7ο ΚΡΗΤΟ-ΚΥΠΡΙΑΚΟ ΣΥΜΠΟΣΙΟ ΡΕΥΜΑΤΟΛΟΓΙΑΣ
Η ΡΕΥΜΑΤΟΛΟΓΑ ΣΗΜΕΡΑ-
ΠΡΑΚΤΙΚΑ ΠΡΟΒΛΗΜΑΤΑ ΤΗΣ ΚΑΘΗΜΕΡΙΝΗΣ ΚΛΙΝΙΚΗΣ ΠΡΑΞΗΣ
Κύπρος 23 Οκτωβρίου-25 Οκτωβρίου 2015

ΑΝΑΣΤΟΛΕΙΣ ΤΗΣ ΚΑΛΣΙΝΕΥΡΙΝΗΣ: ΔΕΔΟΜΕΝΑ ΣΤΗ ΝΕΦΡΙΤΙΔΑ ΣΕΛ

Ελένη Α. Φράγκου, Νεφρολόγος

24/10/2015

ΠΕΡΙΕΧΟΜΕΝΑ

ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

- 19 year old young woman diagnosed with SLE at the age of 11, with serious organ involvement:

  NPSLE with encephalitis, epilepsy - status epilepticus in 2007

  Lupus nephritis class IIIA *(according to ISN/RPS) in* ***2009***

  Activity index 8 (0-24) and chronicity index 0 (0-12)

  Proteinuria 1.8gr/24h, active urine sediment and normal renal function

- Methylprednisolone IV (3gr), **MMF** 2gr/day, along with prednisolone pos with gradual tapering) and hydroxychloroquine

- Complete remission of nephritis

- She continued MMF until **2012**, **when switched to azathioprine**

ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

- **September 2014:** arthritis, anemia, leukopenia with high inflammatory indices, low C3/C4 and elevated anti-dsDNA titers, **nephritic flare**
- **40mg Prednisolone** (while still on **azathioprine** and hydroxychloroquine)
- Partial improvement
- **February 2015:** worsening with **proteinuria 7.2gr/24h, active urine sediment**, normal renal function (CrCl 90ml/min) and normal blood pressure

ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

- **Kidney biopsy:** Mixed membranous and diffuse segmental proliferative nephritis with mostly active lesions and less chronic lesions, ***class V and IV-S with activity index 15 (0-24) and chronicity index 3 (0-12)***

- Methylprednisolone IV (3gr), 30 mg prednisone PO with gradual tapering. **MMF** 3gr/day (young age, risk of premature ovarian failure)

- **April 2015:** proteinuria 2.7gr/24h

- **July 2015:** proteinuria 4.3gr/24h, stable renal function (CrCl 93ml/min), normal BP, normal C3/C4 and increased anti-dsDNA

ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

Αλλαγή σε iv CYC (NIH ή EUROLUPUS protocol)
ή προσθήκη CNI ;;;;

ΠΕΡΙΕΧΟΜΕΝΑ

ΝΕΦΡΙΤΙΔΑ ΤΟΥ ΣΕΛ

- Σημαντική αιτία νοσηρότητας
- 30-60% των περιπτώσεων ΣΕΛ
- Class III, IV, V, mixed
- **Joint EULAR/ERA Recommendations (2010)**

  Hydroxychloroquine

  Θεραπεία εφόδου σε III/IV: MMF ή low-dose iv CYC

  Κακή ιστολογική εικόνα / προγνωστικοί παράγοντες: high-dose iv CYC

  Θεραπεία εφόδου σε V (MLN): MMF

  Θεραπεία συντήρησης: MMF ή AZA ή CNIs σε MLN
- **Ανεπιθύμητες ενέργειες** (λοιμώξεις, ανεπάρκεια γονάδων)**, αποτυχία θεραπείας, υποτροπές**

ΑΝΑΣΤΟΛΕΙΣ ΚΑΛΣΙΝΕΥΡΙΝΗΣ (CNIs)

CYCLOSPORIN A (CsA), TACROLIMUS (FK506, TAC)

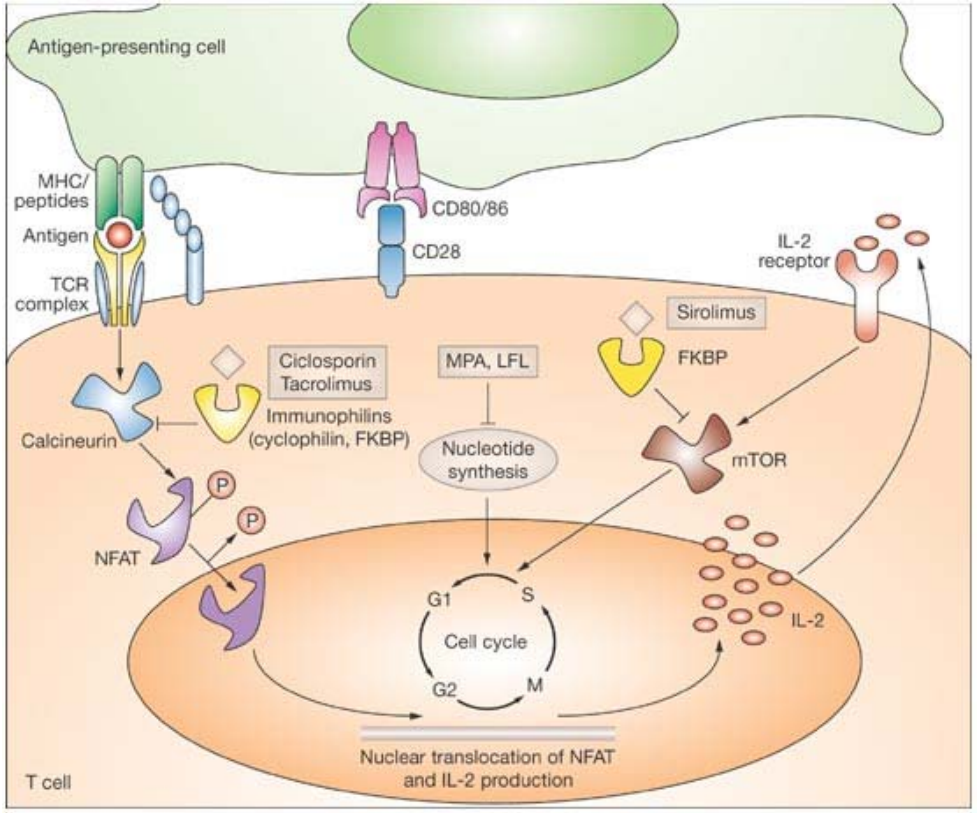
ΜΗΧΑΝΙΣΜΟΣ ΔΡΑΣΗΣ

- Αναστολή πολλαπλασιασμού των T- cells
- Μείωση παραγωγής αυτοαντισωμάτων
- Μείωση παραγωγής κυτταροκινών
- Άμεση αντιπρωτεϊνουρική δράση

ΜΕΤΑΒΟΛΙΣΜΟΣ

Cytochrome P450-3A

(μακρολίδες, αζόλες, non-d-CCB, grapefruit)

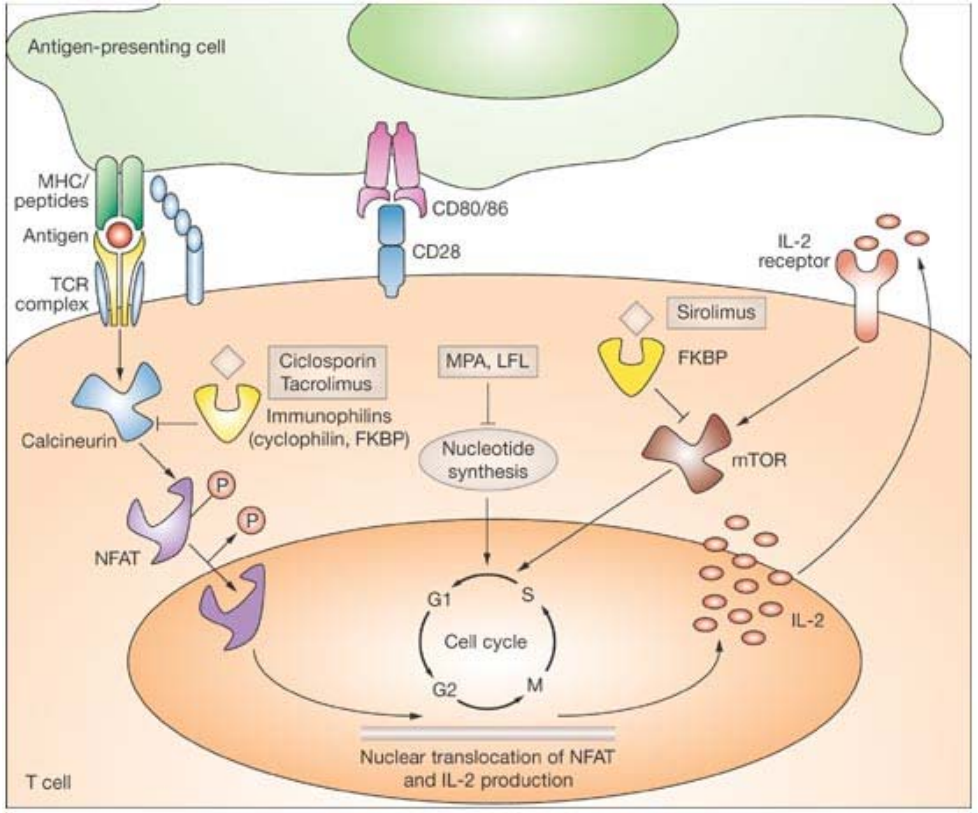


ΑΝΑΣΤΟΛΕΙΣ ΚΑΛΣΙΝΕΥΡΙΝΗΣ (CNIs)

CYCLOSPORIN A (CsA), TACROLIMUS (FK506, TAC)

ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ (ΔΟΣΟΕΞΑΡΤΩΜΕΝΕΣ)

- ΑΥ
- Νεφροτοξικότητα - CsA αρτηριλιοπάθεια
- Ηλεκτρολυτικές διαταραχές
- Υπερτρίχωση, αλωπεκία, υπερτροφία ούλων
- ΓΕΣ διαταραχές
- Διαταραχή ανοχής γλυκόζης
- Δυσλιπιδαιμία
- Υπερουριχαιμία
- Νεοπλασίες



ΑΝΑΣΤΟΛΕΙΣ ΚΑΛΣΙΝΕΥΡΙΝΗΣ (CNIs)

CYCLOSPORIN A (CsA), TACROLIMUS (FK506, TAC)

ΧΟΡΗΓΗΣΗ

- Δόση CsA <4 mg/kg/d, TAC <0.1-0.2 mg/kg/d με άδειο στομάχι
- To<150 ng/ml (CsA), To <6 ng/ml (TAC)

