Journal Club 2024/11/26　　by Dr.大村

Impact of Glucocorticoid Dose on Complete Response, Serious Infections, and Mortality During the Initial Therapy of Lupus Nephritis: A Systematic Review and Meta-Analysis of the Control Arms of Randomized Controlled Trials

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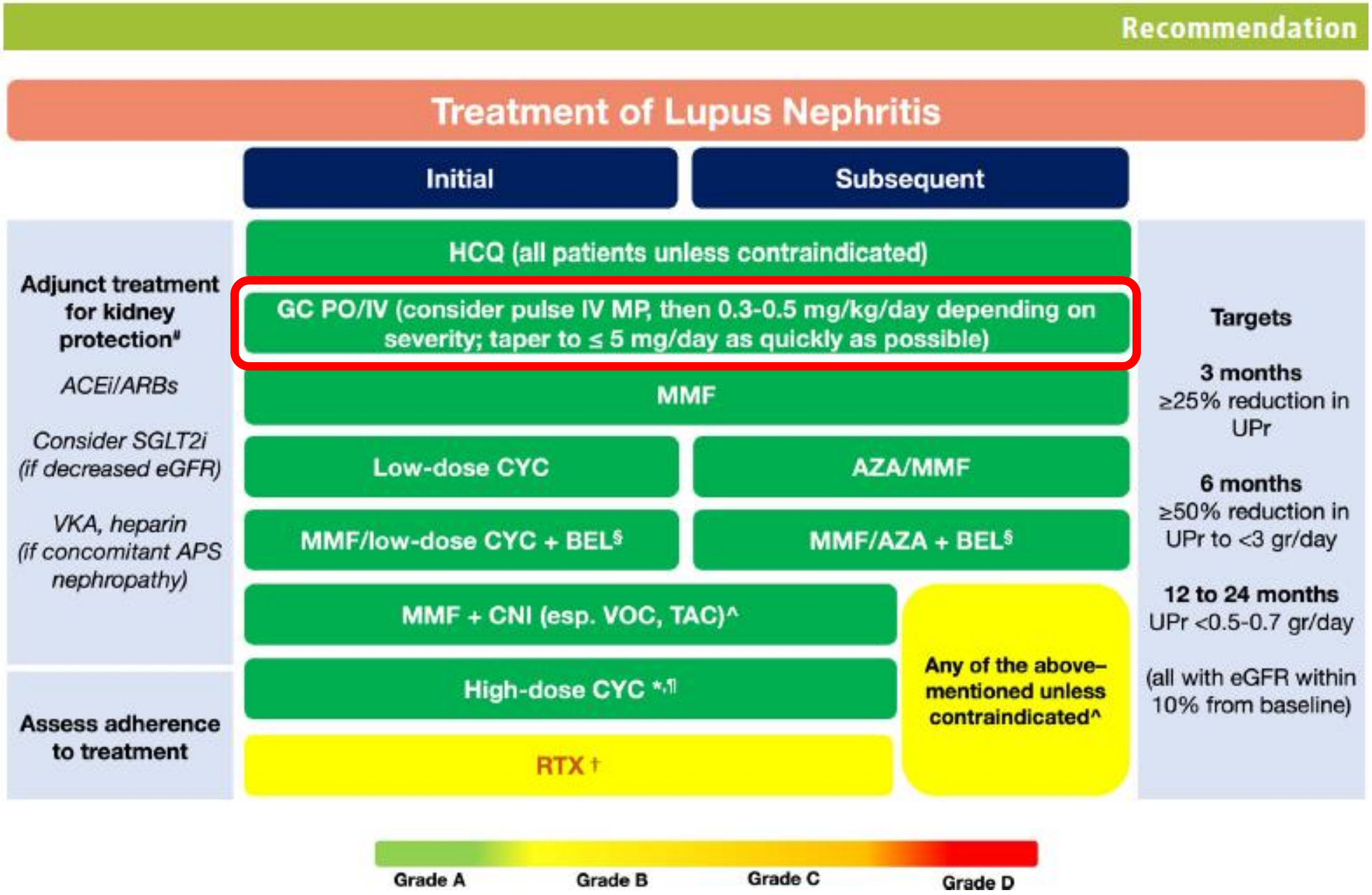
<INTRODUCTION>

LNに対する寛解導入療法に関する推奨

	Eular/ERA-EDTA recommendations 2012	Eular/ERA-EDTA recommendations 2019
Class III/IV	mPSL pulse（計1.5-2.25g） その後PSL 0.5mg/kg/日を4週間 MMF or IVCYを併用 4-6ヶ月以内にPSL 10mg/日以下へ	mPSL pulse（計0.5-2.5g） その後PSL 0.3-0.5mg/kg/日を4週間 MMF or IVCYを併用 3-6ヶ月以内にPSL 7.5mg/日以下へ
Class V	PSL 0.5mg/kg/日 MMF併用	mPSL pulse（計0.5-2.5g） その後PSL 20mg/日 MMF併用（ネフローゼなら＋CNI） 3ヶ月以内にPSL 5mg/日以下へ

