Supplemental Online Content

Zheng Z, Zhang H, Peng X, et al. Effect of tacrolimus vs intravenous cyclophosphamide on complete or partial response in patients with lupus nephritis: a randomized clinical trial. *JAMA Netw Open.* 2022;5(3):e224492. doi:10.1001/jamanetworkopen.2022.4492

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Study Exclusion Criteria

Class II or VI LN or with TMA
Treatment with immunosuppressants (e.g. MMF, ciclosporin, methotrexate, mechlorethamine, chlorambucil, tripterygium preparations, leflunomide) for >1 week within 30 days prior to enrollment
Treatment with tacrolimus (except for topical use) or cyclophosphamide treatment within 30 days prior to enrollment
Methylprednisolone pulse therapy or gamma globulin treatment or plasma exchange within 30 days prior to enrollment
History of allergy to tacrolimus, cyclophosphamide or methylprednisolone
Estimated maintenance dialysis >8 weeks or dialysis for >2 weeks prior to study entry
Previous or planned kidney transplantation
SCr ≥260 μmol/L (or ≥3 mg/dL)
Liver dysfunction (AST or ALT ≥3 x ULN) or bilirubin ≥3 x ULN
Diabetes
History of gastrointestinal bleeding or pancreatitis within 3 months
Uncontrollable hyperkalemia after dietary therapy or reduction of potassium treatment (>ULN)
Lupus pneumonia or lung injury
Anemia (hemoglobin <7 g/dL) or bone marrow suppression (WBC <3.0 x 10^9/L, and/or neutrophils <1.5 x 10^9/L, and/or platelets <50 x 10^9/L) not secondary to SLE
Congenital heart disease, arrhythmia, heart failure and other serious cardiovascular diseases
Refractory hypertension (defined as blood pressure >180/110 mmHg while taking three different types of antihypertensive drugs [including a diuretic])
Recurrent tumours within 5 years
Severe infection requiring intravenous antibiotics within 2 weeks prior to randomization
Active tuberculosis, hepatitis B or hepatitis C virus infection, or severe immunodeficiency diseases (including active CMV [positive CMV IgM antibody], or HIV infection)
Lupus encephalopathy or other life-threatening complications of SLE
Participation in any other clinical trials within 3 months before enrollment
Pregnant, lactating, or unwilling to take contraceptive measures
Any other patient considered not suitable to participate in this study by the investigator

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; HIV, human immunodeficiency virus; LN, lupus nephritis; MMF, mycophenolate mofetil; SCr, serum creatinine; SLE, systemic lupus erythematosus; TMA, thrombotic microangiopathy; ULN, upper limit of normal; WBC, white blood cell.

eTable 2. Sensitivity and Subgroup Analyses of the Primary Efficacy End Point

Sensitivity analyses of response rate carried out by Cochran-Mantel-Haensel test:
FAS LOCF
PPS, completed week 24 response assessment
FAS, completed week 24 response assessment
PPS, based on derived response from laboratory test data, LOCF
FAS, based on derived response from laboratory test data, LOCF
Subgroup analyses performed to assess primary endpoint by:
Sex
BSA (<median at baseline, ≥median at baseline)
Pathological type (III, IV, V, III+V, IV+V)
Duration of LN (≤6 months, >6 months)
SLEDAI score (≥10, <10)
SLEDAI score (≥4, <4)

BSA, body surface area; FAS, full analysis set; LN, lupus nephritis; LOCF, last observation carried forward; PPS, per-protocol set; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

eTable 3. Study Drug Compliance and Exposure in the Safety Population

Parameter	Treatment group, mean±SD	
	Tacrolimus (n=157)	**IVCY (n=142)**
Study drug		
Dosing compliance, %	98.8±4.7	98.6±4.6
Duration, days	159.6±33.6	153.5±40.8
Total dose	774.8±287.2 mg	5.6±1.8 g
Dose	4.8±1.4 mg/day	0.64±0.10 g/m^2/4 weeks
Overall average blood concentration	5.3±2.0 ng/mL	–
Prednisone		
Duration, days	160.3±33.7	152.5±45.4
Total dose, mg	3915.2±755.2	3755.7±1074.5
Daily dose, mg	25.4±5.1	26.4±6.1
Methylprednisolone		
Duration, days	3.4±2.9	5.0±12.2
Total dose, g	1.6±1.2	1.5±0.1

