膠原病 Journal Club　　2021/7/7　住友

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial

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[Lancet. 2021;397(10289):2070-80.]

背景

- ループス腎炎の標準治療ではcomplete renal response rate（U-pro<0.5g/gCr, eGFR>60, rescue therapy-, PSL<10mgなど）は高くない.
- 主に寛解導入早期のHigh-dose steroidに伴う副作用が多い.
- Multitarget(MMF 1000mg+ Tac 4mg: 中国) ではIVCYより高い寛解率を認めた.
- 新規CNI VoclosporinのPhase 2 (AURA-LV) [背景治療: MMF/低用量PSL]ではPlaceboより高いCRRを認めた(n=88/88/89). 27.9mg bidが24w・48wとも高いCRRを認めたため, Phase 3の濃度として選択された.

2019 Update of EULAR/ERA-EDTA Management Recommendation

Recommendation 4：成人LNの治療

寛解導入

4.3. Class III/IVの増殖性病変(±V)ではMMF(2-3g or 同等MPA) (1a/A: ALMS 2009 A&R)か,
low-dose IVCY (500mg/2w, total 6回)(1a/A: EuroLupus 2016 ARD)をステロイド併用しつつ投与する.

4.4. MMF(1-2g)とCNI（特にTac）の併用 (Multitarget: 2015 Ann Intern Med) は選択肢になる.
特にnephrotic rangeの蛋白尿例の場合 (1a/B)

4.5. 腎不全のリスクが高い患者（GFR低下, 半月体形成, fibrinoid necrosis+, 重度の間質炎症）
(2b/B)では4.3-4.の他にhigh-dose IVCY (0.5-0.75g/m^2/月 *6)も考えられる(1a/B)

4.6. 累積ステロイド量を減らすために, mPSL pulse(500-2500mg)後のPSL (0.3-0.5mg/kg)は
4wまで，3-6か月で7.5mg以下にすることが推奨される(2b/C)

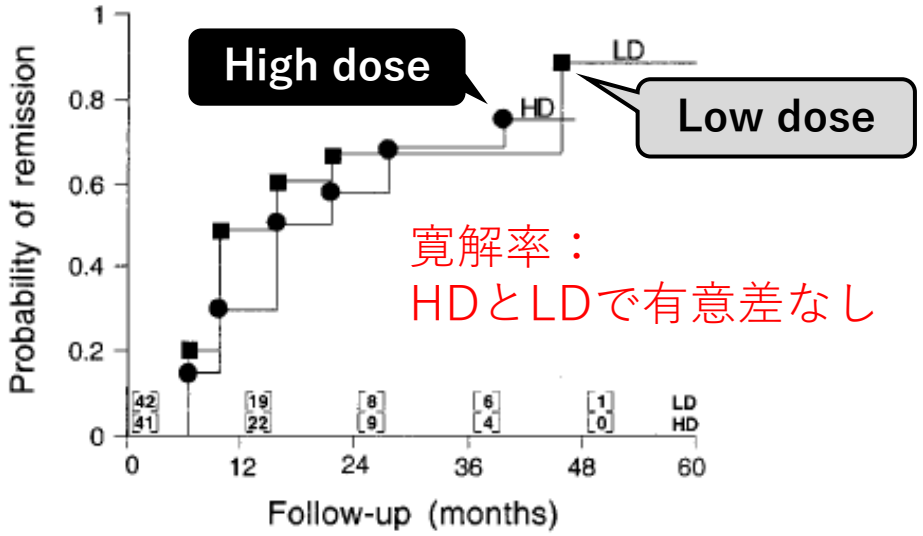
寛解導入
Low vs Hi IVCY

Euro-Lupus (2002)

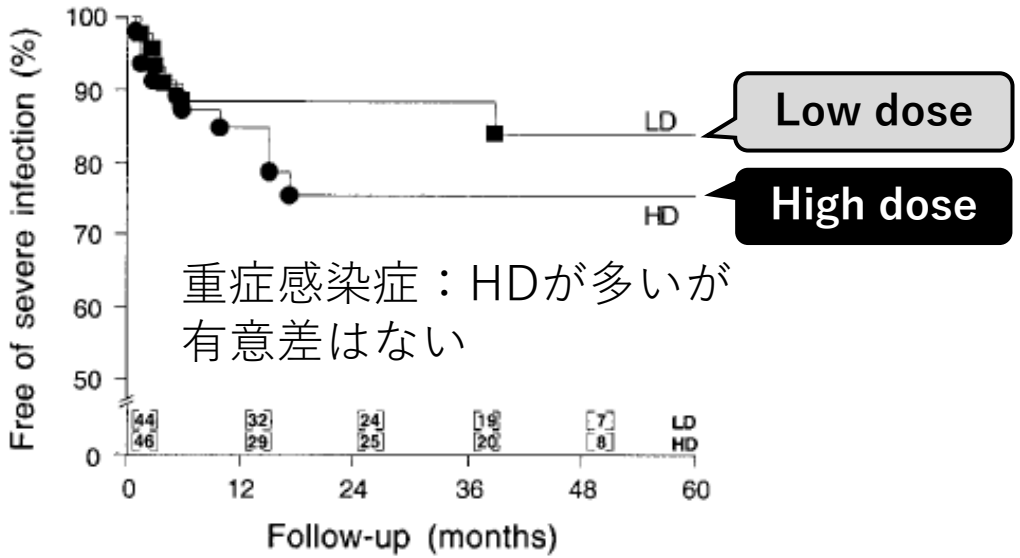
[Arthritis Rheum. 2002;46(8):2121-31.]