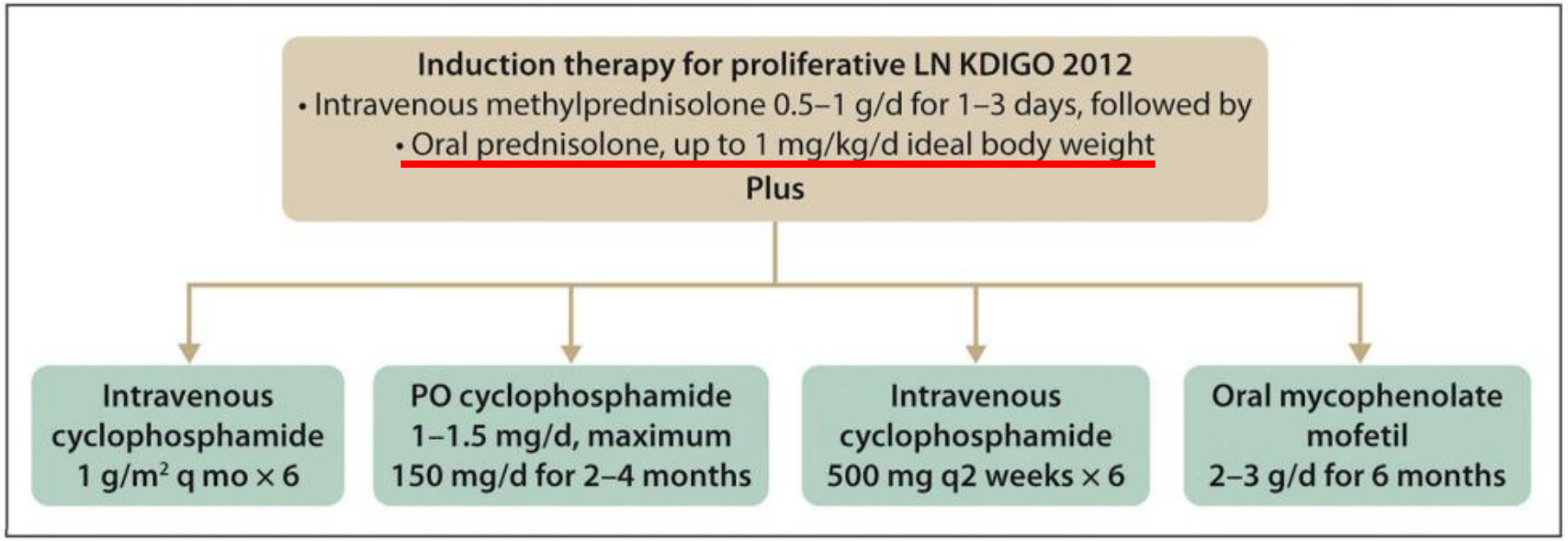
Eular recommendations 2023



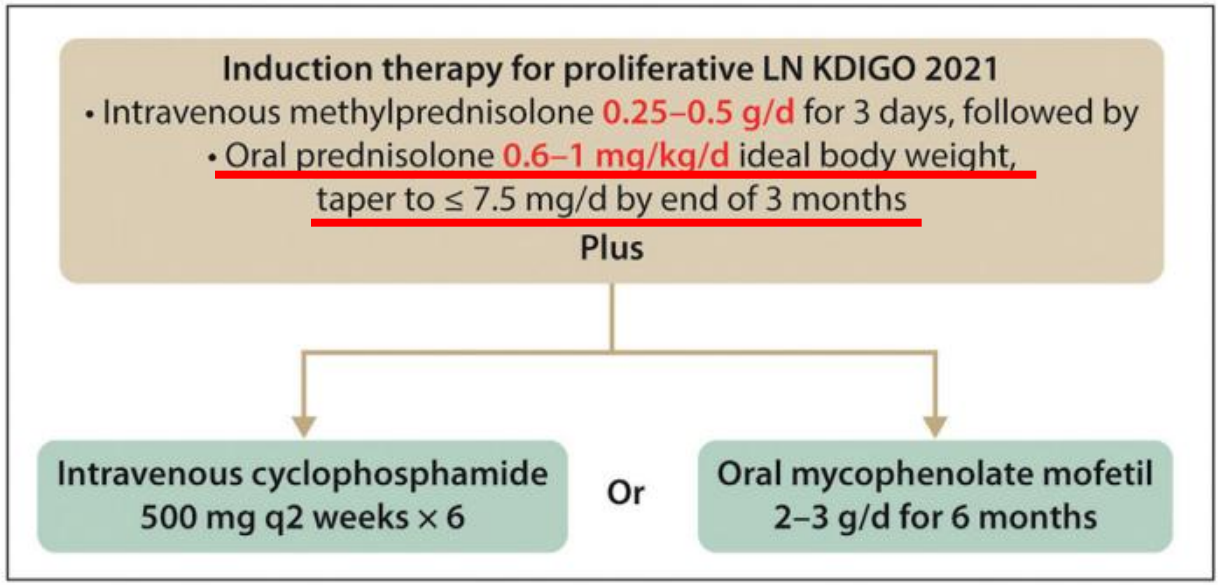
寛解導入療法

LN(III/IV)寛解導入療法に関する推奨（KDIGO 2021）

KDIGO 2012



KDIGO 2021



Comparison of recommended initial first-line treatment of proliferative LN in the 2012 versus KDIGO 2021 guideline.