ΠΡΟΦΥΛΑΞΕΙΣ

Μείωση D αν Creatinine >30%, διακοπή εάν Creatinine >50%

Προσοχή στις αλληλεπιδράσεις με άλλα φάρμακα

ΑΝΤΕΝΔΕΙΞΕΙΣ

Cl Cre <60 ml/min

Αρρύθμιστη ΑΥ

Προχωρημένη σωληναριοδιάμεση νόσος στη βιοψία νεφρού

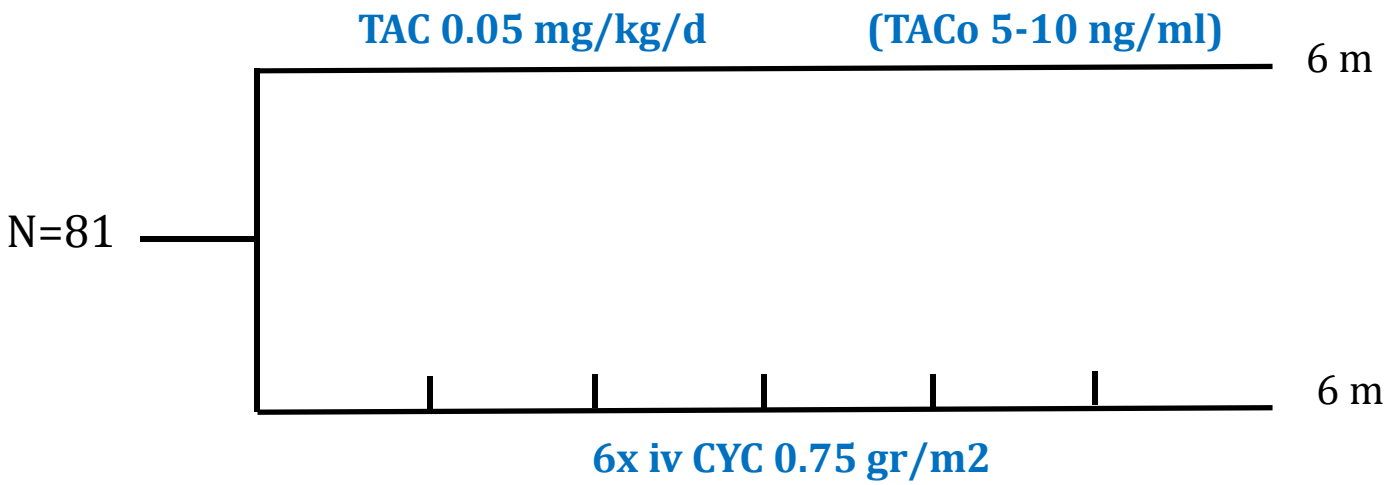
ΠΕΡΙΕΧΟΜΕΝΑ

#6

Short-term Outcomes of Induction Therapy With Tacrolimus Versus Cyclophosphamide for Active Lupus Nephritis: A Multicenter Randomized Clinical Trial

Wei Chen, MD, PhD,[1] Xueqing Tang, MD,[1]* Qinghua Liu, MD, PhD,[1]*

9 centers in China, LN class III, IV, V (activity index ~7, chronicity index ~2)



Am J Kidney Dis. 57(2):235-244. © 2011

Short-term Outcomes of Induction Therapy With Tacrolimus Versus Cyclophosphamide for Active Lupus Nephritis: A Multicenter Randomized Clinical Trial

Wei Chen, MD, PhD,[1] Xueqing Tang, MD,[1]* Qinghua Liu, MD, PhD,[1]*

Table 3. ANCOVA and Adjusted Mean Values for Laboratory and Clinical Parameters of the 2 Groups After the 1-Month Induction Therapy

Variables	TAC Group		IVC Group		*P*[a]
	No.	Adjusted Mean (95% CI)	No.	Adjusted Mean (95% CI)	
Proteinuria (g/24 h)	39	0.01 (−0.12 to 0.13)	32	0.23 (0.09 to 0.37)	0.02
Serum albumin (g/dL)	39	0.54 (0.51 to 0.57)	32	0.50 (0.47 to 0.53)	0.05
Serum creatinine (mg/dL)	37	−0.04 (−0.08 to −0.01)	33	−0.08 (−0.12 to −0.04)	0.2
MDRD Study eGFR (mL/min)	39	1.84 (1.81 to 1.88)	34	1.88 (1.85 to 1.93)	0.1
Serum C3 (mg/dL)	38	1.85 (1.79 to 1.90)	30	1.82 (1.76 to 1.89)	0.5

Table 4. ANCOVA and Adjusted Mean Values for Laboratory and Clinical Parameters of the 2 Groups After the 6-Month Induction Therapy

Variables	TAC Group (n = 39)	IVC Group (n = 34)	*P*[a]
	Adjusted Mean (95% CI)	Adjusted Mean (95% CI)	
Proteinuria (g/24 h)	−0.33 (−0.52 to −0.13)	−0.28 (−0.48 to −0.07)	0.7
Serum albumin (g/dL)	0.62 (0.61 to 0.64)	0.60 (0.59 to 0.62)	0.1
Serum creatinine (mg/dL)	−0.05 (−0.09 to −0.01)	−0.10 (−0.14 to −0.06)	0.09
MDRD Study eGFR (mL/min)	1.91 (1.87 to 1.95)	1.97 (1.92 to 2.01)	0.06
Serum C3 (mg/dL)	−0.04 (−0.08 to −0.01)	−0.10 (−0.14 to −0.06)	0.02

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Table 5. Adverse Events in Patients With Lupus Nephritis in the 2 Groups

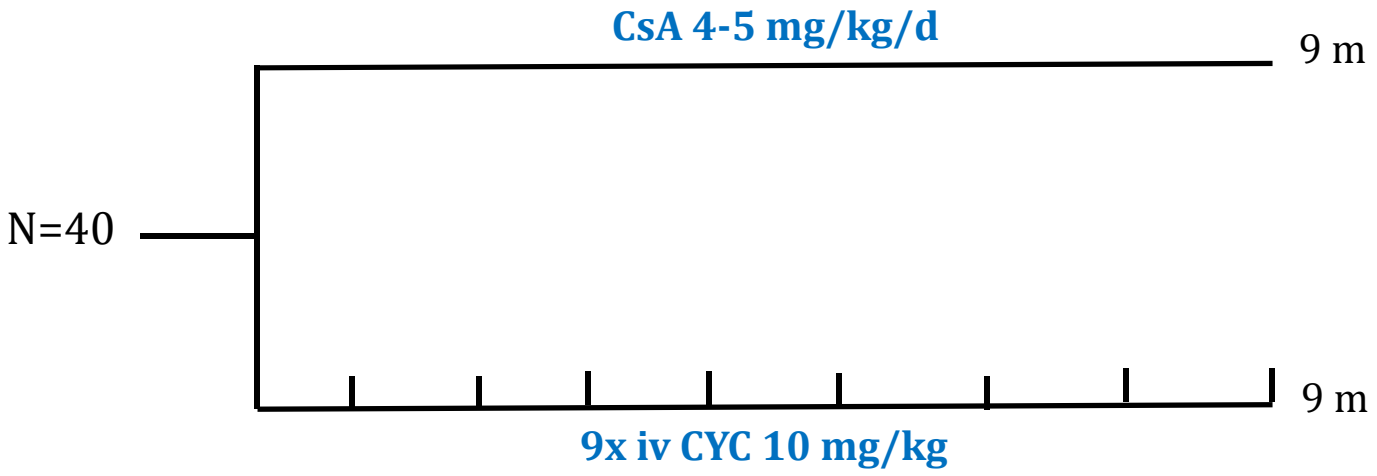
Adverse Effects	TAC Group (n = 39)	IVC Group (n = 34)	*P*
Infection			
No. of patients	5	4	0.9
No. of episodes	12	7	0.3
Types of infection			
Upper respiratory tract	3	2	0.9
Pulmonary	1	1	0.9
Urinary tract	3	2	0.9
Herpes zoster	5	2	0.4
Other			
Leukopenia[a]	0	5	0.02
Gastrointestinal symptoms	4	10	0.04
Hair loss	0	3	0.1
Liver function disorder[b]	3	4	0.7
Amenorrhea	0	2	0.2
Hyperglycemia[c]	7	6	0.9
Transient increase in SCr[d]	3	1	0.6
Death	0	1	0.5

Am J Kidney Dis. 57(2):235-244. © *2011*

Cyclosporine A or intravenous cyclophosphamide for lupus nephritis: the Cyclofa-Lune study

J Závada[1,*], SS Pešičková[2,*], R Ryšavá[2], M Olejárova[1], P Horák[3], Z Hrnčíř[4], I Rychlík[5], M Havrda[5], J Vítová[6], J Lukáč[7], J Rovenský[7], D Tegzova[1], J Böhmova[8], J Zadražil[3], J Hána[6], C Dostál[1] and V Tesar[2]

7 centers in Czech, 1 center in Slovakia, LN class III, IV (activity index ~9, chronicity index ~3)



Lupus (2014) 23, 69–74
Lupus (2010) 0, 1–9

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Table 2 Outcomes of treatment

Parameter	*Month 9* *CPH (n = 21)*	*CyA (n = 19)*	p-*value*	*Month 18* *CPH (n = 21)*	*CyA (n = 19)*	p-*value*
Remission	5 (24%)	5 (26%)	0.86	3 (14%)	7 (37%)	0.15
Response	11 (52%)	8 (43%)	0.52	8 (38%)	11 (58%)	0.21
Remission or Response criterion met						
– stable/improved serum creatinine	18 (86%)	9 (47%)	0.02	12 (57%)	11 (58%)	0.96
– 50% decrease in urinary protein[a]	13 (62%)	16 (84%)	0.24	11 (52%)	14 (74%)	0.16
– urinary protein <0.3	8 (38%)	13 (68%)	0.06	8 (38%)	14 (74%)	0.02
– inactive urinary sediment	12 (57%)	15 (79%)	0.19	14 (67%)	15 (79%)	0.49
– normal/improved C3	18 (86%)	15 (79%)	0.57	16 (76%)	16 (84%)	0.53
Treatment failure	7 (33%)	3 (16%)	0.28	6 (29%)	3 (16%)	0.46
Treatment failure criterion met						
– serum creatinine (increase >50 µmol/l)	1 (5%)	0 (0%)	1.00	2 (10%)	1 (5%)	1.00
– urinary protein >3.5 g/24 h	2 (9%)	0 (0%)	0.49	2 (10%)	1 (5%)	1.00
– persistent nephritic activity[b]	4 (19%)	3 (16%)	1.00	4 (19%)	1 (5%)	0.34

N=40

Lupus (2014) 23, 69–74
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N=40

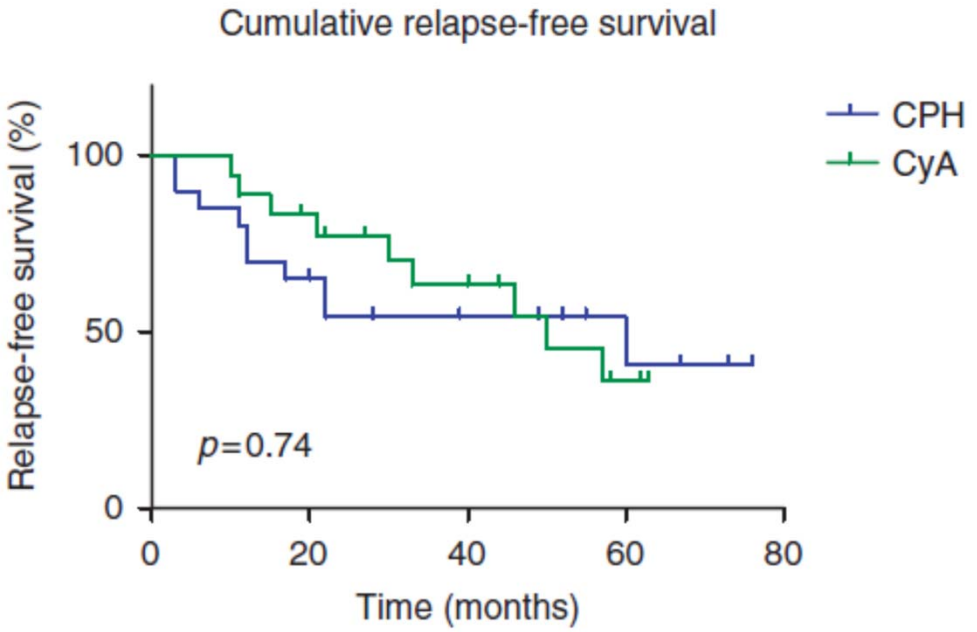

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Table 4 Adverse events (patients who experienced at least one adverse event)

Parameter	*CPH* n *(%)*	*CyA* n *(%)*
Deaths	0 (0%)	0 (0%)
Leukopenia	4 (20%)	2 (11%)
Hair loss	1 (5%)	0 (0%)
Increased facial hair	0 (0%)	1 (5%)
Increased blood pressure	6 (29%)	10 (53%)
Amenorrhea	1 (5%)	0 (0%)
Transient increase in serum creatinine	0 (0%)	3 (16%)
Generalized seizure	0 (0%)	1 (5%)
Herpes Zoster infection	2 (10%)	1 (5%)
Urinary tract infection	1 (5%)	1 (5%)
Sepsis	1 (5%)	0 (0%)
Perianal abscess	0 (0%)	1 (5%)
Transient ischemic attack	0 (0%)	1 (5%)

CPH, cyclophosphamide; CyA, Cyclosporine A.

