only 27% with IS
- 38% with history of LN

Outcome:

- *Mostly mild / moderate flares*
- *2 vs. 1 renal flare (LN V)*
- *No difference in damage accrual*



CORTICOLUP: Mathian et al. Ann Rheum Dis 2020;79:339–346.

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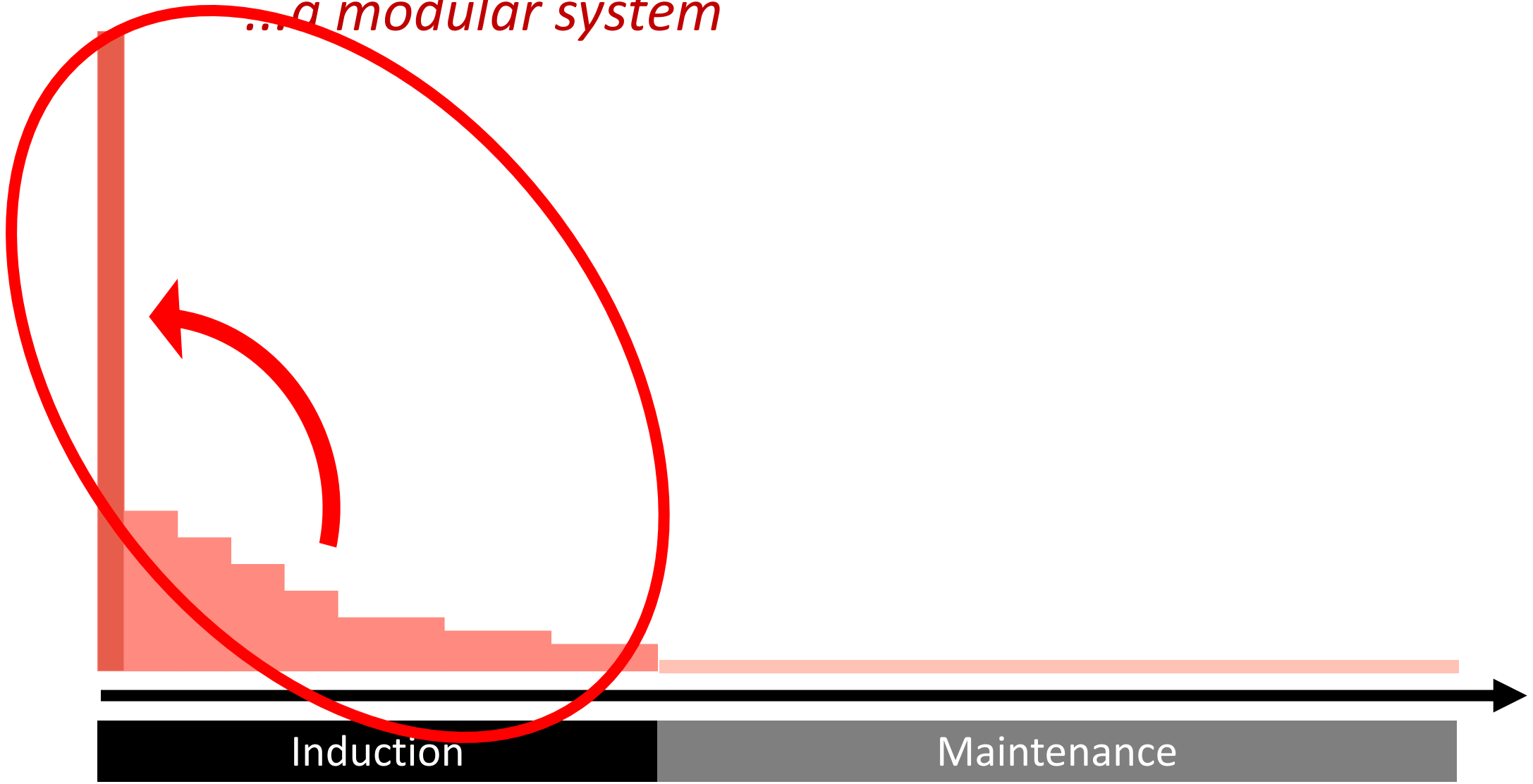
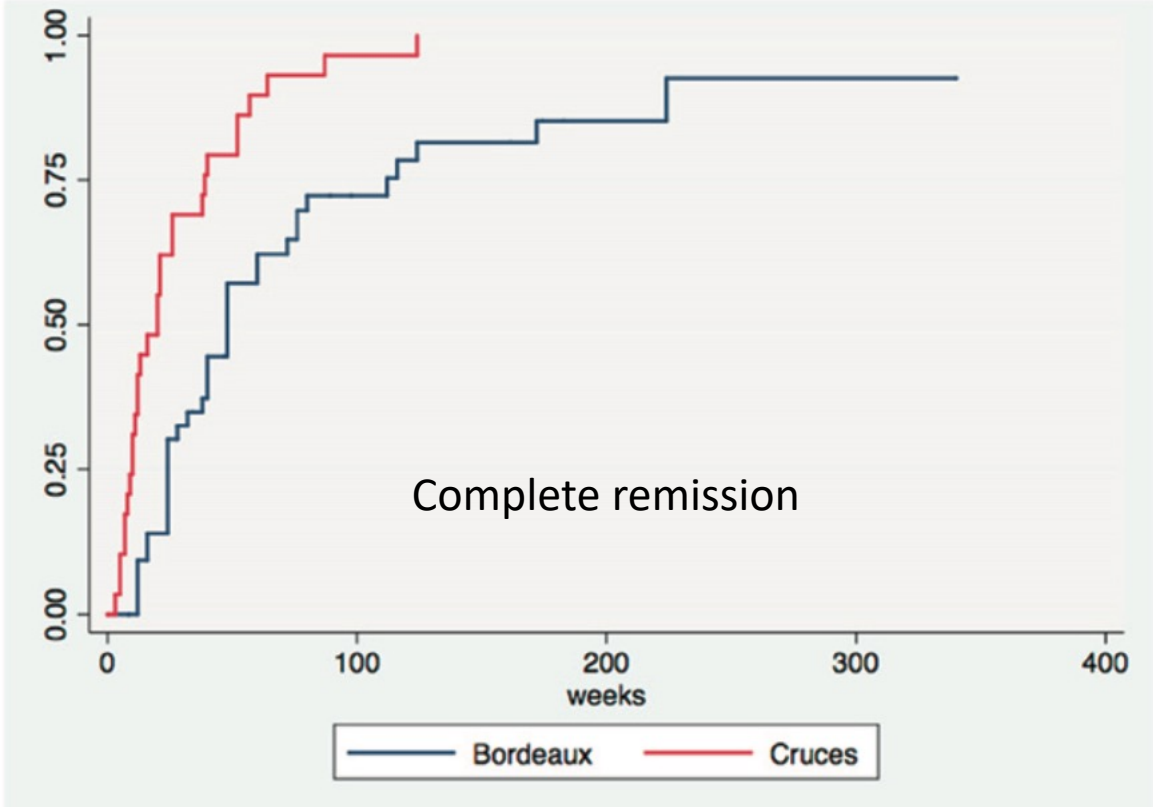


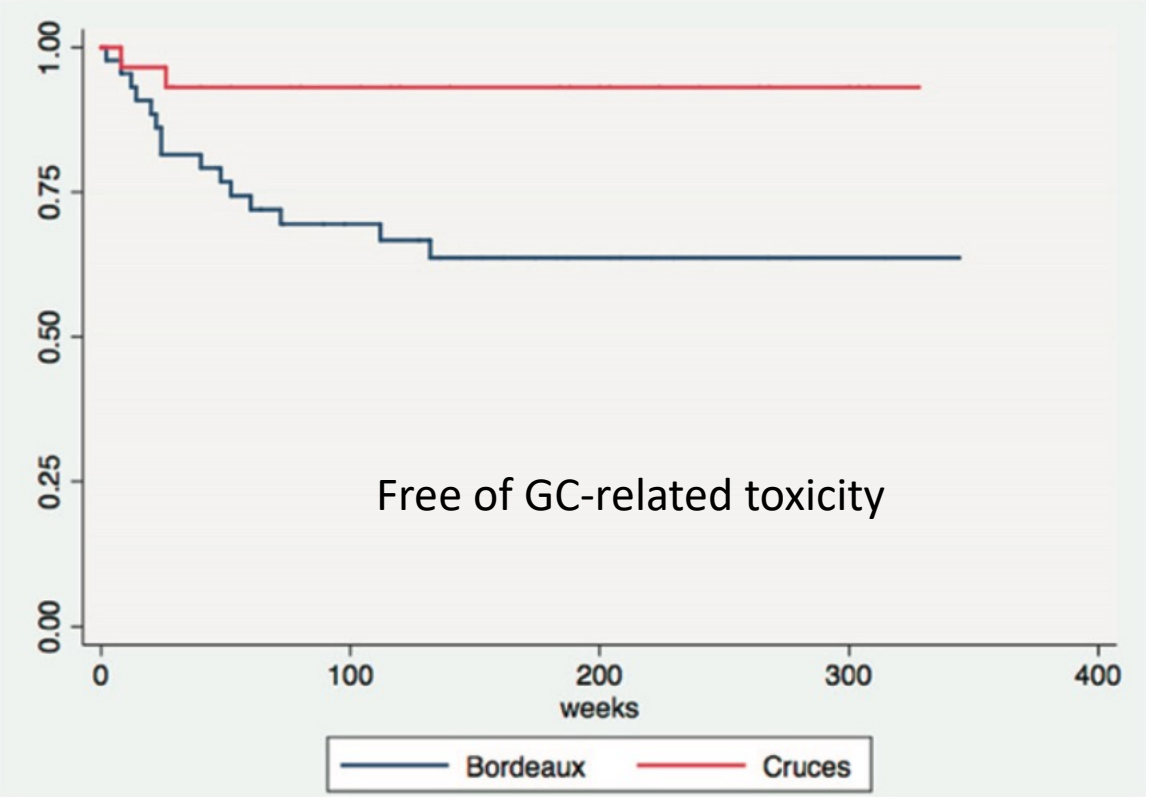
Lupus-Cruces protocol

CYC + 125mg MPDN pulses every 2w + low dose oral PDN

Mean 8.3 ± 1.6 mg/d vs. 21.0 ± 11.7 mg/d PDN dose over 6 months

IV pulses in 100% vs. 75% patients, mean 9.3 ± 3.3 vs. 3 ± 0.5 pulses, mean total dose 1.7 vs. 1.9 g