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

Glucocorticoids

Methylprednisolone i.v. 0.25–0.50 g/d for 1–3 days as appropriate depending on disease severity and rate of progression, then prednisone p.o. at approximately 0.35–1.0 mg/kg/d (not to exceed 80 mg/d) and taper over a few months to maintenance dose (the lower steroid dosing option referring to the reduced-dose regimen in the voclosporin trials)† (Practice Point 10.2.3.1.1)

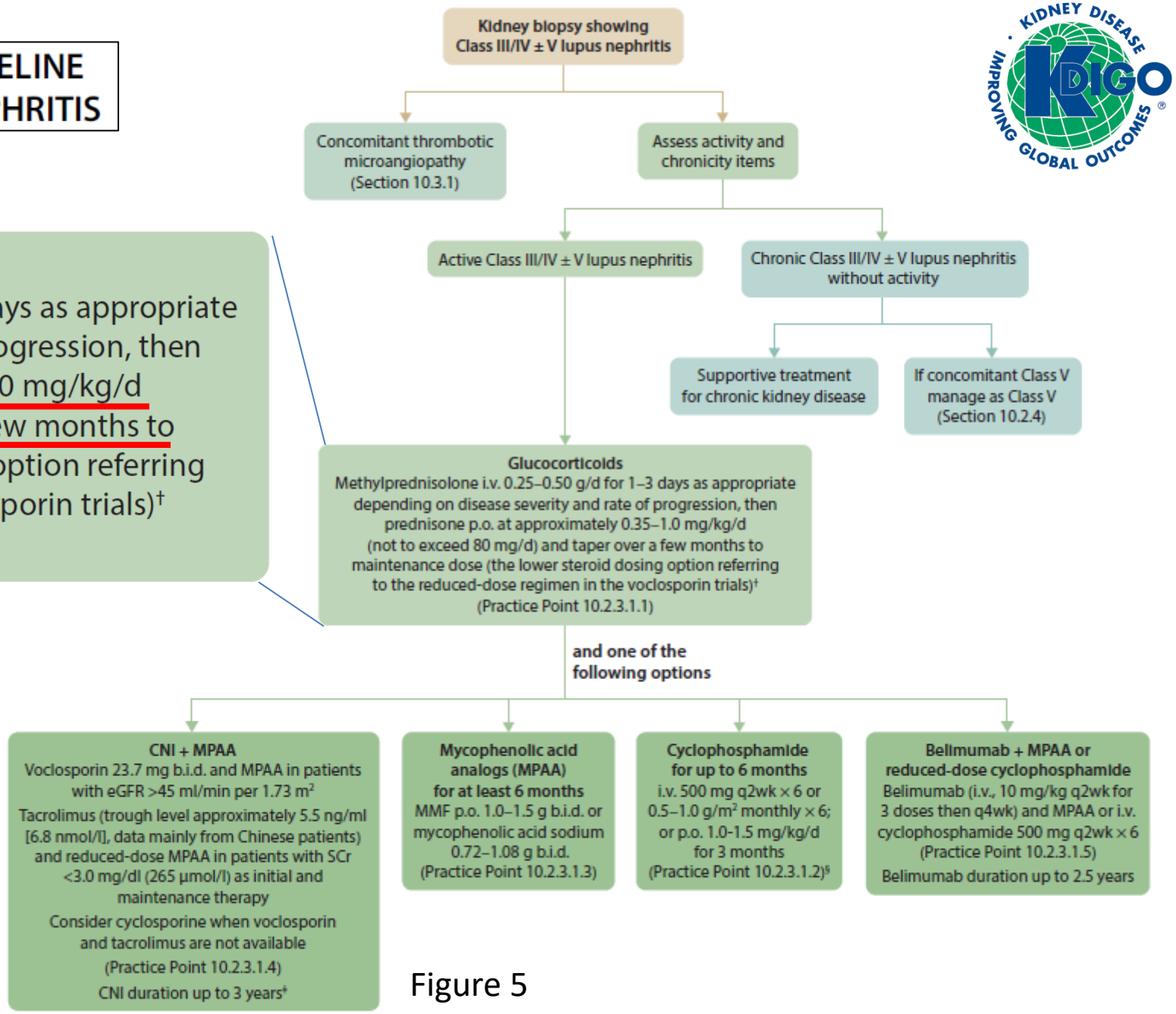


Figure 5

KDIGO 2024 CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF LUPUS NEPHRITIS

Practice Point 10.2.3.1.1: A regimen of reduced-dose glucocorticoids following a short course of methylprednisolone pulses may be considered during the initial treatment of active LN when both the kidney and extrarenal disease manifestations show satisfactory improvement (Figure 7).