IVCY, intravenous cyclophosphamide; SD, standard deviation

eTable 4. Results of Sensitivity Analyses of Response Rate at Week 24

Parameter	Treatment group, n (%)		% difference (95% CI) tacrolimus–IVCY
	Tacrolimus	IVCY	
FAS, LOCF			
n	157	142	
Complete response	72 (45.9)	47 (33.1)	
Partial response	50 (31.8)	48 (33.8)	
Response rate	122 (77.7)	95 (66.9)	10.7 (0.5, 20.6)
PPS, completed week 24 response assessment			
n	141	124	
Complete response	70 (49.6)	45 (36.3)	
Partial response	47 (33.3)	45 (36.3)	
Response rate	117 (83.0)	90 (72.6)	9.6 (−0.5, 19.5)
FAS, completed week 24 response assessment			
n	157	142	
Complete response	72 (45.9)	47 (33.1)	
Partial response	48 (30.6)	45 (31.7)	
Response rate	120 (76.4)	92 (64.8)	11.5 (1.2, 21.6)
PPS, based on derived response from laboratory test data, LOCF			
n	141	124	
Complete response	69 (48.9)	46 (37.1)	
Partial response	47 (33.3)	48 (38.7)	
Response rate	116 (82.3)	94 (75.8)	5.6 (−4.2, 15.4)
FAS, based on derived response from laboratory test data, LOCF			
n	157	142	
Complete response	71 (45.2)	48 (33.8)	
Partial response	50 (31.8)	50 (35.2)	
Response rate	121 (77.1)	98 (69.0)	7.9 (−2.1, 17.8)

CI, confidence interval; FAS, full analysis set; IVCY, intravenous cyclophosphamide; LN, lupus nephritis; LOCF, last observation carried forward; PPS, per-protocol set

eTable 5. Subgroup Analyses: Response Rate by Different Pathological Types of LN at Week 24 (PPS; LOCF).

Pathological type	Treatment group, n (%)		% difference (95% CI) tacrolimus–IVCY
	Tacrolimus (n=141)	IVCY (n=124)	
Type III			
Complete response	5/8 (62.5)	3/7 (42.9)	
Partial response	3/8 (37.5)	3/7 (42.9)	
Response rate	8/8 (100.0)	6/7 (85.7)	–
Type IV			
Complete response	36/59 (61.0)	22/48 (45.8)	
Partial response	18/59 (30.5)	18/48 (37.5)	
Response rate	54/59 (91.5)	40/48 (83.3)	8.2 (−4.5, 22.0)
Type V			
Complete response	7/19 (36.8)	3/18 (16.7)	
Partial response	6/19 (31.6)	5/18 (27.8)	
Response rate	13/19 (68.4)	8/18 (44.4)	24.0 (−7.3, 49.6)
Type III+V			
Complete response	1/14 (7.1)	4/15 (26.7)	
Partial response	9/14 (64.3)	4/15 (26.7)	
Response rate	10/14 (71.4)	8/15 (53.3)	18.1 (−15.9, 46.8)
Type IV+V			
Complete response	21/41 (51.2)	13/36 (36.1)	
Partial response	11/41 (26.8)	18/36 (50.0)	
Response rate	32/41 (78.0)	31/36 (86.1)	−8.1 (−24.8, 9.7)

IVCY, intravenous cyclophosphamide; LN, lupus nephritis; LOCF, last observation carried forward; PPS, per-protocol set.

