



Lupus Nephritis

KDIGO

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Singapore Nov2017

- *Recent data on Tacrolimus*
- *Long-term MPA → Flare & Outcome data*
- *Corticosteroid dosing*

Recent data on Tacrolimus

KDIGO

Tacrolimus vs ivCTX as Induction Rx in III/IV LN

Pred+TAC (42) vs Pred+ivCTX (39)

III/IV+/-V V (11%)

TAC trough blood level 5-10 ng/mL

6-month outcome –

CR 52.4% vs 38.5% P=0.2

Response 90.5% vs 82.1% P=0.7

TAC → lower proteinuria level after 1 mon

Adverse effects less frequent in Tac group

TAC ≈ esp useful for class V

Pred+TAC vs Pred+MMF as Induction Rx

open-label randomized prospective controlled trial
induction Rx **6 mon** III / IV / V (pure V 19%)
responders maintained with pred+AZA (approx 80%)

Baseline CrCl ~80 mL/min

TAC (n=74) started at 0.1 mg/kg/D

TAC trough → >5 µg/L, **achieved level 7.8+/-3.9 µg/L**

MMF (n=76) dose could go up to 3 g/D

Table 3 Overall renal response at month 6

Renal response at month 6	MMF (N=76)	TAC (N=74)	Difference (95% CI)*	p Value
CR	45 (59%)	46 (62%)	3% (-12% to 18%)	0.71
PR	16 (21%)	20 (27%)	6% (-8% to 19%)	
NR	15 (20%)	8 (11%)	-9% (-20% to 3%)	
CR (ACR)†	8 (11%)	10 (14%)	3% (-8% to 14%)	0.59

*With reference to MMF.

†Definition: creatinine clearance ≥ 90 mL/min+urine protein/creatinine <0.2 +inactive urinary casts.

ACR, American College of Rheumatology; CR, complete response; MMF, mycophenolate mofetil; NR, no response; PR, partial response; TAC, tacrolimus.

TAC \Rightarrow numerically higher response rate than MMF in Class V

Major infections – MMF 9.2%; TAC 5.4% (p=0.53)

1 death (infection); MMF \Rightarrow more zoster (18% vs 3%) and diarrhea

CrCl did not change in TAC group but improved in MMF group

**Some patients in Tac group had *reversible SCr increase by 30%*

FU 60.8±26 months

Proteinuric flares

Nephritic flares

≥30%↓CrCl/≥CKD4/death

MMF-AZA

24%

18%

21%

TAC-AZA

35%

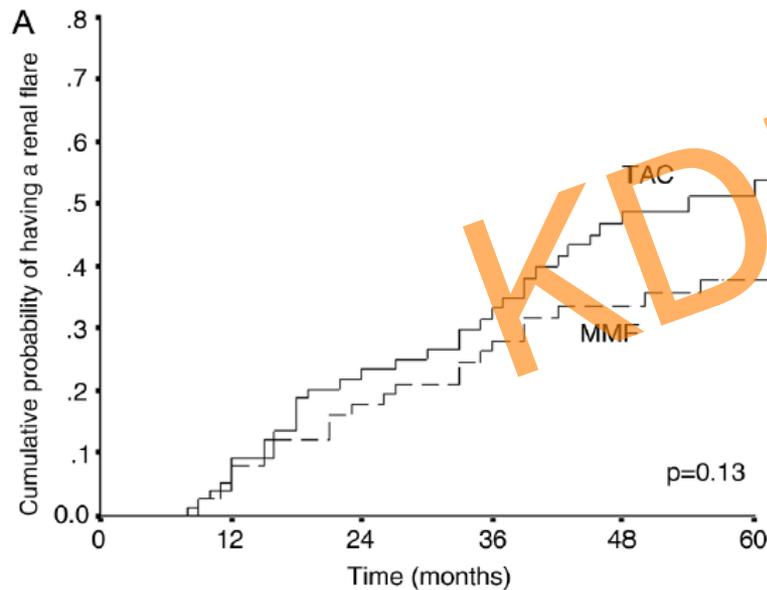
27%

22%

p

0.12

0.21



Renal Flare	M-A	T-A
1-yr	8%	9%
3-yr	28%	33%
5-yr	38%	54%
	p=0.13	
Deaths	6	5

number of patients remaining

MMF	76	68	49	40	32	24
TAC	74	67	49	40	25	15

Present era –

- Rate of renal flare ?
- Renal survival ?
- Patient survival ?

Survival Analysis and Causes of Death

n = 230 Chinese lupus nephritis patients in HK

Follow-up 4076 pat-yr (17.7+/-8.9 yr)

24 deaths (10.4%) – 85% after 10 yrs of follow-up

<i>Survival</i> –	Patient	Renal
5-yr	98.6%	99.5%
10-yr	98.2%	98.0%
20-yr	90.5%	89.7%

Causes of death - infection (50%), cardiovascular (20.8%), malignancy (12.5%)

SMR - ESRD 26.1, malignancy 12.9, cardiovascular 13.6

Relapse-free survival at 5-yr

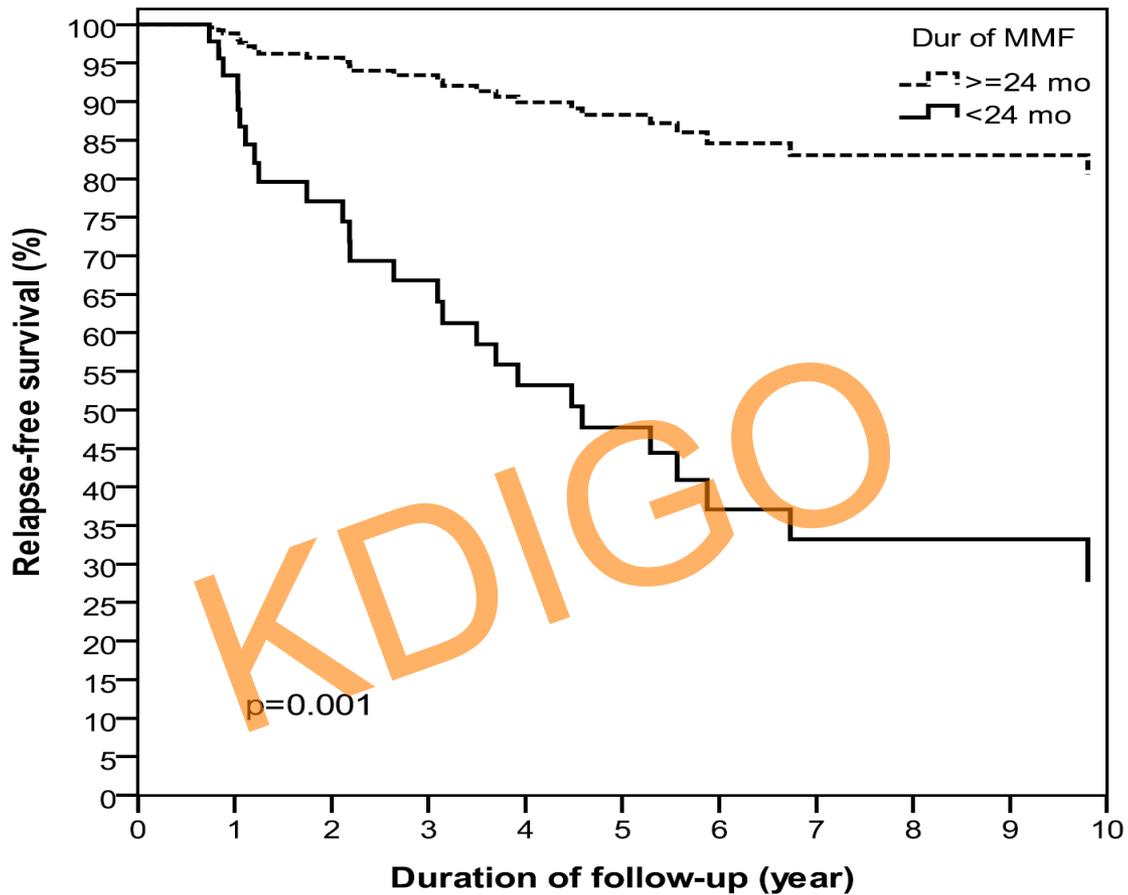
MMF-MMF 76%

MMF-AZA 56%

Yap DYH, et al. Rheumatology 2013; 52: 480-6

Chan TM. Lupus 2008; 17: 617-21

Chan TM. Am J Med 2012; 125: 642-8



Survival % (no. at risk)

MMF ≥ 24 mo 100% (28)

88% (15)

81% (1)

MMF < 24 mo 100% (37)

48% (12)

28% (3)

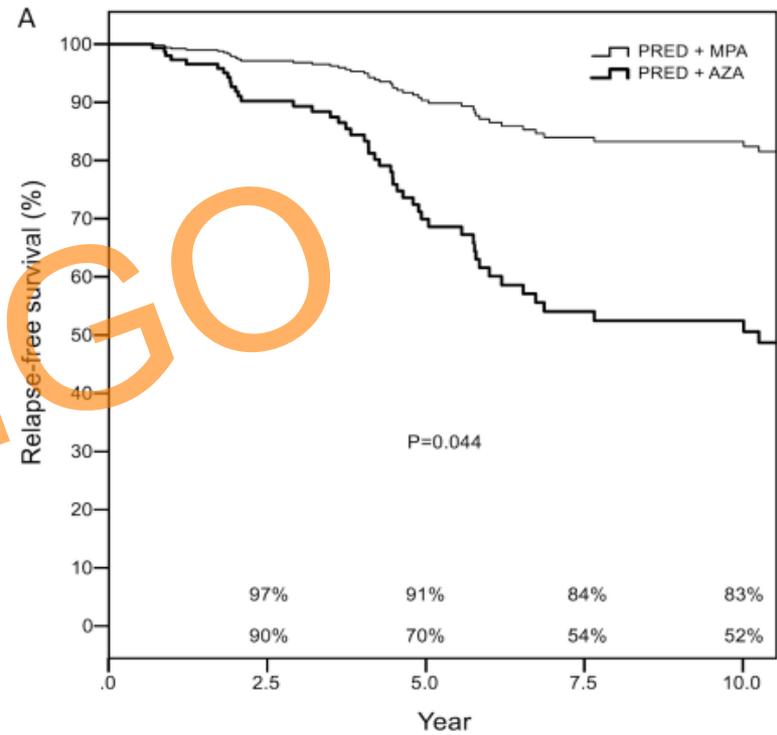
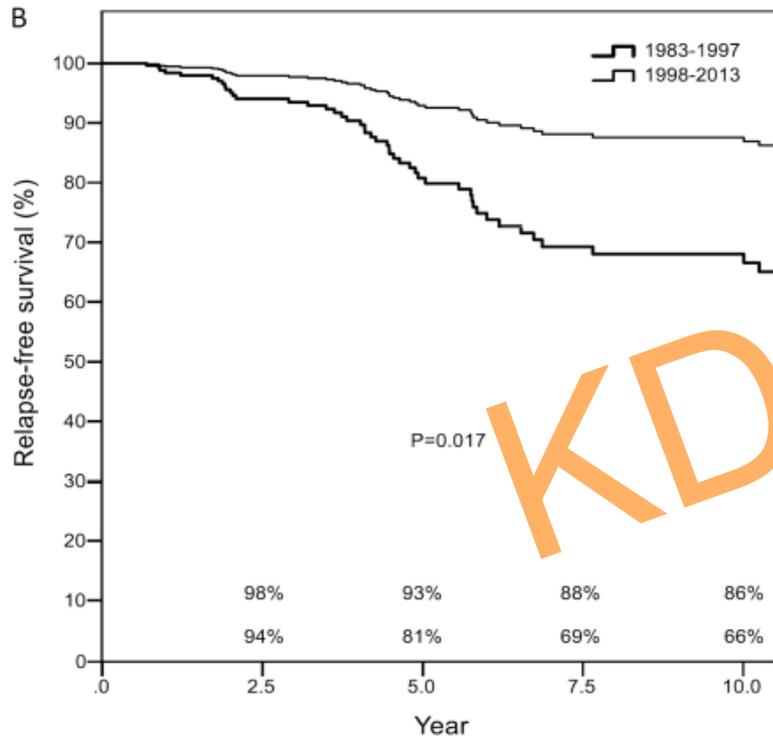
Disease Flares in LN in the Recent Era