	High-dose scheme	Moderate-dose scheme	Reduced-dose scheme
Methylprednisolone intravenous pulses	Nil or 0.25–0.5 g/day up to 3 days as initial treatment	0.25–0.5 g/day up to 3 days often included as initial treatment	0.25–0.5 g/day up to 3 days usually included as initial treatment
Oral prednisone equivalent (/day)			
Week 0–2	0.8–1.0 mg/kg (max 80 mg)	0.6–0.7 mg/kg (max 50 mg)	0.5–0.6 mg/kg (max 40 mg)
Week 3–4	0.6–0.7 mg/kg	0.5–0.6 mg/kg	0.3–0.4 mg/kg
Week 5–6	30 mg	20 mg	15 mg
Week 7–8	25 mg	15 mg	10 mg
Week 9–10	20 mg	12.5 mg	7.5 mg
Week 11–12	15 mg	10 mg	5 mg
Week 13–14	12.5 mg	7.5 mg	2.5 mg
Week 15–16	10 mg	7.5 mg	2.5 mg
Week 17–18	7.5 mg	5 mg	2.5 mg
Week 19–20	7.5 mg	5 mg	2.5 mg
Week 21–24	5 mg	<5 mg	2.5 mg
Week >25	<5 mg	<5 mg	<2.5 mg