G. Ruiz-Irastorza et al. / Autoimmunity Reviews 16 (2017) 826–832

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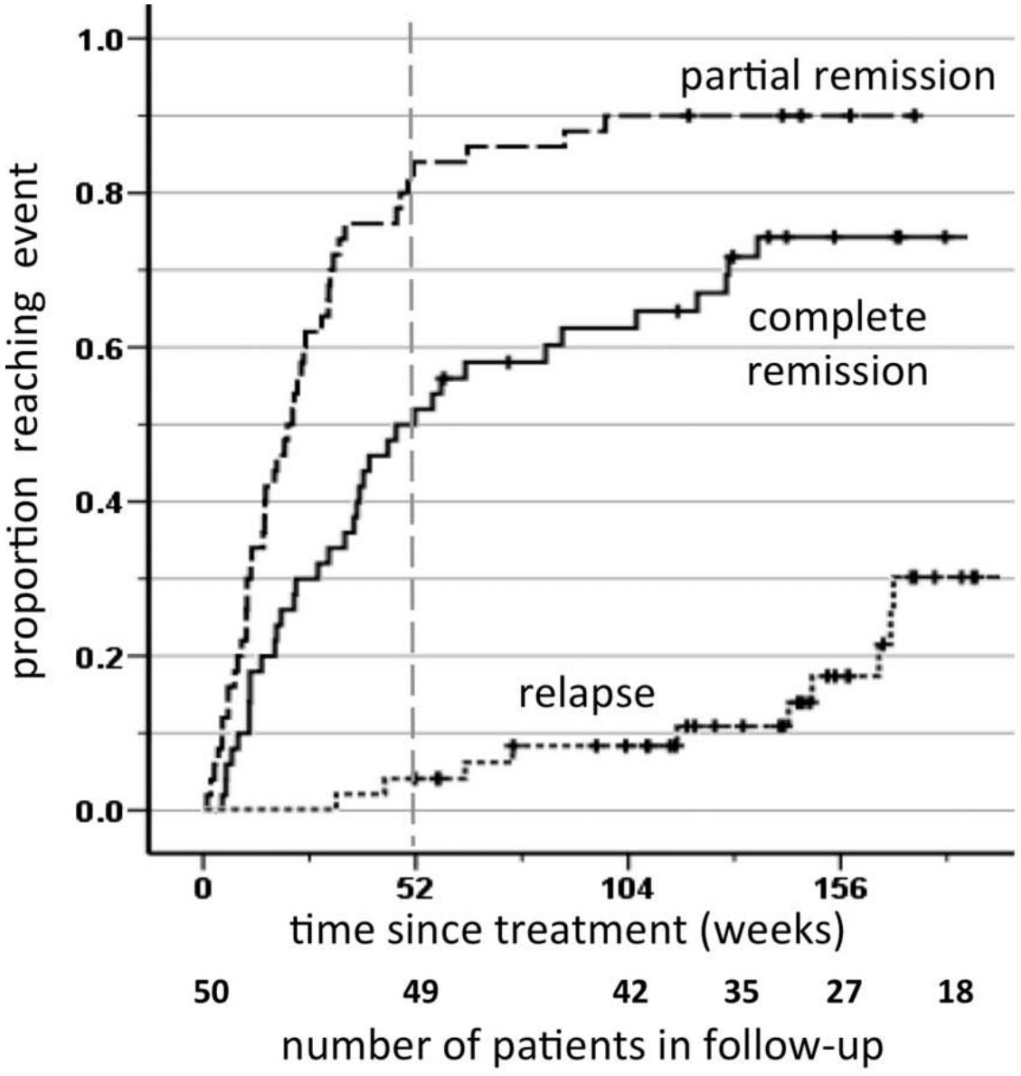
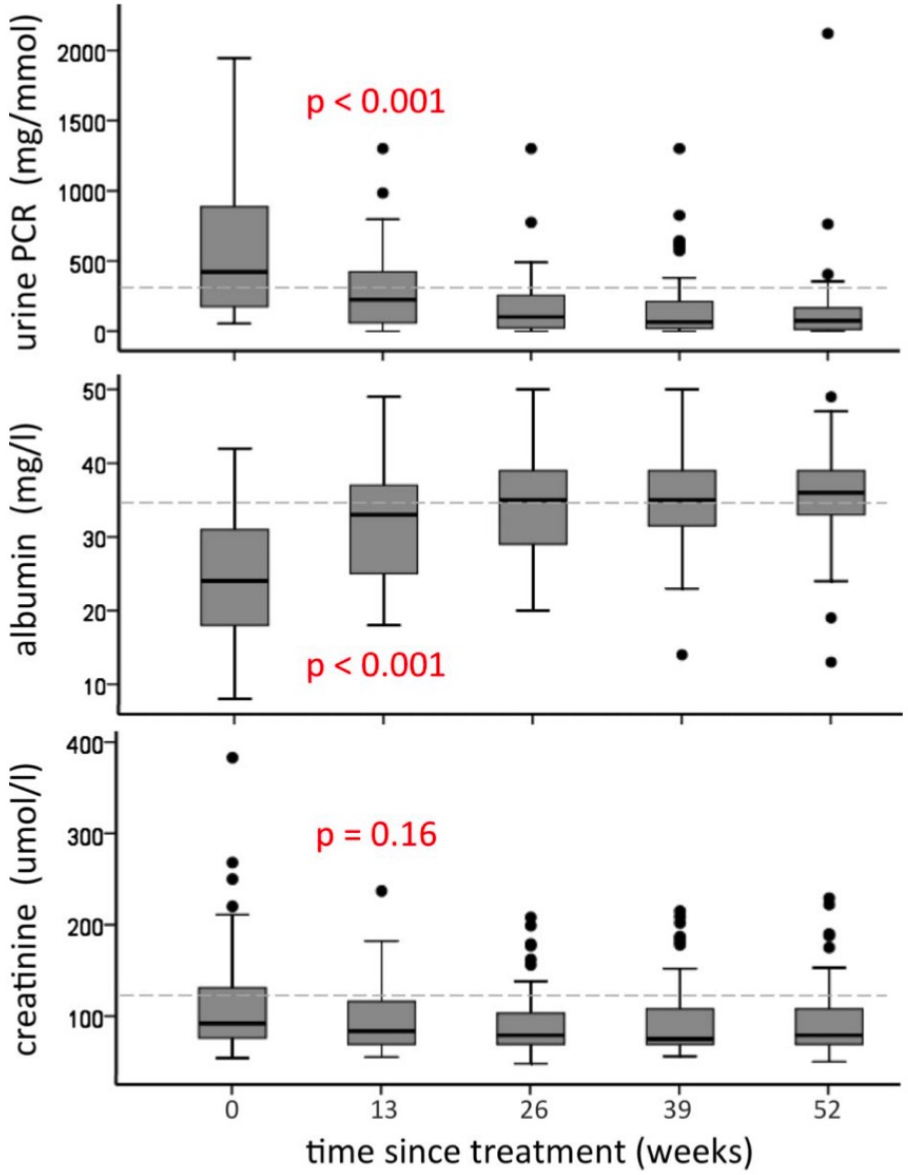
RITUXILUP: MMF + 2x1g RTX + 2x0.5g MPDN, no oral GC





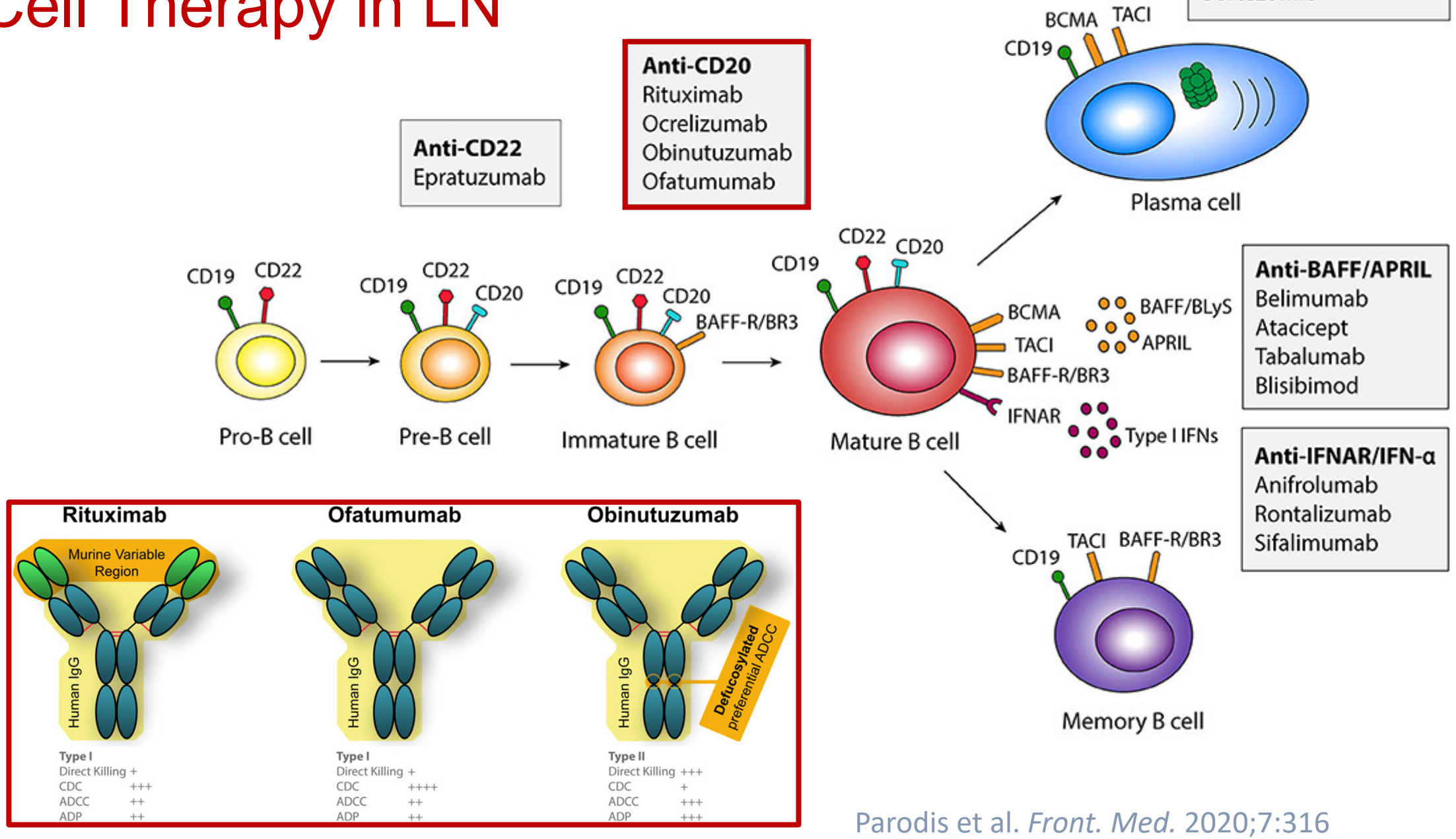
Condon et al., Ann Rheum Dis 2013;72:1280–1286