Immunosuppressive Therapy in Lupus Nephritis

The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide



寛解率：
HDとLDで有意差なし



重症感染症：HDが多いが
有意差はない

- Open-label, multicenter, 治療6M/合計1年間観察RCT
- 90人増殖型LN (III, IV, Vc, Vd)をmPSL 750mgパルス後, PSL 0.5mg/kg4週投与→漸減.
- High-dose CY(46人): IVCY q1M*6回+q3M*2回; 計8回. 初期量0.5mg/m^2, nadirみて250mgずつ増量 (max 1.5g)
- Low-dose CY(44人): 500mg q2w*6回; 累計3g
- 平均40か月観察, 両群ともIVCY後AZA(2mg/kg)で維持.
- High-dose CY: 20%治療failure, 54%寛解, 27%腎再燃
  Low-dose CY: 16%治療failure, 71%寛解, 29%腎再燃.
  いずれも有意差なし.
- 両群とも1年間でCr/C3/U-pro/DAS改善した
- 重症感染症はHigh doseはLow doseの2倍 (有意差-)
- 結論: Low dose IVCYはHigh dose IVCYに劣らない

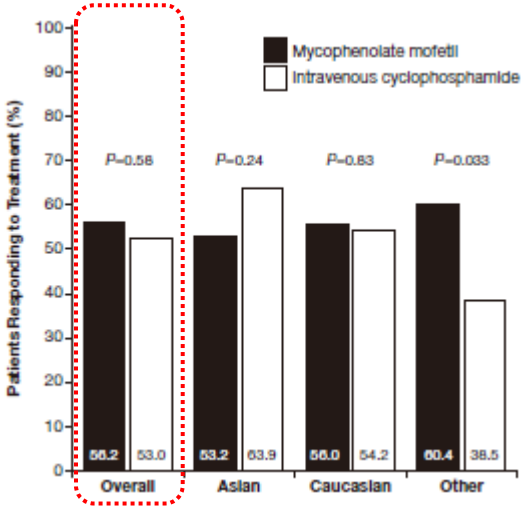
寛解導入
MMF vs IVCY

ALMS (2009)

[J Am Soc Nephrol. 2009;20(5):1103-12.]

Mycophenolate Mofetil *versus* Cyclophosphamide for Induction Treatment of Lupus Nephritis

Gerald B. Appel,* Gabriel Contreras,† Mary Anne Dooley,‡ Ellen M. Ginzler,§ David Isenberg,‖ David Jayne,¶ Lei-Shi Li,** Eduardo Mysler,†† Jorge Sánchez-Guerrero,‡‡ Neil Solomons,§§ David Wofsy,‖ and the Aspreva Lupus Management Study Group



MMFとIVCYの寛解導入の反応性に有意差はない
人種差もない

Parameter	MMF (n = 185)	IVC (n = 185)	Odds Ratio (95% CI)
Responders with renal biopsy class III or IV	88 (56.4)[b]	83 (53.9)[c]	1.1 (0.7 to 1.8)
Patients with renal biopsy class V	16 (55.2)[d]	15 (48.4)[e]	
Renal remission criterion met			Treatment difference (% [95% CI])
serum creatinine	130 (70.3)	125 (67.6)	2.7 (−6.7 to 12.1)
urine protein	44 (23.8)	50 (27.0)	−3.2 (−12.1 to 5.6)
urine sediment	58 (31.4)	44 (23.8)	7.6 (−1.5 to 16.6)
all three criteria	16 (8.6)	15 (8.1)	0.5 (−5.1 to 6.2)
Renal and extrarenal remission			
complete absence of BILAG As and Bs	54 (29.7)[f]	45 (24.9)[g]	4.8 (4.3 to 14.0)
SELENA-SLEDAI			Difference between means (95% CI)
change in score from baseline to end point (mean ± SD)	−6.2 ± 10.1[h]	−6.6 ± 8.0[i]	0.41 (−1.48 to 2.30)
Anti-dsDNA			
patients with dsDNA >60 IU/ml at baseline[j]	117 (67.2)[k]	124 (72.5)[l]	
patients with dsDNA >60 IU/ml at end point	72 (41.4)[k]	91 (53.2)[l]	
C3			
patients with low C3 at baseline[m]	125 (71.0)[n]	139 (79.9)[k]	
patients with low C3 at end point[m]	70 (39.8)[n]	90 (51.7)[k]	
C4			
patients with low C4 at baseline[o]	104 (59.1)[n]	125 (72.3)[p]	
patients with low C4 at end point[o]	51 (29.0)[n]	72 (41.6)[p]	

