Treatment of Class III/IV/V Lupus Nephritis

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- Overview of immunosuppressive Rx for severe LN
- Chinese/Asian data & ongoing studies
- Recent developments

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

Survival rates – [Renal Survival]

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

Yap DYH, et al. Nephrol Dial Transplant 2012; 27: 3248-3254

Severe Proliferative LN

Class III/IV±V

Treatments for Lupus Nephritis

Pre-1970 – corticosteroids alone; adverse effects+ & unsatisfactory efficacy

1970s – addition of cyclophosphamide improved renal outcome

1980s – iv cyclophosphamide pulses; sequential regimen

1990s to 2000s – mycophenolic acid

Now – corticosteroids + MPA or CTX then MPA or AZA; CNI; biologics & others ?

Induction Rx for Severe Prolif LN – why is *Remission* important?

Response to induction Rx → Long-term renal survival

Houssiau FA, et al. Arthritis Rheum 2004; 50: 3934-40
Chan TM, et al. Lupus 2005; 14: 265-72

Remission → renal & patient survival

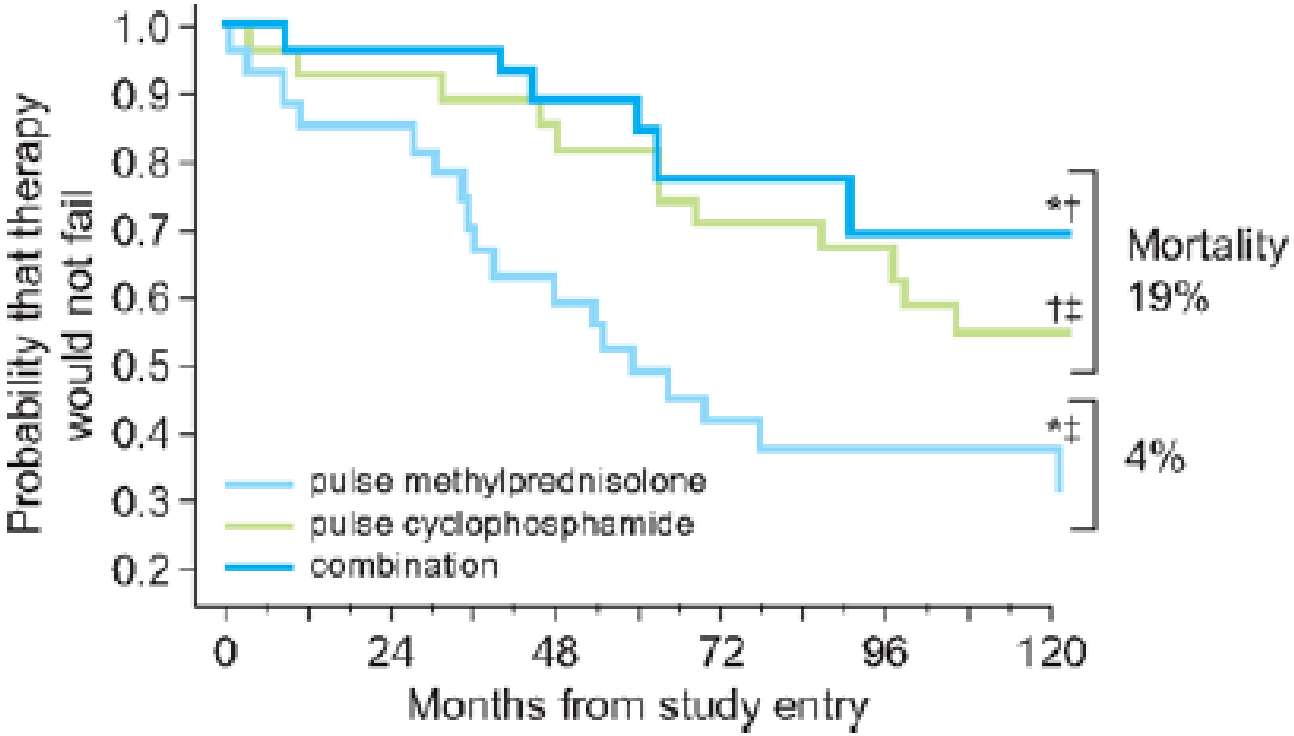
	Renal survival		*Patient survival*	
Remission	5-yr	10-yr	5-yr	10-yr
Yes	94%	94%	95%	95%
No	46%	31%	69%	60%

Korbet SM, et al. Am J Kidney Dis 2000; 35: 904-14

Results with iv CTX

- Renal outcome better with ivCTX + Pred (*vs* Pred)
- Complete response 73/145; partial response 19/145; 41 (45%) renal relapse & 11 ESRF over 117 months
- Importance of maintenance immunosuppression
- *'Prolonged FU'* necessary to examine the impact of treatment on renal survival
- ↓adverse effects with iv CTX vs prolonged p.o., but still considerable
- Sub-optimal renal / patient survival *long-term*

Illei GG, et al. Arthritis Rheum 2002; 46: 995-1002



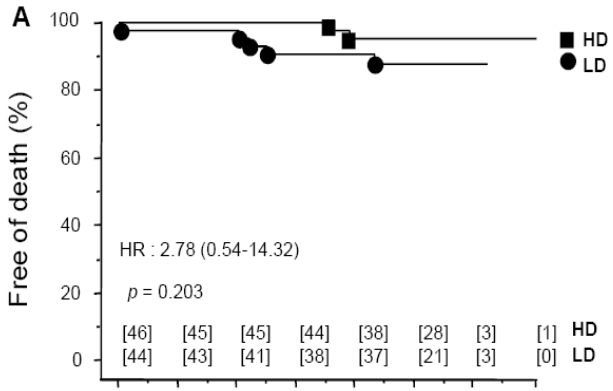
Illei GG, et al. Ann Intern Med 2001; 135: 248-57

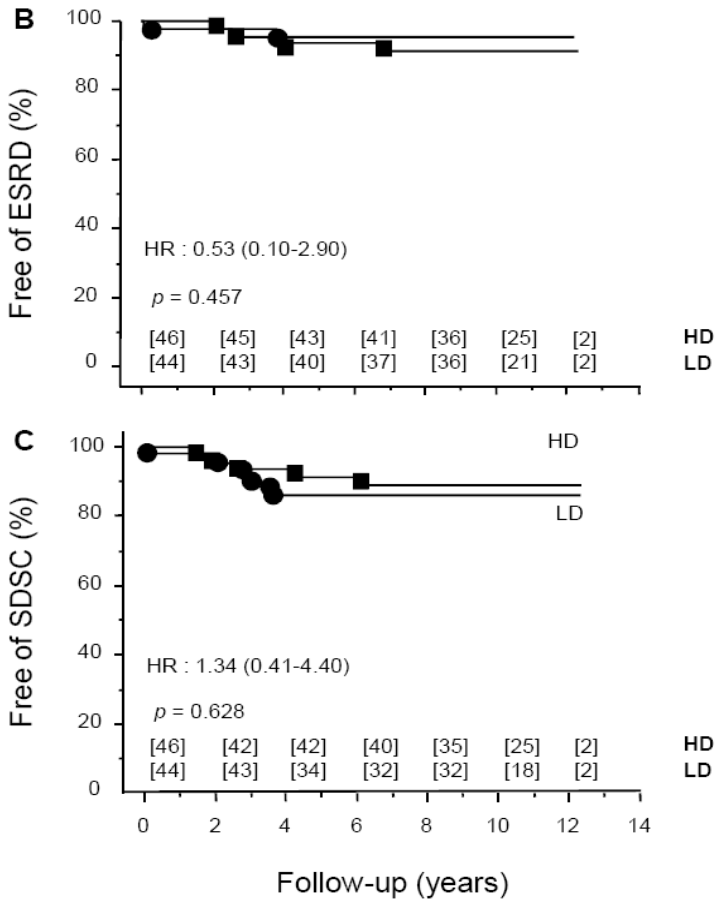
Euro-Lupus Study – 10-yr Data

n = 84 FU 115+/-30 months

7 deaths

6 ESRD





Houssiau FA, et al. Ann Rheum Dis 2010; 69: 2083-89

Euro-Lupus Treatment Regimen

CTX iv + pred

low dose (500 mg q2wk x6) vs high dose (6 q1m + 2 q3m)

followed by azathioprine

FU 41.3 months n = 90

Remission 71% vs 54%, p = n.s.