B Cell Therapy in LN

Proteasome inhibition
Bortezomib

Anti-CD20
Rituximab
Ocrelizumab
Obinutuzumab
Ofatumumab

Anti-CD22
Epratuzumab



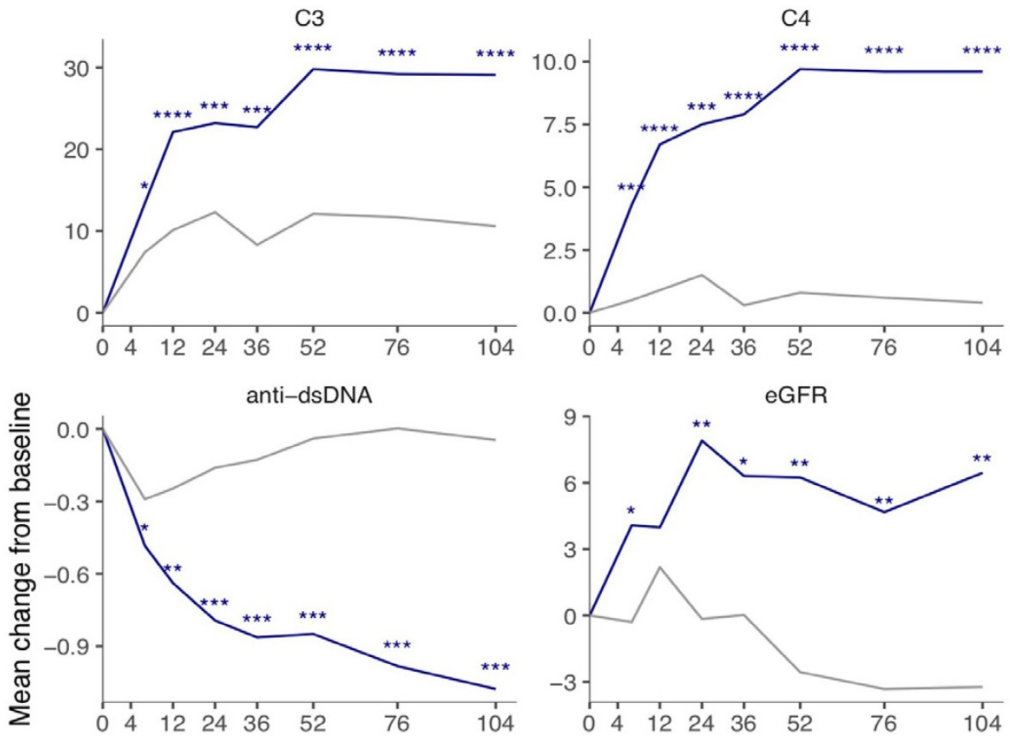
Anti-BAFF/APRIL
Belimumab
Atacicept
Tabalumab
Blisibimod

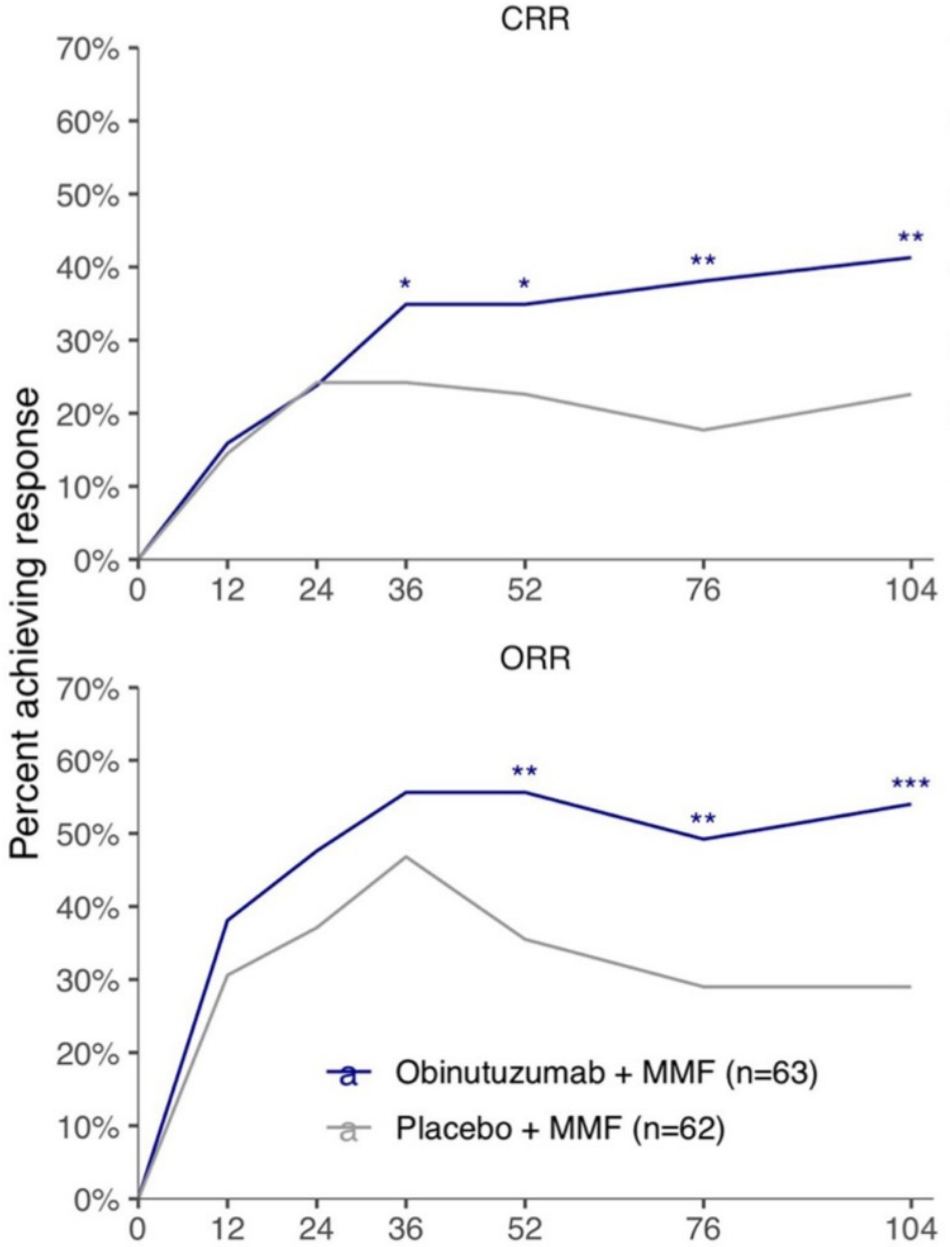
Anti-IFNAR/IFN-α
Anifrolumab
Rontalizumab
Sifalimumab

Parodis et al. *Front. Med.* 2020;7:316

NOBILITY: Obinutuzumab

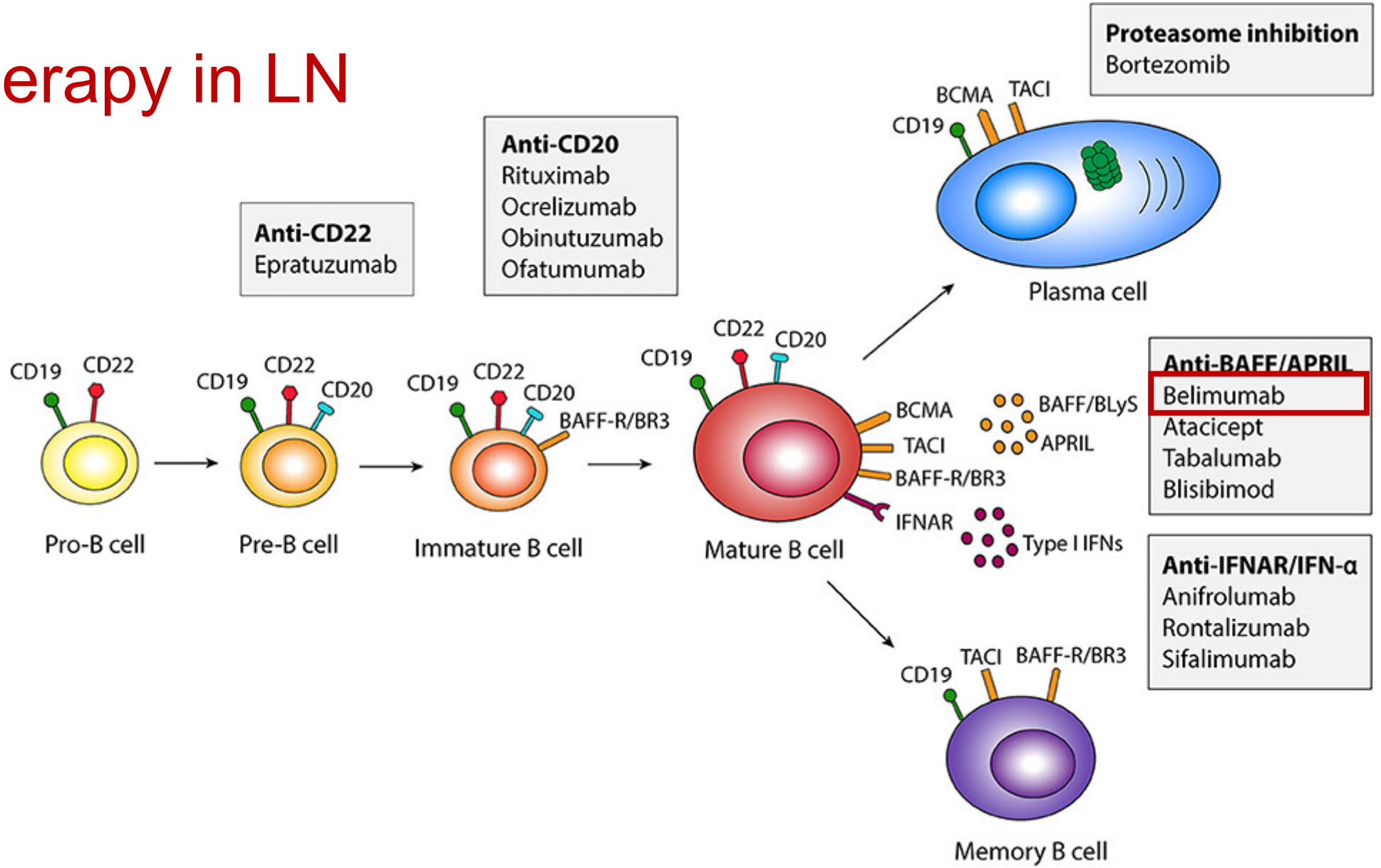
- RCT, n = 125, 1:1 plac vs. obi 1000 mg w 0, 2, 24, 26
- MMF (target dose 2–2.5g/d)
- Methylprednisolone (total 1000–3000mg IV)
- PDN initial 0.5mg/kg/d, maximum 60mg/d, taper to 7.5mg/d by week 12