n = 139 Chinese lupus nephritis III/IV±V patients in HK

Dx 1983-2013 FU 112.5+/-88.4 mon

135 episodes of renal flare \Rightarrow 0.108 per patient-yr

	1-yr	2-yr	3-yr	4-yr	5-yr	10-yr
<i>Survival free of renal flare</i>	96%	90%	86%	80%	69%	57%
<i>Survival (no-flare)</i>		5-yr	10-yr		5-yr	10-yr
<i>pred+MPA</i>		91%	83%	98-13	93%	86%
<i>pred+AZA</i>		70%	52%	83-97	81%	66%



	MPA	CR	'98 to '13
<i>Flare risk OR</i>	0.314	0.329	0.305
P value	0.049	0.016	0.005

Yap DYH, et al. J Rheumatol 2017; 44:1375-83

FU 60.8±26 months

Proteinuric flares

Nephritic flares

≥30%↓CrCl/≥CKD4/death

MMF-AZA

24%

18%

21%

TAC-AZA

35%

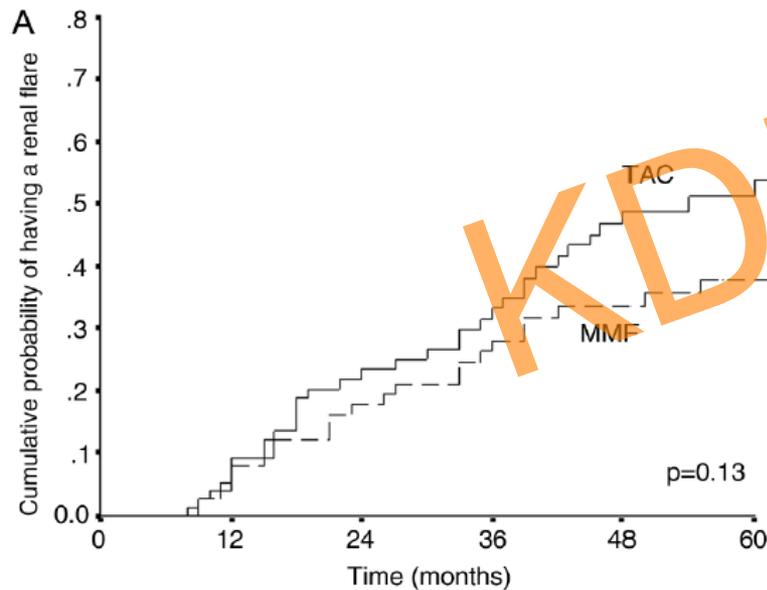
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0.12

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Pred & MMF+TAC vs ivCTX for Class IV+V LN

N=40 UP \geq 1.5 g/d & Cr \leq 265 μ mol/L

6 mon (continued for 9 mon when response suboptimal)

MP 0.5g/D x3 \rightarrow Pred both groups

TAC 5-7 ng/mL

MMF 0.75-1.0 g/d

MPA AUC_{0-12h} 20-45 mg.h/L

ivCTX 0.5-1.0 g/m²

MP-Pred+MMF+TAC (MT, 20) vs MP-Pred+ivCTX (20)

TAC trough blood level 5-7 ng/mL

MMF 0.5 g bid, MPA AUC_{0-12h} 20-45 mg.h/L

Treatment duration 6-9 months

Outcome –

CR/PR	multi-target	Pred+ivCTX
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6-mon	50%/40%	5%/40%
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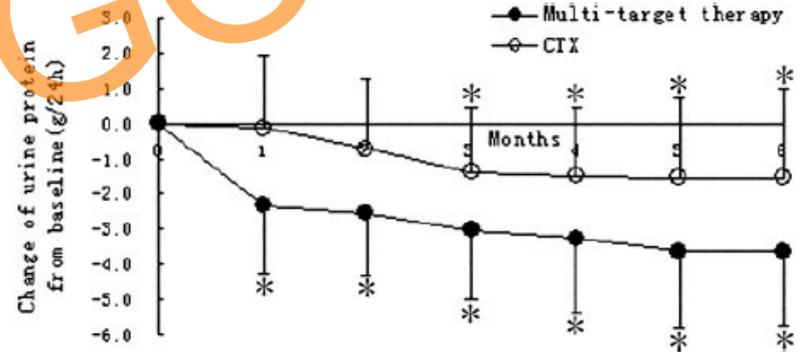
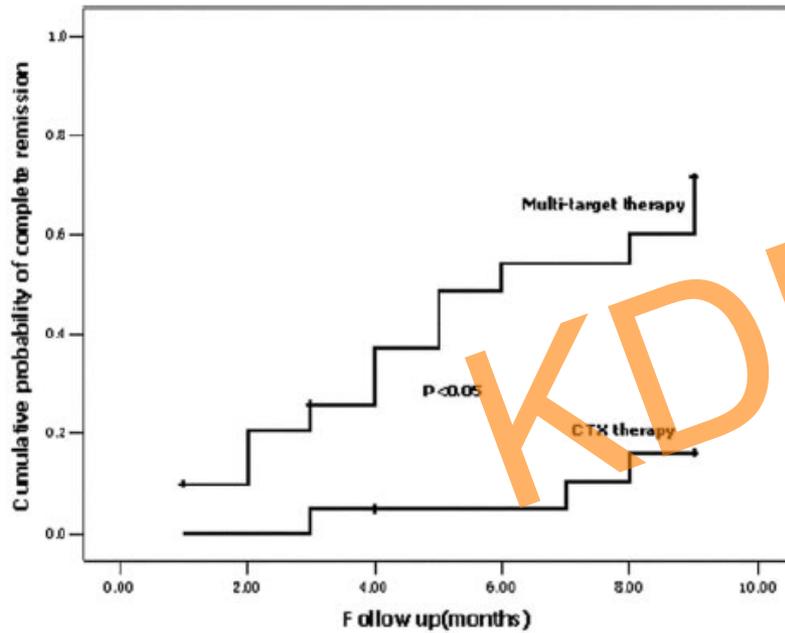
9-mon	65%/30%	15%/40%
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MT triple imsup regimen better tolerated than Pred+ivCTX

↑ Creat with Pred+TAC+MMF

[65% vs 15% at 9 mon]

hypertension asso with TAC



Bao H, et al. J Am Soc Nephrol 2008; 19: 2001-10

Pred & MMF+TAC vs ivCTX as Induction Rx for III/IV/V LN

ivMP 0.5 g/D for 3 days then pred 0.6 mg/kg/D +

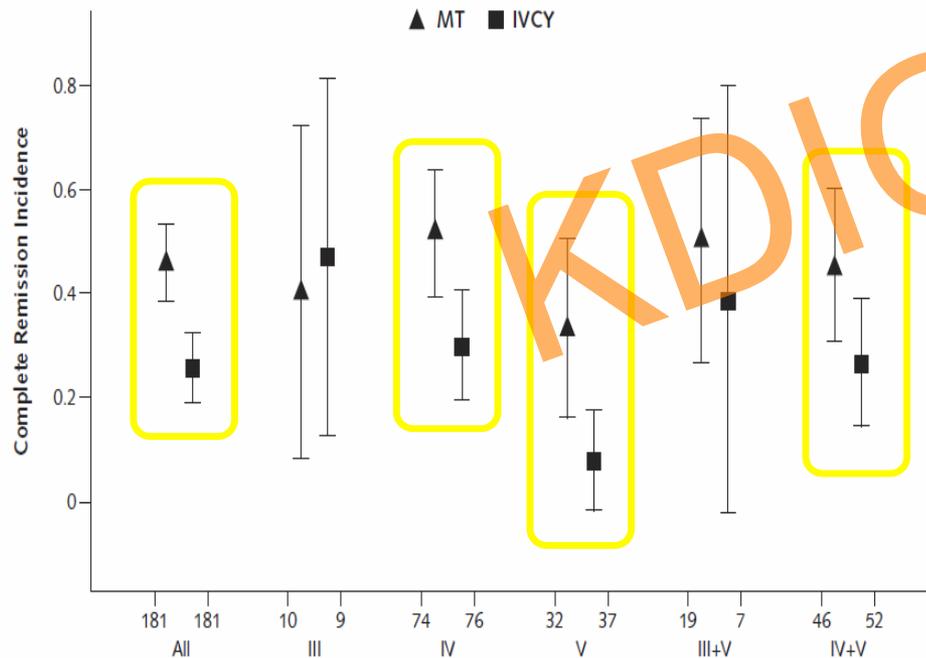
(1). TAC 2 mg bid, MMF 0.5 g bid (n=181)

(2). ivCTX 0.75 g/m² q4wk (n=181) FU 6 mon

- Excluded patients with previous treatment using MMF, CTX, TAC, or high-dose MP, or creat >265.2 micromol/L
- “Drug dosages were adjusted according to the concentration or adverse events.” [mean TAC trough level 5.5 (4 wk), 5.24 (12 wk), 5.49 (24 wk)]

Pred & MMF+TAC vs ivCTX as Induction Rx for III/IV/V LN

1°Endpoint: CR after 24 wks of treatment \Rightarrow MT superior (45.9% vs 25.6%, $p < 0.001$) [response 83.5% vs 63.0%, $p < 0.001$]



368 randomized

362 data analyzed

155 completed 24 wks

26 in each group early discount

Serious AE

MT 7.2% vs CTX 2.8%

AE related drop-out

MT 5.5% vs CTX 1.7%

Pred & MMF+TAC vs AZA as Maintenance Rx for LN

24-wk *Responders* ⇒

MT → MT + pred 10 mg/D (n=116, out of 155)

ivCTX → AZA + pred 10 mg/D (n=90, out of 155)