Infection seemed more frequent in high dose group

Similar efficacy

Houssiau FA, et al. Arthritis Rheum 02; 46: 2121-31

MMF vs CTX as Induction Rx for IV+/-V LN

	n	*endpoint*
Chan-HK	64	12 mon [MMF 2 g/d]
Hu-China	46	6 mon [MMF 1-1.5 g/d]
Ong-Malaysia	44	6 mon [MMF 2 g/d]
Ginzler-USA	140	6 mon [MMF 3 g/d; 63%; M 2.68 g/d]
ALMS	370	6 mon [MMF 3 g/d; M 2.6 g/d]

Chan TM, et al. N Engl J Med 2000; 343: 1156-62

Chan TM, et al. J Am Soc Nephrol 2005; 16: 1076-84

Hu W, et al. Chin Med J (Engl) 2002; 115: 705-9

Ong LM, et al. Nephrology 2005; 10: 504-510

Ginzler EM, et al. N Engl J Med 2005; 353: 2219-28

Appel GB, et al. J Am Soc Nephrol 2009; 20: 1103-12

Chan TM, in *Lupus Nephritis*, 2nd ed., Lewis EJ, Schwartz MM, Korbet SM, & Chan TM, Oxford University Press, 2010

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

MMF in Class IV Lupus Nephritis

MMF (2 g/d) + Pred as induction therapy

→ high efficacy (CR >80%), *similar* to Pred+CTX

→ *fewer* adverse effects vs CTX (alopecia, amenorrhea, leukopenia, infection)

→ *better* QoL (rehabilitation)

Chan TM, et al. N Engl J Med 2000; 343: 1156-62
Chan TM, et al. J Am Soc Nephrol 2005; 16: 1076-84
Tse KC, et al. Lupus 2006; 15: 371-9
Yap DYH, et al. Rheumatology (Oxford) 2013; 52: 480-6

ALMS - Induction Phase Results

Response (endpoint): ↓ proteinuria & stable/improved creatinine

MMF dose achieved → mean 2.6 g/d median CTX 0.75 g/m^2

1. response rate (*week 24*)

   MMF 104/185 (*56.2%*) CTX 98/185 (*53.0%*) p=0.58

2. remission, proteinuria, creatinine – no significant difference

3. tolerability

- *CTX 40.6% more adverse events (episodes)*
- serious AE - MMF 27.7% & CTX 22.8%
- infection - MMF 12.0% & CTX 10.0%
- withdrawal due to AE - MMF 13.0% & CTX 7.2% (p=0.07)
- deaths - MMF 9 & CTX 5 (infections, 7 MMF deaths Asians)

Appel GB, et al. J Am Soc Nephrol 2009; 20: 1103-12

ALMS - Induction Phase Data

Response	MMF	CTX	
Asian	53.2%	63.9%	
White	56.0%	54.2%	
Other	60.4%	38.5%	p=0.03
Black	53.9%	40.0%	
Hispanic	60.9%	38.8%	p=0.011
Latin American	60.7%	32.0%	p=0.003

Isenberg D, et al. Rheumatology 2010; 49: 128-40

Patients with very severe disease

Pooling data of patients with Class III/IV and –

- >15% crescents
- abnormal serum creatinine at presentation

[ALMS, Chan, Ginzler, Mok, Hooi, …]

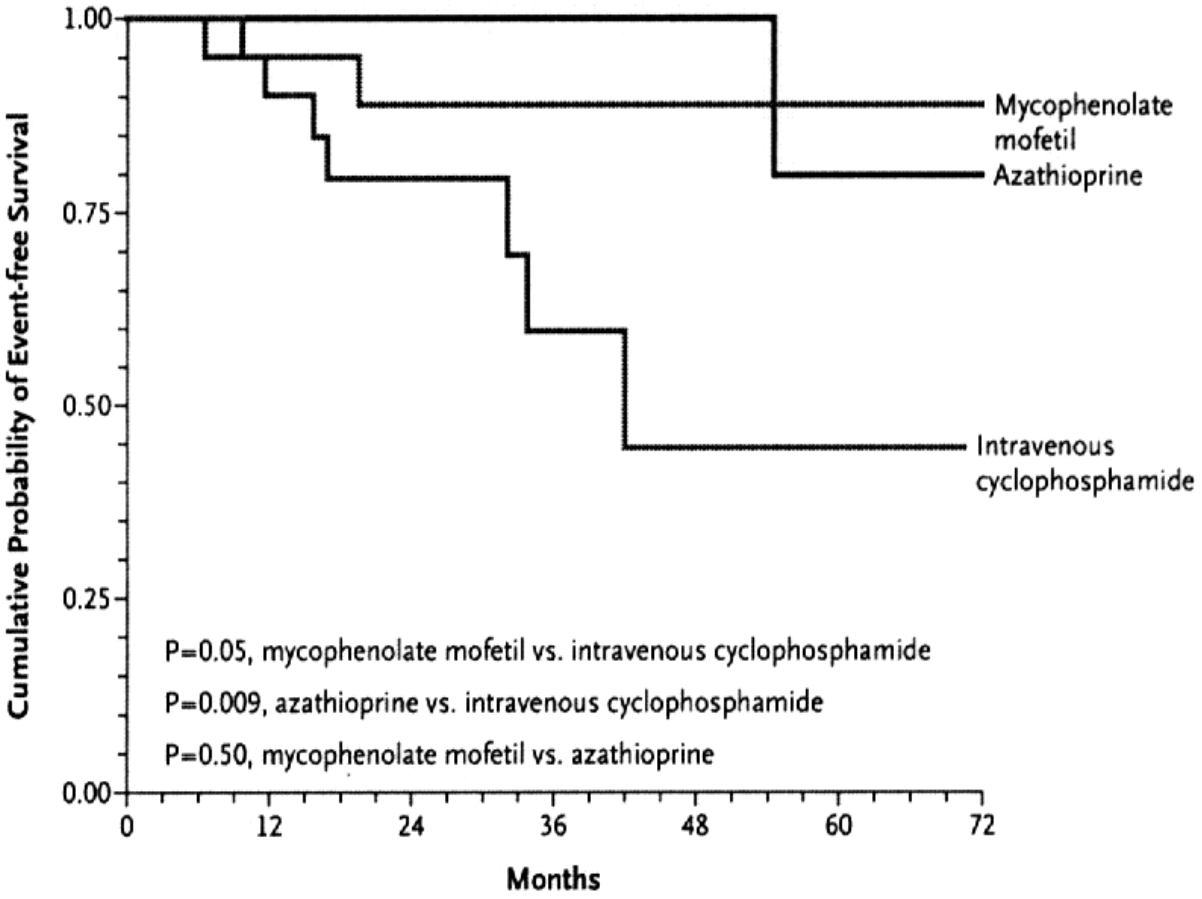
Findings -

Pred + CTX / MMF – similar early response

CTX $\Rightarrow$? fewer disease flares and less renal failure

Rovin BH, et al. Clin J Am Soc Nephrol 2013; 8: 147-53

Maintenance Immunosuppression



No. at Risk

Azathioprine	19	19	15	10	9	4	2
Intravenous cyclophosphamide	20	19	12	6	3	2	1
Mycophenolate mofetil	20	20	14	11	6	2	2

Contreras G, et al. N Engl J Med 2004; 350: 971-80

MMF vs AZA as Maintenance Rx of Lupus Nephritis - MAINTAIN Trial

N=105 III/IV +/-V

Euro-Lupus induction immunosuppression

Maintenance from Wk12 with steroid +
AZA (2 mg/kg/d, n=52) or MMF (2 g/d, n=53)

Median FU 53 months (24 drop-outs):

1. renal flare in 13 AZA patient and 9 MMF patient
2. AZA vs MMF ***similar*** → time to flare (renal or systemic); renal remission; infection
3. cytopenia more with AZA
4. doubling of baseline creatinine - 4 AZA and 3 MMF

Houssiau FA, et al. Ann Rheum Dis 2010; 69: 2083-89

Aspreva Lupus Management Study (ALMS)