Lupus (2014) 23, 69–74
Lupus (2010) 0, 1–9

Calcineurin inhibitors may be a reasonable alternative to cyclophosphamide in the induction treatment of active lupus nephritis: A systematic review and meta-analysis

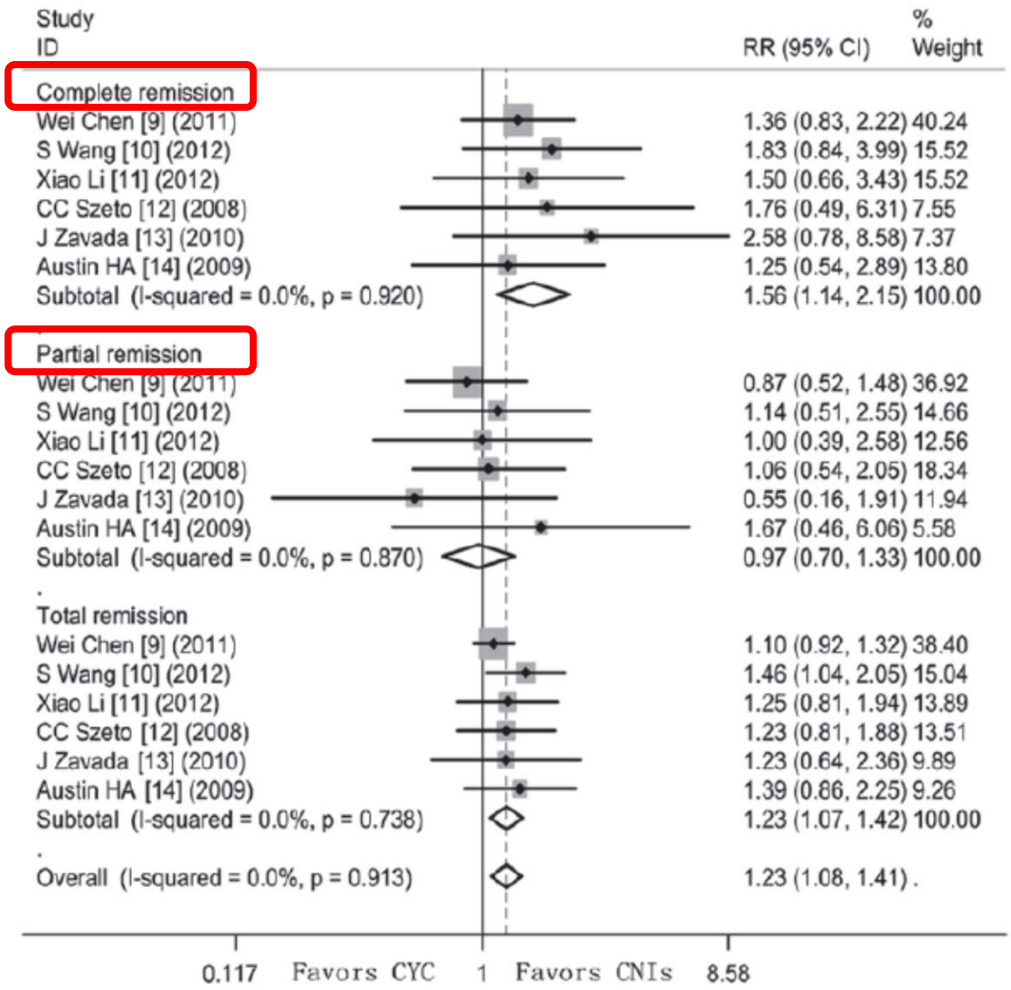
MIN YANG[1*], MIN LI[1*], WEI HE[2], BIN WANG[1] and YONG GU[3]

N=265

Table II. Trial characteristics and qualities.

Study (ref.)	Country or area	Study type	Number enrolled	Age (years)	Comparison	Renal pathology type	Follow-up duration (months)
Chen *et al* (9)	China	RCT	TAC 42 CYC 39	32±10.8 31.9±10.1	TAC+Pred vs. IV CYC+Pred	Class III, IV, V	6
Wang *et al* (10)	China	CS	TAC 20 CYC 20	32±7.7 35.7±11.4	TAC+Pred vs. IV CYC+Pred	Class III, IV, V	21.25±15.25 16.83±15.85
Li *et al* (11)	China	RCT	TAC 20 CYC 20	29 (17-50) 33 (17-64)	TAC+Pred vs. IV CYC+Pred	Class III, IV, V	6
Szeto *et al* (12)	Hong Kong	CC	TAC 18 CYC 19	38.2±10.4 36.5±12.2	TAC+Pred vs. PO CYC+Pred	Class V	6
Zavada *et al* (13)	Czech Republic and Slovakia	RCT	CsA 19 CYC 21	30±9 28±5	CsA +Pred vs. IV CYC+Pred	Class III, IV	9
Austin *et al* (14)	USA	RCT	CsA 12 CYC 15	34 (13-56) 41 (17-60)	CsA +Pred vs. IV CYC+Pred	Class V	12

Calcineurin inhibitors may be a reasonable alternative to cyclophosphamide in the induction treatment of active lupus nephritis: A systematic review and meta-analysis

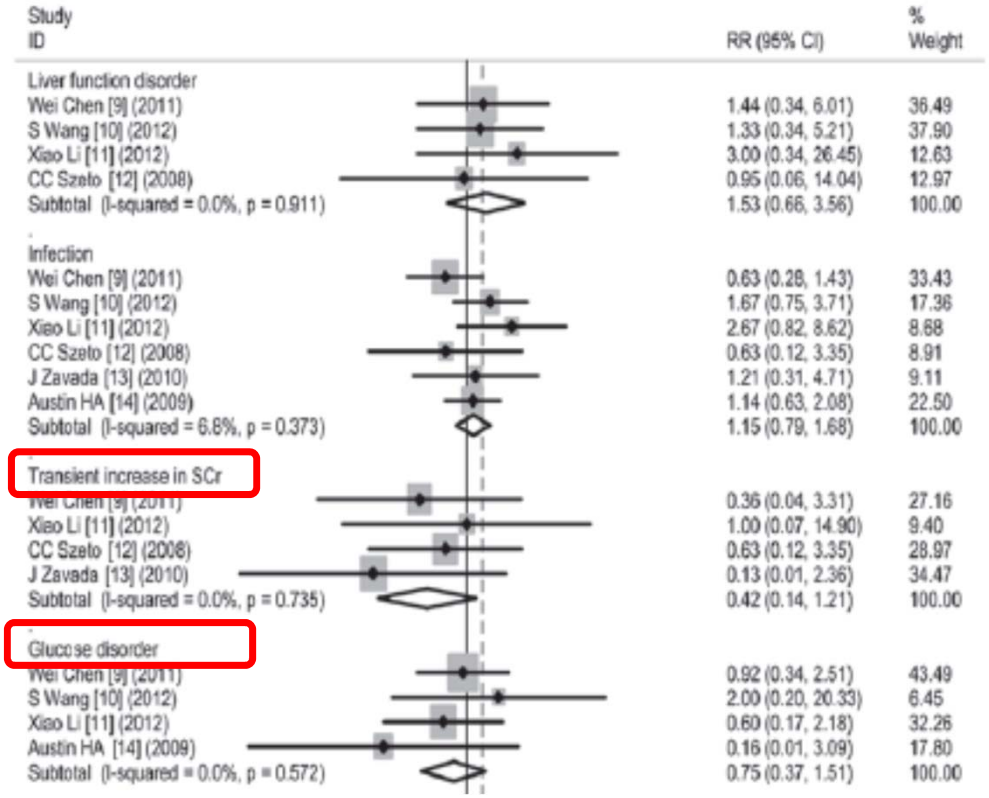


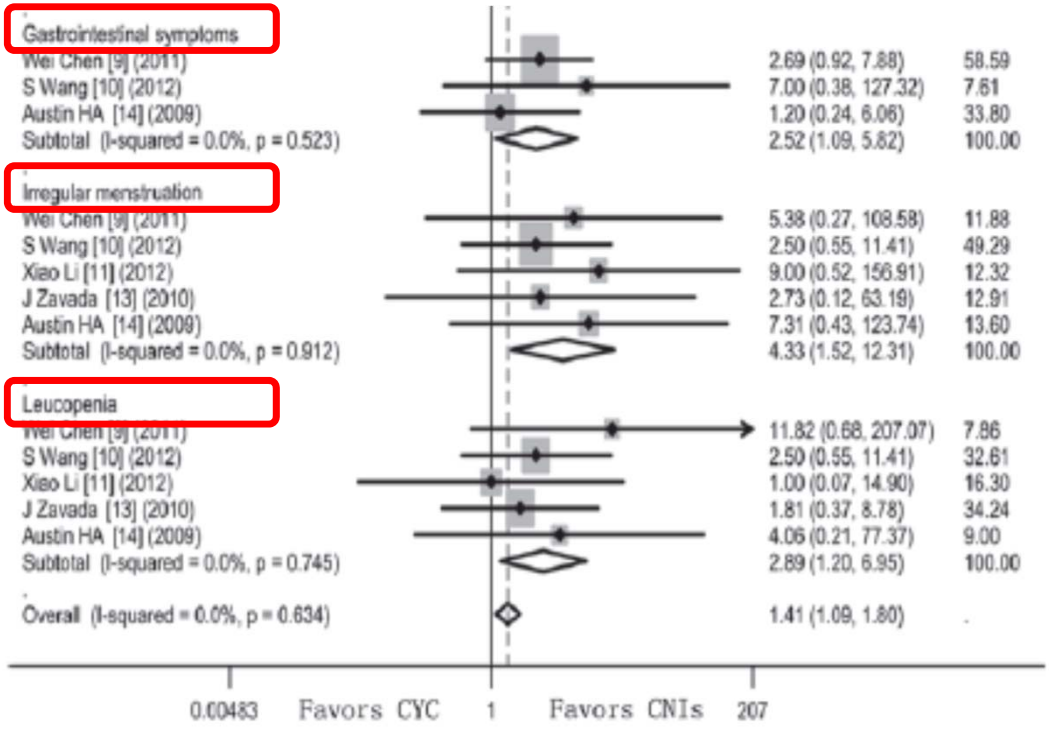
N=265

EXPERIMENTAL AND THERAPEUTIC MEDICINE 7: 1663-1670, 2014

Calcineurin inhibitors may be a reasonable alternative to cyclophosphamide in the induction treatment of active lupus nephritis: A systematic review and meta-analysis