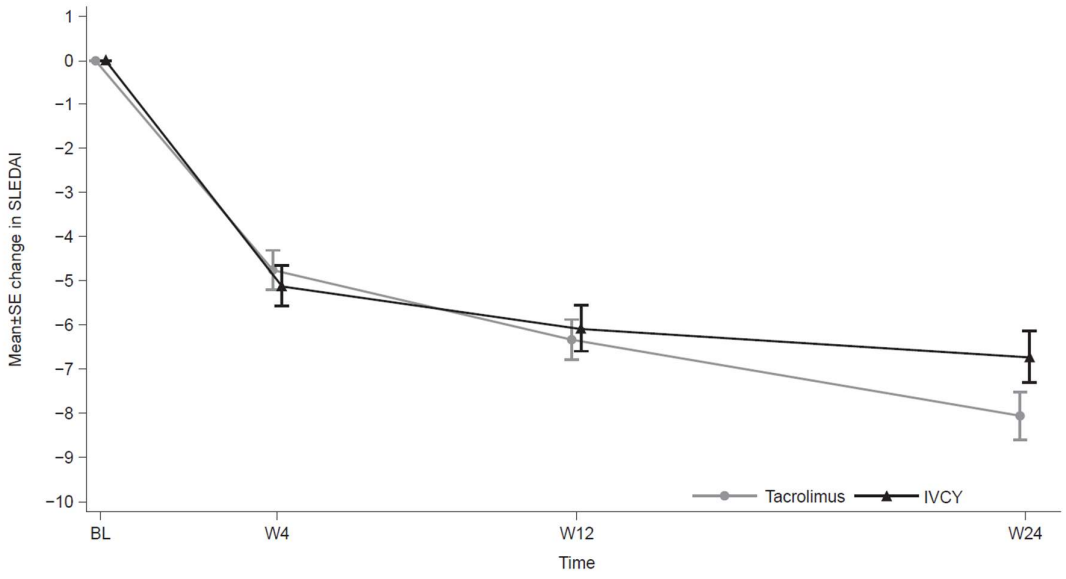
eTable 6. Mean SCr Level and Mean Change from Baseline to Week 24 (PPS)

Time point	Treatment group, mean±SD			
	Tacrolimus (n=141)		IVCY (n=124)	
	SCr, μmol/L	Change from baseline	SCr, μmol/L	Change from baseline
Baseline	74.1±38.59	–	69.8±34.90	–
Week 1	78.1± 52.78	4.0±34.06	68.1±29.23	−1.4±21.63
Week 2	77.2±51.57	3.2±34.90	66.2±24.27	−3.6±23.34
Week 4	76.8±49.13	2.8±35.06	64.5±21.49	−5.2±25.99
Week 8	78.1±47.88	4.0±35.61	63.9±21.99	−5.9±29.06
Week 12	78.0±48.95	4.0±38.35	65.0±23.85	−4.7±28.95
Week 16	79.3±49.22	5.3±38.44	64.5±20.47	−5.2±28.38
Week 20	83.5±58.61	9.5±47.81	65.3±22.05	−4.4±26.36
Week 24	82.9±57.89	8.8±48.54	64.3±20.67	−5.4±26.56

IVCY, intravenous cyclophosphamide; PPS, per-protocol set; SCr, serum creatinine; SD, standard deviation

eFigure 1. Mean (SE) Change from Baseline to Week 24 in SLEDAI Score (PPS)

IVCY, intravenous cyclophosphamide; PPS, per-protocol set; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SE, standard error.