➤ TAC 2-3 mg/D, MMF 0.5-0.75 g/D, AZA 2 mg/kg/D

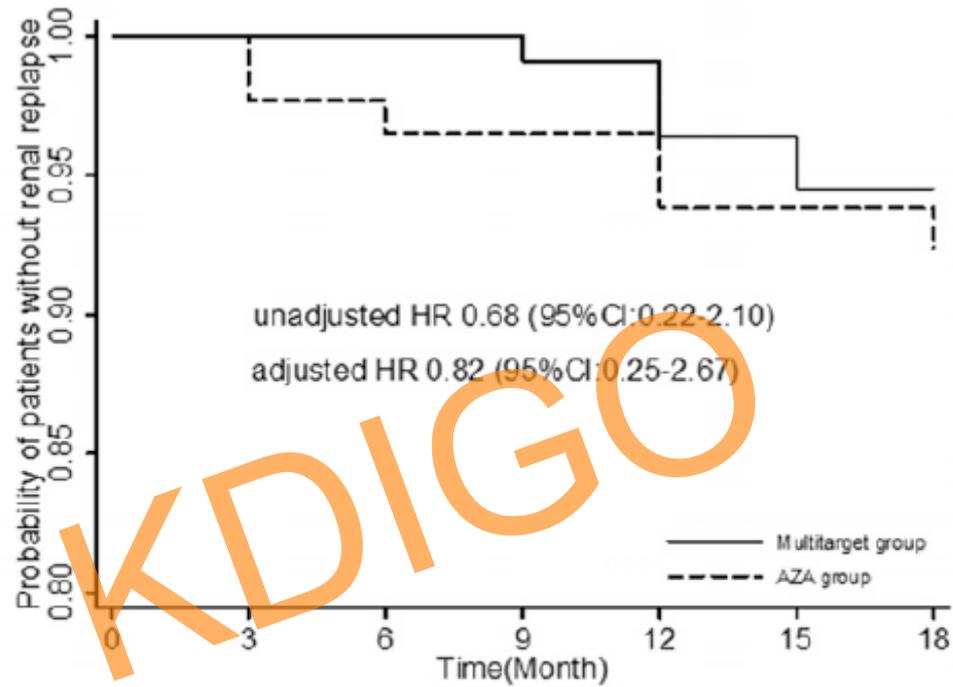
Renal Flare Rate after FU 18 mon (MT 101, AZA 64) -

MT-MT 5.47% HR 0.82, 95% CI 0.25-2.67, P=0.74

CTX-AZA 7.62%

	<u>AE</u>	<u>Withdrawal (AE)</u>
MT	16.4%	1.7%
AZA	44.4%	8.9%
P	<0.01	0.02

mean TAC trough level
3.55 ng/mL at 18 mon



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

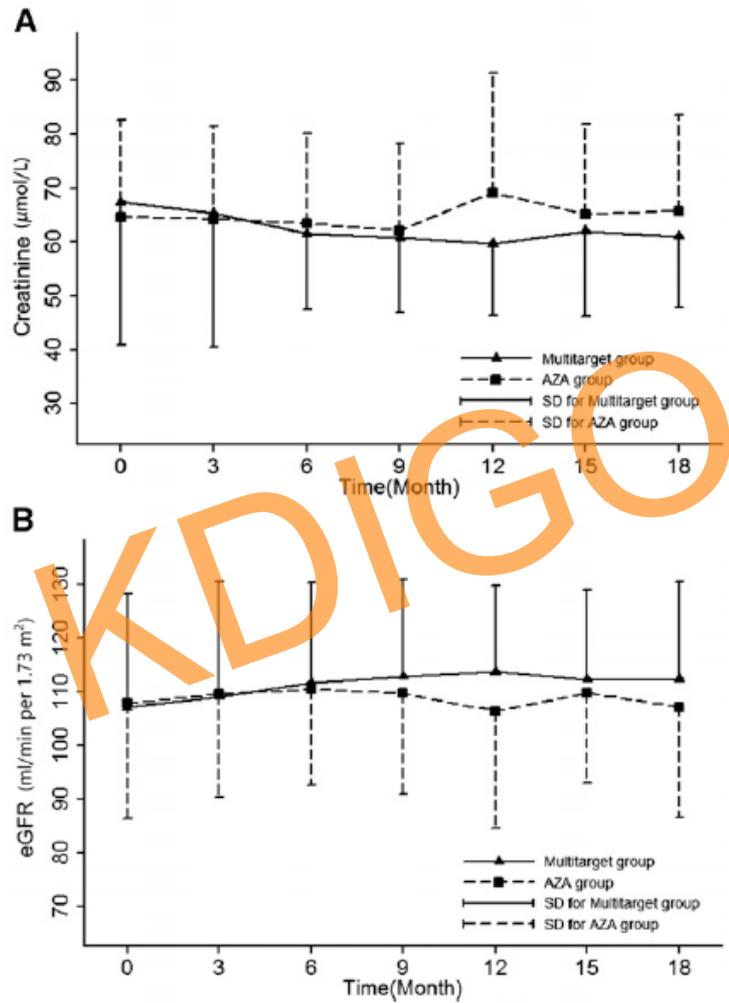


Table 2. Adverse events during the maintenance treatments

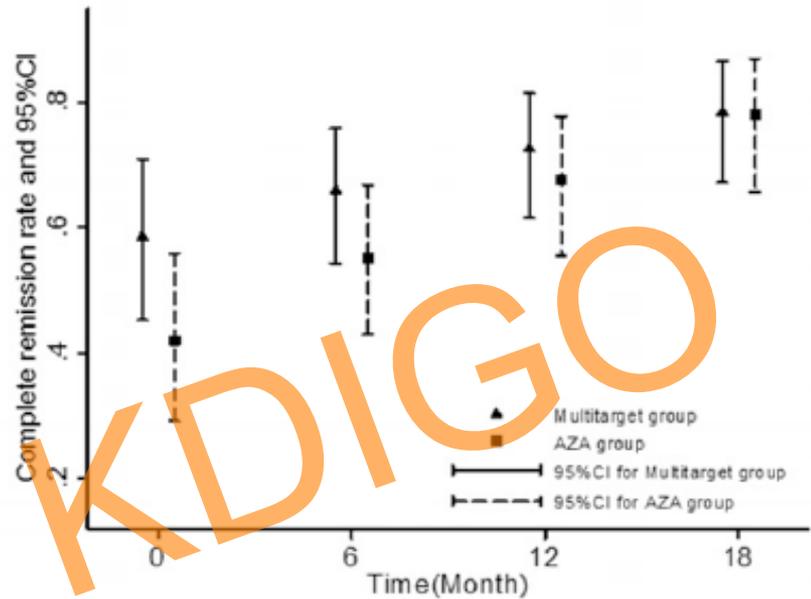
Adverse events	Multitarget, n=116			AZA, n=90		
	Event No.	Crude Rate, %	Rate per 100 patient-yr	Event No.	Crude Rate, %	Rate per 100 patient-yr
AEs (includes SAEs) ^a	19	16.4	11.59	40	44.44	35.57
Infection	12	10.3	7.32	9	10.0	8
Herpes zoster	2	1.7	1.22	2	2.2	1.78
Pneumonia	2	1.7	1.22	0	0	0
Upper respiratory tract infection	7	6.0	4.27	6	6.7	5.34
Herpes simplex	1	0.9	0.61	0	0	0
Urinary tract infection	0	0	0	1	1.1	0.89
Liver dysfunction ^b	1	0.9	0.61	6	6.7	5.34
Leukopenia ^a	9	7.8	5.49	23 ^c	25.6	20.45
Osteonecrosis	1	0.9	0.61	1	1.1	0.89
Upper gastrointestinal symptoms	1	0.9	0.61	5	5.6	4.45
Menstrual disorder	0	0	0	2	2.2	1.78
SAEs	2	1.7	1.22	3	3.3	2.67
Pneumonia	2	1.7	1.22	0	0	0
Liver dysfunction	0	0	0	1	1.1	0.89
Leukopenia	0	0	0	2	2.2	1.78

Leukopenia was defined as a peripheral white blood cell count <4000 cells per 1 μ l. The definition of liver dysfunction was a serum alanine aminotransferase and/or aspartate transaminase level >50 U/L. The crude rates were compared using the Fisher exact method. AE, adverse event; SAE, serious adverse event.

^aP<0.01.

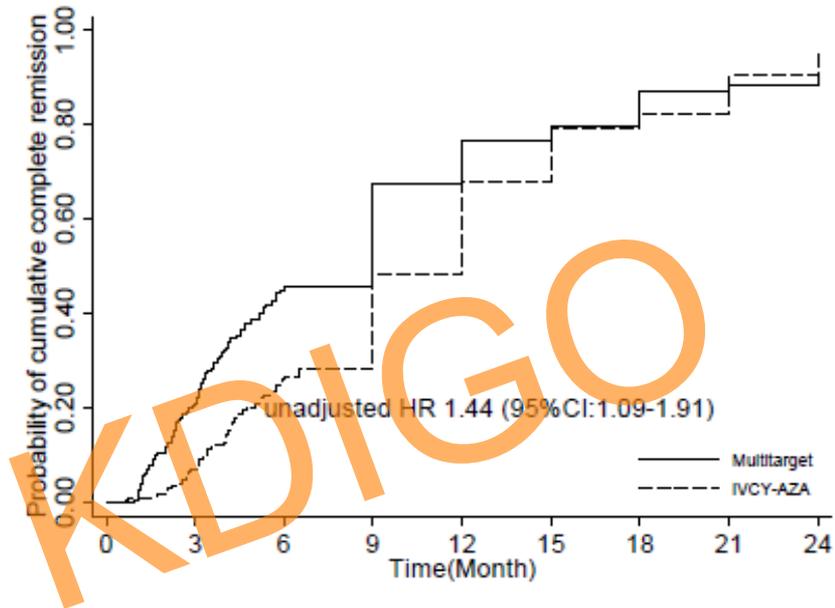
^bP<0.05.

^cOnly one patient with leukopenia experienced an infection (herpes zoster); the other 22 patients with leukopenia underwent transient withdrawal or an alteration in the AZA dose.



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	

Supplemental Figure 2. The cumulative probability of achieving CR during multitarget therapy and IVCY-AZA treatments. Cumulative CR data were analyzed using Kaplan-Meier curves and between-group differences were compared using the log-rank test. The frailty model was used to estimate the HRs.