<RESULTS>　　**＜目的：GCレジメンの違いによるRenal Response、感染、死亡との関連を明らかにする＞**

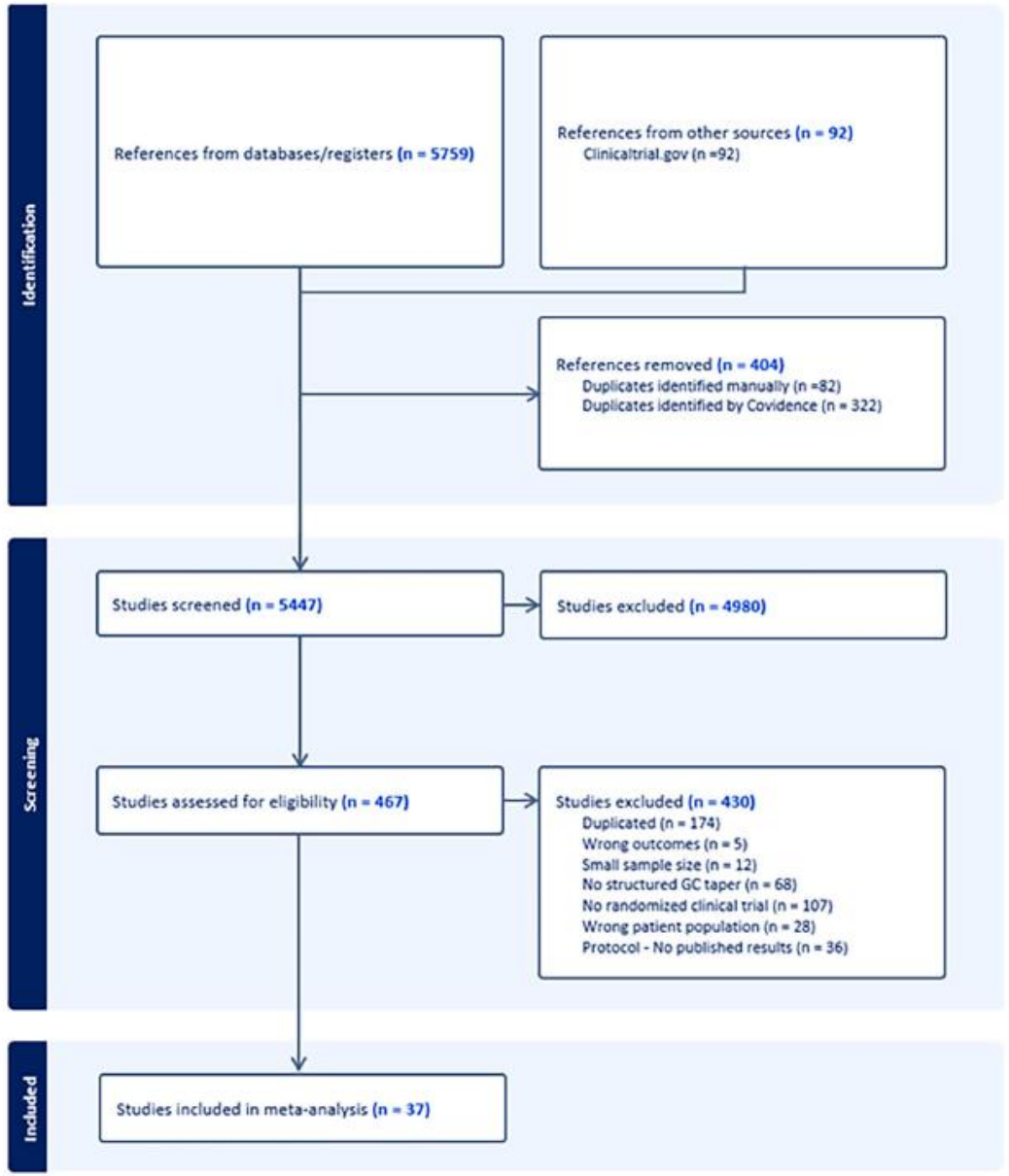


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for the identification, selection, and inclusion of studies. GC, glucocorticoids. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.42920/abstract.

＜解析に含めた論文＞

・10人以上の生検所見のあるLN患者を含んだRCT
・2023/9/22までに出版された論文
・最低6カ月間の観察期間
・初期治療としてMPAA or CYC(AZA or MPAA維持)による標準療法
・GCのprotocolized regimenがある

＜最終解析対象論文＞

・ 37 RCTs: 3231人、50 RCT arms
・ initial PSL dose ≦30mg/day (**Low dose**)
　633 Pts, 12 arms,
・ initial PSL dose >30mg/day (**High dose**)
　2598 Pts, 38 arms,
・ **Fast taper** (PSL≦7.5mg at 16w)
　586 Pts, 8 arms
・ **Slow taper** (PSL>7.5mg at 16w)
　2645 Pts, 42 arms
・ with mPSL pulse 1949 Pts, 34 arms
・ w/o mPSL pulse 1282 Pts, 16 arms

メタ回帰モデルによる初期PSL量と6M後、12M後のCR、重症感染症、死亡との関連

Table 1. Meta-regression models for complete response, serious infections, and death and their associations with the starting glucocorticoid dosage*

Outcome	Complete response		Serious infections		Death	
	β (95% CI)	*P* value	β (95% CI)	*P* value	β (95% CI)	*P* value
6 mo						
Unadjusted model	0.019 (0.001 to 0.036)	0.03	0.027 (0.001 to 0.053)	0.04	0.068 (0.018 to 0.118)	0.008
Adjusted model 1[a]	0.031 (0.013 to 0.050)	<0.001	0.027 (0.001 to 0.053)	<0.001	0.073 (0.022 to 0.124)	0.005
Adjusted model 2[b]	0.022 (0.006 to 0.039)	0.008	0.041 (0.009 to 0.073)	0.01	0.076 (0.023 to 0.131)	0.006
Adjusted model 3[c]	0.023 (0.009 to 0.037)	0.003	–	–	–	–
12 mo						
Unadjusted model	0.022 (−0.001 to 0.045)	0.06	0.008 (−0.017 to 0.035)	0.52	0.003 (−0.053 to 0.060)	0.93
Adjusted model 1[a]	0.017 (−0.011 to 0.045)	0.23	0.023 (−0.006 to 0.052)	0.12	0.032 (−0.047 to 0.110)	0.43
Adjusted model 2[d]	0.018 (−0.013 to 0.048)	0.25	–	–	–	–

* β coefficients represent the logit proportion of change per unit increase of glucocorticoid dose (mg of prednisone) in the corresponding outcome. Meta-regression was not performed in blank cells because we required 5–10 studies per covariable to be included in the models. CI, confidence interval.
[a] Adjusted for the administration of glucocorticoid pulses.
[b] Adjusted for the administration of glucocorticoid pulses, underlying immunosuppressant, and baseline proteinuria.
[c] Adjusted for the administration of glucocorticoid pulses, underlying immunosuppressant, baseline proteinuria, and publication year.
[d] Adjusted for the administration of glucocorticoid pulses and underlying immunosuppressant.

<Complete Response (CR)>
・Uprot <0.5g/day or equivalent
・Stabilization of sCre ±25% from baseline