NOBILITY: Furie RA, et al. Ann Rheum Dis 2021;0:1–8

B Cell Therapy in LN



Parodis et al. *Front. Med.* 2020;7:316

BLISS-LN: Belimumab

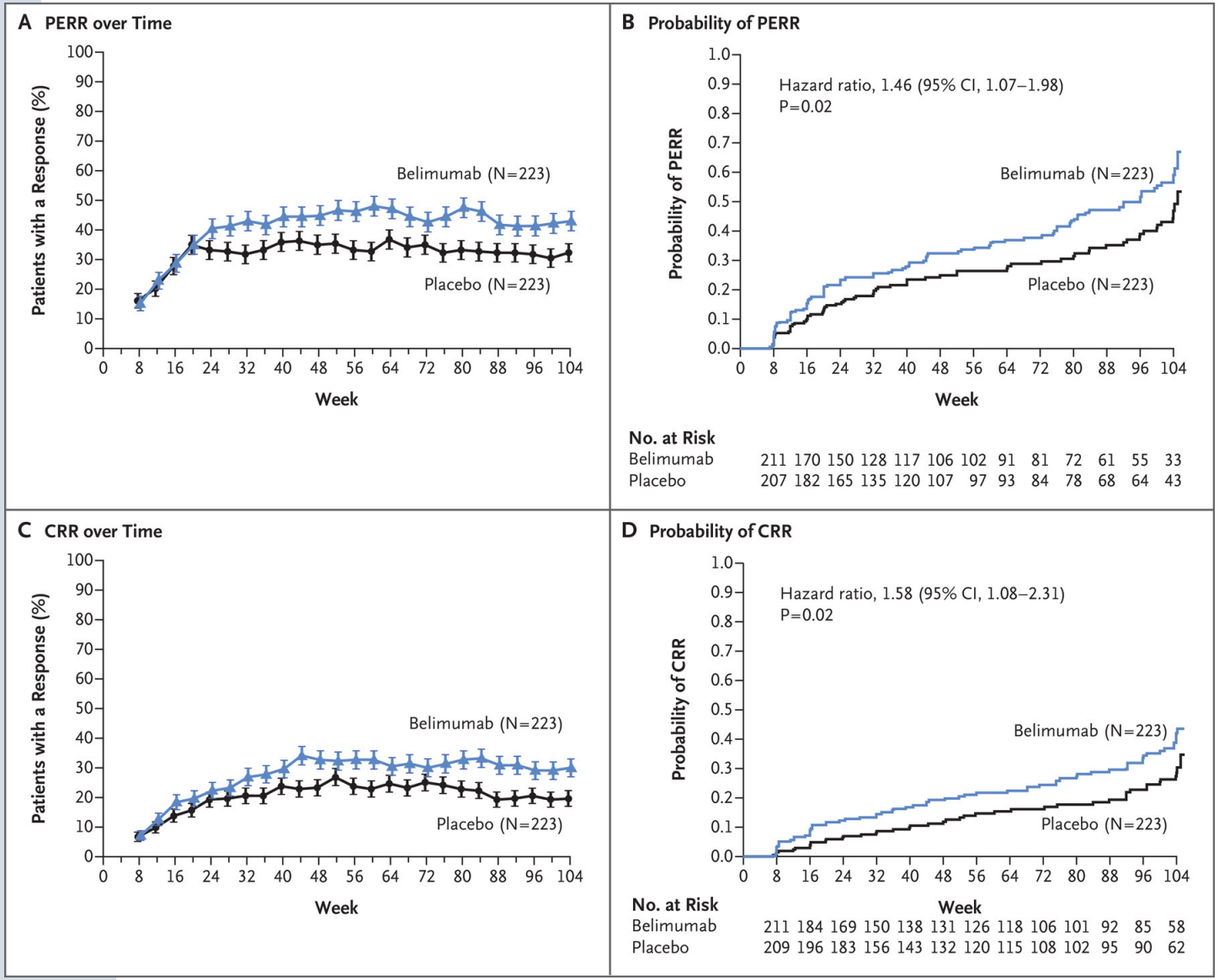
- RCT; n = 448; 1:1 placebo vs. belimumab d 1, 15, 29, then every 28 d x 104 w
- Inclusion criteria:
  - SLE (ACR)
  - LN III/IV/V within 6 months of inclusion with active lesions
  - UPCR ≥ 1
  - Induction therapy started within 60 days of enrollment
- Background therapy:
  - CYC-AZA (EUROLUPUS) or MMF (ALMS)
  - Steroid regimen not specified (but target PDN ≤ 10mg at week 24)
- Endpoints:
  - Primary: PERR (UPCR ≤ 0.7; eGFR ≥ 60 / ≥ 80% pre-flare; no rescue therapy at week 104)
  - Secondary: PERR at 52 weeks; CRR; time to renal-related event / death; ...)

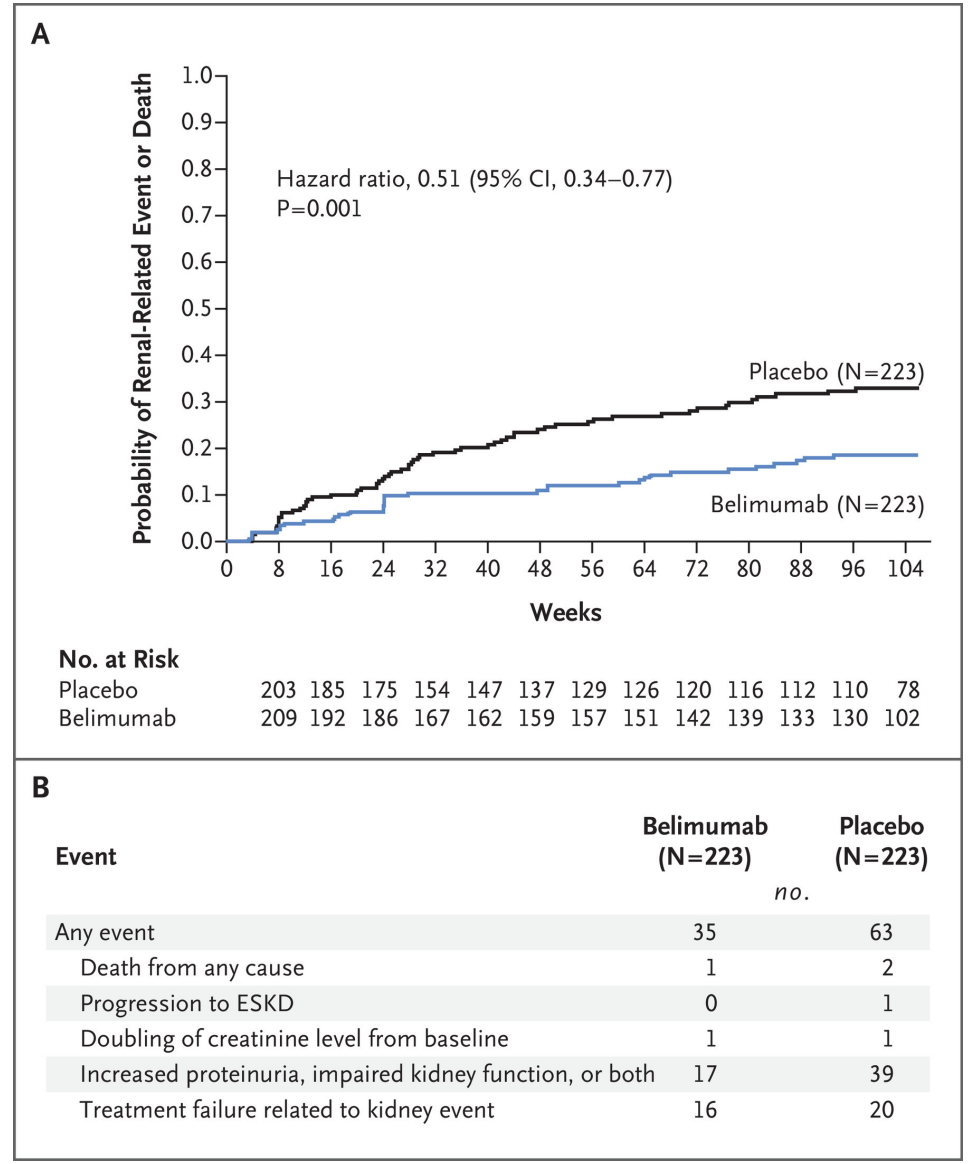
BLISS-LN: Baseline Characteristics

Characteristic	Belimumab (N = 223)	Placebo (N = 223)	Total (N = 446)
Female sex — no. (%)	197 (88)	196 (88)	393 (88)
Age — yr	33.7±10.7	33.1±10.6	33.4±10.7
Kidney-biopsy lupus nephritis class — no. (%)§			
III or IV	126 (56)	132 (59)	258 (58)
III and V or IV and V	61 (27)	55 (25)	116 (26)
V	36 (16)	36 (16)	72 (16)
Ratio of urinary protein to creatinine	3.2±2.7	3.5±3.6	3.4±3.2
Ratio of urinary protein to creatinine ≥3 — no. of patients (%)	91 (41)	92 (41)	183 (41)
Estimated GFR — ml per minute per 1.73 m^2	100.0±37.7	101.0±42.7	100.5±40.2
Estimated GFR category — no. (%)			
≥60 ml per minute per 1.73 m^2	190 (85)	182 (82)	372 (83)
≥90 ml per minute per 1.73 m^2	131 (59)	133 (60)	264 (59)