No. at risk

Multitarget	181	132	80	50	29	21	17	9	7
IVCY-AZA	181	152	108	50	34	20	13	11	5

No. with complete remission

Multitarget	0	36	39	20	8	3	6	1	1
IVCY-AZA	0	12	31	15	13	7	2	5	3

Log-rank test statistic 7.69, $P=0.006$

- *Merits vs Concerns about CNI*
- *Long-term CNI data important*
- *Duration of CNI ?*

Calcineurin Inhibitors (CNI)

- cyclosporine, tacrolimus, voclosporin, ...
- effective immunosuppression (T lymphocyte)
- standard immunosuppressive therapy in kidney transplantation ⇒ corticosteroids + CNI + MPA
- reduce proteinuria (effect on podocyte) → efficacy in MN, FSGS, relapsing MCD
- side-effects in addition to over-immunosuppression - **CNI nephrotoxicity** (acute/chronic), ↑BP, metabolic, tremor, ...
- therapeutic window - TDM

Long-term Data on TAC in LN

retrospective TAC treatment >6 mon target trough 4-6 $\mu\text{g/L}$

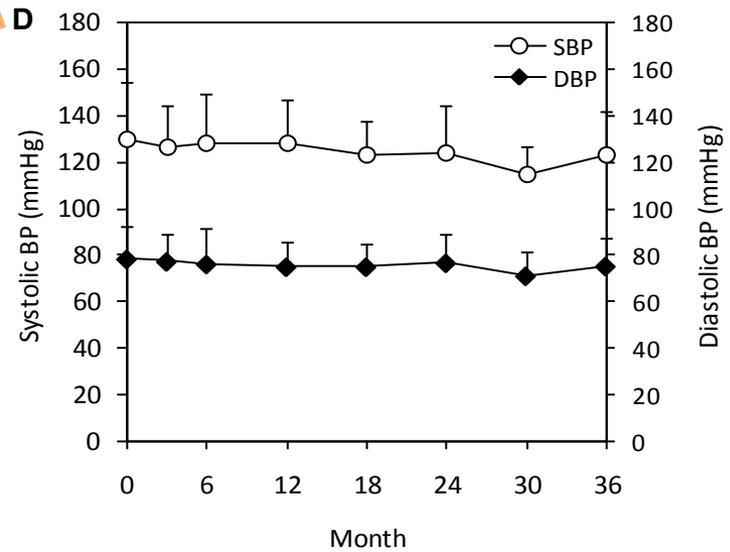
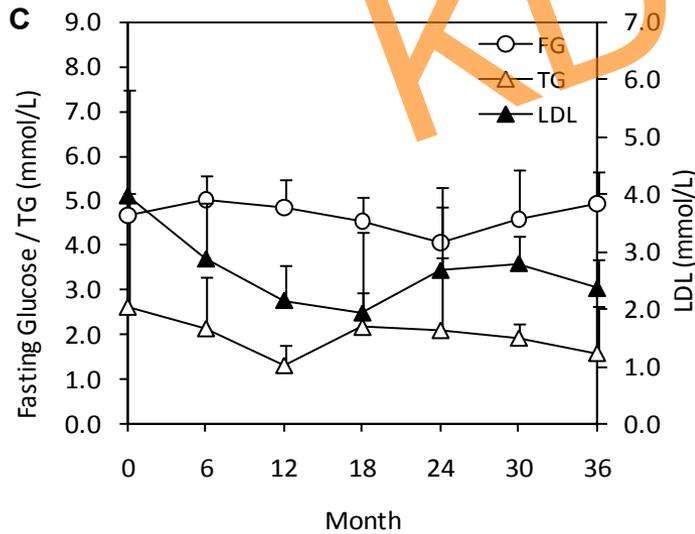
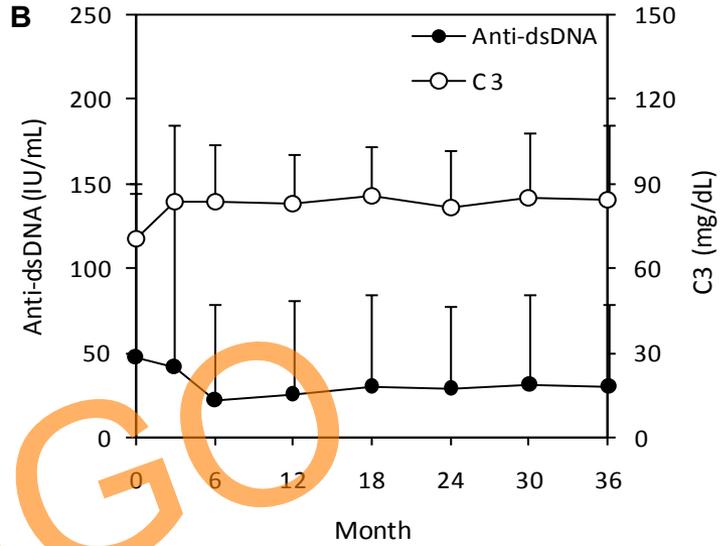
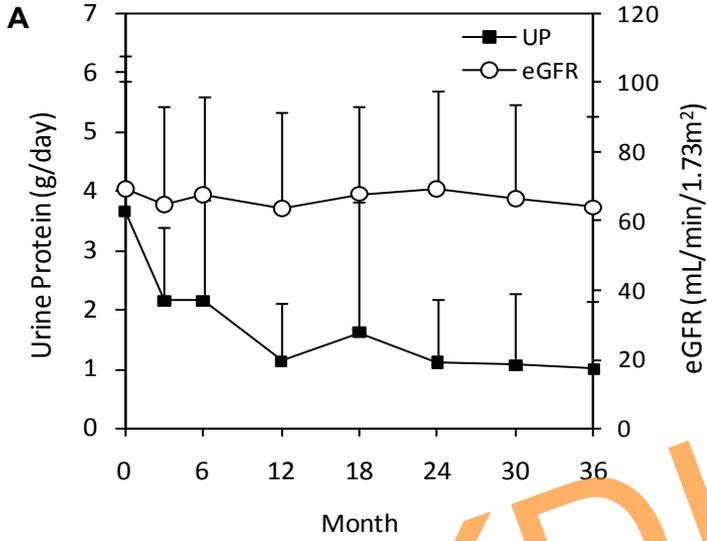
N=29 [41.2 \pm 9.2 yr; 24F 5M]

17 III/IV \pm V \rightarrow TAC added to pred+MMF

10 V \rightarrow Pred+TAC 2 relapsing podocytopathy

TAC duration 46.9 \pm 37.9 mon [18(62.1%) >36 mon]

TAC	<u>6 mon</u>	<u>12 mon</u>
Dose	3.39 \pm 1.91	3.41 \pm 1.72 mg/D
Trough	4.72 \pm 2.9	4.17 \pm 1.91 $\mu\text{g/L}$



Long-term Data on TAC in LN

Renal Response –

Complete UP \leq 0.5 g/D, creat \pm 15% of baseline

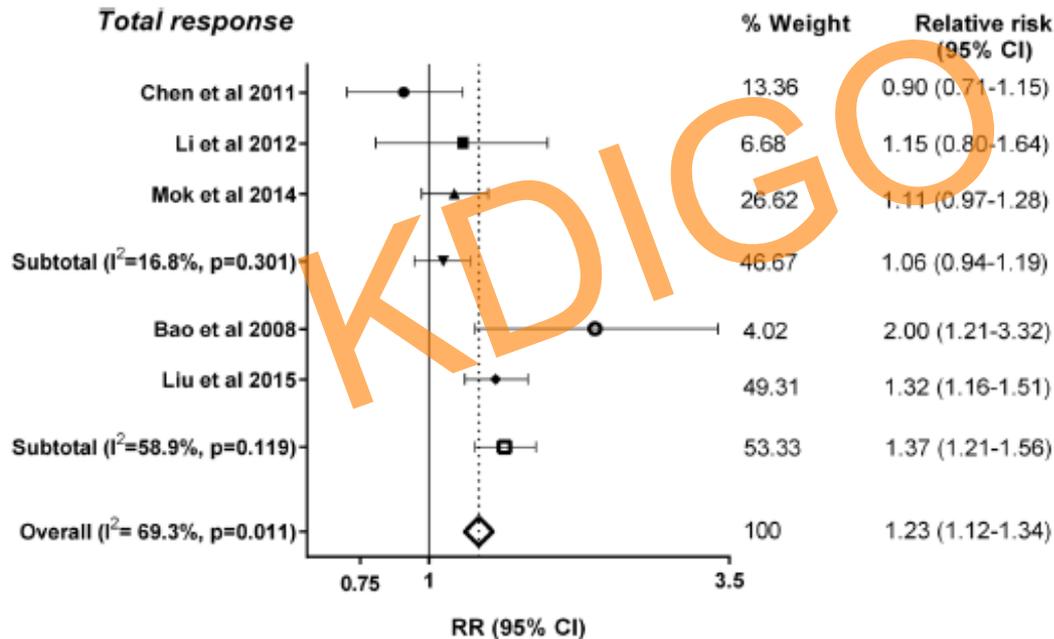
Partial UP \downarrow by 50%, non-nephrotic, stable creat

<i>Response rate</i>	<u>Complete</u>	<u>Partial</u>	
Class III/IV \pm V	40%	26.7%	[12-mon]
	46.7%	33.3%	[24-mon]
Class V	30%	30%	
	50%	40%	

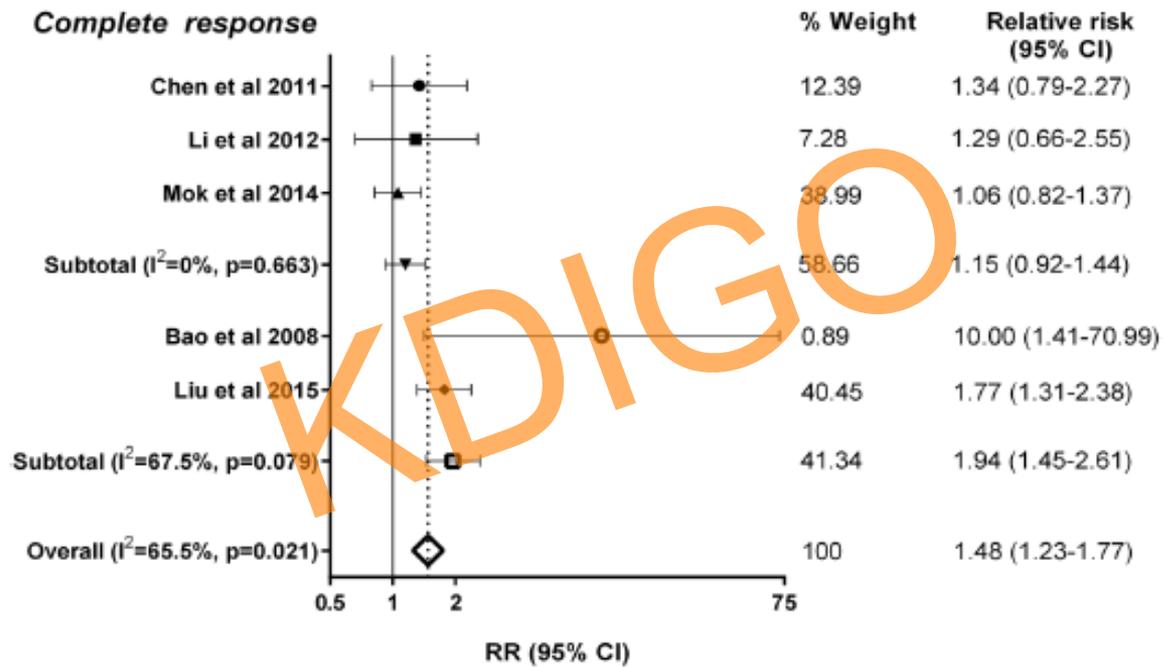
37.9% had UP \downarrow by 50% after 6 months of TAC

Meta-analysis of Tacrolimus in LN

23 clinical studies (induction 70%; maintenance 35%)
[6 RCT – all Asian]