III, IV, V or mixture

Induction (n=370) → MMF (3 g/d) vs iv CTX (1 g/m^2) q4wk

+ steroid (up to 60 mg/d)

Responders re-randomized at Week 24 (n=227)

→ MMF 1 g bid (n=116) or AZA 2 mg/kg/d (n=111) + steroid

Maintenance phase lasted 36 months

Outcome: Time to 'treatment failure' [death, ESRD, doubling of baseline creatinine, renal flare, rescue therapy]

Result [55.9% completed the study]

MMF regimen better than AZA

- 'time to treatment failure' – HR 0.44, CI 0.25-0.77, P=0.003
- 'time to renal flare' – HR 0.50, CI 0.26-0.93, P=0.03
- 'time to rescue therapy' – HR 0.39, CI 0.18-0.87, P=0.02

- 'treatment failure' - 16.4% [MMF] vs 32.4% [AZA]
- renal flare - 12.9% [MMF] vs 23.4% [AZA]
- rescue treatment - 7.8% [MMF] vs 17.1% [AZA]
- withdrawal due to adverse events more with AZA

(39.6% vs 25.2%, P=0.02)

Dooley MA, et al. N Engl J Med 2011; 365: 1886-95

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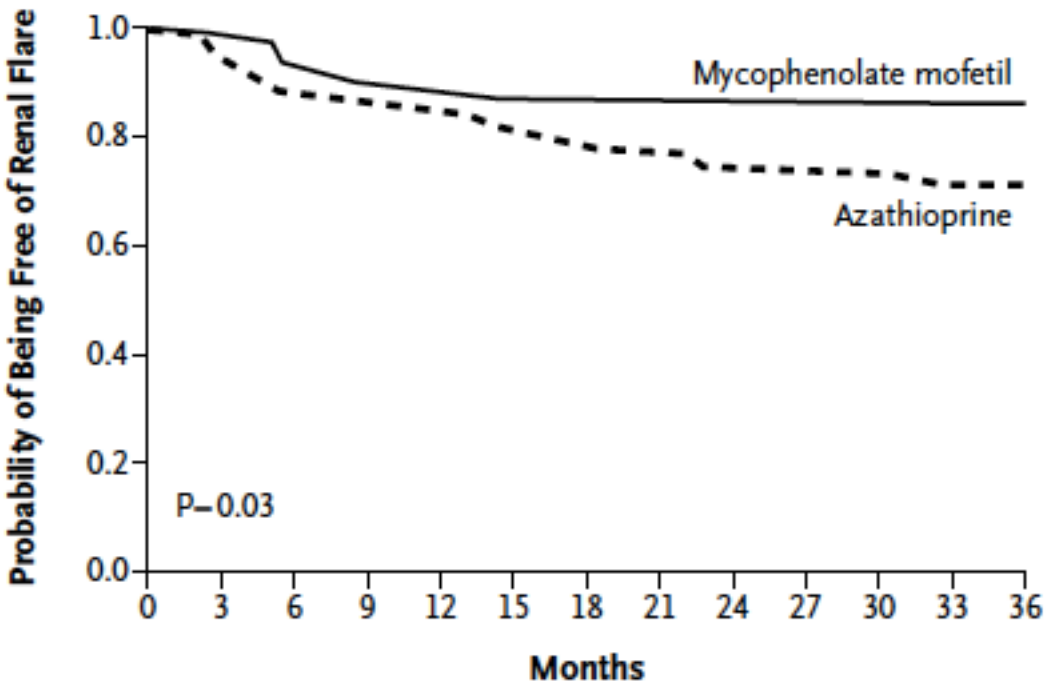


No. at Risk

Mycophenolate mofetil	116	109	102	92	89	88	82	80	78	75	74	73
Azathioprine	111	101	89	82	77	71	65	62	60	58	56	54

Dooley MA, et al. N Engl J Med 2011; 365: 1886-95

Long-term Results with Pred+MMF in LN

65 patients with Class III/IV+/-V LN FU 92+/-48 months

- Treated with Pred+MMF continuously from the early (induction) phase to the maintenance phase
- MMF → AZA and/or CNI in 34 patients

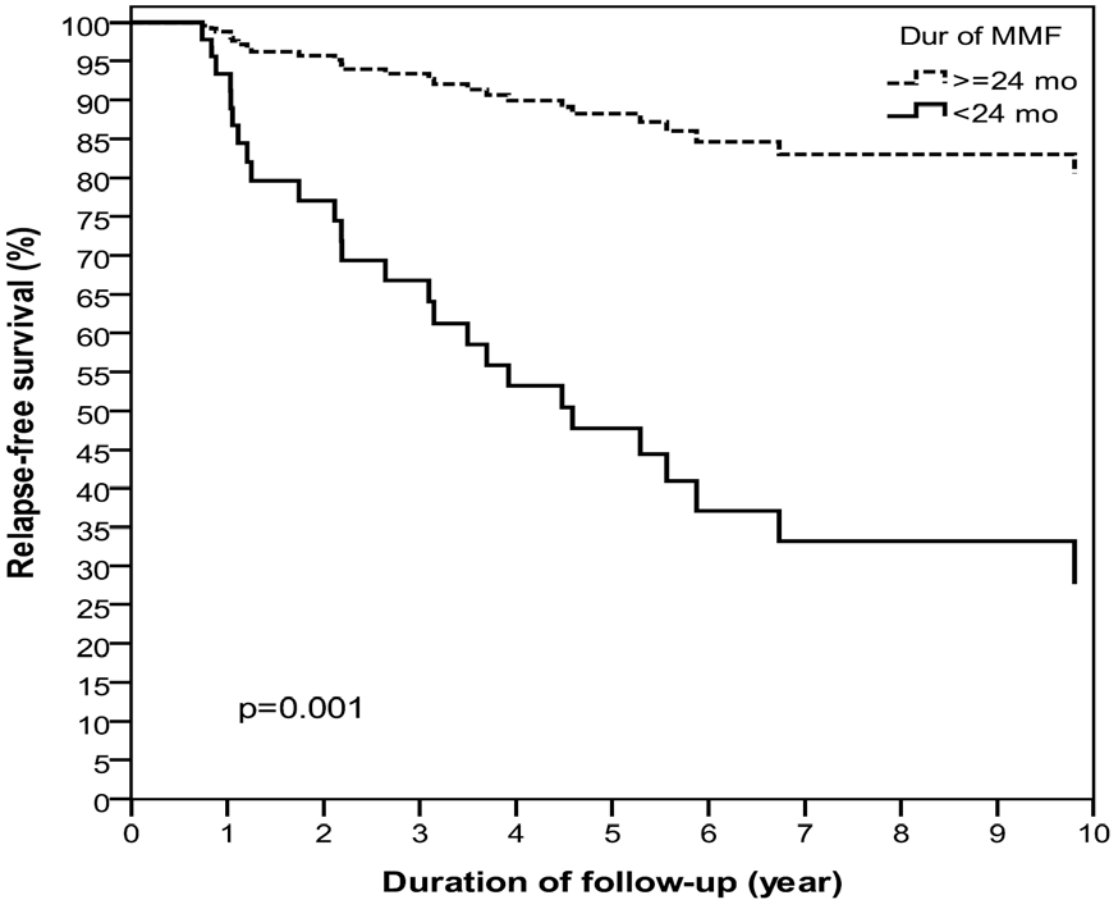
Yap DYH, et al. Rheumatology 2013; 52: 480-6