Furie R et al., N Engl J Med 2020; 383:1117

BLISS-LN: Results





B

Event	Belimumab (N=223)	Placebo (N=223)
	no.	
Any event	35	63
Death from any cause	1	2
Progression to ESKD	0	1
Doubling of creatinine level from baseline	1	1
Increased proteinuria, impaired kidney function, or both	17	39
Treatment failure related to kidney event	16	20

Furie R et al., N Engl J Med 2020; 383:1117

BLISS-LN: Adverse Events

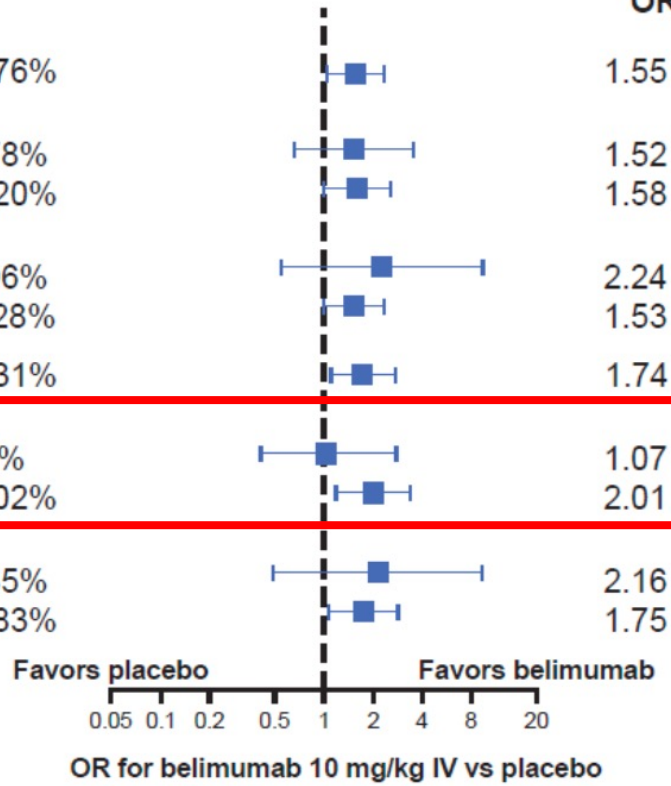
Table 3. Adverse Events, Adverse Events of Special Interest, and Suicidality in the Safety Population.*

Event	Belimumab (N=224)	Placebo (N=224)
	no. of patients (%)	
All adverse events†	214 (96)	211 (94)
All treatment-related adverse events†	123 (55)	119 (53)
Upper respiratory tract infection	26 (12)	24 (11)
Urinary tract infection	15 (7)	13 (6)
Herpes zoster	13 (6)	10 (4)
Bronchitis	11 (5)	10 (4)
Nasopharyngitis	8 (4)	8 (4)
Headache	9 (4)	5 (2)
Nausea	8 (4)	5 (2)
Rash	6 (3)	5 (2)
All serious adverse events†	58 (26)	67 (30)
All treatment-related serious adverse events†	23 (10)	25 (11)
Most common treatment-related serious adverse events, according to system organ class, occurring in ≥1% of patients in either group		
Infections and infestations	15 (7)	18 (8)
Respiratory, thoracic, and mediastinal disorders	5 (2)	1 (<1)
Blood and lymphatic system disorders	3 (1)	2 (1)
Nervous system disorders	0	3 (1)

Furie R et al., N Engl J Med 2020; 383:1117

BLISS-LN: Subgroup Analysis

		Response rate (%)		Treatment difference (%)	OR (95% CI)	p-value
		Placebo n=223	Belimumab 10 mg/kg IV n=223			
PERR	Overall	72/223 (32.3%)	96/223 (43.0%)	10.76%	1.55 (1.04, 2.32)	0.03
	Induction					
	Cyclophosphamide	16/59 (27.1%)	20/59 (33.9%)	6.78%	1.52 (0.66, 3.49)	
	Mycophenolate mofetil	56/164 (34.1%)	76/164 (46.3%)	12.20%	1.58 (1.00, 2.51)	
	Race					
	Black	5/32 (15.6%)	7/31 (22.6%)	6.96%	2.24 (0.55, 9.19)	
	Non-black	67/191 (35.1%)	89/192 (46.4%)	11.28%	1.53 (1.01, 2.33)	
CRR	Overall	44/223 (19.7%)	67/223 (30%)	10.31%	1.74 (1.11, 2.74)	0.02
	Induction					
	Cyclophosphamide	11/59 (18.6%)	11/59 (18.6%)	0%	1.07 (0.41, 2.78)	
	Mycophenolate mofetil	33/164 (20.1%)	56/164 (34.1%)	14.02%	2.01 (1.19, 3.38)	
	Race					
	Black	4/32 (12.5%)	6/31(19.4%)	6.85%	2.16 (0.49, 9.43)	
	Non-black	40/191 (20.9%)	61/192 (31.8%)	10.83%	1.75 (1.08, 2.83)	



Furie R et al., N Engl J Med 2020; 383:1117

CNI: „Multitarget Therapy“

Induction:

n = 362 (all Chinese)

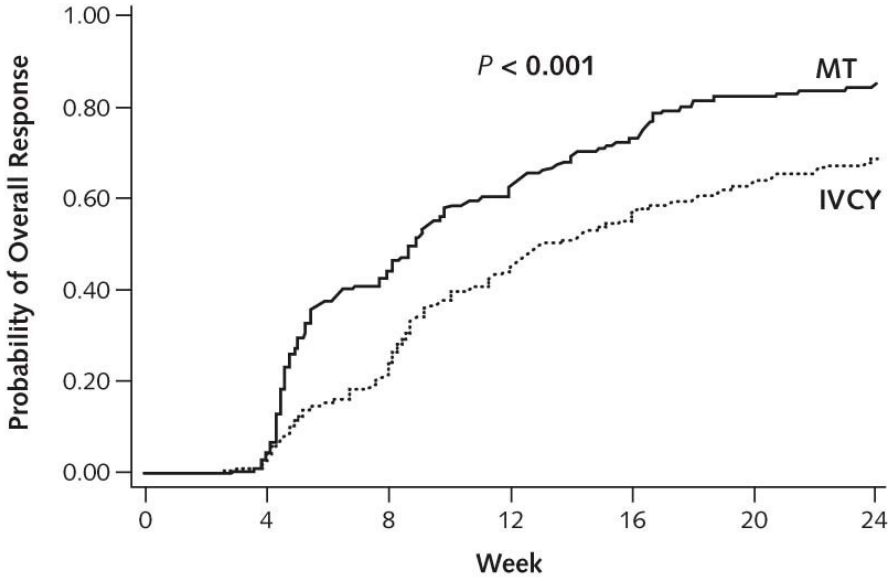
CYC + PDN

vs.

Tac + low dose MMF (2x500mg) + PDN

26 weeks

Liu Zet al. Ann Intern Med, 2015;162:18



Patients at risk, *n*							
MT	181	175	98	67	45	29	20
IVCY	181	176	132	91	71	58	45

Maintenance (extension):

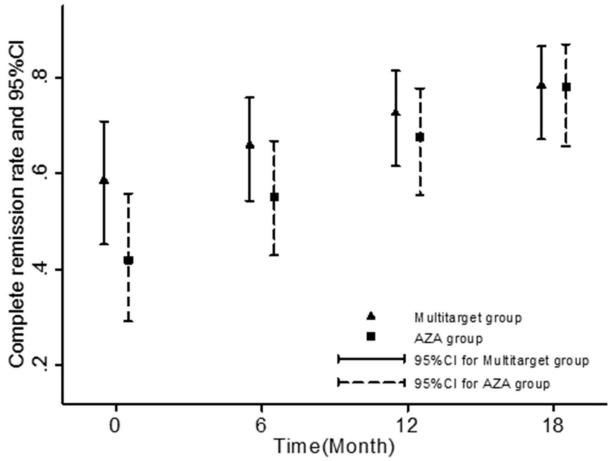
n = 206

AZA + PDN (10 mg)

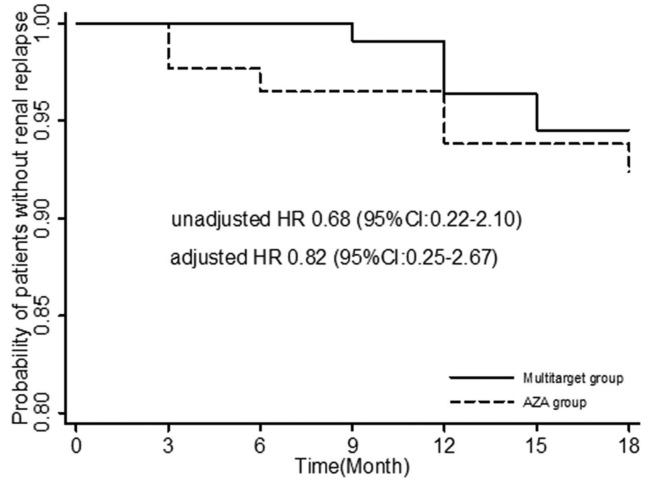
vs.