Kraaij T, et al. Lupus Sci Med 2016;3:e000169.
DOI 10.1136/lupus-2016-000169

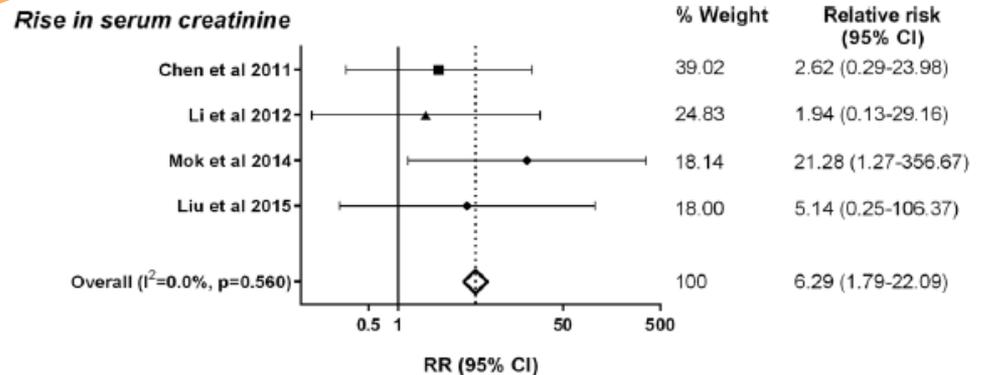
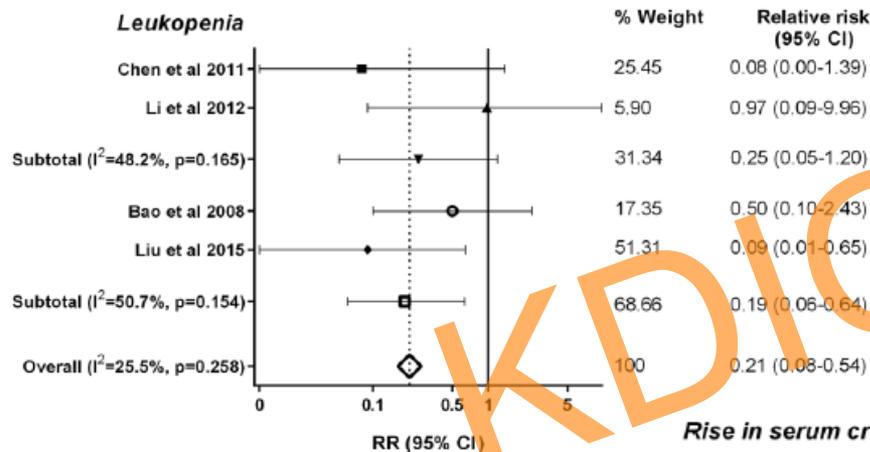


Kraaij T, et al. Lupus Sci Med 2016;3:e000169.
 DOI 10.1136/lupus-2016-000169

TAC ⇒

leucopenia RR 0.21, 95% CI 0.08-0.54, P<0.05

↑creatinine RR 6.29, 95% CI 1.79-22.09, P<0.05



Kraaij T, et al. Lupus Sci Med 2016;3:e000169.
DOI 10.1136/lupus-2016-000169

Tacrolimus in the Treatment of Lupus Nephritis

- ❑ Effective immunosuppressive agent
- ❑ Distinct role in treatment of proteinuria due to podocyte injury
- ❑ Safety in pregnancy (lactation) vs MMF (contraindicated)
- ❑ Drug interactions
- ❑ Optimal patient group / treatment duration?
- ❑ Important to prevent / detect early the adverse effects (especially nephrotoxicity, which can be subclinical)
- ❑ Avoid over-immunosuppression → Role in steroid-sparing ?

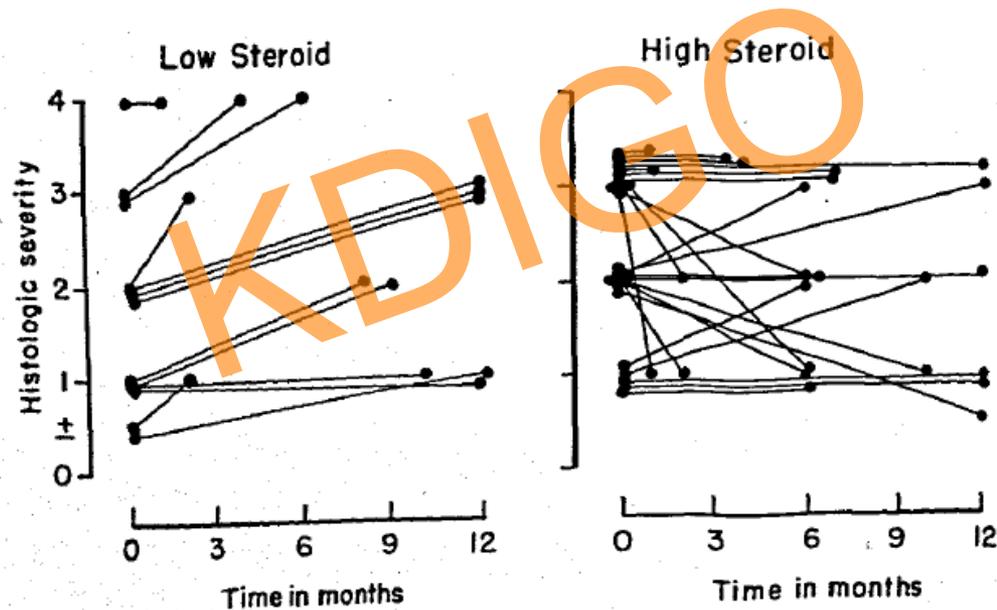
Corticosteroids in severe LN

KDIGO 2012

Corticosteroids in the treatment of class III and IV LN

All regimens use similar corticosteroid dosing: an initial dose of oral prednisone up to 1 mg/kg, tapering according to clinical response over 6–12 months. Additional i.v. methylprednisolone is widely used at the beginning of treatment for more severe disease. However, the dosing and duration of corticosteroids has never been subject to evaluation by RCTs.

high-dose prednisone (n=31) more effective than low-dose prednisone (n=16) in preventing histological progression and death from renal failure (13/31 vs 13/16).



Adverse Effects of Medium- / High-dose GC in SLE – Systematic Review

8 RCTs included 182 SLE patients treated with GC alone
[≥ 30 mg/D = high-dose]

DM 9/100 pat-yr

Infection 25/100 pat-yr

Avas Necrosis 12/100 pat-yr

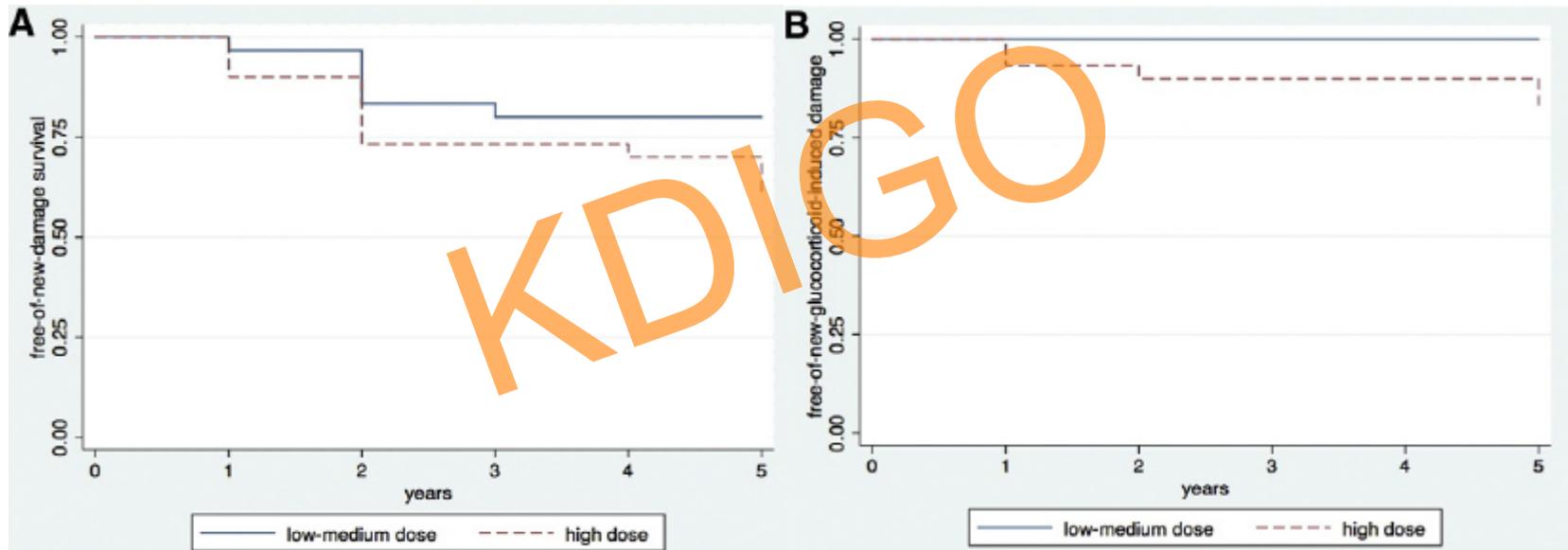
High vs Low-Medium Prednisone in Active SLE

Retrospective comparison of patients with SLEDAI \geq 6 treated with pred \leq 30 mg/D (M, n=30) vs pred $>$ 30 mg/D (H, n=30)

Prolif LN excluded

	Group M (n = 30)	Group H (n = 30)
Women, n/N (%)	26 (86.67)	26 (86.67)
Age at diagnosis, mean (S.D.)	38.8 (17)	32.2 (13)
Anti-Ro, n/N (%)	10 (33)	11 (37)
Anti-La, n/N (%)	7 (23)	5 (17)
Anti-SM, n/N (%)	5 (17)	6 (20)
Anti-RNP, n/N (%)	2 (7)	4 (13)
Anti-DNA, n/N (%)	19 (63)	15 (50)
Antiphospholipid antibodies, n/N (%)	7 (23)	9 (30)
SLEDAI-0, mean (S.D.)	9.86 (2.8)	9.83 (4.5)
SDI-0, mean (S.D.)	0.13 (0.4)	0.13 (0.4)
Main organ systems affected, n (%) ^a		
Serosal	6	11
Articular	14	13
Kidney	4	7
Haematological	2	6
Skin	11	4
CNS	1	1
involvement		involvement
Vasculitis	2	

↓SLEDAI after 1 yr: 4.9 ± 6.4 in H & 5.1 ± 5.2 in M, $p=0.8$
SLICC Damage Index (SDI): H gp HR 3.85 for new damage
GC-related damage: H gp 5 patients, M gp nil