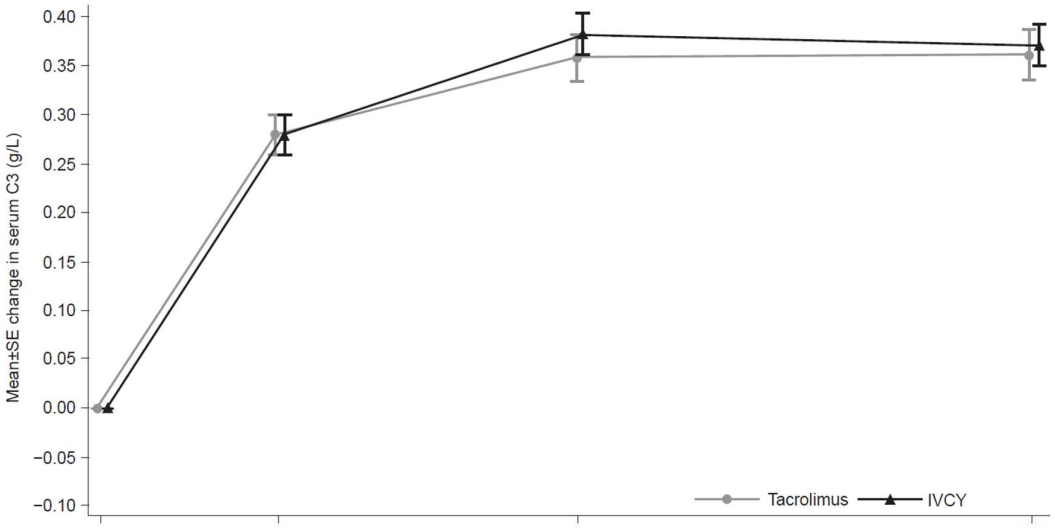


Tacrolimus, n:	139	135	136	133
IVCY, n:	122	119	121	119

eFigure 2. Mean (SE) Change from Baseline to Week 24 in Serum C3 and Serum C4

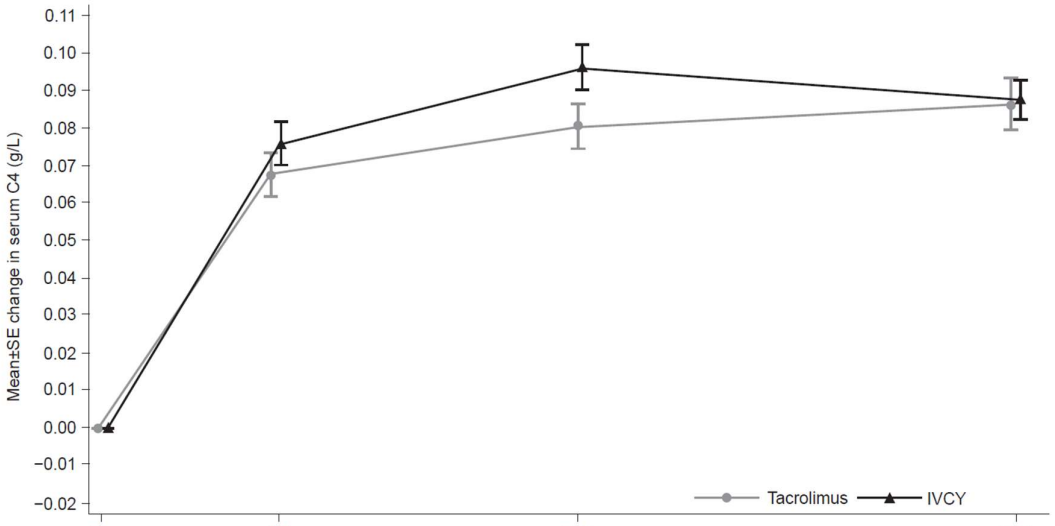
C3, complement C3; C4, complement C4; IVCY, intravenous cyclophosphamide; PPS, per-protocol set; SE, standard error.

(A) Serum C3



Tacrolimus, n:	141	140	140	140
IVCY, n:	124	124	124	124

(B) Serum C4



Tacrolimus, n:	139	136	138	138
IVCY, n:	124	124	124	124