Class3/4の反応性，尿蛋白，SLEDAI，dsDNA-Ab，補体なども差がない

- Open-label, multicenter, RCT (24M観察)
- 活動性LN 370人(WHO IIIorIII＋V, IVorIV＋V, V): MMF (target dose 3g), IVCY (0.5-1.0 g/m2/月) を6か月の寛解加療．両者ともPSL 60mg max後漸減.
- 1次endpoint: 尿蛋白減少とCr改善
- 2次endpoint: CR, SLEDAI/Damage index
- MMF群(185人): Response rate 56.2%
  IVCY群(185人): Response rate 53.0%
  →有意差なし．2次endpointも有意差なし
- 有害事象: MMFで9人・IVCYで5人死亡．有害事象に有意差なし.
- 結論: MMFとIVCYの寛解導入に有意差を認めず
  （当初の想定はMMF>IVCYだった [NEJM 2005;353:2219-28.など小規模の既報から])

寛解導入
MT vs IVCY

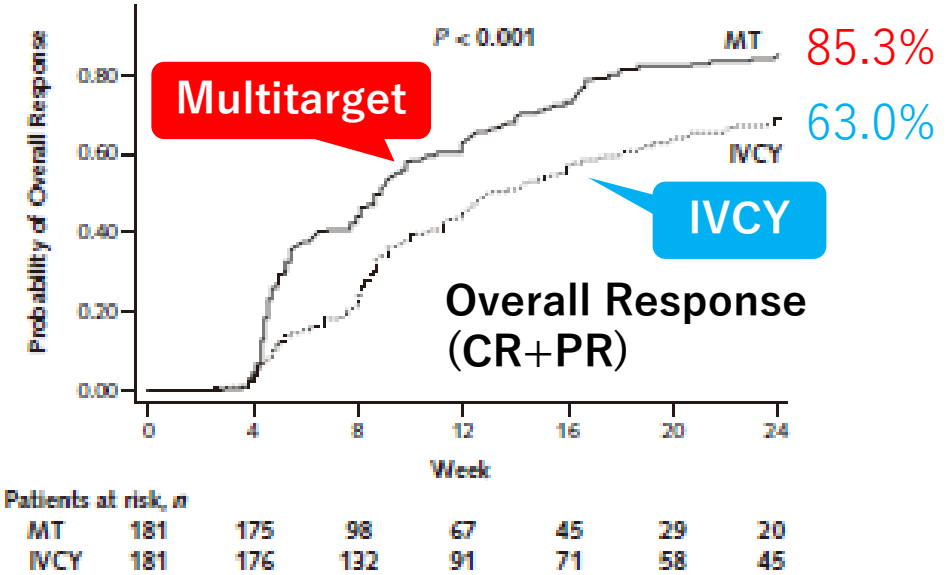
Multitarget (2015)

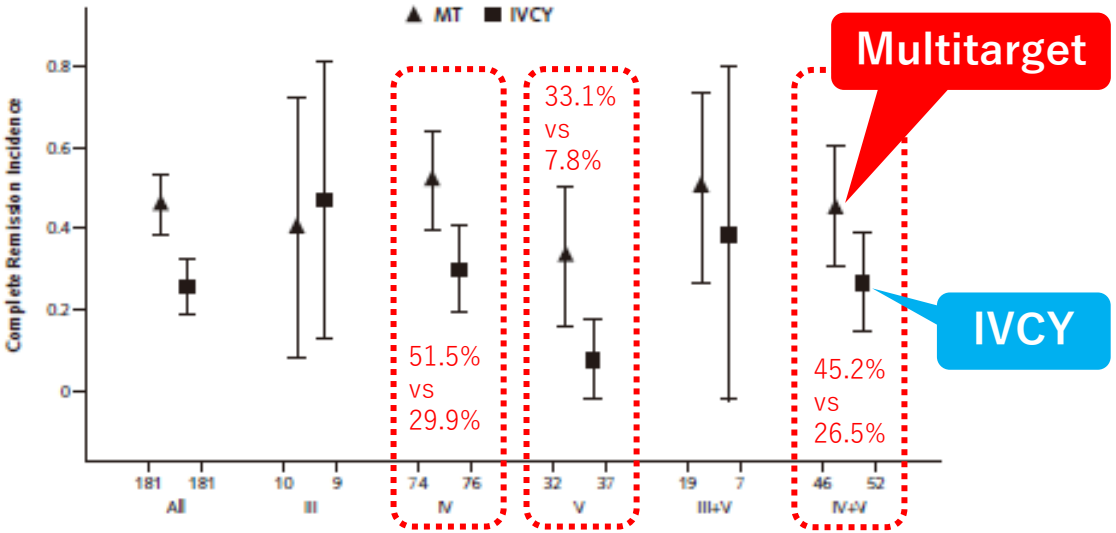
[Ann Intern Med. 2015;162:18.]