Tac + MMF 2-3 x 250mg + PDN

Zhang H et al. JASN 2017;28:3671



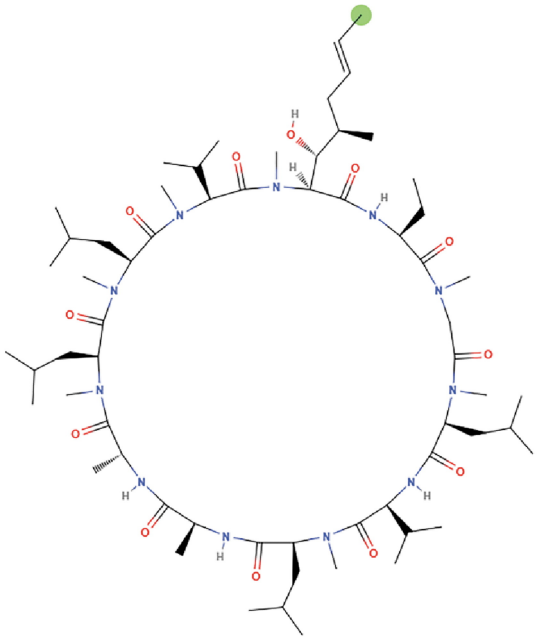
No. at risk				
Multitarget group	116	102	87	101
AZA group	90	72	57	64
No.of complete remission				
Multitarget group	69	65	57	82
AZA group	40	35	28	47



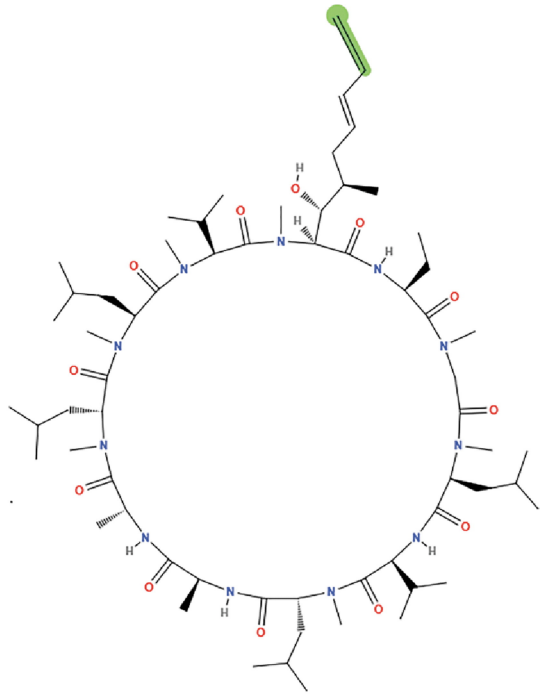
No. at risk							
Multitarget group	116	116	113	112	109	104	101
AZA group	90	87	83	76	72	66	64
No.of relapse							
Multitarget group	0	0	0	1	3	2	0
AZA group	0	2	1	0	2	0	1

Voclosporin*

- Structurally similar to cyclosporine A, with the addition of a single carbon extension with a double-bond that changes how voclosporin binds to calcineurin



Cyclosporin



Voclosporin

- Advantages over cyclosporin A and tacrolimus:
  - Consistent dose-concentration, eliminating the need for therapeutic drug monitoring
  - No dose modification in mild to moderate renal impairment
  - Increased potency compared to cyclosporine A
  - Improved glucose metabolic profile compared to tacrolimus
  - Improved lipid profile compared to cyclosporine A
  - No drug-drug interaction with MMF

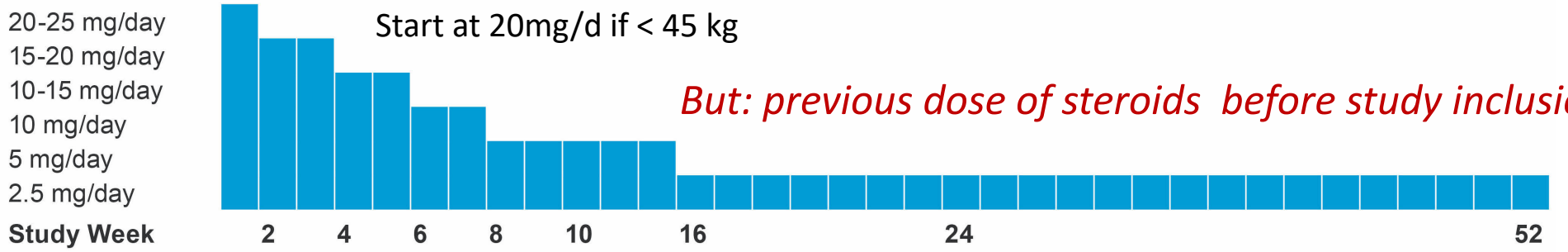
* Voclosporin is not approved by Swissmedic for the treatment of Lupus Nephritis. Remark is valid for all following slides

AURORA: Voclosporin Phase III

- RCT; n = 357; 1:1 placebo vs. voclosporin 23.7 bid
- Inclusion criteria:
  - SLE (ACR)
  - LN III/IV/V within 2 years of inclusion
  - UPCR ≥ 1.5 (≥ 2 for class V LN)
  - Doubling of proteinuria within 6 months if biopsy > 6 months back
- Background therapy («standard of care» ...?):
  - MMF 2 x 1g
  - Low dose glucocorticoid scheme:

IV methylprednisolone 0.5 g/day on Days 1 and 2

Rapid Low-Dose Oral Steroid Taper*



Start at 20mg/d if < 45 kg

But: previous dose of steroids before study inclusion?

Rovin B et al., Lancet 2021; 397: 2070–80

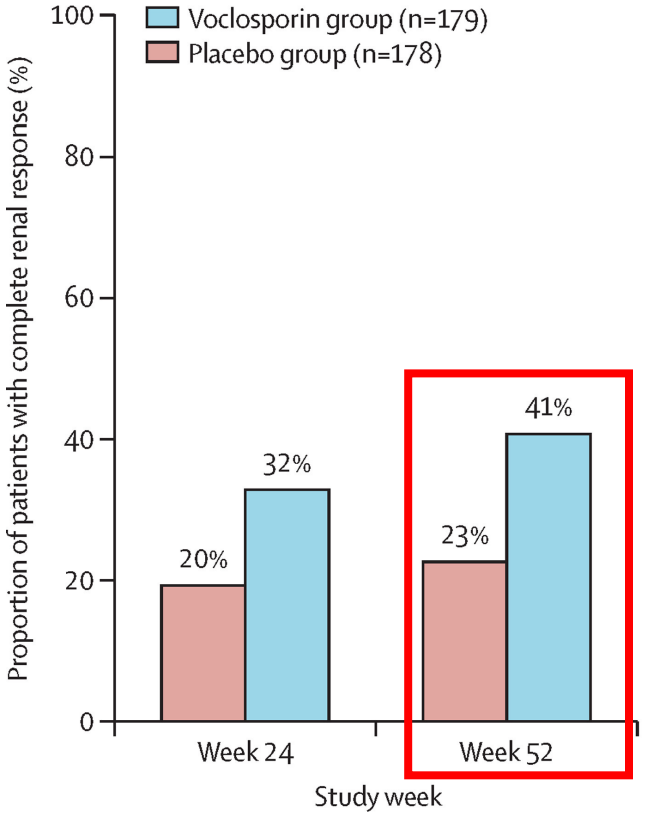
AURORA: Selected Baseline Characteristics

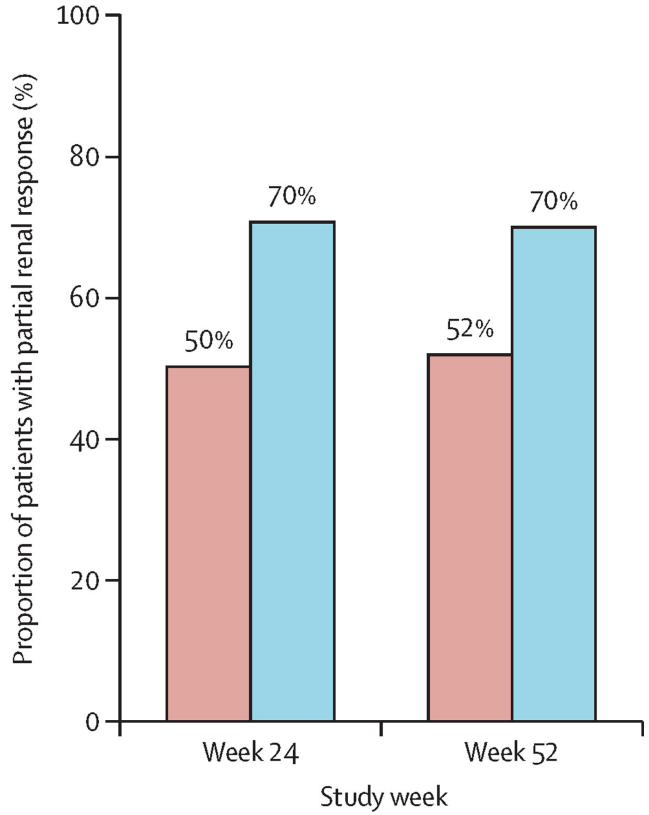
Rovin B et al., Lancet 2021; 397: 2070–80

	Control n=178	Voclosporin n=179
Median age, years (range)	32 (18–72)	31 (18–62)
Sex, n (%)		
Male	26 (14.6)	18 (10.1)
Female	152 (85.4)	161 (89.9)
Mean time since initial lupus nephritis diagnosis, years (SD)	4.7 (4.9)	4.6 (5.1)
eGFR, ml/min/1.73 m^2		
Mean (SD)	90.4 (29.0)	92.1 (30.6)
Median	97.0	91.0
UPCR, mg/mg		
Mean (SD)	3.9 (2.4)	4.1 (2.7)
Median	3.1	3.4
Biopsy Class, n (%)		
Pure class III	29 (16)	20 (11)
Pure class IV	77 (43)	91 (51)
Pure class V	25 (14)	25 (14)
Mixed III or IV + V	46 (26)	43 (24)
Biopsy, n (%)		
Within six months before screening	157 (88)	161 (90)
More than six months before screeing	21 (12)	18 (88)