Corticosteroid Exposure and Clinical Outcome

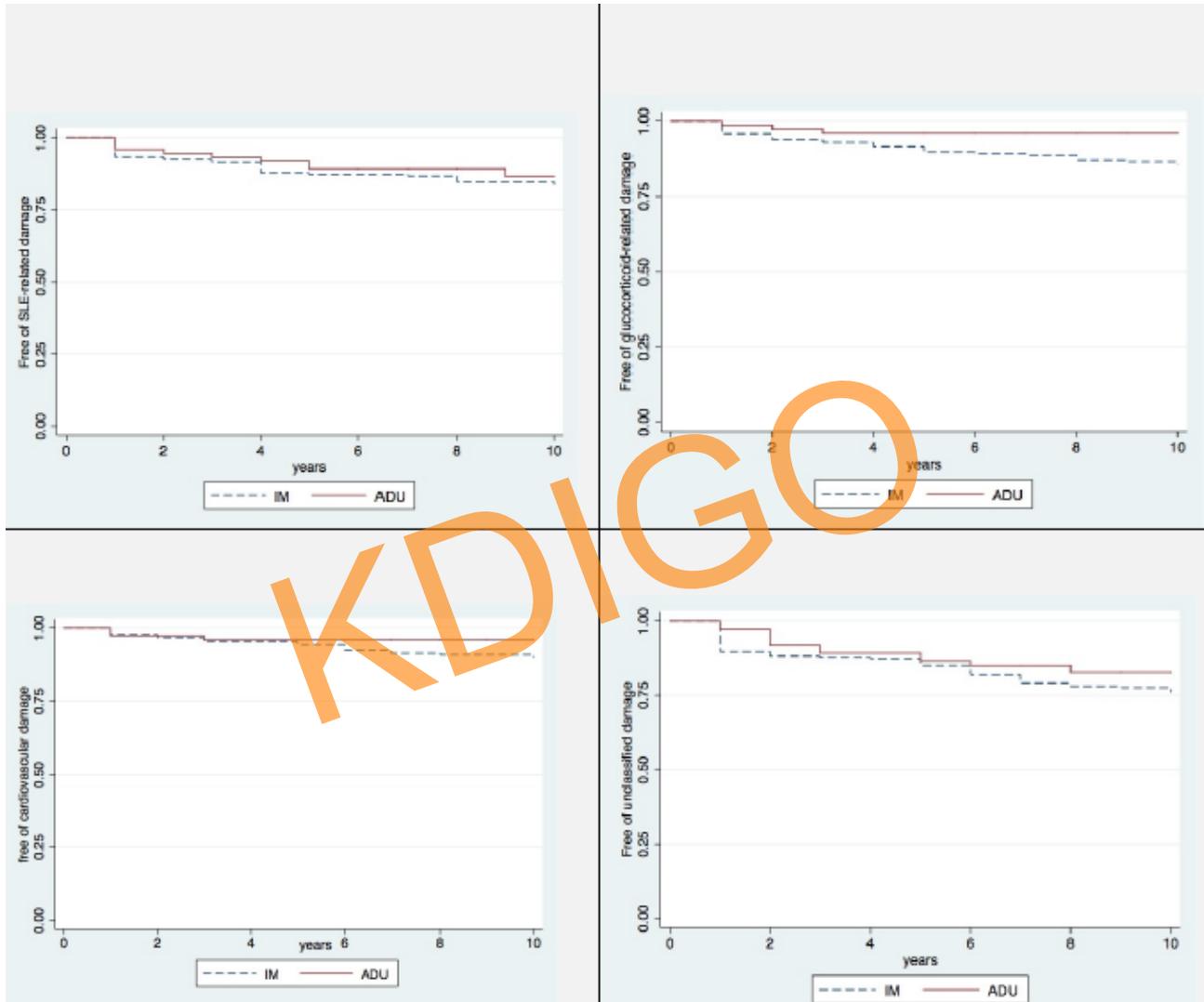
Retrospective comparison of SLE patients treated at Autoimm Dis Unit (ADU) vs other doctors in Internal Medicine (IM)

ADU protocol – oral pred ≤ 30 mg/D; maintenance ≤ 5 mg/D; iv MP pulses; more HCQ and other immunosup

	ADU (n=74)	IM (n=213)	
ANY PRED at year 1, n (%)	47 (63.5)	163 (76.5)	0.03
PREDMAX-1 (mg/d), mean (S.D.)*	15.09 (14.16)	36.8 (27.9)	<0.001
PRED-1 (mg/d), mean (S.D.)*	5.04 (3.4)	16.2 (16.1)	<0.001
ANY PRED at year 5, n (%)	59 (79.7)	180 (84.5)	0.3
PRED-5 (mg/d), mean (S.D.)*	2.8 (2)	9.4 (8.9)	<0.001
ANY MPRED at year 1, n (%)	16 (21)	16 (7.5)	0.001
MPRED-1 cumulative (mg), mean (S.D.)*	905.6 (466.4)	1261 (1443.5)	0.25
ANY MPRED up to year 5, n (%)	24 (32)	25 (12)	<0.001
MPRED-5 cumulative (mg), mean (S.D.)*	1314.7 (1023.4)	1346.8 (1262.4)	0.9

SLEDAI decreased similarly in both groups

ADU group less steroid related damage (HR 0.23)



Ruiz-Arruza I, et al. Arthritis Care Res 2017 Epub. Doi: 10.1002/acr.23322

↓GC with ivMP vs Standard GC, plus CTX, in LN III/IV/V

Retrospective comparison between LN patients treated at Hosp Univ Cruces (CC) and at Bordeaux Univ Hosp (BC)

CC protocol – ivMP 250-500 mg/D x3 then oral pred \leq 30 mg/D ... maintenance 2.5-5 mg/D; also ivCTX 500 mg AND ivMP 125 mg q2wk for 6-9 doses + MMF/AZA

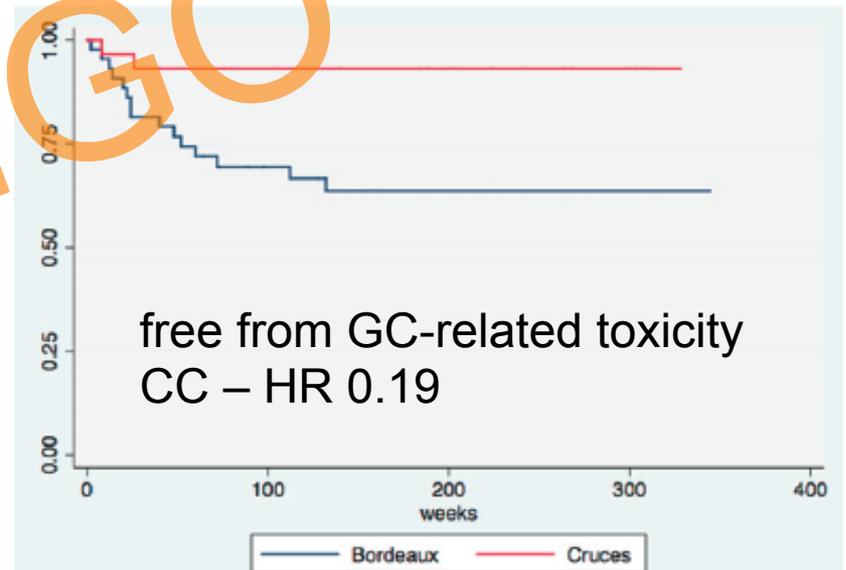
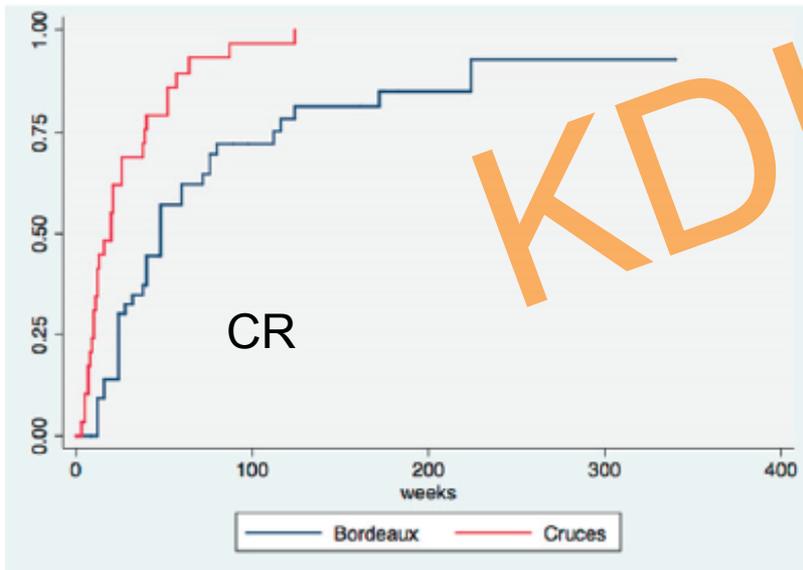
BC protocol – ivMP x1-3 & Euro-Lupus with oral pred 0.7-1.0 mg/kg/D ... maintenance 5-7.5 mg/D + MMF/AZA

Cumulative MP: BC 1.9 g vs CC 1.7 g (p=0.3)

Oral pred: BC 21 ± 11.7 mg/D vs CC 8.3 ± 1.6 mg/D (p<0.001)

CR asso ivMP → OR1.09

	BC Bordeaux (n = 44)	CC Cruces (n = 29)	p
CR at 6 months	13 (30%)	20 (69%)	0.001
CR at 12 months	18 ^a (42%)	25 (86%)	<0.001
CR at the end of follow-up	31 (70.5%)	29 (100%)	0.002
Pr/Cr <0.7 at 12 months	25 ^a (58%)	26 (90%)	0.013
Proteinuria reduction at 6 months (gr) mean (SD)	1.6	2.9	0.05
Proteinuria reduction at 12 months	1.9	3.4	0.06



Standard- vs Reduced-dose GC + ECMPS (MyLupus)

prospective 24-wk open-label multicenter LN III/IV/V

All received ivMP 0.5 g/D x3D

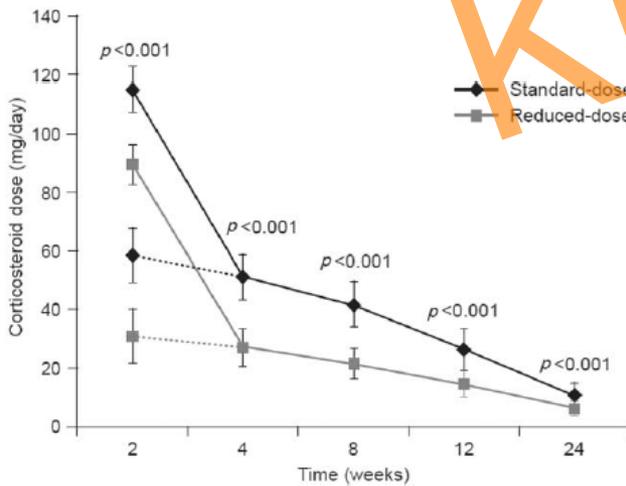
Standard-dose GC (n=42) → 45-50 mg/D ... 5-10 mg/D wk 24

Reduced-dose GC (n=39) → 22.5-25 mg/D ... 2.5-5 mg/D

ECMPS 1440 mg/D x2wk then 2160 mg/D

64.2% White, 16.0% Asian

Similar decrease of BILAG and SLEDAI



	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%)

Table 3 Change in renal function from baseline to week 24 (ITT population)