N=265





EXPERIMENTAL AND THERAPEUTIC MEDICINE 7: 1663-1670, 2014

ΜΟΝΟΘΕΡΑΠΕΙΑ ΜΕ CNIs ΩΣ ΘΕΡΑΠΕΙΑ ΕΦΟΔΟΥ

✓ Οι CNIs είναι **περισσότερο αποτελεσματικοί από την iv CYC** ως προς την πλήρη ύφεση της III-V LN

✓ Οι CNIs προκαλούν **ταχύτερη ύφεση της λευκωματουρίας**

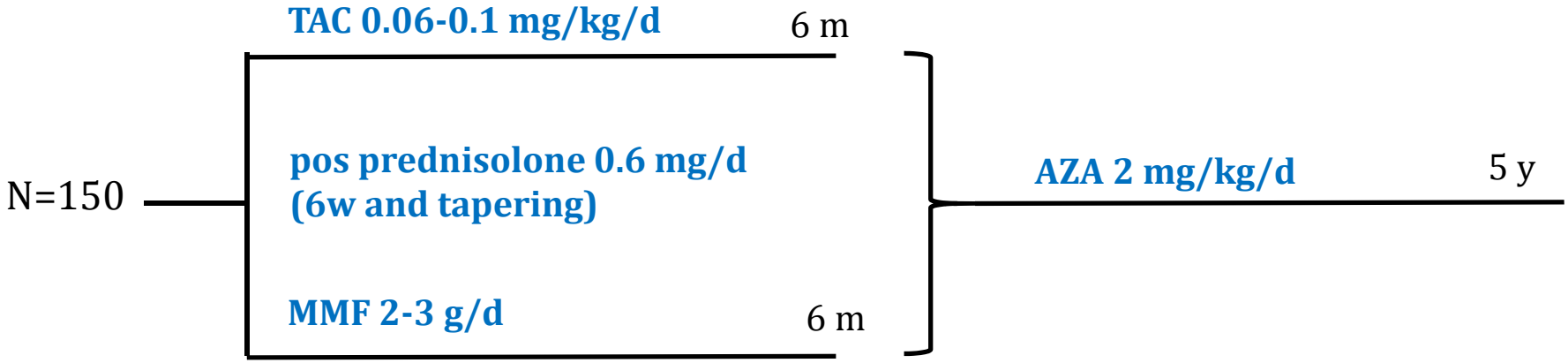
✓ Οι CNIs **έχουν διαφορετικό προφίλ ασφάλειας** σε σχέση με την iv CYC

Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up

#3

Chi Chiu Mok,[1] King Yee Ying,[2] Cheuk Wan Yim,[3] Yui Pong Siu,[1] Ka Hang Tong,[1] Chi Hung To,[1] Woon Leung Ng[3]

LN class III, IV, V (activity index ~10, chronicity index ~3)



Ann Rheum Dis 2014;**0**:1–7.

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Chi Chiu Mok,[1] King Yee Ying,[2] Cheuk Wan Yim,[3] Yui Pong Siu,[1] Ka Hang Tong,[1] Chi Hung To,[1] Woon Leung Ng[3]

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

Ann Rheum Dis 2014;**0**:1–7.

Tacrolimus versus mycophenolate mofetil for induction therapy of lupus nephritis: a randomised controlled trial and long-term follow-up

Chi Chiu Mok,[1] King Yee Ying,[2] Cheuk Wan Yim,[3] Yui Pong Siu,[1] Ka Hang Tong,[1] Chi Hung To,[1] Woon Leung Ng[3]

Table 4 Renal response of pure membranous lupus nephritis

	Baseline	2 months	4 months	6 months	p Value
Urine P/Cr ratio					
MMF	6.32±8.2	2.95±3.2	2.50±2.1	1.45±1.1	0.047
TAC	4.34±2.8	1.44±1.1	1.85±2.9	1.08±0.9	<0.001
p Value*	0.44	0.16	0.65	0.52	
CrCl (mL/min)					
MMF	92.4±36	93.5±35	104±37	102±31	0.19
TAC	100±38	98.8±43	90.9±41	90.8±44	0.07
p Value*	0.57	0.76	0.03	0.04	

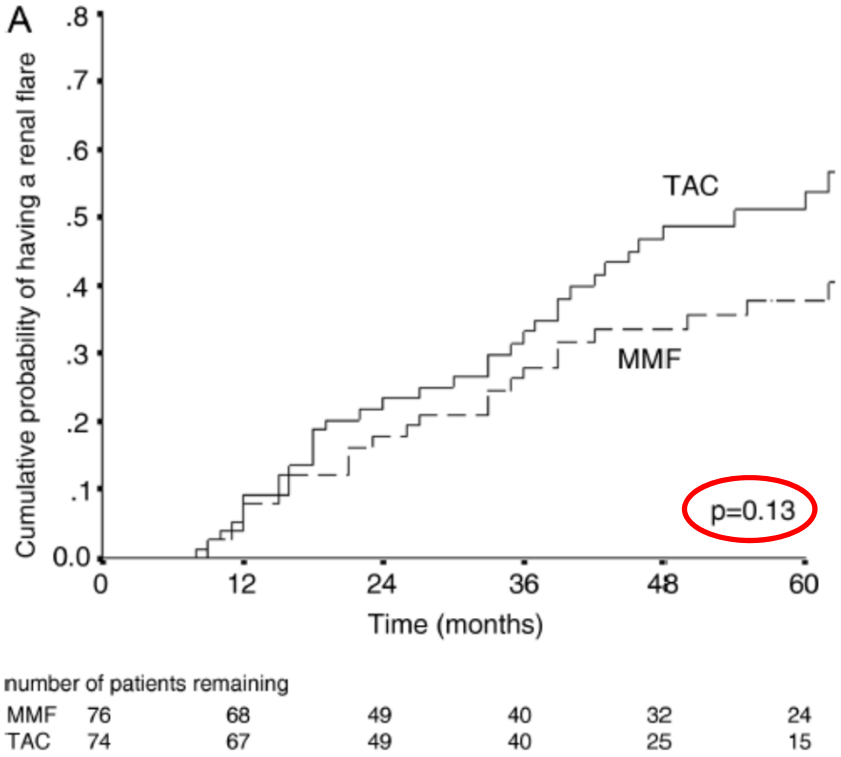
Renal response at 6 months	MMF (N=12)	TAC (N=16)	Difference (95% CI)†	p Value
CR	6 (50%)	9 (56%)	6% (−27% to 38%)	0.09
PR	3 (25%)	7 (44%)	19% (−16% to 47%)	
NR	3 (25%)	0 (0%)	−25% (−53% to 0.2%)	

Ann Rheum Dis 2014;**0**:1–7.

Table 5 Adverse events in the first 6 months

	MMF (N=76)	TAC (N=74)	p Value
Any adverse events	59 (78%)	69 (93%)	0.007
Death	1 (1.3%)	0 (0%)	1.00
Major infection (hospitalisation)	7 (9.2%)	4 (5.4%)	0.53
Minor infection (excluding Herpes)	16 (28%)	12 (16%)	0.45
Upper respiratory tract	10 (13%)	7 (9.5%)	0.48
Urinary tract	3 (3.9%)	1 (1.4%)	0.62
Gynaecological	1 (1.3%)	0 (0%)	1.00
Gastrointestinal	0 (0%)	1 (1.4%)	1.00
Sinusitis	1 (1.3%)	0 (0%)	1.00
Subcutaneous	1 (1.3%)	3 (4.1%)	0.36
Herpes zoster	14 (18%)	2 (2.7%)	0.003
Herpes simplex	0 (0%)	1 (1.4%)	1.00
Nausea	3 (3.9%)	2 (2.7%)	1.00
Diarrhoea	8 (11%)	2 (2.7%)	0.10
Diabetes mellitus	2 (2.6%)	3 (4.1%)	0.68
Alopecia	0 (0%)	6 (8.1%)	0.01
Tremor	0 (0%)	15 (20%)	<0.001
Headache	1 (1.3%)	3 (4.1%)	0.36
Cramps	2 (2.6%)	7 (9.5%)	0.10
Tinnitus	1 (1.3%)	0 (0%)	1.00
Hypertrichosis	0 (0%)	1 (1.4%)	1.00
Reversible increase in SCr by 30%	0 (0%)	10 (14%)	0.001
Others	4 (5.3%)	1 (1.4%)	0.37

MMF, mycophenolate mofetil; SCr, serum creatinine; TAC, tacrolimus.



Ann Rheum Dis 2014;**0**:1–7.

ΜΟΝΟΘΕΡΑΠΕΙΑ ΜΕ CNIs ΩΣ ΘΕΡΑΠΕΙΑ ΕΦΟΔΟΥ

✓ Το TAC **δεν είναι αποτελεσματικότερο από το MMF**
ως προς την μερική ή πλήρη ύφεση της III-V LN

✓ Το TAC συσχετίζεται με
μεγαλύτερη επίπτωση νεφρικής υποτροπής
και έκπτωσης της νεφρικής λειτουργίας
σε σχέση με το MMF

ΠΕΡΙΕΧΟΜΕΝΑ

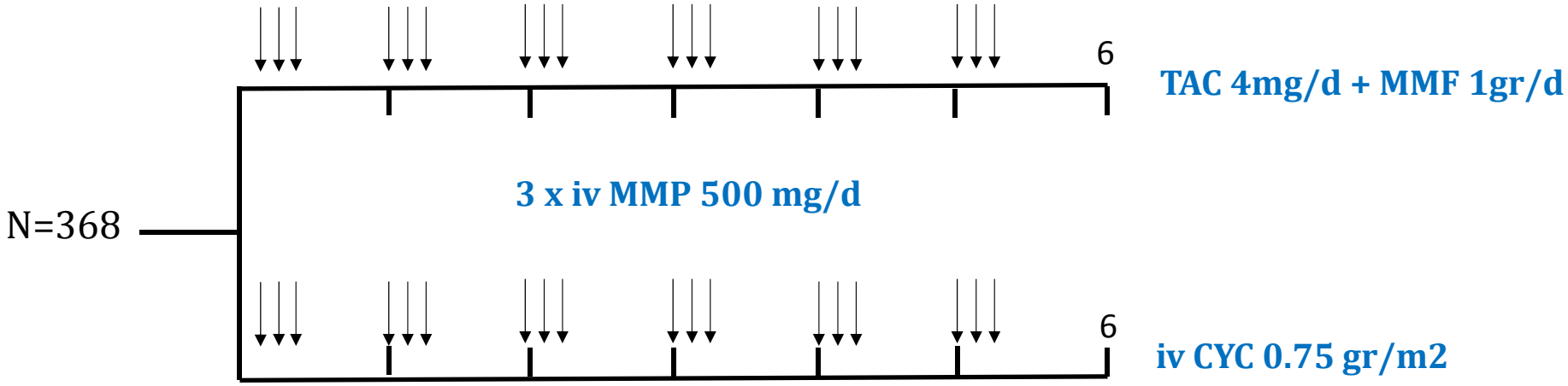
Annals of Internal Medicine ORIGINAL RESEARCH

Multitarget Therapy for Induction Treatment of Lupus Nephritis

A Randomized, Controlled Trial

Zhihong Liu, MD; Haitao Zhang, MD; Zhangsuo Liu, MD; Changying Xing, PhD; Ping Fu, MD; Zhaohui Ni, MD; Jianghua Chen, MD; Hongli Lin, MD; Fuyou Liu, MD; Yongcheng He, MD; Yani He, MD; Lining Miao, MD; Nan Chen, MD; Ying Li, MD; Yong Gu, MD; Wei Shi, MD; Weixin Hu, MD; Zhengzhao Liu, MD; Hao Bao, MD; Caihong Zeng, PhD; and Minlin Zhou, MD

26 centers in China, **mild-moderately severe** LN, (activity index ~7, chronicity index ~1)



Ann Intern Med. doi:10.7326/M14-1030 2014.