10-yr	patient survival	renal survival
	91%	86%

Relapse-free survival at 5-yr

MMF-MMF	76%
MMF-AZA	56%

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

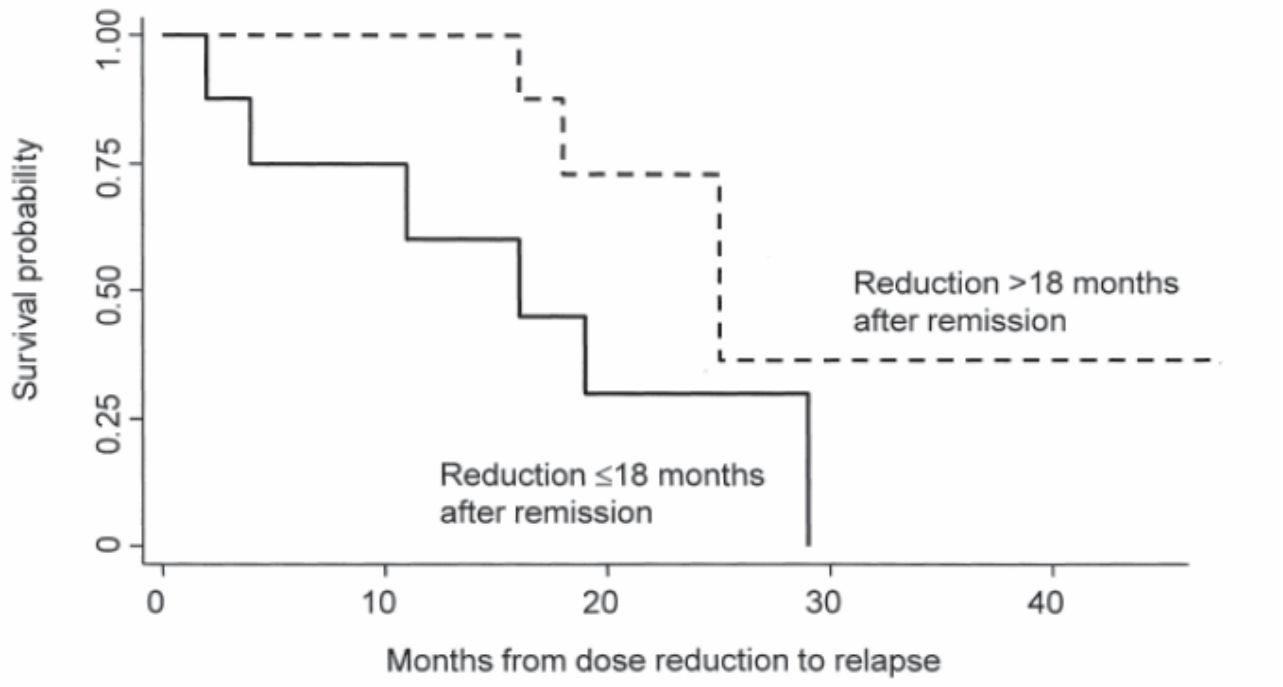


Survival % (no. at risk)

MMF≥24 mo	100% (28)	88% (15)	81% (1)
MMF<24 mo	100% (37)	48% (12)	28% (3)

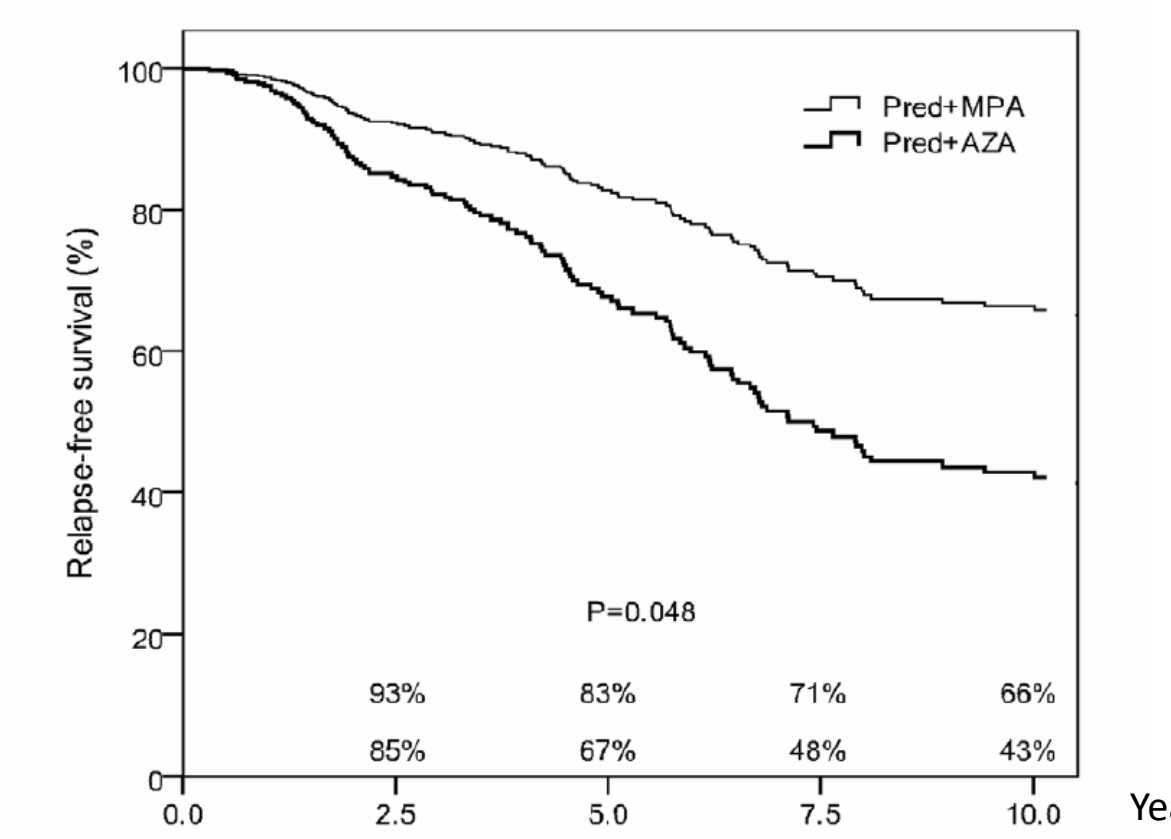
Yap DYH, et al. Rheumatology 2013; 52: 480-6

Reducing MMF dose within 18 months after treatment response $\rightarrow$ 6-fold increase in risk of relapse (p=0.001)



Laskari K, et al. J Rheumatol 2011; 38: 1304-8

N=184 FU 195+/-94 months



Yap DYH, et al. Unpublished data.

Rx of Class III/IV±V LN

Induction – Pred (?MP) + MMF/CTX/?CNI

Maintenance – pred + MMF/AZA/?CNI [+hydroxychloroquine]

Non-immunological $\rightarrow$ renal & vascular outcomes, …

Membranous LN

Class V

Treatment of Membranous Lupus Nephritis

randomized controlled trial

Response Rate at 1 yr –

steroid alone	27%
cyclophosphamide	60%
cyclosporine	84%

Austin HA, et al. J Am Soc Nephrol 2009; 20: 901-11

Effect of Immunosuppressive Treatment in Membranous Lupus Nephritis

meta-analysis of 21 studies

Response rate –

steroid alone <60%

other immunosuppressive agents 83%

[AZA 89%, CTX 77%, MMF 84%, CYA 84%]

Non-response rate –

steroid alone 39%

other immunosuppressive agents 17%

Swan JT, et al. J Investig Med 2011; 59: 246-58

MMF vs CTX as Induction Treatment in Membranous Lupus Nephritis

pooled data from two studies 33 MMF vs 32 IVC

similar efficacy at 24 wk

Study	Group	*N*	Urine protein (g/24 h)	Serum creatinine (μmol/l)	Serum albumin (g/l)	Serum C3 (g/l)	Serum C4 (g/l)	Anti-dsDNA	Nephrotic (%)	Use of RAASI (%)	% Change in urine protein	% Change in serum creatinine
US	MMF	8	1.5 ± 1.1, *P*=0.007	79 ± 9, *P*=0.026	34 ± 6	129 ± 37	36 ± 11	0.1 ± 0.3	0	62.5	−61 ± 29	16 ± 18
	IVC	7	1.6 ± 1, *P*=0.046	66 ± 25, *P*=0.283	34 ± 4	130 ± 35	27 ± 15	0.6 ± 1	0	71	−71 ± 21	9 ± 18
ALMS	MMF	25	1.8 ± 2, *P*<0.001	63 ± 21, *P*=0.073	36 ± 8	111 ± 37	30 ± 17	0.4 ± 0.7	12	80	−63 ± 29	−6 ± 22
	IVC	25	2.7 ± 2.4, *P*=0.001	71 ± 32, *P*=0.539	34 ± 3	71 ± 33	22 ± 12	1 ± 1.1	32	76	−48 ± 51	3 ± 23