Multitarget Therapy for Induction Treatment of Lupus Nephritis

A Randomized 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





組織型ごとの寛解率

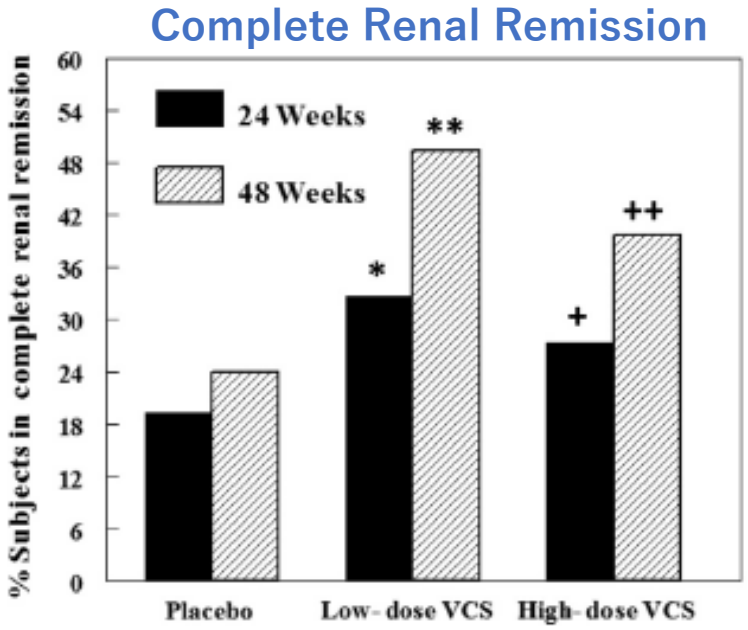
- Open-label, multicenter, 24w RCT
- 新規発症生検済LN (ACR-SLE) 中国人368人. ClassIII 19/IV 150/V 69/III+V 26/IV+V 98人. U-Pro>1.5g かつCr <3mg/dLを組入, Chronicity index>3除外.
- Multitarget(MT)群(181人) : MMF 1000mg+TAC 4mg
- IVCY群(181人): IVCY 750mg/m^2/4w*6
- 両群ともmPSL pulse+ PSL 0.6mg/kg・4w→20mg(-5g/2w)→10mg(-2.5mg/2w)
- 1次endpoint: CR率 (U-pro<0.4g/24h, 沈査-, Alb>3.5, Cr正常).
- 結果: 24wCR率はMTが高い (MT 45.9% vs IVCY 25.6%, p<0.001) . 副作用同等. 組織型ではIV/V/IV+VでMTがCR率高い
- MTはIVCYよりC3とSLEDAIも有意に改善.
- なぜMT?→移植時IVCY/MMF単独のCR率低く拒絶反応治療で多剤使用する援用. CNIがpodocyteのアクチンに保護的に作用(Tだけでなく)[Nat Med. 2008;14:931-8]

寛解導入
Voclosporin

AURA-LV (2019)

[Kidney Int. 2019;95(1):219-231.]

A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis



Forced Corticosteroid Taper

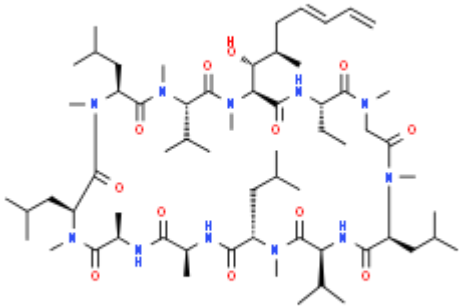
Week	Prednisone (mg/d)
0-2	20-25
2	15-20
4	10-15
6	10
8	5
16-on	2.5

Table 2| Overall summary of adverse events (safety set, *N* = 265)

Distribution across categories of AE	Placebo (*N* = 88) *n* (%)	Voclosporin 23.7 mg BID (*N* = 89) *n* (%)	Voclosporin 39.5 mg BID (*N* = 88) *n* (%)
Any AE	75 (85.2)	82 (92.1)	85 (96.6)
Any serious AE	14 (15.9)	25 (28.1)	22 (25.0)
Any treatment-related AE	15 (17.0)	45 (50.6)	55 (62.5)
Any serious treatment-related AE	1 (1.1)	4 (4.5)	7 (8.0)
Any AE leading to study drug discontinuation	9 (10.2)	16 (18.0)	14 (15.9)
Any AE with outcome of death	1 (1.1)	10 (11.2)	2 (2.3)