Annals of Internal Medicine

ORIGINAL RESEARCH

Multitarget Therapy for Induction Treatment of Lupus Nephritis

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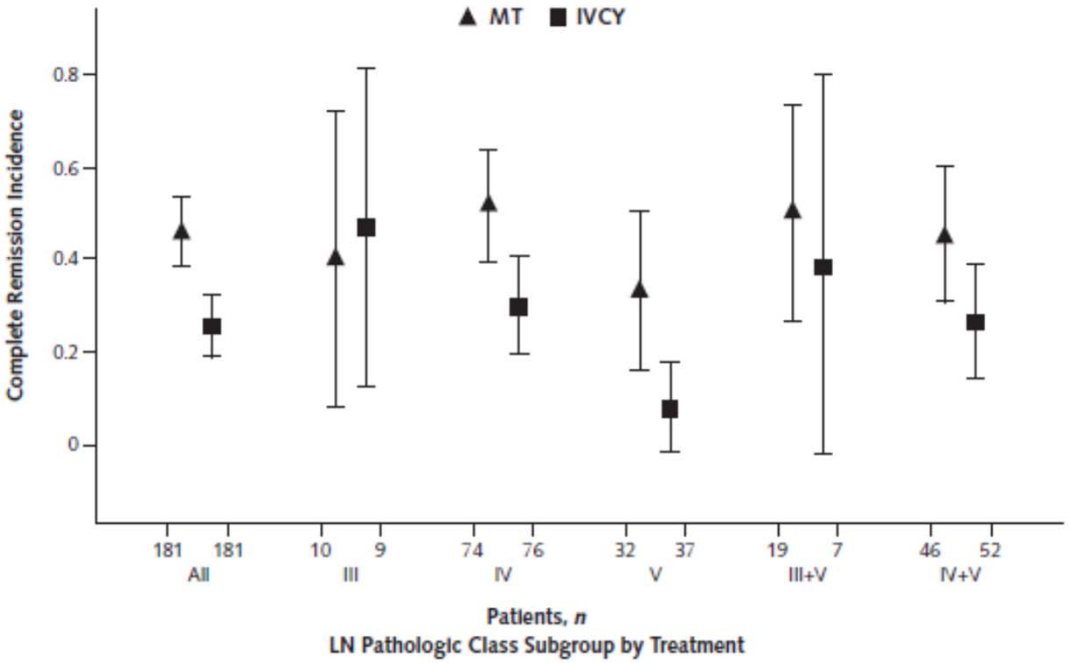

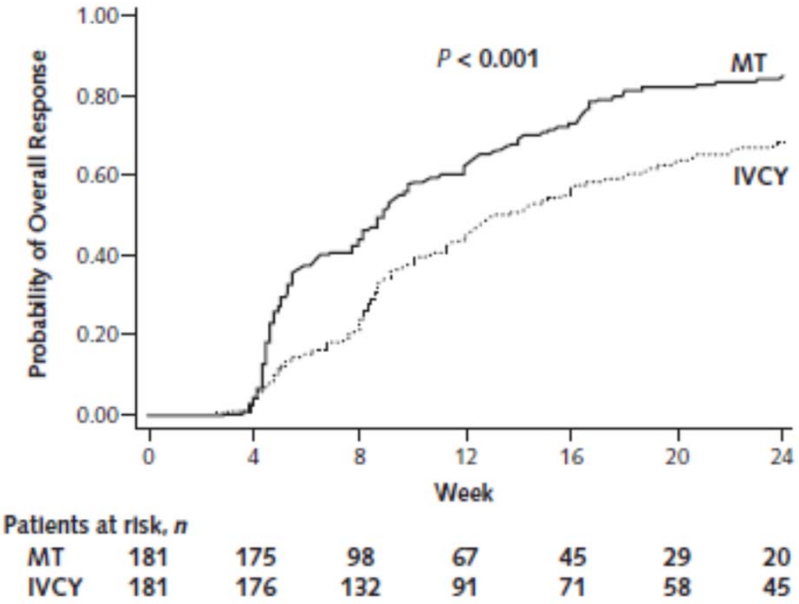

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Table 2. Adverse Experience Data for Multitarget Therapy and Intravenous Cyclophosphamide Therapy*

Variable	Multitarget (*n* = 181), *n* (%)	Intravenous Cyclophosphamide (*n* = 181), *n* (%)
Serious adverse events	13 (7.2)	5 (2.8)
Pneumonia	7 (3.9)	1 (0.6)
Varicella zoster virus	2 (1.1)	1 (0.6)
Upper respiratory tract infection	2 (1.1)	0
Skin and soft tissue infection	0	1 (0.6)
Epilepsy	1 (0.6)	0
Septicemia	0	1 (0.6)
Doubling of serum creatinine level	1 (0.6)	0
Pregnant	1 (0.6)	1 (0.6)
All adverse events (include serious adverse events)	91 (50.3)	95 (52.5)

Ann Intern Med. doi:10.7326/M14-1030 2014.

Annals of Internal Medicine ORIGINAL RESEARCH

Multitarget Therapy for Induction Treatment of Lupus Nephritis

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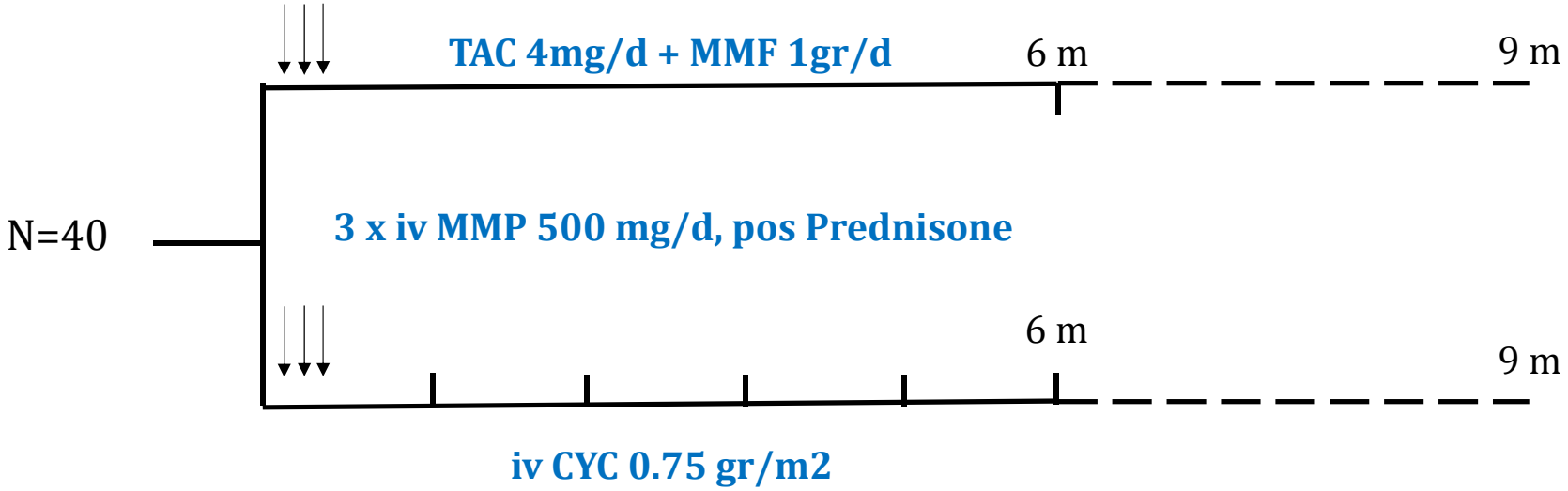
Skin and soft tissue infection	0	1 (0.6)
Epilepsy	1 (0.6)	0
Septicemia	0	1 (0.6)
Doubling of serum creatinine level	1 (0.6)	0
Pregnant	1 (0.6)	1 (0.6)
All adverse events (include serious adverse events)	91 (50.3)	95 (52.5)
Withdrawn because of adverse event	10 (5.5)	3 (1.7)
Pneumonia†	6 (3.3)	0
Varicella zoster virus	1 (0.6)	0
Epilepsy	1 (0.6)	0
Doubling of serum creatinine level	1 (0.6)	0
Arrhythmia	1 (0.6)	0
Leukopenia	0	1 (0.6)
Teratoma	0	1 (0.6)
Septicemia	0	1 (0.6)

Ann Intern Med. doi:10.7326/M14-1030

Successful Treatment of Class V+IV Lupus Nephritis with Multitarget Therapy

Hao Bao, Zhi-Hong Liu, Hong-Lang Xie, Wei-Xin Hu, Hai-Tao Zhang, and Lei-Shi Li

(activity index ~10, chronicity index ~2)



J Am Soc Nephrol 19: 2001–2010, 2008.

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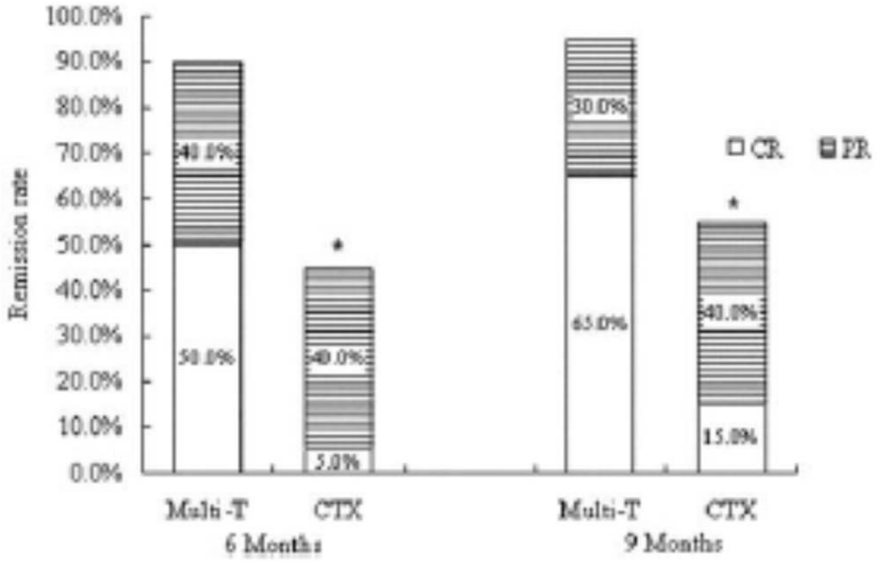


Figure 2. Remission rates in the multitarget therapy and IVCY groups after 6 and 9 mo (intention-to-treat). *$P < 0.05$ versus the multitarget therapy group.

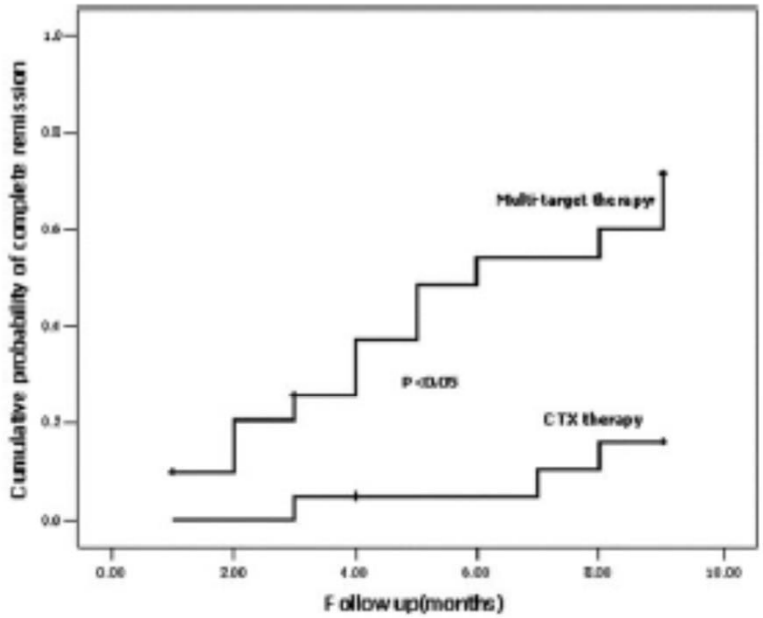


Figure 3. Probability of achieving complete remission for patients treated with multitarget therapy or IVCY. $P < 0.05$ compared between the two groups.