17 MMF & 23 IVC nephrotic → responder 11/17 vs 14/23

Radhakrishnan J, et al. Kidney Int 2010; 77: 152-60

Pred+Tac vs Pred+MMF in LN V with Nephrotic Syndrome

prospective randomized pilot study with 16 patients

[MMF 7, Tac 9] FU 24 months

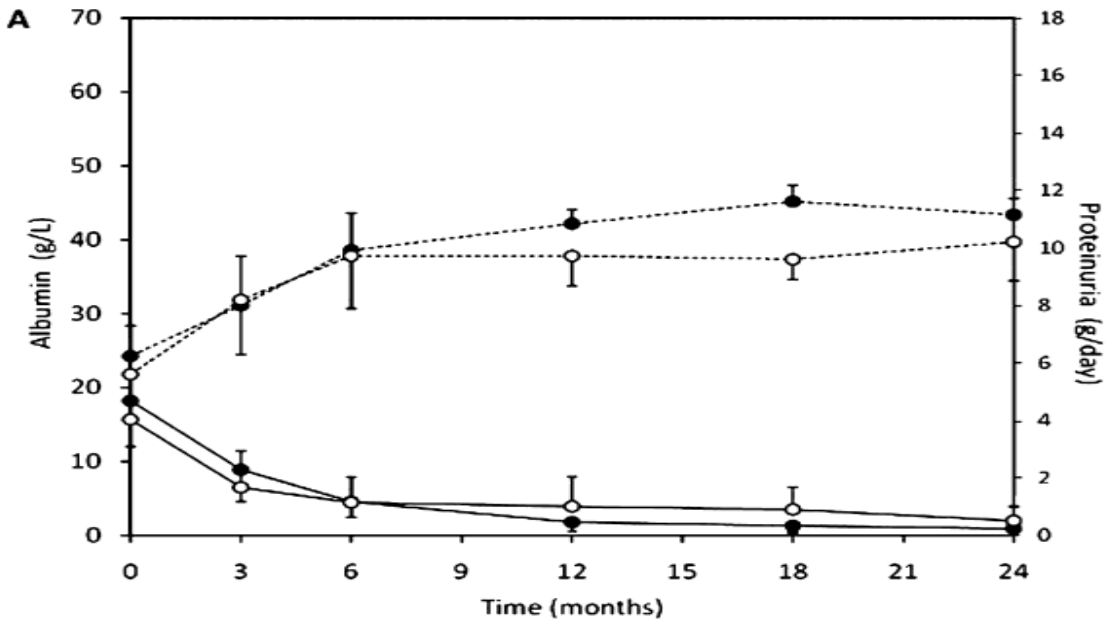
proteinuria 4.7 & 4 g/d at baseline

MMF 0.75-1 g bid Tac trough level 6-8 ng/mL

Yap DYH, et al. Nephrology 2012; 17: 352-357

Pred+Tac vs Pred+MMF in LN V with Nephrotic Syndrome

Response rate 55.6% vs 71.4% P=0.515



Yap DYH, et al. Nephrology 2012; 17: 352-357

ACR & EULAR Guidelines for Class V LN

⇒ Nephrotic → pred + MMF (2-3 g/D)

Rx of Class V LN

Significant proteinuria → immunosuppression

Pred + MMF / CTX / (AZA) / CNI

Recent Developments

Emerging Therapies

Calcineurin Inhibitors (CNI)

- cyclosporine, tacrolimus, …
- effective immunosuppression (T lymphocyte)
- standard immunosuppressive therapy in kidney transplantation $\Rightarrow$ corticosteroids + CNI + MPA
- reduce proteinuria (effect on podocyte) $\rightarrow$ efficacy in MN, FSGS, relapsing MCD

CyA vs ivCTX Induction Rx in III/IV LN (CYCLOFA-LUNE)

Pred+CyA (19) vs Pred+ivCTX (21) III/IV FU 9+9 months

activity 9.3/9.9 chronicity 3.5/4.0 UP 3.8/2.5 g/D

CTX – 10 mg/kg q3wk x2, q4wk x4, q6wk x2

CyA – 4-5 mg/kg/D for 9 m then reduce

Drop-outs: ind phase – 1 CTX & 1 CyA; maint phase – 3 CTX

Response (9 mon): 11/21 CTX vs 8/19 CyA, p=0.75

Response (18 mon): 8 vs 11, p=0.21

38 patients median FU 7.7 yr

CTX vs CyA similar → creat, UP, renal failure, SLICC damage score, adverse events

Zavada J, et al. Lupus 2010; 19: 1281-1289
Zavada J, et al. Lupus 2014; 23: 69-74

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

Chen W, et al. Am J Kidney Dis 2011; 57: 235-44

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

Tac (n=74) dose not guided by TDM (started with 0.1 mg/kg/D)

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

achieved Tac trough 7.8+/-3.9 μg/L

Mok CC, et al. Ann Rheum Dis 2015, in press

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.

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

Tac resulted in numerically higher response rate than MMF in Class V

One death (infection), more zoster (18% vs 3%) and diarrhea in MMF group

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

Mok CC, et al. Ann Rheum Dis 2015, in press

Pred+Tac vs Pred+MMF in Nephrotic Class V LN

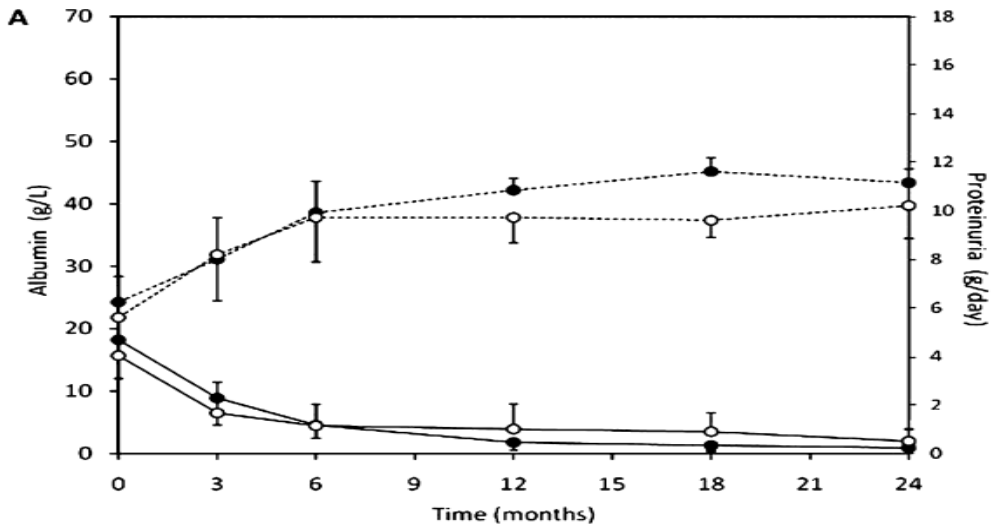
prospective randomized pilot study with 16 patients

[MMF 7, Tac 9] FU 24 months

proteinuria 4.7 & 4 g/d at baseline

MMF 0.75-1 g bid, Tac trough level 6-8 ng/mL

Response rate 71.4% vs 55.6% P=0.515



Yap DYH, et al. Nephrology 2012; 17: 352-7

Pred+MMF+Tac as Induction Rx for IV+V LN

MP-Pred+MMF+Tac (20) vs MP-Pred+ivCTX (20)