- Phase 2, 二重盲検RCT, multicenter (20ヵ国79施設)
- Placeboと2 dose Voclosporin (23.7mg bid or 39.5mg bid)を投与し安全性と有効性をみる (背景治療はMMF 2g/d+ 低容量GC).
- 活動性LN 265人が対象.
- 1次endpoint: 24w complete renal remission (CRR)
- 2次endpoint: 48w CRR
- Low-dose Voclosporin群 (89人): 24w CRR 32.6%
  High-dose Voclosporin群 (88人): 24w CRR 27.3%
  Placebo (88人): 24w CRR 19.7%
  → OR 2.03 (Low-dose vs Placebo)
- 48wでもLow-dose VCSのCRRは持続し, High-dose VCSはPlaceboより有意にCRRが高かった.
- 有害事象: Low-dose VCSで死亡が多い (Low 11.2%, High 2.3%, Placebo 1.1%). ある地域と治療早期に集中する.
- 結論: 急性期LNの寛解導入としてのVoclosporinのMMF+GCへの追加は腎反応性に有用. 死亡を含む有害事象は多かった.

Voclosporinとは？



- 新規カルシニュリン阻害薬 (CNI)
- Lupkynis (Aurinia Pharmaceuticals/大塚)
- 2021/1 FDA認可

- Traditional CNI (CyA, Tac) と比較した利点
  1. 薬物動態が安定しており血中濃度モニタリングが不要
  2. 脂質や血糖に与える影響が少ない
  3. Mycophenolic acidの濃度に影響を与えない.

試験デザイン

- Phase III, 二重盲検ランダム化プラセボ比較試験 (27か国147病院)

P：SLE (ACR基準), スクリーニングの2年以内に腎生検したループス腎炎

* class Ⅲ, Ⅳ, Ⅴ [単独or Ⅲ/Ⅳと並存].
* 腎炎活動性: 尿蛋白UPCR >1.5mg/mg, pure class Ⅴでは≧2mg/mg. スクリーニング6ヶ月以上前に腎生検した患者は, スクリーニング6ヶ月前と比較し尿蛋白2倍以上.
* eGFR<45 mL/min/1.73m^{2}は除外.

I：Voclosporin (23.7mg bid) , 52週間. PSL急速減量+ MMF (1g bid)併用

C：Placebo, 52週間. PSL急速減量+ MMF (1g bid)併用

O：Primary end point; 52週でのcomplete renal response.

* 尿蛋白Cr比≦ 0.5 mg/mg, eGFR≧ 60 mL/min/1·73 m^2 もしくはbaselineから20%以上の減少がない, レスキューの薬剤投与がない, 44～52週でPSL≦10mgを維持（3連日未満か7日未満）

- 安全性も評価された.
- eGFR 30%以上悪化した場合中止.

Rapidly tapered low-dose steroids

Table S3 Dosing Schedule for IV Methylprednisolone and Daily Oral Prednisone

	Patients <45 kg	Patients ≥45 kg
Weeks 1-2*		
Days 1-2†	0·25 g (IV)	0·5 g (IV)
Days 3-13	20 mg (oral)	25 mg (oral)
Week 2 (Day 14)	15 mg (oral)	20 mg (oral)
Week 4 (Day 28)	10 mg (oral)	15 mg (oral)
Week 6 (Day 42)	10 mg (oral)	10 mg (oral)
Week 8 (Day 56)	5 mg (oral)	5 mg (oral)
Week 12 (Day 84)	5 mg (oral)	5 mg (oral)
Week 16 (Day 112)	2·5 mg (oral)	2·5 mg (oral)