J Am Soc Nephrol 19: 2001–2010, 2008.

Successful Treatment of Class V+IV Lupus Nephritis with Multitarget Therapy

Hao Bao, Zhi-Hong Liu, Hong-Lang Xie, Wei-Xin Hu, Hai-Tao Zhang, and Lei-Shi Li

Table 8. Adverse events[a]

Parameter	Multitarget (*n* [%]; *n* = 20)	IVCY (*n* [%]; *n* = 20)
Gastrointestinal syndrome	2 (10.0)	7 (35.0)
Temporary GPT/GOT rise	1 (5.0)	2 (10.0)
Leucopenia	2 (10.0)	4 (20.0)
New-onset hypertension	3 (15.0)	0 (0.0)
Hyperglycemia	1 (5.0)	0 (0.0)
Upper respiratory infection	1 (5.0)	4 (20.0)
Pneumonia	1 (5.0)	1 (5.0)
Herpes zoster or varicella	1 (5.0)	1 (5.0)
Urinary tract infection	1 (5.0)	1 (5.0)
Alopecia	1 (5.0)	4 (20.0)
Irregular menstruation	1 (5.0)	4 (20.0)

[a]GPT/GOT, glutamic-pyruvic transaminase/glutamic oxaloacetic transaminase.

J Am Soc Nephrol 19: 2001–2010, 2008.

MULTITARGET ΘΕΡΑΠΕΙΑ ΜΕ CNIs ΩΣ ΘΕΡΑΠΕΙΑ ΕΦΟΔΟΥ

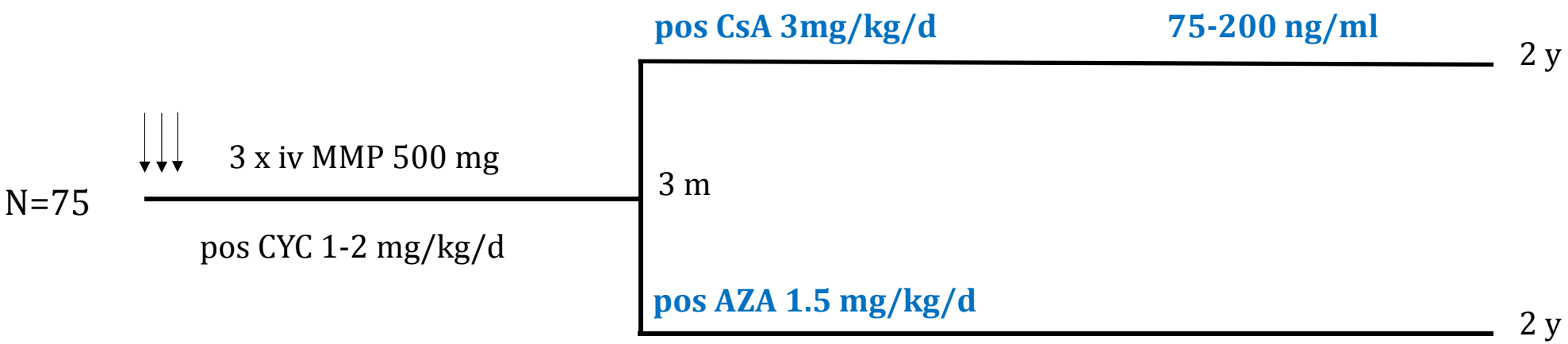
✓ Σε LN με ήπια-μέτρια σοβαρότητα,
η multitarget θεραπεία φαίνεται **αποτελεσματικότερη από την IV CYC**

✓ Χρειάζονται μελέτες και σε άλλες φυλές
και σε LN με χειρότερους ιστολογικούς δείκτες ή με αυξημένη Cre

ΠΕΡΙΕΧΟΜΕΝΑ

A Randomized Pilot Trial Comparing Cyclosporine and Azathioprine for Maintenance Therapy in Diffuse Lupus Nephritis over Four Years

Gabriella Moroni,* Andrea Doria,† Marta Mosca,‡ Ornella Della Casa Alberighi,§ Gianfranco Ferraccioli,‖ Silvano Todesco,† Carlo Manno,¶ Paolo Altieri,** Roberto Ferrara,†† Simona Greco,†† and Claudio Ponticelli*‡‡



Clin J Am Soc Nephrol 1: 925–932, 2006.

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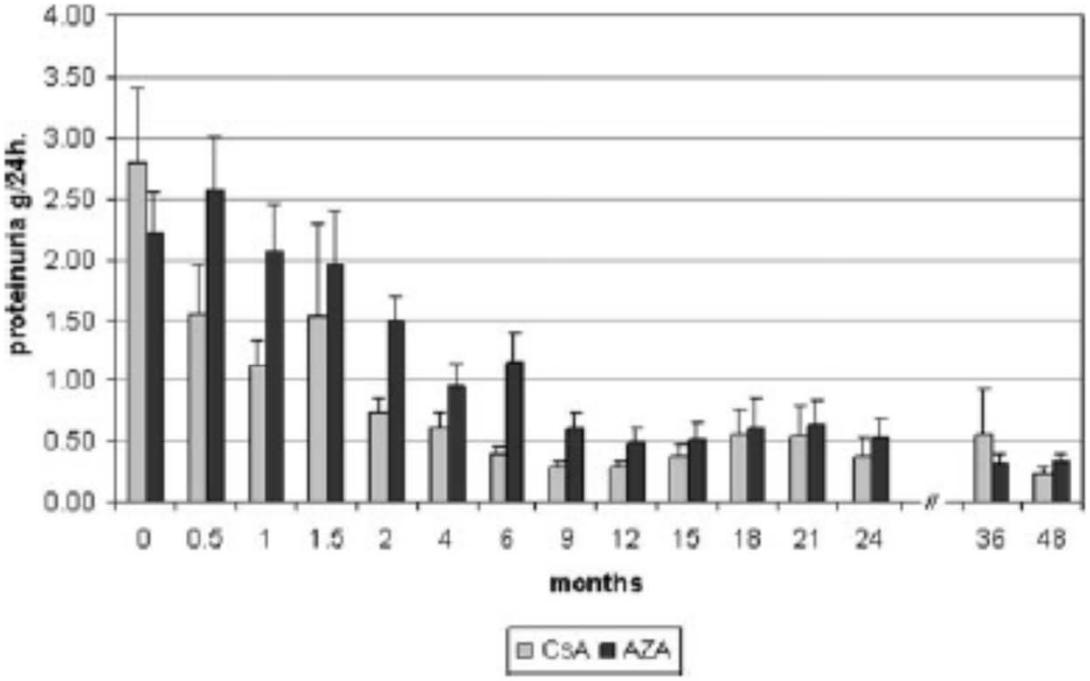

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Table 4. Adverse events recorded during the core study, regardless of event severity[a]

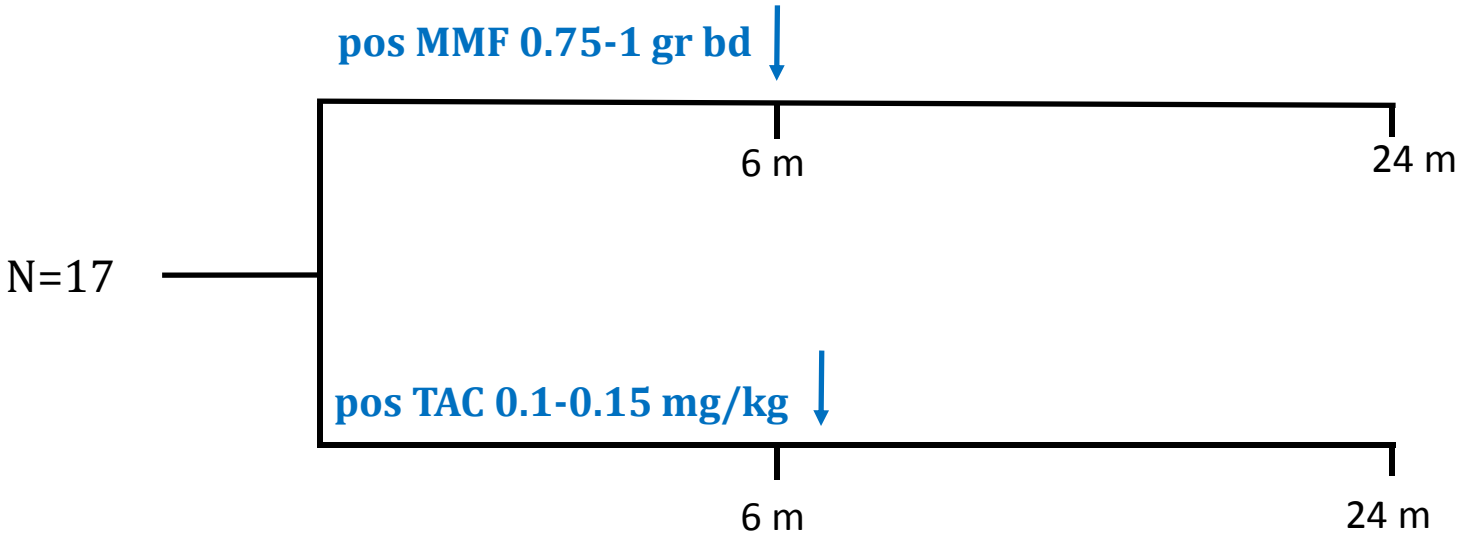
	Cyclosporine		Azathioprine	
	n (%)	Incidence Density[b]	*n* (%)	Incidence Density[b]
No. of patients	36		33	
Leukopenia	4 (11.1)	6.1	10 (30.3)	16.7
Anemia	5 (13.9)	7.6	5 (15.2)	8.4
Hypertension	7 (19.4)	10.6	5 (15.2)	8.4
Hypercholesterolemia	2 (5.6)	3.0	4 (12.1)	6.7
Gum hyperplasia	2 (5.6)	3.0	0	0.0
Hypertrichosis	2 (5.6)	3.0	0	0.0
Diabetes	0	0.0	1 (3.0)	1.7
Hyperkalemia	1 (2.8)	1.5	0	0.0
Hypertensive crisis	1 (2.8)	1.5	0	0.0
Infections	7 (19.4)	10.6	14 (42.4)	23.4
Arthralgias	14 (38.9)	21.2	3 (9.1)	5.0
Gastrointestinal disorders	11 (30.6)	16.7	3 (9.1)	5.0

[a]In no case hospitalization was required. Numbers shown are the counts of patients who reported each adverse event. Patients reporting multiple events are therefore counted for each reported adverse event.
[b]Number of events per 100 patients-years of follow-up.

Clin J Am Soc Nephrol 1: 925–932, 2006.