Tac trough blood level 5-7 ng/mL

MMF 0.5 g bid, MPA AUC0-12h 20-45 mg.h/L

Treatment duration 6-9 months

Outcome –

CR/PR	MT	Pred+ivCTX
6-mon	50%/40%	5%/40%
9-mon	65%/30%	15%/40%

Triple regimen better tolerated than Pred+ivCTX

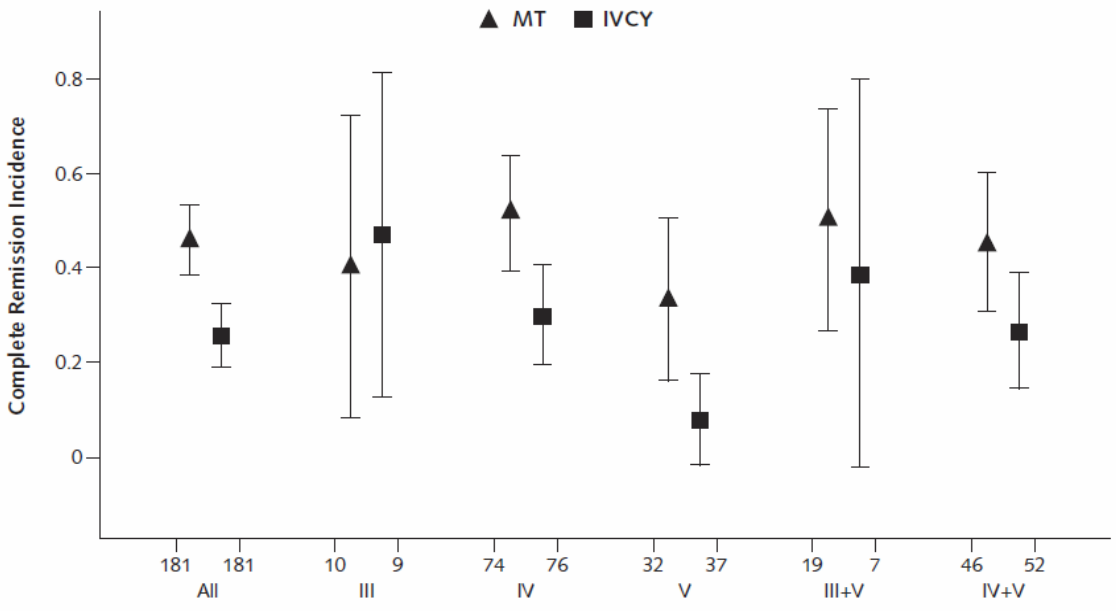
Bao H, J Am Soc Nephrol 2008; 19: 2001-10

Pred+ MMF+Tac *vs* ivCTX as Induction Rx for III/IV/V LN

Tac 4 mg/D, MMF 0.5 g bid *vs* ivCTX 0.75 g/m^2 q4wk for 6 mon

ivMP 0.5 g/D for 3 days creat ≤265.2 micromol/L

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



368 randomized

24 lost to FU

28 discont assigned Rx

<u>Serious AE</u>

MT 7.2% vs CTX 2.8%

<u>AE related drop-out</u>

MT 5.5% vs CTX 1.7%

Liu ZH, et al. Ann Intern Med 2015; 162: 18-26

Tacrolimus vs AZA as Maintenance Rx in III/IV LN

70 patients with III/IV+/-/V after response to induction Rx

Pred+Tac (34) vs Pred+AZA (36)

Tac trough blood level 4-6 ng/mL AZA 2 mg/kg/D

6-month outcome

renal flare - 2 in AZA group, none in Tac

AZA asso with leukopenia and liver abnormality

Chen W, et al. Lupus 2012; 21: 944-952

Long-term Data on Tac in LN

retrospective Tac treatment >6 mon target trough 4-6 μg/L

N=29 [41.2±9.2 yr; 24F 5M]

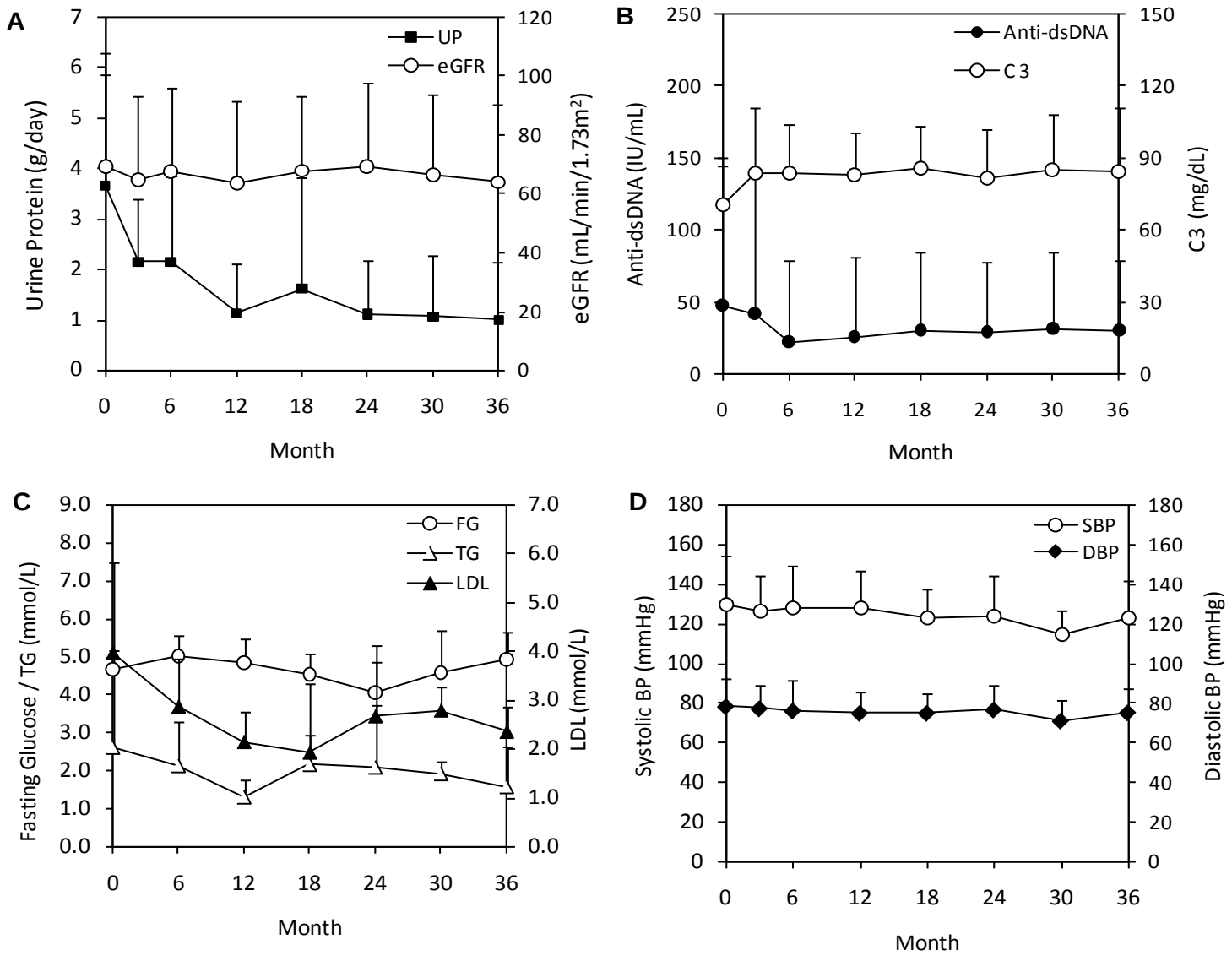
17 III/IV±V → Tac added to pred+MMF

10 V → Pred+Tac 2 relapsing podocytopathy

Tac duration 46.9±37.9 mon [18(62.1%) >36 mon]

Tac	*6 mon*	*12 mon*
Dose	3.39±1.91	3.41±1.72 mg/D
Trough	4.72±2.9	4.17±1.91 μg/L

Yap DYH, et al. Rheumatology 2014; 53: 2232-7



Yap DYH, et al. Rheumatology 2014; 53: 2232-7

Long-term Data on Tac in LN

Renal Response –

Complete UP ≤0.5 g/D, creat ±15% of baseline

Partial UP↓ by 50%, non-nephrotic, stable creat

Response rate	*Complete*	*Partial*
Class III/IV±V	40%	26.7% [12-*mon]*
	46.7%	33.3% [24-*mon]*
Class V	30%	30%
	50%	40%

37.9% had UP↓ by 50% after 6 months of Tac

Yap DYH, et al. Rheumatology 2014; 53: 2232-7

Biologics

- anti-CD20
- atacicept
- abatacept
- belimumab
- Others – e.g. PKC inhibitors

- Importance of Proteinuria response to treatment
- What level of Proteinuria should one target

CSG Data

Remission achieved ?