メタ回帰モデル解析では
初回GC量は6カ月後のCR達成、重症感染症、死亡と関連
12カ月後のCR達成、重症感染症、死亡とは関連しない

回帰式による初期PSL量（±mPSLパルス）による6M後のCR、重症感染症、死亡予測

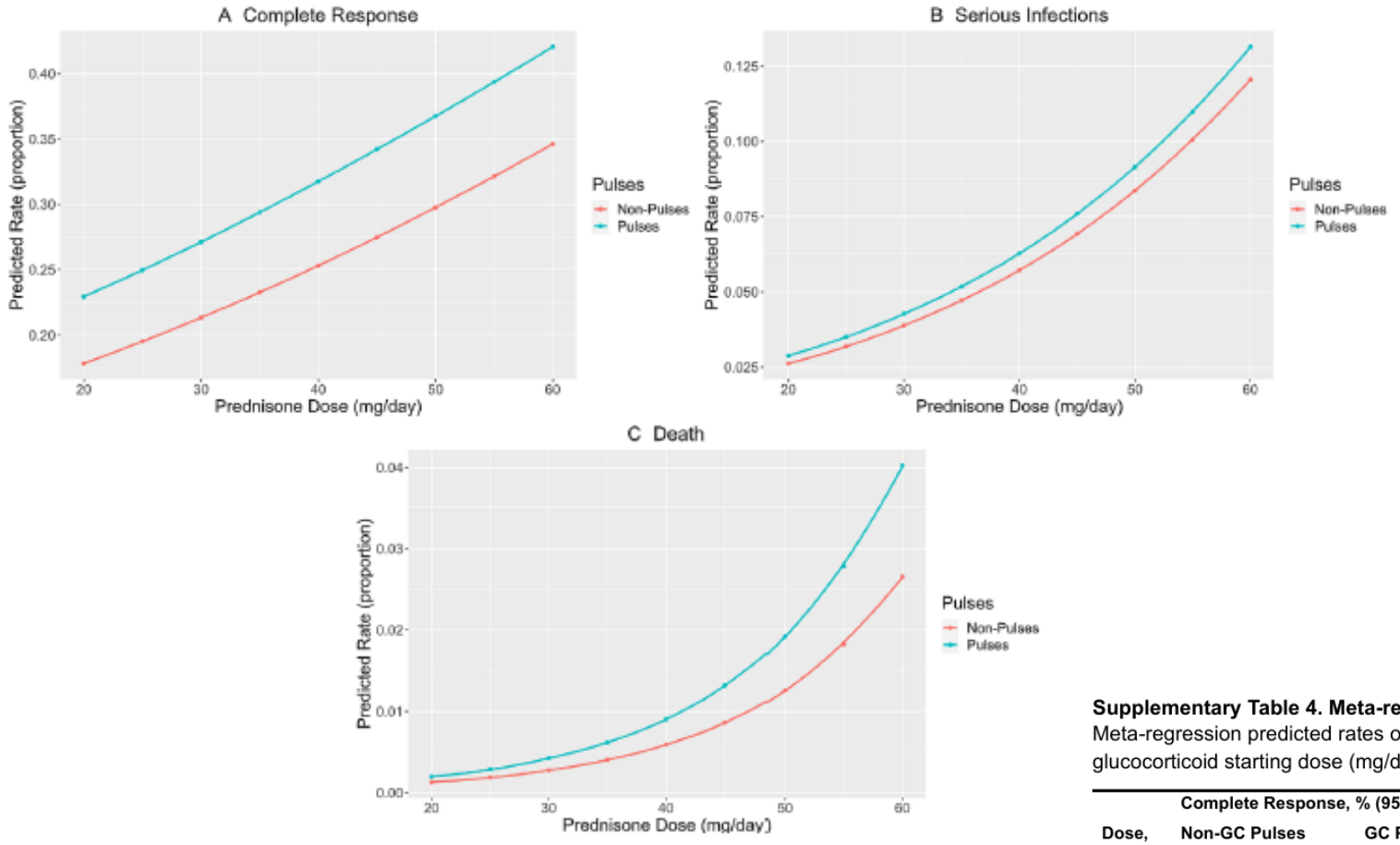


Figure 2. Meta-regression predicted rates of (A) complete response, (B) serious infections, and (C) mortality corticoid initial dosage (mg/day) and whether glucocorticoid pulses were administered.

Supplementary Table 4. Meta-regression predicted rates

Meta-regression predicted rates of complete response, serious infections, and death at six months according to glucocorticoid starting dose (mg/day) and use or not of glucocorticoid pulses.

	Complete Response, % (95% CI)		Serious Infections, % (95% CI)		Death, % (95% CI)	
Dose, mg/day	Non-GC Pulses	GC Pulses	Non-GC Pulses	GC Pulses	Non-GC Pulses	GC Pulses
20	17.8 (6.5–29.2)	22.9 (9.2–36.7)	2.6 (2.0, 3.3)	2.9 (2.2, 3.6)	0.1 (0.0–0.3)	0.2 (0.0–0.4)
25	19.5 (7.3–31.5)	25.0 (10.4–39.6)	3.2 (2.4–4.0)	3.5 (2.6–4.4)	0.2 (0.0–0.4)	0.3 (0.0–0.6)
30	21.3 (8.3–34.4)	27.1 (11.7–42.5)	3.9 (3.0–4.9)	4.3 (3.2–5.3)	0.3 (0.0–0.6)	0.4 (0.0–0.8)
35	23.3 (9.4–37.2)	29.4 (13.2–45.6)	4.7 (3.5–6.0)	5.2 (3.9–6.5)	0.4 (0.0–0.8)	0.6 (0.0–1.2)
40	25.3 (10.6–40.0)	31.7 (14.8–48.7)	5.7 (4.3–7.1)	6.3 (4.7–7.8)	0.6 (0.0–1.2)	0.9 (0.0–1.8)
45	27.5 (11.9–43.0)	34.2 (16.6–51.8)	6.9 (5.2–8.6)	7.6 (5.8–9.4)	0.9 (0.0–1.7)	1.3 (0.0–2.6)
50	29.8 (13.4–46.1)	36.7 (18.5–55.0)	8.4 (6.4–10.4)	9.2 (7.0–11.3)	1.3 (0.0–2.5)	1.9 (0.0–3.8)
55	32.1 (15.1–49.2)	39.4 (20.6–58.1)	10.1 (7.7–12.4)	11.0 (8.4–13.6)	1.8 (0.0–3.6)	2.8 (0.1–5.6)
60	34.6 (16.9–52.3)	42.1 (22.9–61.2)	12.1 (9.3–14.9)	13.1 (10.1–16.2)	2.7 (0.0–5.3)	4.0 (0.1–7.9)