Pilot 24 month study to compare mycophenolate mofetil and tacrolimus in the treatment of membranous lupus nephritis with nephrotic syndrome

DESMOND YH YAP,[1] XUEQING YU,[2] XIANG-MEI CHEN,[3] FUMING LU,[5] NAN CHEN,[6] XUE-WANG LI,[4] COLIN SO TANG[1] and TAK MAO CHAN[1]



Nephrology **17** (2012) 352–357

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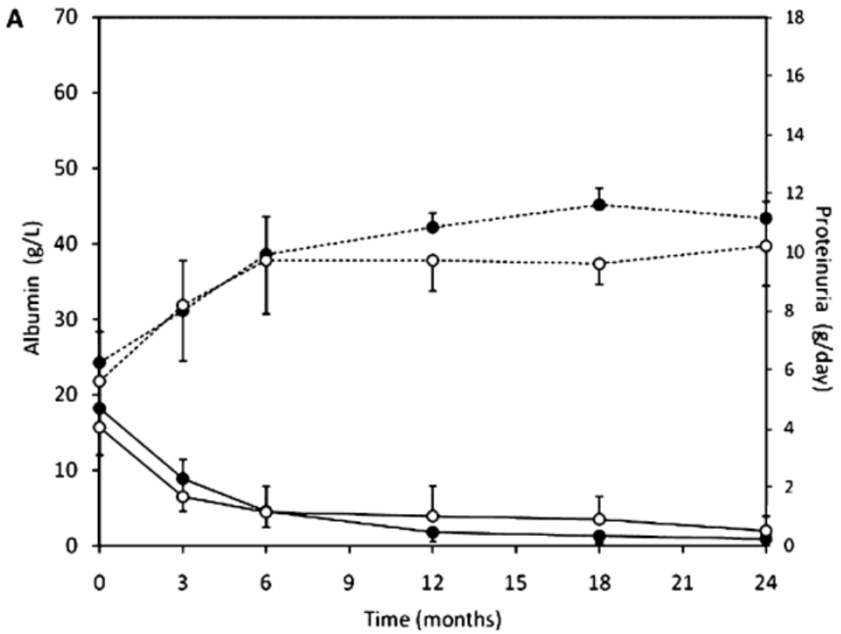

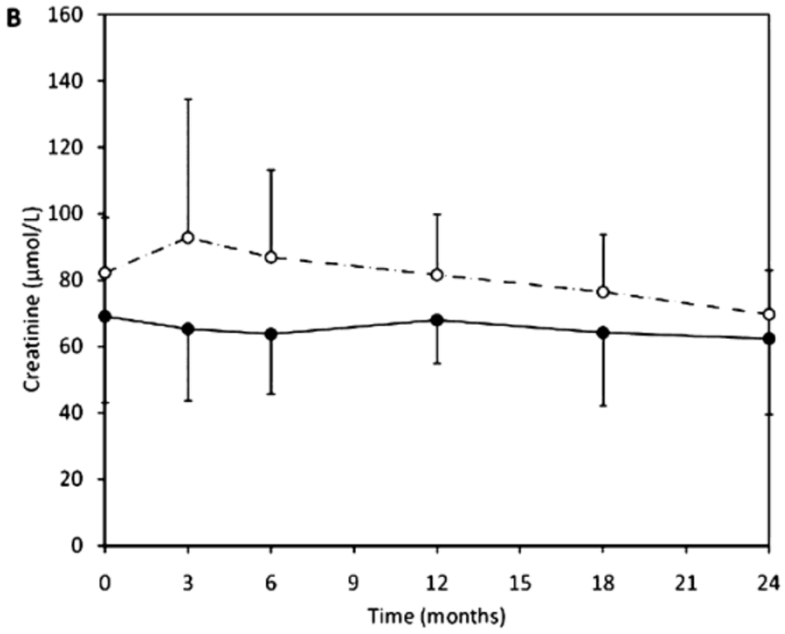

Nephrology **17** (2012) 352–357

CNIs ΩΣ ΘΕΡΑΠΕΙΑ ΣΥΝΤΗΡΗΣΗΣ

✓ Οι CNIs είναι **εξίσου αποτελεσματικοί με AZA και MMF**
ως προς τη διατήρηση της ύφεσης της LN

✓ Η εναλλαγή των σκευασμάτων
αυξάνει τις μακροπρόθεσμες θεραπευτικές επιλογές

ΠΕΡΙΕΧΟΜΕΝΑ

Combination therapy of mycophenolate mofetil and tacrolimus in lupus nephritis

CM Lanata[1], T Mahmood[2], DM Fine[1] and M Petri[1]
[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA; and [2]St Agnes Hospital, Baltimore, MD, USA

Since most lupus nephritis patients have an incomplete response to mycophenolate mofetil, combination regimens may improve outcomes. Tacrolimus (FK506) has shown some benefit in lupus nephritis in small trials, and combined with mycophenolate mofetil is standard immunosuppression in transplant patients. We investigate the addition of FK506 to mycophenolate mofetil, in patients who were mycophenolate mofetil failures. All patients were part of a prospective cohort, but evaluated retrospectively. Seven lupus nephritis patients (mean age 27.1, 100% female, 42% Caucasian and 42% African American) were evaluated. Three patients had combined ISN class III and V, two ISN class IV, one ISN class V and II and one ISN class IV and V. Six were taking an ACE-inhibitor or angiotensin receptor blocker, 6 hydroxychloroquine and 5 prednisone (mean dose 11.5 mg; range 0–30 mg). Mean mycophenolate mofetil dose at time of tacrolimus addition was 2.8 g (range 2–3 g). Mean tacrolimus dose was 3.4 mg (range 2–8 mg) titrated to a mean level of 4.67 ng/dl (range 2.2–11.8 ng/dl) for a mean of duration of 16 months (range 2–54 months). Two patients continued both therapies,

Lupus (2010) 19, 935–940

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a mean of duration of 16 months (range 2–54 months). Two patients continued both therapies, while five discontinued therapy. One patient achieved a complete renal remission, while three achieved partial remission with 82.9%, 77.1%, 55.3% reductions in proteinuria. Toxicity limited the use of combination therapy: diabetic ketoacidosis (one patient), pneumonia (two) and muscle pain (two). These data suggest that adding tacrolimus in patients refractory to mycophenolate mofetil might have some benefit, although complete responses were rare. Unfortunately, tacrolimus toxicity appeared to be prevalent in these systemic lupus erythematosus patients, limiting its long term use. *Lupus* (2010) **19**, 935–940.

Lupus (2010) 19, 935–940

Combined low-dose mycophenolate mofetil and tacrolimus for lupus nephritis with suboptimal response to standard therapy: a 12-month prospective study

CC Mok, CH To, KL Yu and LY Ho
Department of Medicine, Tuen Mun Hospital, Hong Kong, China

Objective: The objective of this paper is to evaluate the efficacy of combined mycophenolate mofetil (MMF) and tacrolimus (TAC) for lupus nephritis with suboptimal response to standard therapy. **Methods:** Inclusion criteria for patients: (1) biopsy-confirmed active lupus nephritis; and (2) inadequate response to ≥2 immunosuppressive regimens. While prednisolone (≤10 mg/day) and angiotensin-converting enzyme inhibitors were continued, immunosuppressive agents were replaced by combined MMF (1 g/day) and TAC (4 mg/day). Patients were followed every 2 months for the clinical response and adverse events at 12 months. **Results:** Twenty-one patients were recruited (20 women; age 35.8 ± 9.2 years; systemic lupus erythematosus (SLE) duration 111 ± 51 months). The histological classes of lupus nephritis were: IV/III (33%), V + III/IV (33%) and pure V (33%). The creatinine clearance (CrCl), urine protein-

Lupus (2013) 22, 1135–1141

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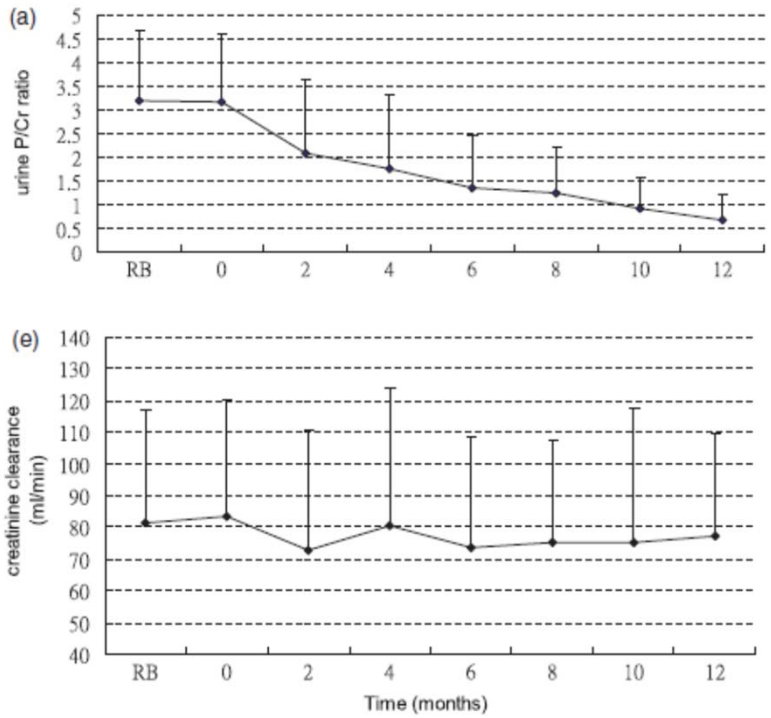


Table 2 Adverse events reported by participants

Adverse events	*Number (%)*
Serious infection requiring hospitalization	2 (6)
Infection not requiring hospitalization (excluding herpes)	12 (27)
Herpes infection (simplex/zoster)	3 (9)
Diarrhea	4 (12)
Cramps	3 (9)
Dyspepsia	2 (6)
Transient increase in serum creatinine	2 (6)
Alopecia	1 (3)
Facial twitching	1 (3)
Tremor	1 (3)
Diabetes mellitus	1 (3)
Others	4 (12)
Total	33 (100)

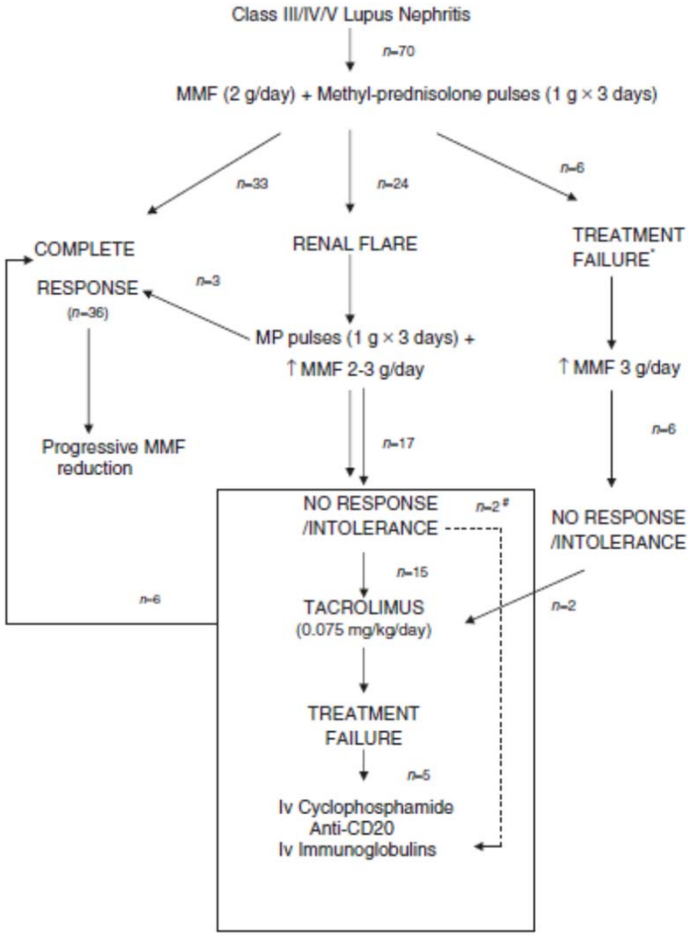
Lupus (2013) 22, 1135–1141

Long-term outcomes—mycophenolate mofetil treatment for lupus nephritis with addition of tacrolimus for resistant cases

Josefina Cortés-Hernández[1], María Teresa Torres-Salido[1], Alfonso Segarra Medrano[2], Miquel Vilardell Tarrés[1] and Josep Ordi-Ros[1]

(activity index ~14, chronicity index ~2)

Methods. We report, in this observational study, our long-term experience treating 70 patients with biopsy-proven LN, with MMF as continuous induction-maintenance therapy, who were followed up prospectively over a 5-year period. As rescue therapy for MMF-resistant cases, tacrolimus (0.075 mg/kg/day) was added. The study primary end point was complete response (CR). Secondary end points included partial response (PR), treatment failure, relapse and side effects. Predictor factors associated to renal outcome were analysed by Cox regression analysis.