YES ⇒ renal & patient survival >90%

NO ⇒ renal survival 46% / 31% at 5 / 10 years

patient survival 69% / 60% at 5 / 10 years

Korbet SM, et al. Am J Kid Dis 2000; 35: 904–14

Proteinuria reduced by 50% or more after Rx for 6 months ?

YES ⇒ 5- / 10-yr ESRF rate 15% / 26%

NO ⇒ 5- / 10-yr ESRF rate 41% / 50%

Korbet SM, et al. Nephrol Dial Transplant 2013; 28: 2313–8

ALMS Data

baseline eGFR <30mls/min ⇒ worse renal prognosis

C3 normalize / ↓proteinuria of >25% by 8 weeks ⇒ favorable outcome

Dall'Era M, et al. Arthritis Care Res 2011; 63: 351–7

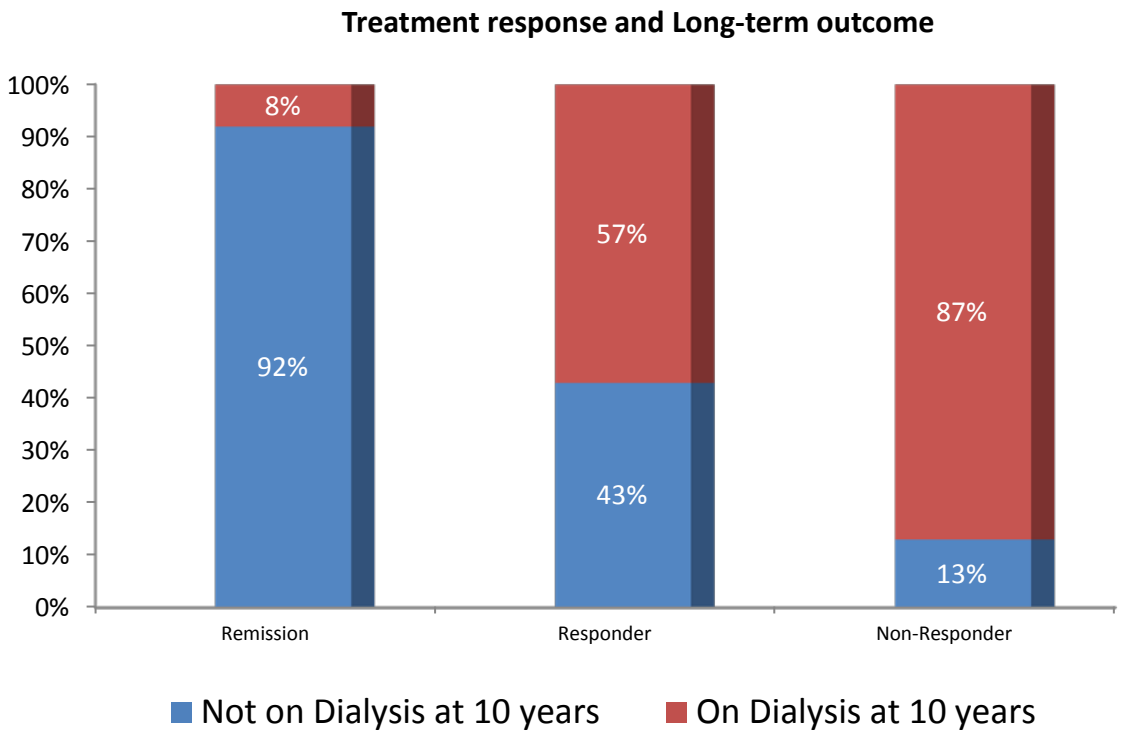


Diagram courtesy of
N Solomon, Aurinia Pharm

ELNT & MAINTAIN Data

Follow-up (MAINTAIN): 110 months (median) [range 18-156 mon]

↓Proteinuria more rapid ⇒ better long-term renal prognosis

↓Proteinuria alone (vs creat vs creat+uRBC) drives PPV of 12-mon treatment response on 10-yr renal prognosis – 92% (vs 94% vs 93%)

Proteinuria at 12-mon –

<0.8 g/D (ELNT) →	good long-term renal outcome (defined as 7-yr creat ≤1 mg/dL) [sens 81%; spec 78%]
<0.7 g/D (MAINTAIN) →	good long-term renal outcome [sens 71%; spec 75%; PPV 94%; NPV 29%]

Dall'Era M, et al. Arthritis Rheumatol 2015; 67: 1305-13
Tamirou F, et al. Ann Rheum Dis 2015, in press
Tamirou F, et al. Lupus Sci Med 2015, in press

↓IgG and Infection in LN Patients

Pre-mature termination of APRIL LN Study 28113 after three of four atacicept-treated patients showed IgG <3 g/L, with pneumonia/bacteraemia affecting two patients

Ginzler EM, et al. Arthritis Res Ther 2012; 14: R33

Pred+MMF Does Not Lead to ↓↓IgG in LN Patients

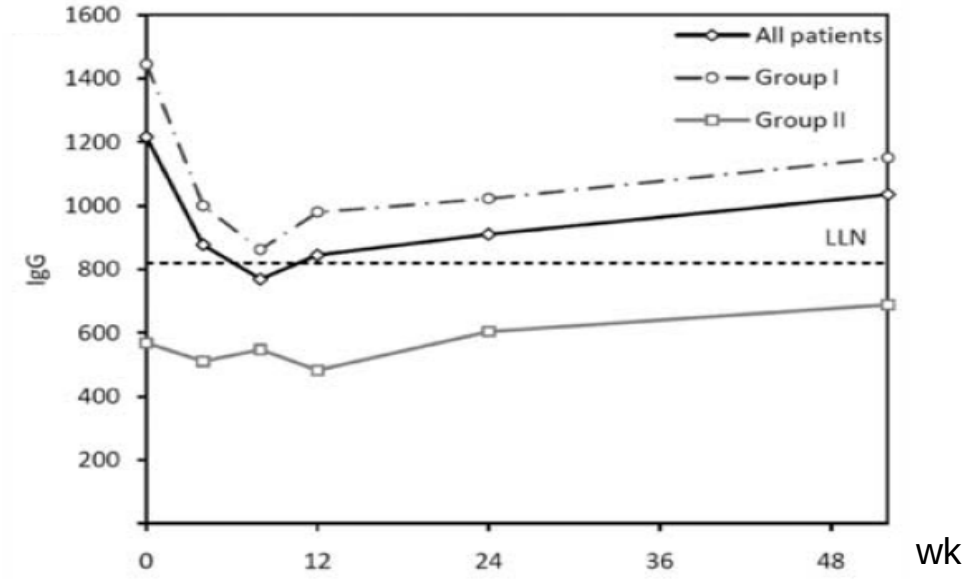
N=46 26.1% had low IgG level at baseline (none below 3 g/L)

Low IgG level asso with heavier proteinuria (6.8 vs 4.4 g/D)

After Rx ⇒ ↓IgG level after 2 wks, trough at 8 wks, then increase

One patient had IgG <3 g/L after Rx

5/12 infections asso ↓IgG (RR 1.863, CI 0.466-6.818, p=0.28)