	<i>All patients</i>			<i>Standard-dose steroids</i>		<i>Reduced-dose steroids</i>		<i>Change from baseline</i>		
	<i>Baseline</i>	<i>24 months</i>	<i>p value^d</i>	<i>Baseline</i>	<i>24 months</i>	<i>Baseline</i>	<i>24 months</i>	<i>Standard-dose steroids</i>	<i>Reduced-dose steroids</i>	<i>p value^d</i>
Serum creatinine ($\mu\text{mol/L}$)	75.2 \pm 31.6	70.9 \pm 28.9	0.097	74.8 \pm 35.6	73.3 \pm 35.0	75.7 \pm 27.1	68.2 \pm 20.7	-1.5 \pm 15.9	-7.4 \pm 20.0	0.24
Creatinine clearance (mL/min) ^b	112 \pm 50	117 \pm 50	0.17	112.0 \pm 48.2	111.3 \pm 42.4	112.6 \pm 52.2	122.8 \pm 57.9	-0.7 \pm 21.6	10.1 \pm 27.9	0.13
GFR ($\text{mL}/\text{min}/1.73\text{m}^2$) ^c	91.7 \pm 34.1	104.7 \pm 33.2	<0.001	91.8 \pm 34.5	100.9 \pm 33.5	91.5 \pm 34.1	106.7 \pm 33.0	9.0 \pm 19.7	15.2 \pm 22.3	0.11
Urine protein:creatinine ratio (g/g)	1.9 \pm 1.3	0.8 \pm 1.1	<0.001	2.0 \pm 1.3	0.8 \pm 0.8	1.8 \pm 1.5	0.9 \pm 1.4	-1.2 \pm 0.9	-0.8 \pm 1.4	0.023

Table 4 Adverse events occurring in $\geq 5\%$ of patients in either treatment group (safety population)

	<i>All patients (n = 81)</i>	<i>Standard-dose steroids (n = 2)</i>	<i>Reduced-dose steroids (n = 39)</i>
Any adverse event	65 (80.2%)	35 (83.3%)	30 (76.9%)
Any serious adverse event	12 (14.8%)	8 (19.0%)	4 (10.3%)
Any infection	42 (51.6%)	25 (59.5%)	17 (43.6%)
Diarrhoea	18 (22.2%)	10 (23.8%)	8 (20.5%)
Oedema peripheral	10 (12.3%)	5 (11.9%)	5 (12.8%)
Herpes zoster	7 (8.6%)	7 (16.7%)	0 (0%)
Insomnia	8 (9.9%)	4 (9.5%)	4 (10.3%)
Vomiting	8 (9.9%)	4 (9.5%)	4 (10.3%)
Hypertension	6 (7.4%)	3 (7.1%)	3 (7.7%)
Upper respiratory tract infection	6 (7.4%)	4 (9.5%)	2 (5.1%)
Cough	5 (6.2%)	3 (7.1%)	2 (5.1%)
Abdominal pain upper	4 (4.9%)	1 (2.4%)	3 (7.7%)
Anaemia	4 (4.9%)	1 (2.4%)	3 (7.7%)
Headache	4 (4.9%)	2 (4.8%)	2 (5.1%)
Muscle spasms	4 (4.9%)	3 (7.1%)	1 (2.6%)
Nausea	4 (4.9%)	3 (7.1%)	1 (2.6%)
Constipation	4 (4.9%)	3 (7.1%)	1 (2.6%)
Tachycardia	3 (3.7%)	1 (2.4%)	2 (5.1%)
Folliculitis	2 (2.5%)	0 (0%)	2 (5.1%)
Gastritis	2 (2.5%)	0 (0%)	2 (5.1%)

Corticosteroids in the Treatment of LN

- Effective combined immunosuppressive regimen
⇒ Time to consider ↓ GC exposure ?
- ivMP ⇒ Opportunity to ↓ oral GC & maintain /
increase treatment efficacy ?

- *Lupus podocytopathy*
- *Other drugs in LN Rx ?*
- *Clinical trials in LN*

Lupus Podocytopathy

KDIGO 2012

12.2: Class II LN (mesangial-proliferative LN)

12.2.1: Treat patients with class II LN and proteinuria <1 g/d as dictated by the extrarenal clinical manifestations of lupus. (2D)

12.2.2: We suggest that class II LN with proteinuria >3 g/d be treated with corticosteroids or CNIs as described for MCD (Chapter 5). (2D)

Rationale

Podocytopathies, characterized histologically by diffuse foot process effacement in the absence of glomerular capillary wall immune complex deposition or endocapillary proliferation, have been observed in patients with class II LN. Podocyte injury in class II LN does not appear related to the extent of mesangial immune complex deposition.⁵⁹⁸ While there have been no prospective studies of the treatment of nephrotic-range proteinuria in class II LN, it is reasonable to treat such patients as for MCD/FSGS in case of nephrotic syndrome, or if proteinuria cannot be controlled using RAS blockade.

Lupus Podocytopathy

retrospective single-center median FU 62 mon

53 (1.41%) of 3750 LN kidney bx [Jan 2000 to Dec 2013]

50 ARA SLE criteria + nephrotic at presentation FU \geq 6 mon

Steroid (30) / Combined IS (20 – CTX, TAC, MMF, TW, AZA, LFM)

⇒ Remission rate 94% after 12 weeks

CR 76% [76.7% S vs 75% CIS, p=0.9]

median time to CR [4(2-6) wk S vs 8(3.7-12) wk CIS, p=0.076]

Relapse 57.4% [89.5% S vs 35.7% CIS maintenance, p<0.001]

no ESRD or death

<i>Characteristics</i>	<i>Total (n = 50)</i>	<i>GC monotherapy (n = 30)</i>	<i>Combination therapy (n = 20)</i>	<i>p value</i>
Age (years)	29.9 ± 12.4	29.0 ± 11.9	31.1 ± 13.3	0.569
Female sex	45 (90.0)	27 (90.0)	18 (90.0)	0.9
Proteinuria (g/24 h)	6.0 ± 3.0	6.5 ± 3.0	5.3 ± 2.8	0.135
Serum albumin (g/l)	23.5 ± 5.3	22.4 ± 5.6	25.3 ± 4.4	0.059
Serum creatinine (mg/d)	0.69 (0.38–7.23)	0.79 (0.41–7.23)	0.65 (0.38–2.37)	0.239
ANA positive	50 (100)	30 (100)	20 (100)	0.9
Anti-dsDNA positive	13 (26)	5 (16.7)	8 (40.0)	0.100
Serum C3 (g/l)	0.7 ± 0.3	0.7 ± 0.4	0.6 ± 0.3	0.482
Serum C4 (g/l)	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.466
Prednisone dose (mg/kg/d)	0.81 ± 0.16	0.91 ± 0.08	0.65 ± 0.10	0.000

Mizoribine

(trade name Bredinin)

- imidazole nucleoside isolated from mould *Eupenicillium brefeldianum*
- selective inhibition of inosine monophosphate synthetase and guanosine monophosphate synthetase → inhibits guanine nucleotide synthesis without incorporation into nucleotides, arresting DNA synthesis in the S phase
- commonly used in Japan in the treatment of lupus, rheumatological & kidney diseases incl kidney transplant; usually at 'low' dose as maintenance treatment in LN
- advantage being few side-effects
- higher doses investigated for the treatment of active LN

Mizoribine

Post-marketing surveillance of 559 Japanese LN patients

2010-15 [steroid 99.3%; imsup 51.2%; TAC 43.8%]

2-year: 26.5% CR, 63.3% CR or PR; ADR 17.5% (major 3.2%)

Flares: 1st year 18.6%; 2nd year 16.4%

Progressive improvement of disease activity

Progressive worsening of kidney function (after 12 mon)

Takeuchi T, et al. Mod Rheumatol 2017 Jul 19: 1-10

11 Chinese LN patients

Mizoribine (150 mg/D, increased to 200 mg in one patient)

as part of induction Rx FU 6-9 mon

Remission 72.7% at 6-mon (2 CR, 9 PR)

No adverse event

Zhang M, et al. Rheumatol Int 2013; 33: 2737-42

Leflunomide

(trade name Arava)

- a pyrimidine synthesis inhibitor by inhibiting dihydroorotate dehydrogenase, an important enzyme in de novo synthesis of uridine monophosphate which is required for DNA and RNA synthesis → inhibits lymphocyte proliferation
- active metabolite teriflunomide (70%) → inhibits DHODH and tyrosine kinases; relative selectivity for activated lymphocytes ; viral suppressive effect on CMV, HSV1, BKV by interfering with nucleocapsid tegumentation in virion assembly
- adverse effects – liver damage (esp when used with methotrexate), interstitial pneumonitis, marrow suppression, anaphylaxis, ...

Leflunomide + Prednisone as Induction Rx for LN

110 Chinese LN III/IV/V patients

[70 leflunomide vs 40 ivCTX]

not strictly randomized

6-mon result – CR PR

leflunomide 21% 52%

CTX 18% 55%

similar rate of adverse events

	<i>LEF (N = 70)</i>		<i>CYC (N = 40)</i>		<i>P value</i>
	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	
Infections	13	18.6	6	15	NS
No. of episodes	15		10		
Herpes zoster	8		4		
Herpes simplex	1		0		
CMV infection	1		0		
Lung infection	1		1		
Acute pyelonephritis	0		1		
Upper respiratory tract infection	2		1		
Other infection ^a	2		3		
Hypertension	8	11.4	1	2.5	NS
Diarrhoea	4	5.7			NS
Palpitation	4	5.7	1	2.5	NS
Alopecia	11	15.7	7	17.5	NS
Leukopenia	4	5.7	1	2.5	NS
Elevated liver enzymes	5	7.1	3	7.5	NS
GI symptoms	1	1.4	14	35	< 0.001

Rituximab (anti-CD20) – LUNAR Trial

144 LN Class III/IV [Black/Hispanic 60+%) 1:1 →

rituximab (1 g D₁, D₁₅, D₁₆₈, D₁₈₂) vs placebo

Background imsup: MP 1 g x2 then pred + MMF 3 g/D

52-wk Renal Response:

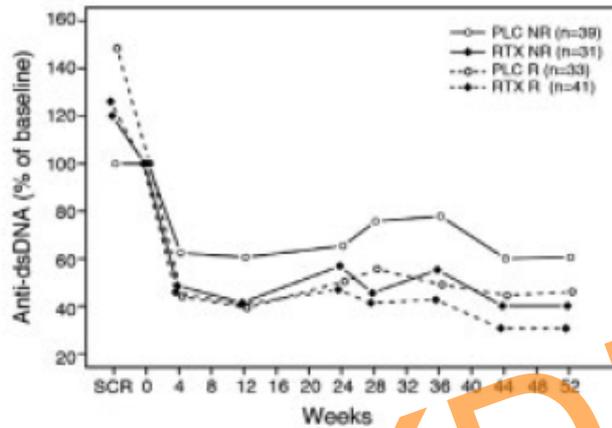
[C+P RR] 56.9% Ritux vs 45.8% placebo, p=0.18

Ritux – more neutropenia and hypotension

Serious infections: 16.6 Ritux vs 19.9/100 pt-yr placebo

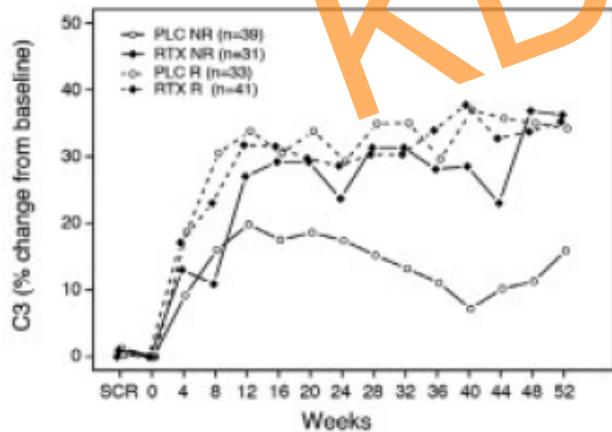
2 deaths, both in Ritux – Staph infection; lung hemorrhage