GC: glucocorticoids; CI: confidence interval.

サブグループメタ解析による
GC初期量や減量スピードと6M後、12カ月後のCRとの関連

Table 2. Subgroup meta-analysis for CR, serious infections, and mortality rates at 6 and 12 mo according to glucocorticoid starting dosage, taper speed, and administration of pulses during the initial therapy of lupus nephritis*

Outcomes and subgroups	RCTs/arms, n	Rate (95% CI), %[a]	Events/patients, n	I^2, %	$P_{subgroups}$
CR at 6 mo					
Starting dosage					0.98
High dosage	22/29	29.8 (24.0–36.4)	613/1,980	82	
Low dosage	10/11	29.7 (21.2–39.9)	173/633	79	
Taper speed					0.77
Slow	24/34	30.4 (25.6–36.2)	687/2,169	79	
Fast	6/6	27.9 (15.5–44.9)	99/444	85	
Glucocorticoid pulses					0.35
Yes	20/27	31.5 (24.7–39.1)	465/1,597	80	
No	11/13	26.8 (20.7–34.0)	321/1,016	83	
CR at 12 mo					
Starting dosage					0.11
High dosage	12/15	36.7 (28.9–45.3)	387/1,166	79	
Low dosage	5/5	27.3 (20.4–35.6)	134/482	79	
Taper speed					0.17
Slow	12/15	36.4 (29.4–44.1)	402/1,178	75	
Fast	5/5	27.3 (18.3–38.6)	119/470	82	
Glucocorticoid pulses					0.26
Yes	13/16	31.6 (26.4–37.3)	399/1,314	73	
No	4/4	46.0 (23.3–70.5)	122/334	90	

サブグループメタ解析による
GC初期量や減量スピードと6M後、12カ月後の重症感染症との関連

Table 2. Subgroup meta-analysis for CR, serious infections, and mortality rates at 6 and 12 mo according to glucocorticoid starting dosage, taper speed, and administration of pulses during the initial therapy of lupus nephritis*

Outcomes and subgroups	RCTs/arms, n	Rate (95% CI), %[a]	Events/patients, n	I^2, %	$P_{subgroups}$
Serious infections at 6 mo					
Starting dosage					0.21
High dosage	16/22	10.4 (8.8–12.1)	139/1,341	48	
Low dosage	3/3	6.3 (2.9–13.4)	6/95	0	
Taper speed					0.21
Slow	15/23	10.4 (8.9–12.2)	137/1,318	44	
Fast	2/2	6.8 (3.4–13.0)	8/118	42	
Glucocorticoid pulses					0.41
Yes	9/13	9.4 (7.5–11.8)	66/700	45	
No	8/12	10.7 (8.7–13.2)	79/736	48	
Serious infections at 12 mo					
Starting dosage					0.26
High dosage	6/8	12.9 (9.9–16.6)	50/387	78	
Low dosage	3/3	10.2 (7.3–14.0)	32/315	0	
Taper speed					0.53
Slow	5/7	12.6 (9.3–16.9)	37/294	0	
Fast	4/4	11.0 (8.3–14.5)	45/408	55	
Glucocorticoid pulses					0.18
Yes	7/9	12.2 (9.9–15.0)	78/639	0	
No	2/2	6.4 (2.4–15.7)	4/63	62	

サブグループメタ解析による
GC初期量や減量スピードと6M後、12カ月後の死亡との関連

Table 2. Subgroup meta-analysis for CR, serious infections, and mortality rates at 6 and 12 mo according to glucocorticoid starting dosage, taper speed, and administration of pulses during the initial therapy of lupus nephritis*