AURORA: Endpoints

- Primary: CRR at week 52:
  - UPCR ≤ 0.5
  - eGFR ≥ 60 / ≥ 80% BL
  - no rescue therapy
- Key secondary:
  - UPCR ≤ 0.5
  - PRR (≥ 50% proteinuria reduction from BL) at week 24 and 52
  - Time to PRR
  - CRR at week 24





	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

Rovin B et al., Lancet 2021; 397: 2070–80

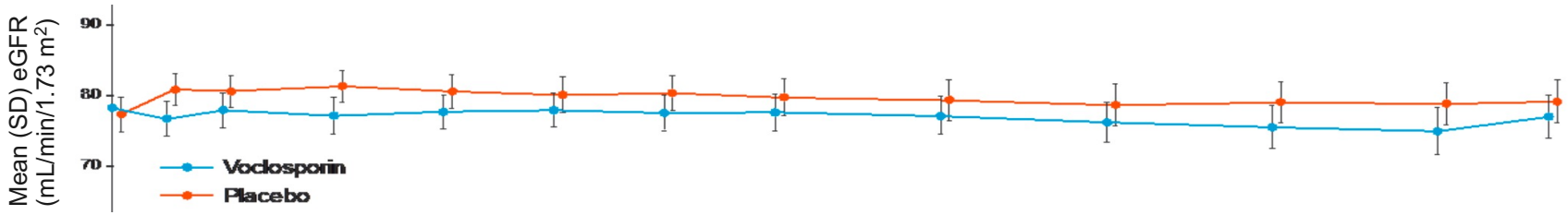
AURORA: Adverse Events

	Control (n=178) n (%)	Voclosporin (n=179) n (%)
Adverse Event (AE)	158 (89)	162 (91)
Serious Adverse Event (SAE)	38 (21)	37 (21)
SAE System Organ Class of Infection	20 (11)	18 (10)
Treatment-related SAE	8 (4)	8 (4)
AE leading to study drug discontinuation	26 (15)	20 (11)
Death*	5 (3)	1 (<1)
Treatment-related AE leading to death	0	0

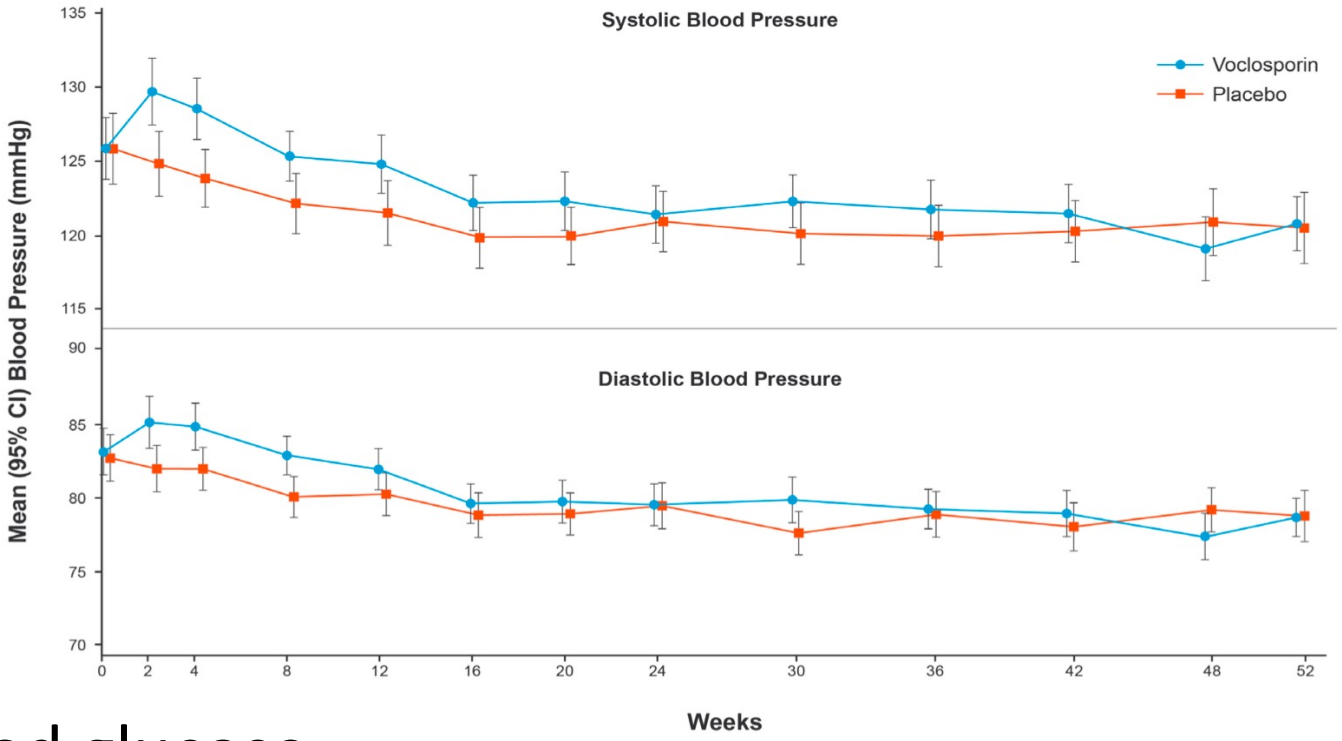
Rovin B et al., Lancet 2021; 397: 2070–80

Effect of Voclocporin on eGFR and Cardiovascular Risk Factors

- GFR:



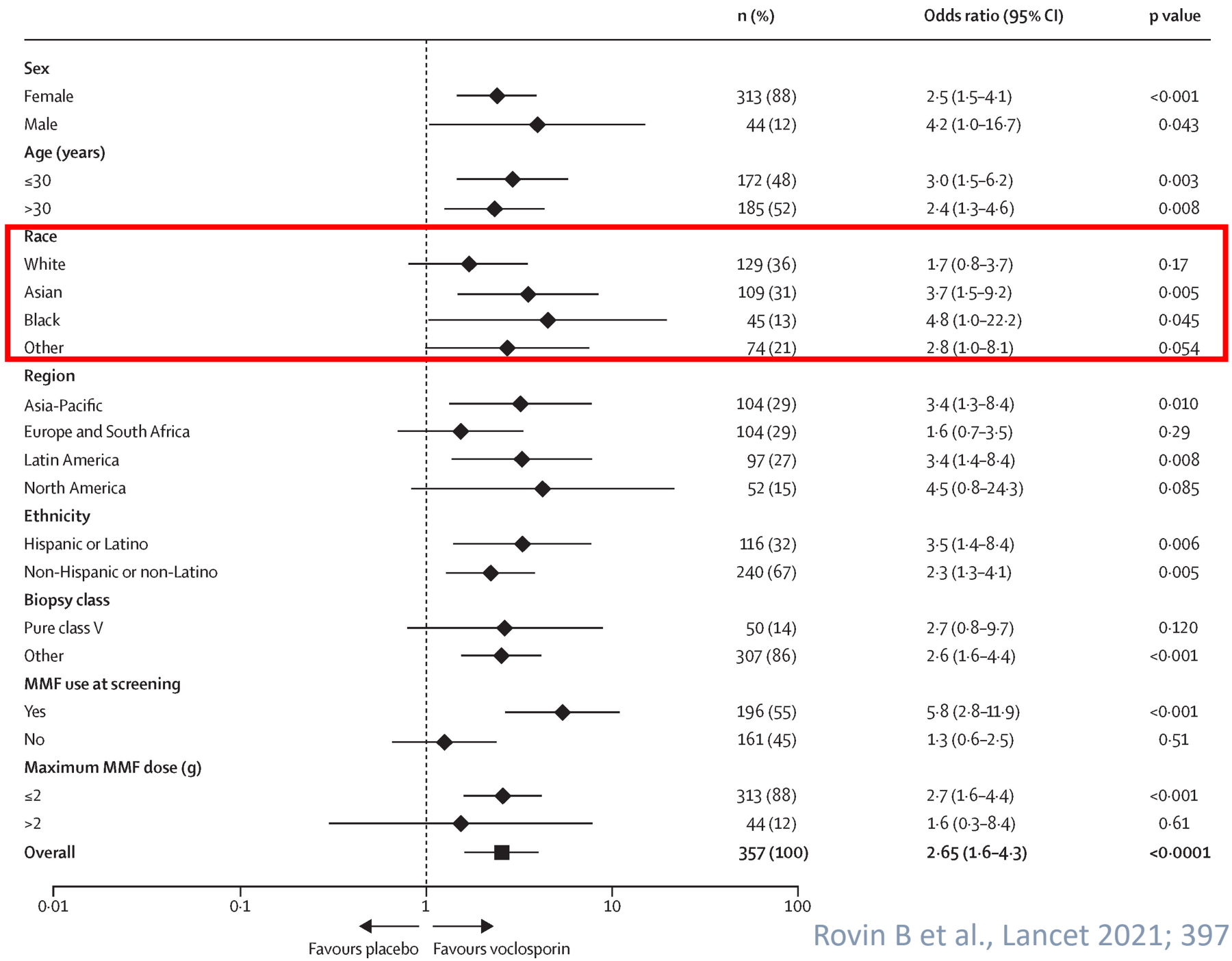
- Blood pressure:



- No effect on blood glucose
- Positive effect on blood lipids

Rovin B et al., Lancet 2021; 397: 2070–80

AURORA: Subgroup analysis



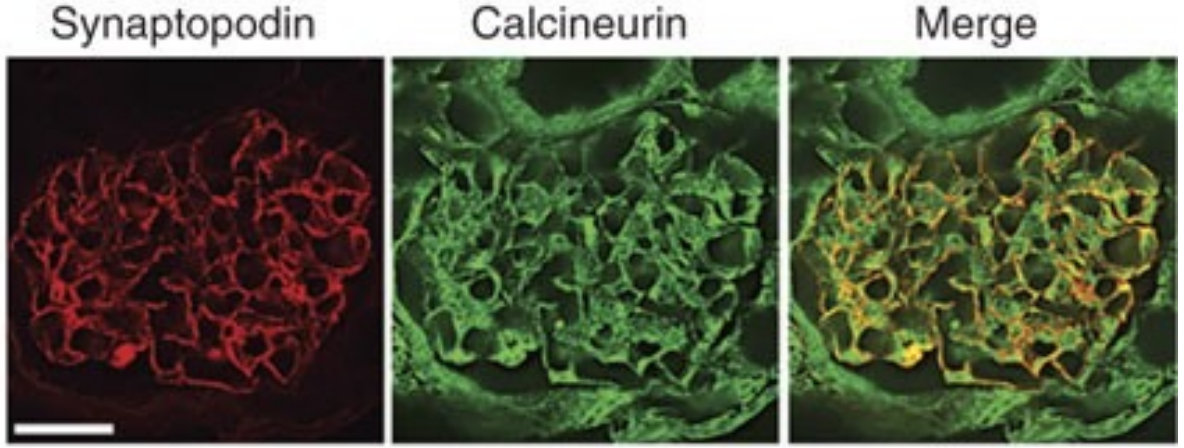
Rovin B et al., Lancet 2021; 397: 2070–80

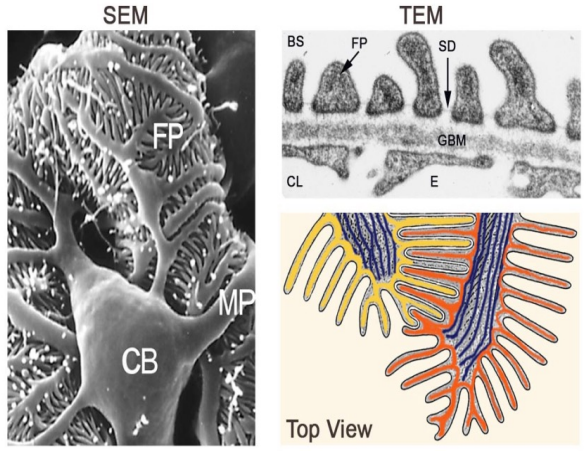
AURORA: Effect on SLEDAI and Serological Activity Parameters

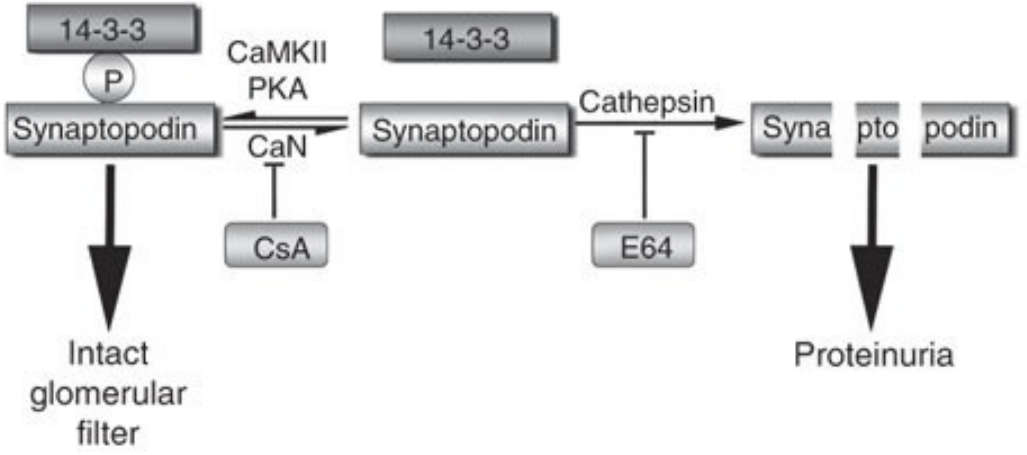
Visit (n/n)	Voclosporin (n=179) LS Mean (95% CI)	Placebo (n=178) LS Mean (95% CI)	LS Mean Difference vs· Placebo (95% CI)	p-value
SELENA-SLEDAI Index Score				
Week 24 (167/172)	-4·5 (-5·4, -3·7)	-4·1 (-5·0, -3·2)	-0·5 (-1·6, 0·6)	0·375
Week 52 (150/160)	-6·0 (-6·7, -5·2)	-5·5 (-6·3, -4·7)	-0·5 (-1·4, 0·4)	0·277
Complement C3 (mg/dL)				
Week 24 (174/169)	14·6 (10·3, 19·0)	13·4 (9·0, 17·8)	1·2 (-3·9, 6·3)	0·634
Week 52 (161/149)	15·8 (11·1, 20·5)	13·1 (8·2, 18·0)	2·7 (-3·0, 8·5)	0·352
Complement C4 (mg/dL)				
Week 24 (174/169)	3·8 (2·2, 5·3)	3·3 (1·7, 4·9)	0·5 (-1·4, 2·4)	0·620
Week 52 (161/149)	3·4 (1·9, 4·9)	3·0 (1·4, 4·5)	0·4 (-1·3, 2·2)	0·629
Anti-dsDNA (IU/mL)				
Week 24 (173/169)	-44·1 (-55·6, -32·5)	-33·4 (-45·1, -21·8)	-10·6 (-24·4, 3·1)	0·129
Week 52 (159/149)	-54·1 (-65·1, -43·0)	-42·2 (-53·7, -30·8)	-11·9 (-25·0, 1·3)	0·077

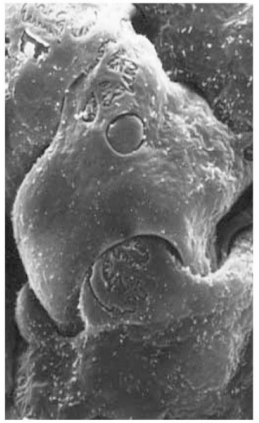
Rovin B et al., Lancet 2021; 397: 2070–80

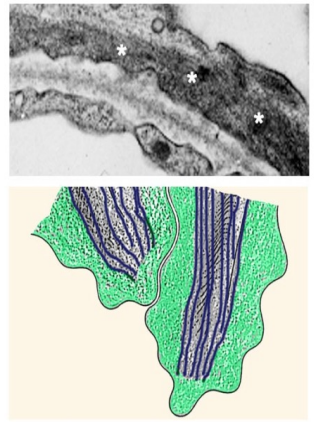
Non-immune Effects of CNI on Proterinuria











Faul C et al., Nat Med 2008;14:931

Lessons from NOBILITY, BLISS-LN and AURORA for Steroid Dosing in LN

- Not real steroid replacement trials
- But: “Triple“ Immunosuppression as a means to reduce GC?
- BLISS-LN and NOBILITY used „standard“ GC-regimen
- AURORA: largest LN study with a defined low dose GC regimen
- Respons rates in AURORA placebo arm similar to other studies with higher dose GC, *however...*
  - *Comparability between studies (inclusion criteria, end point definition)?*
  - *Pre-randomization steroid treatment?*

AURA (voclosporin Phase II) vs. ALMS

Dall'Era et al., Lupus 2019;28:591

AURA, placebo arm vs. ALMS both arms
Propensity matched

	ALMS		*AURA*		
	Mean	*(95% CI)*	*Mean*	*(95% CI)*	p-*value*
Mean glucocorticoid dose, mg/day, p.o. only	25.2	(23.2, 27.2)	10.0	(8.7, 11.3)	<0.0001
Total glucocorticoid dose, mg, p.o. only	3709.2	(3394.5, 4023.9)	1496.0	(13192, 1672.8)	<0.0001
Total glucocorticoid dose, mg, p.o. and i.v.	3709.2	(3394.5, 4023.9)	2630.9	(2.3664, 2895.4)	<0.0001
MMF dose, g/day	2.6	(2.45, 2.77)	1.9	(1.73, 1.96)	<0.0001

	ALMS			*AURA*			*AURA* vs. *ALMS*		
	n	N	%	n	N	%	*Odds ratio*	*(95% CI)*	p-*value*
Week 24 response[a]	34	63	54.0	28	63	44.4	0.68	(0.34, 1.38)	0.2857
Week 24 remission[b]	10	63	15.9	9	63	14.3	0.88	(0.33, 2.35)	0.8035
Week 24 partial remission[c]	34	63	54.0	31	63	49.2	0.83	(0.41, 1.66)	0.5932
C3 normalization, week 12[d]	15	55	27.3	13	56	23.2	0.81	(0.34, 1.90)	0.6628
C4 normalization, week 12[e]	25	55	45.5	18	56	32.1	0.57	(0.26, 1.23)	0.1516
C3 and C4 normalization, week 12	9	55	16.4	9	56	16.1	0.98	(0.36, 2.69)	0.9667
C3 or C4 normalization, week 12	31	55	56.4	22	56	39.3	0.50	(0.24, 1.07)	0.0731
C4 normalization, week 24[f]	19	47	40.4	5	42	11.9	0.20	(0.07, 0.60)	0.0041
Anti-dsDNA pos, ≥30 IU/ml, week 24	26	48	52.4	25	51	49.0	0.81	(0.37, 1.79)	0.6087
>25% decrease proteinuria, week 24	28	52	53.8	33	60	55.0	1.05	(0.50, 2.21)	0.9027
UPCR ≤ 1 at week 24	32	48	66.7	24	53	45.3	0.41	(0.18, 0.93)	0.0323

KDIGO 2021 Recomendation

	Standard-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

Figure 90 | Example of glucocorticoid regimens for LN. LN, lupus nephritis.

Conclusions and Take Home Messages

- Very few data available on the optimal steroid regimen in LN
- Starting with 1mg/kg may be too high
- Spectrum of therapeutic effects and adverse effects is dose-dependent (different mechanisms of action)
- Cumulative dose of GC is of limited value, particularly if adding pulse IV and oral GC
- Pulse IV methylprednisolone allows lower oral GC-dosing and may help reduce overall GC-related adverse effects
- Do not use low dose oral GC schemes w/o IV pulses for severe disease

Conclusions and Take Home Messages

- Triple therapy as a means to spare steroids and increase response rate:
  - B-cell depletion (rituximab, obinutuzumab)
  - Anti-BLyS (belimumab)
  - CNI (voclosporin)
  - more to come...

Thank you for listening!

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