- Day 1-2: 250 or 500mg IV mPSL
- Day 3から20/25mg PSL
- 減量はAURA-LVと同じ

Forced Corticosteroid Taper

Week	Prednisone (mg/d)
0-2	20-25
2	15-20
4	10-15
6	10
8	5
16-on	2.5

AURA-LVのprotocol

患者背景

	Voclosporin group (n=179)	Placebo group (n=178)
Median age, years	31 (18–62)	32 (18–72)
Sex		
Male	18 (10%)	26 (15%)
Female	161 (90%)	152 (85%)
Mean weight, kg	66·49 (17·07)	66·55 (16·11)
Race*		
White	68 (38%)	61 (34%)
Black	26 (15%)	19 (11%)
Asian	53 (30%)	56 (31%)
Other†	32 (18%)	42 (24%)
Ethnicity*		
Hispanic or Latino	57 (32%)	59 (33%)
Non-Hispanic or non-Latino	122 (68%)	118 (66%)
Unknown	0	1 (1%)
Region		
North and Latin America	75 (42%)	74 (42%)
Europe and South Africa	52 (29%)	52 (29%)
Asia-Pacific	52 (29%)	52 (29%)
Mean time since initial lupus nephritis diagnosis, years	4·6 (5·1)	4·7 (4·9)
Mean time since systemic lupus erythematosus diagnosis, years	6·6 (6·4)	6·9 (6·1)‡
Biopsy class		
Pure class III	20 (11%)	29 (16%)
Pure class IV	91 (51%)	77 (43%)
Pure class V	25 (14%)	25 (14%)
Class II and V only	0	1 (<1%)
Class III and V only	24 (13%)	20 (11%)
Class IV and V only	19 (11%)	26 (15%)

(Table 1 continues in next column)

	Voclosporin group (n=179)	Placebo group (n=178)
(Continued from previous column)		
Baseline eGFR		
Mean, mL/min per 1·73 m²	92·1 (30·6)	90·4 (29·0)
High (≥60 mL/min per 1·73 m²)	146 (82%)	144 (81%)
Mean baseline UPCR, mg/mg	4·14 (2·71)	3·87 (2·36)
Complement 3		
Mean, mg/dL	81·6 (34·73)	86·9 (36·42)
Low (<90 mg/dL)	105 (59%)	99 (55%)
Complement 4		
Mean, mg/dL	16·6 (11·5)	16·8 (9·7)
Low (<10 mg/dL)	50 (28%)	45 (25%)
Anti-double-stranded DNA		
Mean, IU/mL	105·2 (127·7)	94·7 (124·4)
High (>10 IU/mL)	133 (74%)	118 (66%)
SELENA-SLEDAI		
n	177	177
Mean	13·2 (6·5)	11·8 (6·1)
MMF use at screening		
Yes	100 (56%)	96 (54%)
No	79 (44%)	82 (46%)

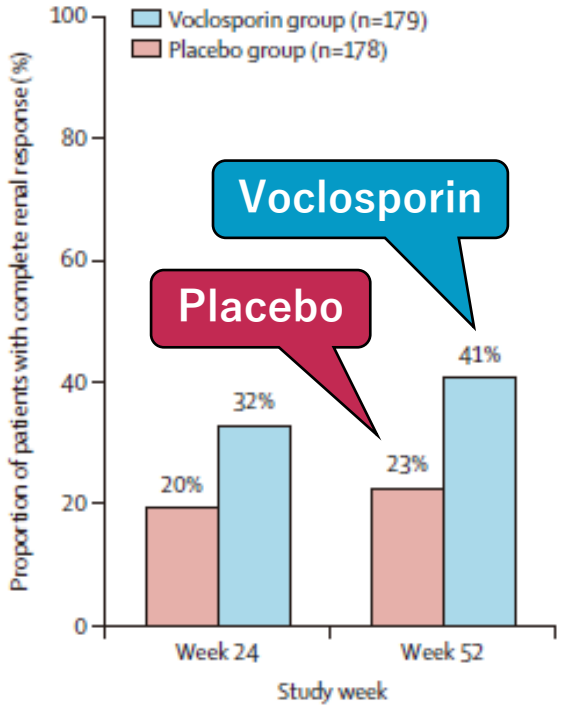
Data are median (range), n (%), or mean (SD), unless stated otherwise. Percentages might not add up to 100% because of rounding. eGFR=estimated glomerular filtration rate. UPCR=urine protein creatinine ratio. SELENA-SLEDAI=Safety of Estrogens in Systemic Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index. MMF=mycophenolate mofetil. *Analyses for race and ethnicity were post hoc. †Other races include American Indian, Alaska Native, Native Hawaiian, Pacific Islander, and other or mixed races except mixed Black race. ‡Data missing for one patient.

Table 1: **Demographic and baseline patient characteristics in the intention-to-treat population**

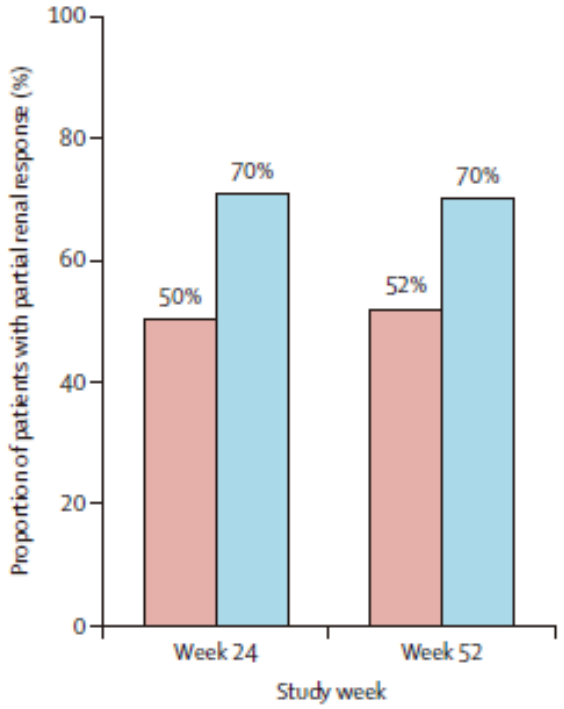
- Voclosporin群に179名, Placebo群に178名が組み入れられた.
- 患者背景：組織型, 治療内容, 地域などは調整して振り分けられている.
- Pure Class III 11/16%, Pure Class IV 51/43%, Pure Class V 14/14%
- Upro: 4.14/3.87 mg/mg
- eGFR: 92.1/90.4
- SELENA-SLEDAI 13.2/11.8
- Screening時55%でMMF使用.