Outcomes and subgroups	RCTs/arms, n	Rate (95% CI), %[a]	Events/patients, n	I^2, %	$P_{subgroups}$
Death at 6 mo					
Starting dosage					0.20
High dosage	22/29	2.0 (1.5–2.8)	38/1,864	0	
Low dosage	5/7	0.8 (0.2–3.2)	2/249	0	
Taper speed					0.42
Slow	23/33	2.0 (1.4–2.7)	39/1,997	0	
Fast	3/3	0.9 (0.1–5.9)	1/116	0	
Glucocorticoid pulses					0.57
Yes	16/23	1.7 (1.1–2.7)	19/1,097	0	
No	9/13	2.1 (1.4–3.2)	21/1,016	0	
Death at 12 mo					
Starting dosage					0.20
High dosage	10/11	2.6 (1.7–4.0)	20/774	0	
Low dosage	4/5	1.4 (0.6–3.1)	6/420	0	
Taper speed					0.01
Slow	10/12	1.4 (0.8–2.5)	11/786	0	
Fast	4/4	3.7 (2.2–6.0)	15/408	34	
Glucocorticoid pulses					0.16
Yes	10/12	2.6 (1.7–3.9)	22/860	0	
No	4/4	1.2 (0.5–3.2)	4/334	17	

* CI, confidence interval; CR, complete response; RCT, randomized controlled trial.
[a] Results from meta-analyses.

解析結果の確からしさに関するアセスメント

Table 3. Summary of findings for the administration of low versus high starting dosages of glucocorticoids in patients with lupus nephritis who received the standard of care for initial therapy*

	Certainty assessment					
Follow-up (participants; studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias, large effect, dose response, or residual confounding	Overall certainty of evidence
Complete response						
6 mo (n = 2,613; 40 RCT arms[a])	Not serious	Not serious[b]	Not serious[c]	Not serious	Dose–response gradient[d]	Moderate
12 mo (n = 1,648; 20 RCT arms[a])	Not serious	Not serious[b]	Not serious[c]	Not serious	None	Low
Serious infections						
6 mo (n = 1,436; 25 RCT arms[a])	Not serious	Not serious[b]	Not serious[c]	Not serious	Dose–response gradient[d]	Moderate
12 mo (n = 702; 11 RCT arms[a])	Not serious	Not serious[b]	Not serious[c]	Serious[e]	None	Very low
Death						
6 mo (n = 2,113; 36 RCT arms[a])	Not serious	Not serious[b]	Not serious[c]	Serious[e]	Dose–response gradient[d]	Low
12 mo (n = 1,194; 16 RCT arms[a])	Not serious	Not serious[b]	Not serious[c]	Serious[e]	None	Very low

* RCT, randomized controlled trial.
[a] Equivalent to observational studies.
[b] Inconsistency in the underlying immunosuppression but no impact in the estimates.
[c] Across-study comparison is the primary analysis.
[d] Meta-regression analysis showed positive association.
[e] Rare events, and confidence interval is very wide.

Revised Cochrane risk of bias tool for RCTs (RoB 2)を用いた評価

Discussion（I）

- 70年のGC使用歴史においていまだにGC量や減量法の最適化ができていない。ガイドラインもevidence-basedではない。今回の結果（用量依存性に効果と副作用が上昇する）から、GC投与法は個別に適用されるべきだろう。
- 一方、初期量PSL30mgより上、下で２つに分けたサブグループ解析においてはCR,重症感染症、死亡における差がなかった
- 過去の報告(ALMSとAURA）のpropensity sore解析でも高容量PSLと低用量PSL群に有効性と副作用に差はなかった(Lupus 2019)
- 我々は連続変数による解析を行っており、より強い統計解析力をもち、よりexplanatory informationを保持し、バイアスを減らし、同じ効果をみるのにより少ない観察値を必要とするため2値解析より優れている

Discussion (2)

- Tseliosら (ACR 2022)は12カ月以上f/uできたstudyを初期PSL≦30mg/日かPSL≧40mg/日に分け、高容量の方がCR率がよかったと報告している
- 高容量GCでaggressiveに治療する方が深い寛解を得られ、結果的に少ないGC量で疾患コントロールできるかどうかは、まだわからない
- GC減量スピードに関しては、数字の上では緩徐減量群の方が6ヶ月でも12カ月でもCR率、重篤感染症、死亡率も高かったが、12カ月の死亡率のみは有意に急速減量群で多かった。理由は不明だが、早く減量してCRに入らなかった患者が合併症を起こした可能性
- 今回の結果よりmPSLパルスに続くPSL 40mg (0.6-0.7mg/kg/日)がPopulation levelでは推奨されるのではないか

Discussion (Limitation)

- GC用量の異なる群でHead-to-head comparisonをしたわけではない
- アウトカムの定義を事前にしているとはいえ、スタディ間の多様性はある
- できる限りGC用量がうまく調和するようにしたが、過度の肥満など予測容量やカテゴリーと一致しない場合がある
- GC用量とアウトカムの関連が非線形となるような解析は行っていない
- 6ヶ月と12カ月のデータに限られており（ESRDやGIOPなどみてない）、他のGC関連副作用はみていない
- 低用量GCを用いたRCTはMPAAを使用しているものが圧倒的に多い