Nephrol Dial Transplant (2010) 25: 3939–3948

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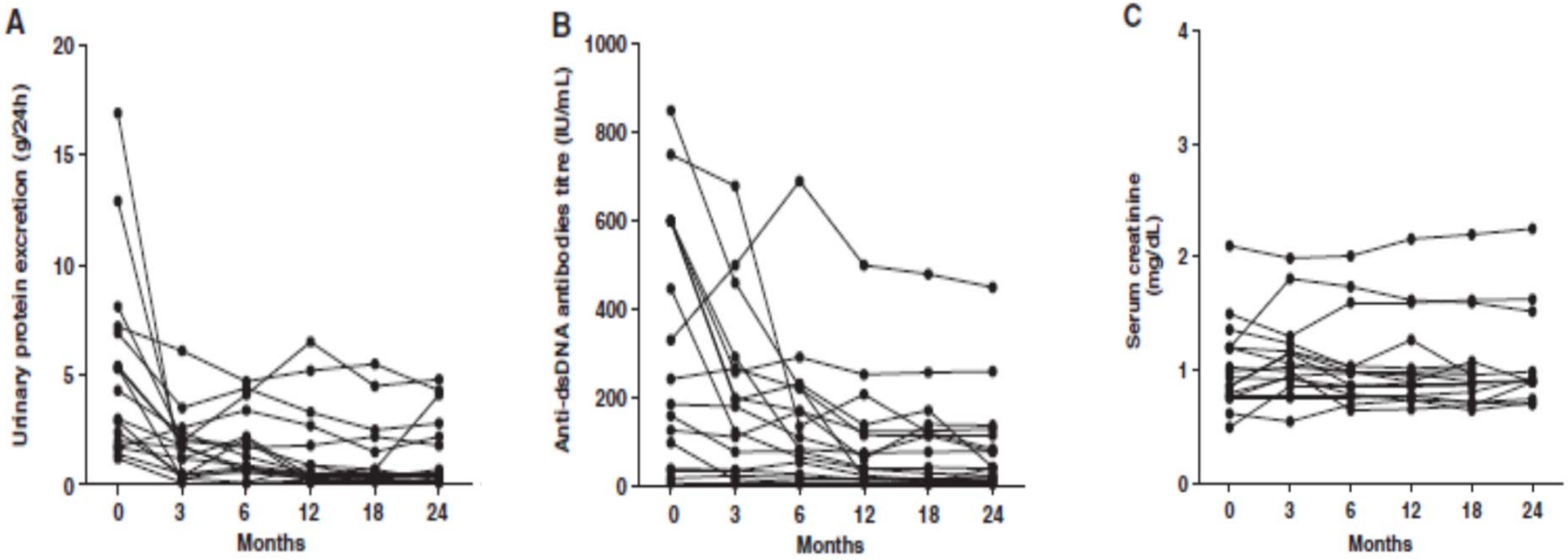

29% υποτροπή

Nephrol Dial Transplant (2010) 25: 3939–3948

CNIs ΣΤΗΝ ΑΝΘΕΚΤΙΚΗ LN

✓ Ο **συνδυασμός των CNIs με το MMF**
αποτελεί **επιλογή** στην ανθεκτική LN

✓ Απαιτούνται περισσότερες μελέτες με μεγαλύτερη διάρκεια για να επιβεβαιωθεί η αποτελεσματικότητα και η ασφάλειά τους

ΠΕΡΙΕΧΟΜΕΝΑ

Tacrolimus is an effective treatment for lupus nephritis in pregnancy

P Webster[1], A Wardle[1], K Bramham[2], L Webster[2], C Nelson-Piercy[2] and L Lightstone[1]
[1]Imperial College Healthcare NHS Trust Lupus Centre, Hammersmith Hospital, London, UK; and [2]Division of Women's Healthy, Women's Health Academic Centre, King's College London, UK

	Class LN	*Length of disease quiescence prior to pregnancy (months)*	*Stage of CKD entering pregnancy*	*Gestation at flare (wks/40)*	*Urine PCR at flare*	*Treatment at time of flare*	*Gestation Tac started (wks/40)*	*Treatment concurrent with Tac*	*Gestation at Remission*	*Gestation at delivery (wks)*	*Birth Weight (g)/Sex*	*Birth Weight Centile*
1	V	>12	1	No Flare	–	No Flare	Pre-conception	Aza	N/A	39	3460/F	50–75
2	IV-G (A/C)	>12	3	No flare	–	No flare	Pre-conception	Aza	N/A	36	2512/F	25–50
3	IV-G (A/C)	0	2	No flare	–	No flare	Pre-conception	Pred	**CR** 12/12 PP	39	2786/F	9–25
4	IV-G (A/C)	>12	2	18	1514	Aza Pred	18	Aza Pred MPred	**PR** 32/40 **CR** 5/12 PP	37	2476/F	25
5	IV-G (C)	>12	3	8	384	Aza Pred	30	Pred	**PR** 1/12 PP **CR** 8/12 PP	37	2988/M	50
6	IV	>12	3	8	602	Aza HCQ	8	Aza HCQ	**CR** 3/12 PP	30	1130/F	25
7	V	>12	1	10	769	Nil	10	MPred Aza HCQ	**PR** 19/40 **CR** 30/40	38	3320/F	75
8	IV-G (C)	>12	3	8	570	Pred Aza	20	Pred	**PR** 1/12 PP	35	2912/M	75–91
9	V	New diagnosis in pregnancy	No CKD	12	1116	Pred Aza HCQ	21	Pred HCQ	**PR** 6/12 PP **CR** 12/12 PP	33	1400/M	2–9

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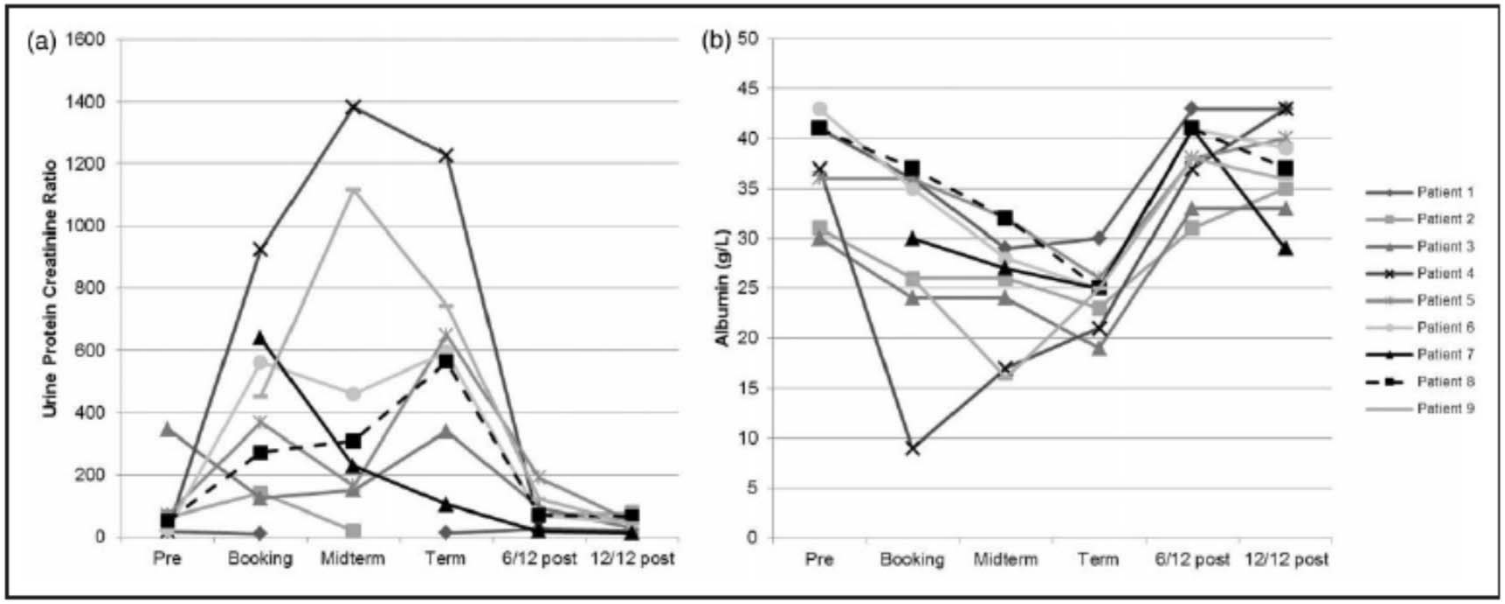

Lupus (2014) 23, 1192–1196

ΠΕΡΙΕΧΟΜΕΝΑ

ΣΥΜΠΕΡΑΣΜΑΤΑ

- ✓ Ως **θεραπεία εφόδου**, οι CNIs είναι αποτελεσματικοί στις τάξεις III-V LN, με **καλύτερα ποσοστά ύφεσης σε σχέση με την iv CYC αλλά ίδια με αυτά του MMF**

- ✓ Ως **θεραπεία εφόδου**, οι CNIs προκαλούν **ταχύτερη μείωση της πρωτεϊνουρίας** και προτιμώνται σε ασθενείς με νεφρωσικό σύνδρομο ή MLN

- ✓ Η **multitarget θεραπεία** είναι αποτελεσματικότερη της IVCYC ως **θεραπεία εφόδου** σε Ασιάτες με **ήπια-μέτρια** σοβαρότητα LN

ΣΥΜΠΕΡΑΣΜΑΤΑ

- ✓ Ως **θεραπεία συντήρησης**, οι CNIs είναι **εξίσου αποτελεσματικοί με AZA και MMF** ως προς τη διατήρηση της ύφεσης της LN και, χορηγούνται σε αυτούς που **δε μπορούν να λάβουν MMF ή AZA** και **στην MLN**

- ✓ Οι CNIs χορηγούνται στην **εγκυμοσύνη**

- ✓ Η **multitarget θεραπεία** αποτελεί μία επιλογή στην **ανθεκτική LN**

- ✓ Οι CNIs έχουν **παρόμοιο προφίλ ασφάλειας** σε σχέση με τα άλλα φάρμακα

ΠΡΟΟΠΤΙΚΕΣ ΓΙΑ ΤΟ ΜΕΛΛΟΝ

- ✓ Μελέτες για αξιολόγηση του μακροπρόθεσμου αποτελέσματος
- ✓ Μελέτες σε πολλές και διαφορετικές φυλές (διαφορετική φαρμακοκινητική)
- ✓ Αξιολόγηση εξωνεφρικών εκδηλώσεων ΣΕΛ
- ✓ Μεγαλύτερες μελέτες

ΚΛΙΝΙΚΗ ΠΕΡΙΠΤΩΣΗ

LN class V and IV-S
with activity index 15 (0-24) and chronicity index 3 (0-12)
and NS

IV-CYC

ΕΥΧΑΡΙΣΤΩ

Prof D.T. Boumpas

Dr G. Bertsias

Dr P. Verginis

Dr M. Zavros