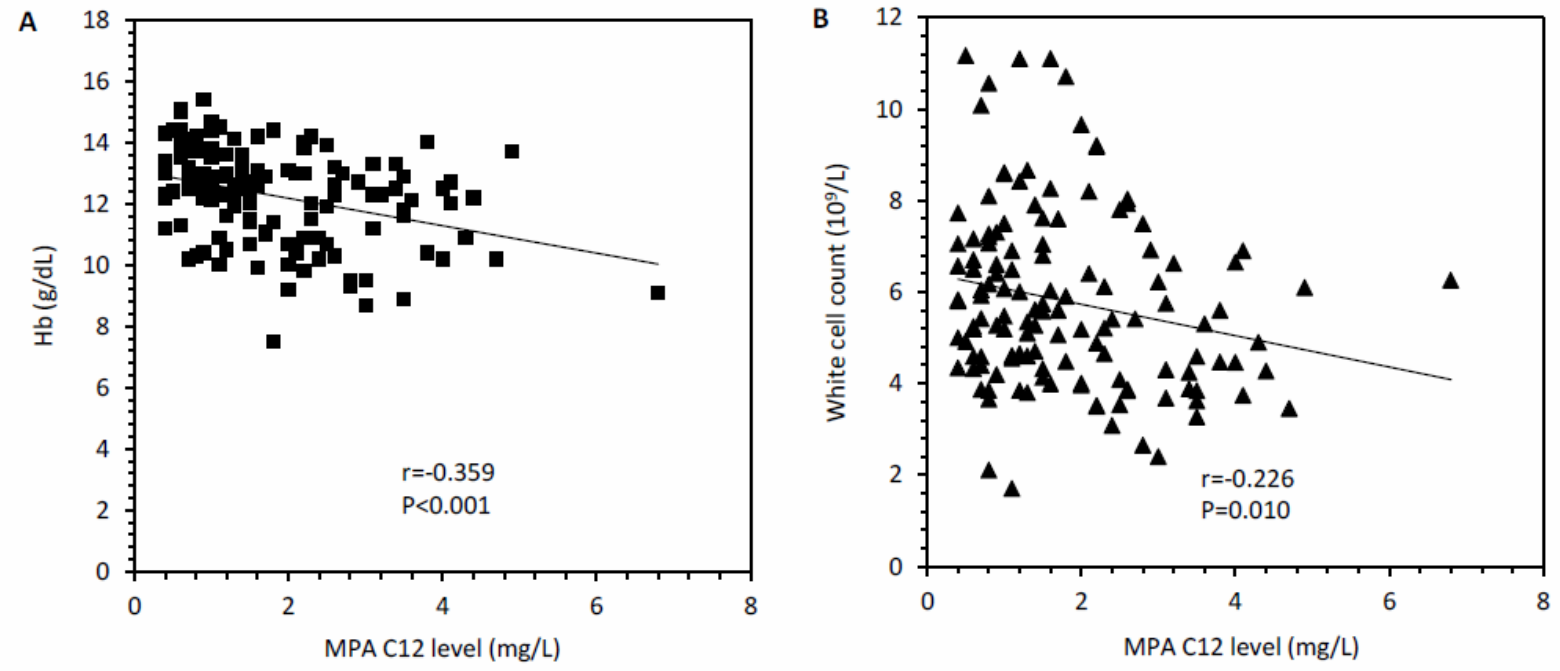
Yap DYH, et al.
Lupus 2014; 23: 678-83

MPA Therapeutic Drug Monitoring

MPA Therapeutic Drug Monitoring in LN Treatment

- MPA pharmacokinetics vary between patients
- MMF (not EC-MPS) $\rightarrow$ relatively good correlation between trough (other single time-point) MPA level and AUC
- Drug exposure ~more related to efficacy than adverse events
- [SLE/Vasculitis] AUC 35-45 mg.h/L or Trough MPA 3.5-4.5 mg/L $\cong$ favorable clinical outcome [MMF dose approx 1.8 g/D]; Trough MPA 3 mg/L $\rightarrow$ 92% NPV for flare

de Winter BC, et al. Ther Drug Monit 2009; 31: 585-91
Weber LT, et al. J Am Soc Nephrol 2002; 13: 759-68
Neumann I, et al. Nephrol Dial Transplant 2008; 23: 3514-20
Zahr N, et al. Arthritis Rheum 2010; 62: 2047-54
Djabarouti S, et al. Arthritis Res Ther 2010; 12: R217
Lertdumrongluk P, et al. Kidney Int 2010; 78: 389-95



Yap DYH, et al. Unpublished data.

Concentration-controlled MPA Treatment Regimen

N=19, III/IV MMF dose commenced at 1.5 g/D

Target MPA-C1 >13 mg/L

Response rate –

24 Wk 17/19 (89%) [4 CR]

48 Wk 8 CR

78% achieved MPA-$AUC_{0\text{-}12h}$ target 45 mg.h/L

Required MMF dose $\Rightarrow$ $\geq$2 g/D in 83.3%

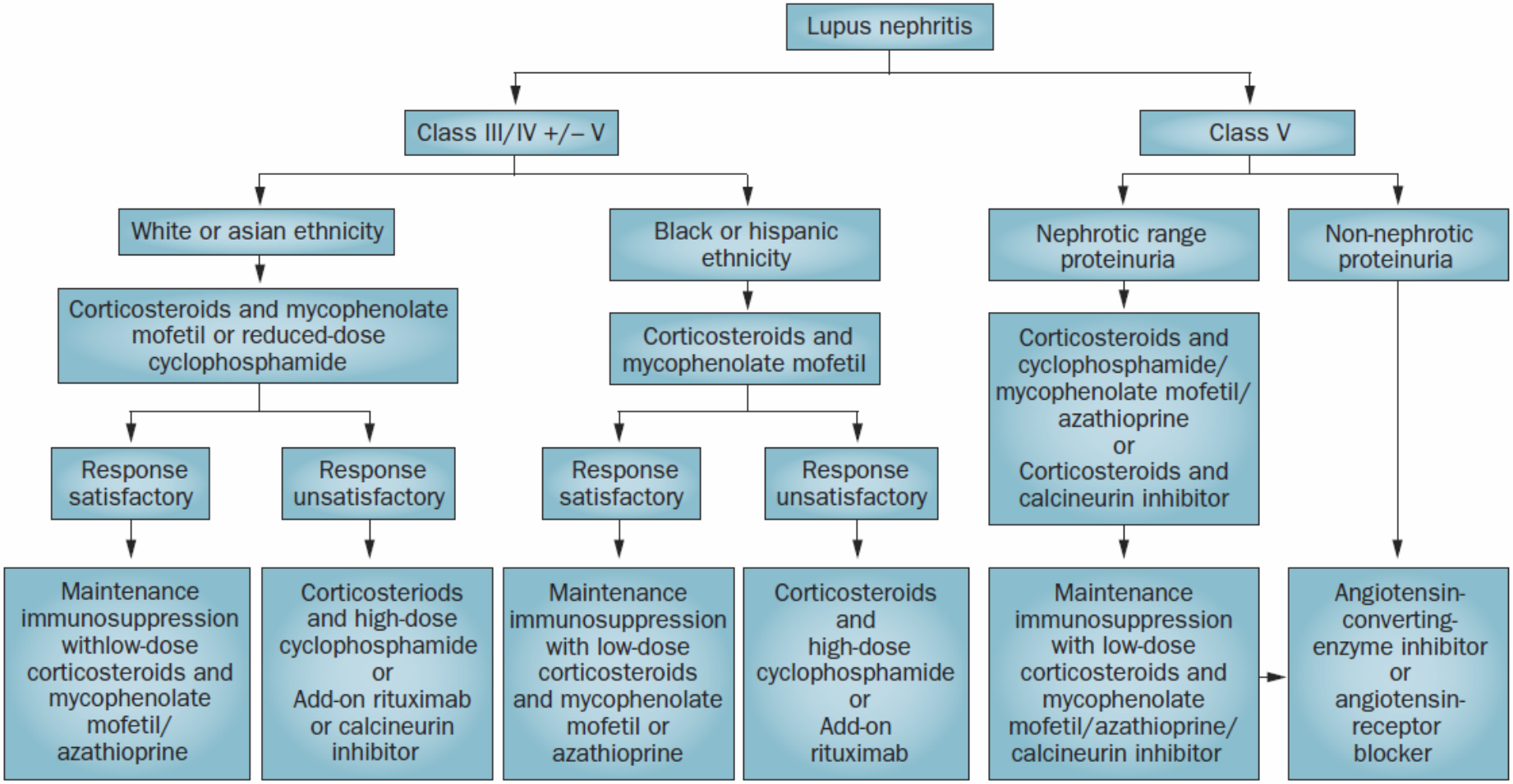
Lertdumrongluk P, et al. Kidney Int 2010; 78: 389-95

Kittanamongkolchai W, et al. Lupus 2013; 22: 727-32

Treatment of Lupus Nephritis

Then : corticosteroids → corticosteroids + CTX; suboptimal efficacy; morbidities; unsatisfactory long-term outcomes

Now : corticosteroids + MPA or CTX then MPA or AZA; additional choices e.g. CNI & biologics etc; ↓ dependency on corticosteroids; individualization



Chan TM. Nat Rev Nephrol 2015; 11: 46-61

Thank you