Primary endpointは達成

Complete renal response



Partial renal response



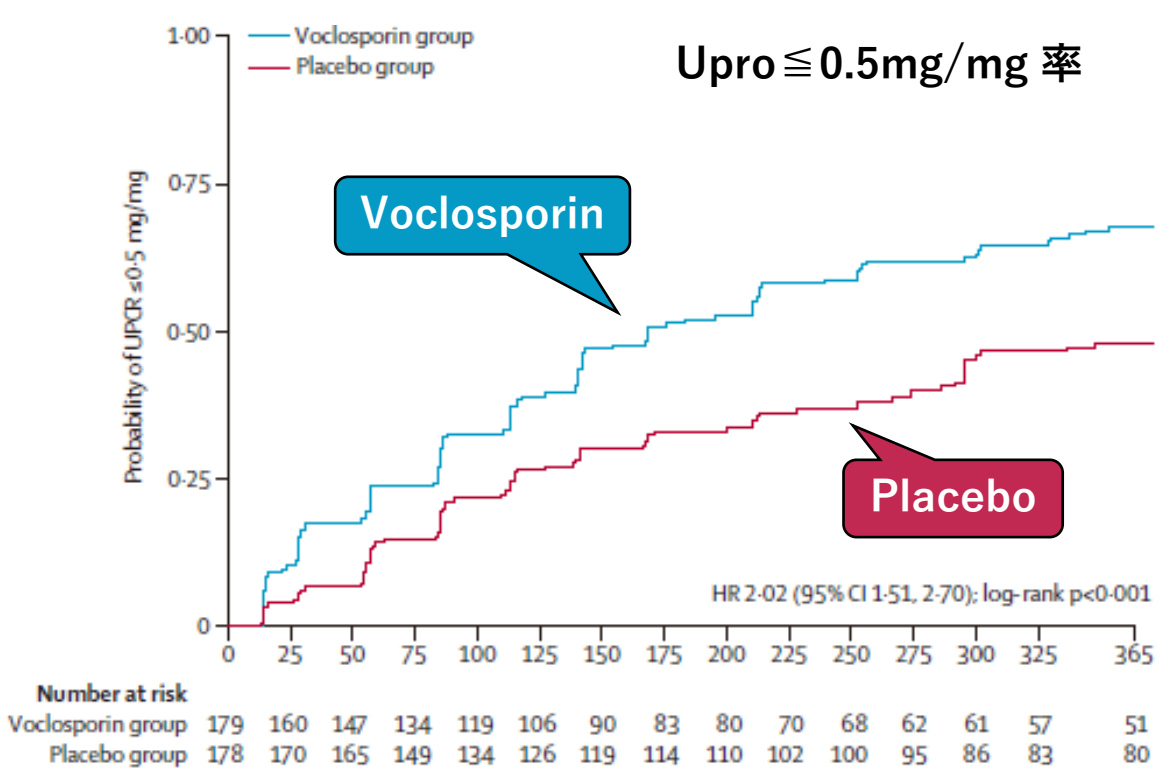
	Voclosporin group (n=179)	Placebo group (n=178)	OR or HR (95% CI)	p value
Primary endpoint*				
Complete renal response at 52 weeks	73 (41%)	40 (23%)	OR 2·65 (1·64–4·27)	<0·0001
Secondary endpoints				
Complete renal response at 24 weeks	58 (32%)	35 (20%)	OR 2·23 (1·34–3·72)	0·002
Partial renal response at 24 weeks	126 (70%)	89 (50%)	OR 2·43 (1·56–3·79)	<0·001
Partial renal response at 52 weeks	125 (70%)	92 (52%)	OR 2·26 (1·45–3·51)	<0·001
Time to UPCR ≤0·5 mg/mg, days	169 (141–214)	372 (295–NC)	HR 2·02 (1·51–2·70)	<0·001
Time to 50% reduction in UPCR, days	29 (29–32)	63 (57–87)	HR 2·05 (1·62–2·60)	<0·001