A



greater serological improvement in rituximab treated subjects

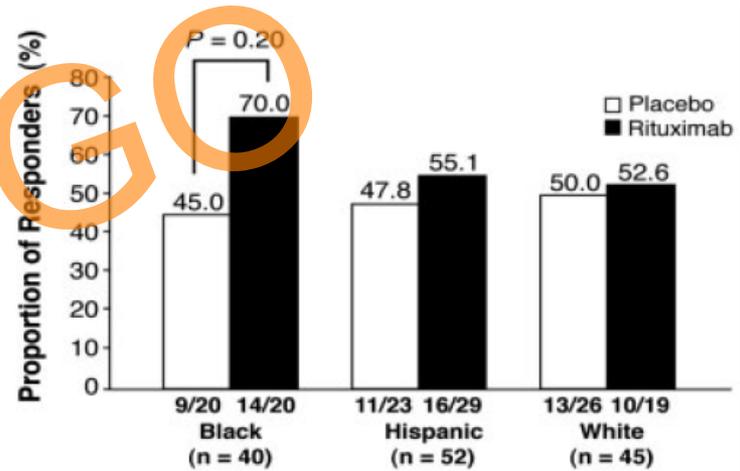
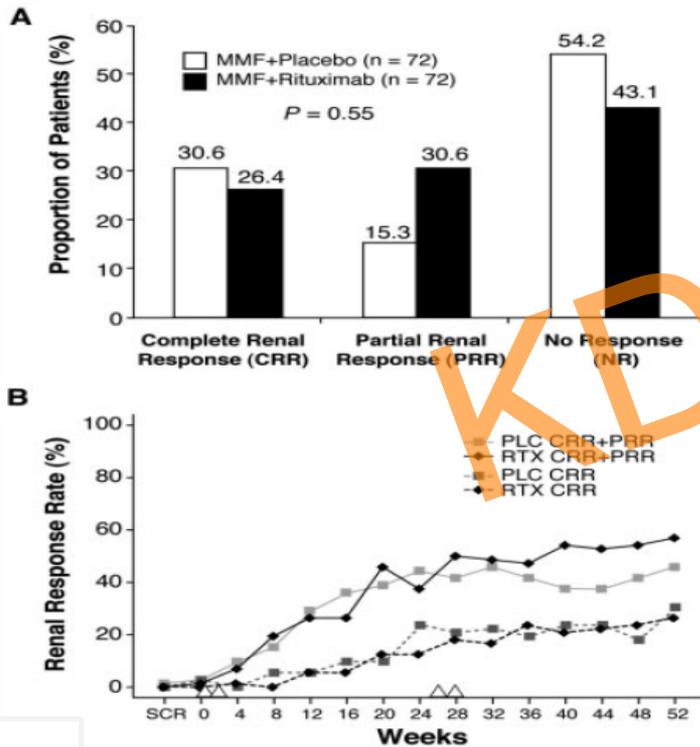
D



Rovin BH, et al.
Arthritis Rheum 2012; 64: 1215-26

C+P RR 52-wk: 56.9% vs 45.8%, p=0.18

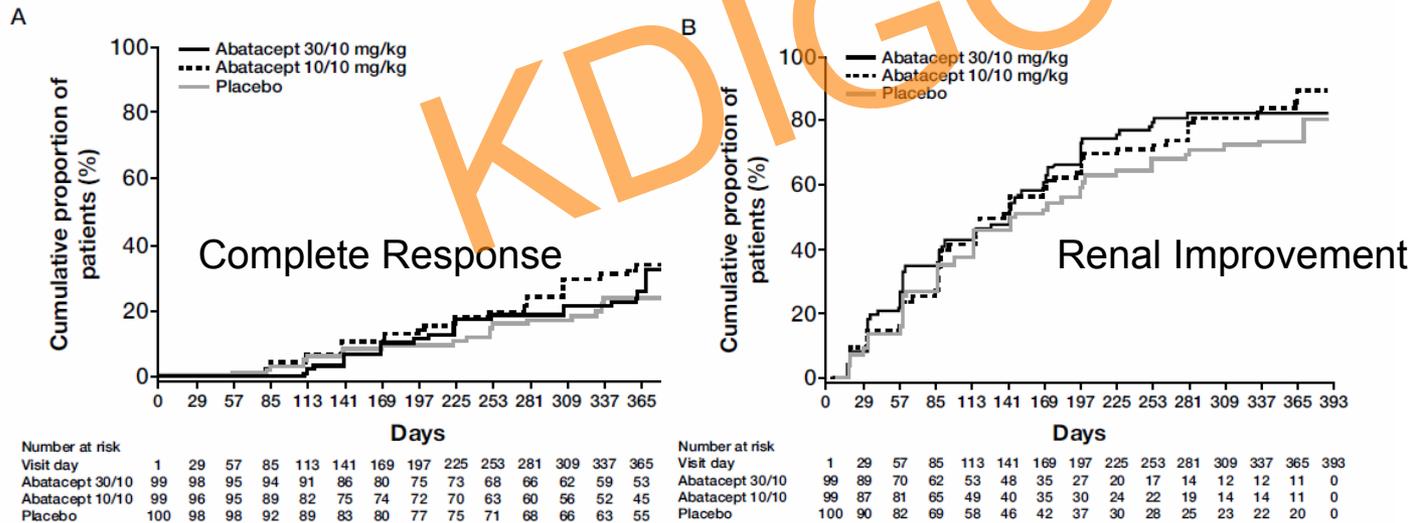
CTX rescue: 0 rituximab vs 8 placebo

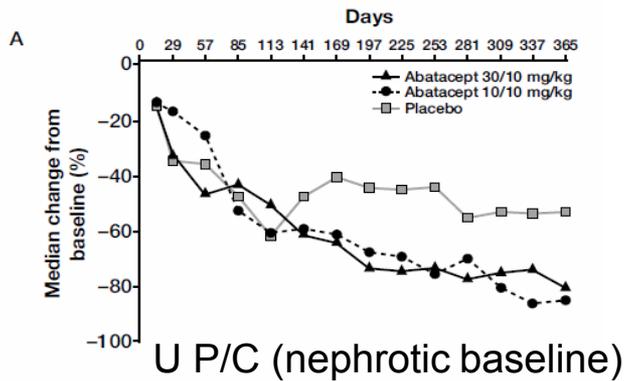


Abatacept

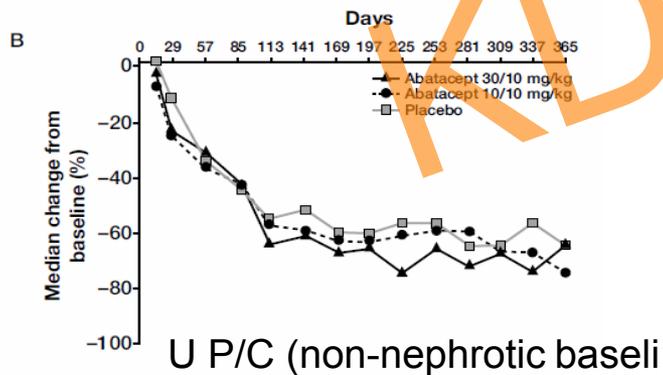
Phase II/III; 298 patients LN III/IV; Asian 50-60%, AA 3-6%, White 28-46%; 1:1:1 → abatacept# 30/10 mg/kg, 10/10 mg/kg, placebo, & pred+MMF, 52 weeks; #D_{1, 15, 29, 57} then D_{85, 113, 141, 169, 197, 225, 253, 281, 309, 337}

abatacept → ↑gastroenteritis (5%), herpes zoster (6%) [vs 0-2%]

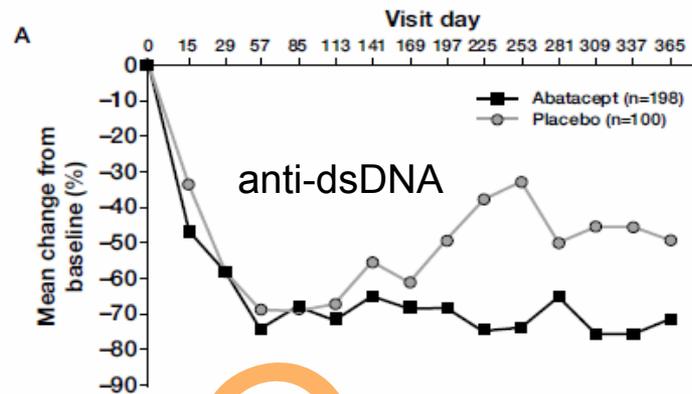




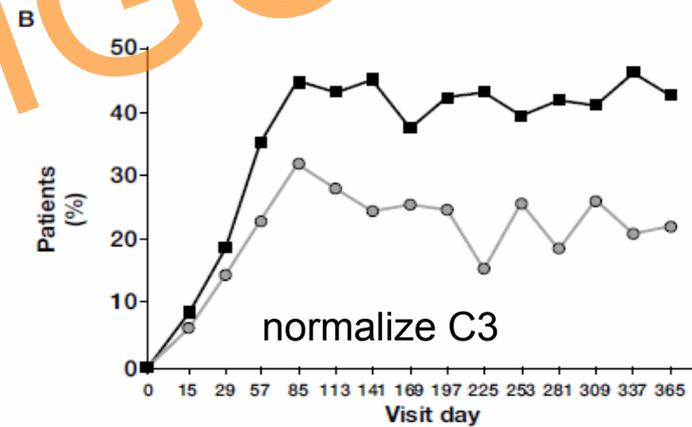
Visit day	15	29	57	85	113	141	169	197	225	253	281	309	337	365
Abatacept 30/10	38	38	38	32	35	34	33	33	31	30	31	29	29	30
Abatacept 10/10	34	36	31	33	30	31	30	30	30	27	27	26	26	25
Placebo	43	44	42	41	41	40	37	37	36	34	34	34	34	33



Visit day	15	29	57	85	113	141	169	197	225	253	281	309	337	365
Abatacept 30/10	60	59	57	57	57	55	51	51	52	49	45	47	44	45
Abatacept 10/10	58	59	56	59	53	52	53	52	51	49	51	49	47	49
Placebo	53	53	54	52	51	51	48	48	48	46	45	45	46	45



Visit day	15	29	57	85	113	141	169	197	225	253	281	309	337	365
Abatacept, n	179	183	176	173	167	159	156	155	154	145	148	143	139	138
Placebo, n	90	89	90	87	83	84	77	80	77	76	72	68	73	68



Visit day	15	29	57	85	113	141	169	197	225	253	281	309	337	365
Abatacept, n	162	168	157	158	150	147	144	141	143	134	130	127	124	126
Placebo, n	84	84	82	80	77	75	71	72	69	67	64	65	67	64

- biological vs clinical efficacy
- clinical efficacy of background therapy (SOC)
- study instrument – how endpoints are defined
- patient heterogeneity → appropriate target population

Thank you

KDIGO