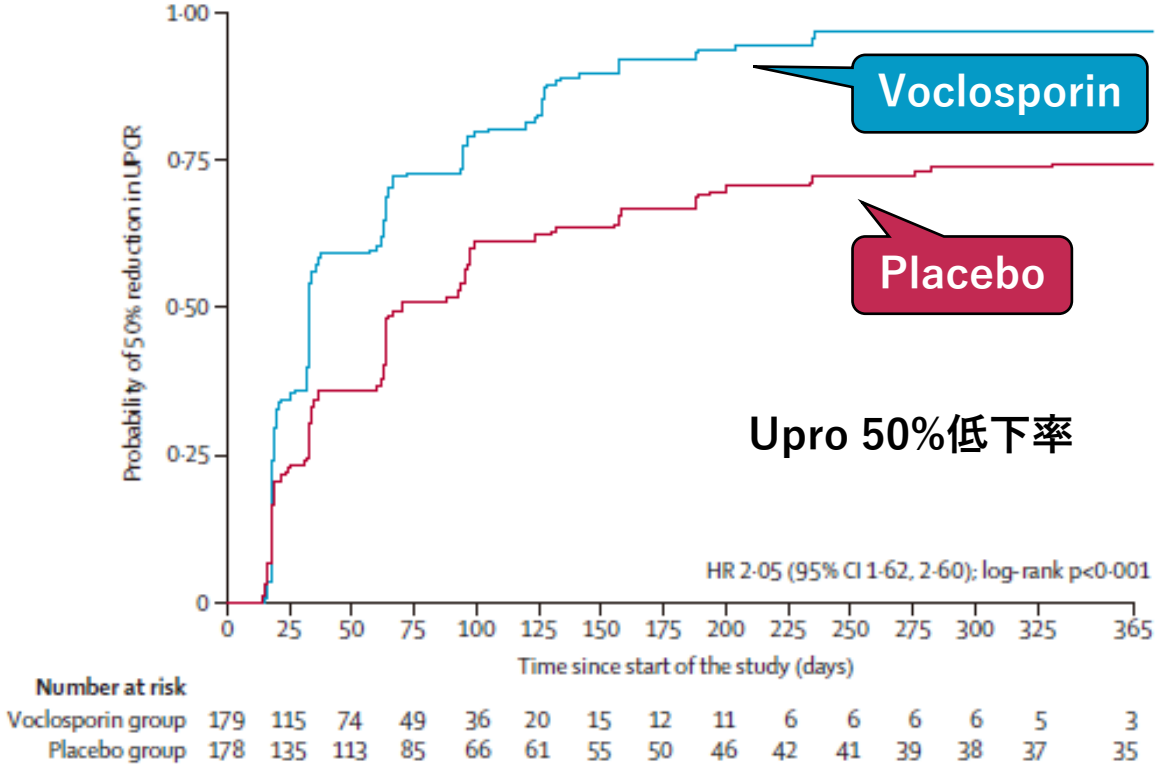
Data are n (%) or median (95% CI), unless otherwise specified. OR=odds ratio. HR=hazard ratio. UPCR=urine protein creatinine ratio. NC=non-calculable. *The model is based on a logistic regression with terms for treatment, baseline UPCR, biopsy class, mycophenolate mofetil use at baseline, and region.

Table 2: **Summary of complete and partial renal responses at weeks 24 and 52 (intention-to-treat population)**

- Secondary endpointもVoclosporin群は達成している.

Time-to event curve





- 両群の差は1か月後から開き始めている(早期治療効果の可能性).

有害事象について

	Voclosporin group (n=178)	Placebo group (n=178)
Adverse event summary		
Adverse event	162 (91%)	158 (89%)
Serious adverse event	37 (21%)	38 (21%)
Serious adverse event of infections and infestations	18 (10%)	20 (11%)
Treatment-related serious adverse event	8 (4%)	8 (4%)
Adverse event leading to study drug discontinuation	20 (11%)	26 (15%)
Death*	1 (<1%)	5 (3%)
Treatment-related adverse event leading to death	0	0

- 重篤な有害事象(SAE)発生率は同じ(Voclosporin 21% vs Placebo 21%).
- 最も頻度の高いSAEは肺炎(Voclosporin 4% vs Placebo 4%).
- 死亡はVoclosporin 1名, Placebo 5名だった.
- 治療関連死の事例はなかった.

本試験の意味

- VoclosporinをMMF+低容量ステロイドと併用する治療は, MMF単剤+低容量ステロイドよりも6カ月/12カ月のCRRが有意に改善する.
- 今回の高いCRRは, 従来の標準治療よりはるかに低容量のステロイドと中等量のMMFで実現している.
- 比較的安全に使用できた (Phase 2における高い死亡率とは大きく異なっていた).
- Activeなループス腎炎の治療に重要な知見をもたらす.