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Avacopan for the Treatment of ANCA-Associated Vasculitis

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膠原病 Journal Club
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本論文のPICO

P:　新たに診断/再発　GPA or MPAに対してIVCY or RTXを投与

I:　avacopan 30mg 1日2回

C:　PSL on a tapering regimen

O: ①臨床的寛解 26週時点でのBVAS 0, 直近4週のステロイド投与なし
②持続的寛解 26週と52週時点でそれぞれ寛解しており、
52週の直近4週でステロイド投与なし

Study Design

- 多国籍・多施設 (143施設; 日本から30施設が参加)
- Phase 3 A Randomized, Double-Blind, Placebo-Controlled trial
- 期間: 2017年5月から2019年11月
- 患者数: 386人

Randomization

- 参加者はPSL群とAvacopan群へ1:1に割付け
- 層別化は新規/再発,MPO/PR3,IV or POCY/RTXに基づいた
- ランダム化は層別化したアルゴリズムを用いて、中央でWebベースで行われた
- PSLとAvacopanは二重盲検化されている

Inclusion Criteria

- 18歳以上でChapell-Hill分類で診断された GPA or MPA(再発例も含む)
- MPO or PR3 ANCAが陽性
- BVASで1つ以上の大項目,3つ以上の小項目, 少なくとも２つ以上の腎項目を満たす
- eGFR＞15ml/分
- 全ての免疫抑制薬は参加前に中止

Exclusion criteria

- 人工呼吸器管理を要する肺胞出血を認める
- 自己免疫性疾患を合併する(EGPA,SLE,SjS,IgA vasculitis, cryoglobulinemic vasculitisなど)
- 12週以内に透析や血漿交換を行った
- 4週以内に3g以上のステロイドパルスを行われた (protocolに基づいた重症例は認められた)
- 6週以上に渡りPSL換算 10mg以上の投与
- 12週以内に生物学的製剤の投与を受けた
- 12週以内に心筋梗塞,脳梗塞,心不全の診断治療を受けた
- 5年以内に悪性腫瘍の既往がある

Intervention / comparison

Avacopan 30mg 1日2回

Body weight	Initial CCX168/placebo dose	CCX168 Plasma AUC_{0-6} (ng•hr/mL) on Day 1	CCX168 Dose Adjustment
<40 kg (88 lb)	10 mg (1 capsule) twice daily	≥351	None
		<351	Increase dose to 20 mg (2 capsules) twice daily
40-55 kg (88-121 lb)	20 mg (2 capsules) twice daily	351 to 699	None
		<351	Increase dose to 30 mg (3 capsules) twice daily
		>699	Decrease dose to 10 mg (1 capsule) twice daily
>55 kg (121 lb)	30 mg (3 capsules) twice daily	≤699	None
		>699	Decrease dose to 20 mg (2 capsules) twice daily

ステロイド tapering regimen

Study Day	Avacopan Group	Prednisone Group			
	Daily Prednisone Dose*				
	All†	Adults		Adolescents	
		≥55 kg	<55 kg	>37 kg	≤37 kg
Week 1	0	60 mg	45 mg	45 mg	30 mg
Week 2	0	45 mg	45 mg	45 mg	30 mg
Week 3	0	30 mg	30 mg	30 mg	30 mg
Week 4 to 6	0	25 mg	25 mg	25 mg	25 mg
Week 7 and 8	0	20 mg	20 mg	20 mg	20 mg
Week 9 and 10	0	15 mg	15 mg	15 mg	15 mg
Week 11 to 14	0	10 mg	10 mg	10 mg	10 mg
Week 15 to 20	0	5 mg	5 mg	5 mg	5 mg
≥ Week 21	0	0	0	0	0

Treatment

■ IVCY
15mg/kg 0,2,4,7,10,13
15週目からAZA 2mg/kg

■ POCY
2mg/kg 14週目まで継続
15週目からはAZA 2mg/kg

Age (years)	Oral Cyclophosphamide Dose (mg/kg/day)		IV Cyclophosphamide Dose (mg/kg)	
	Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)		Estimated Glomerular Filtration Rate (mL/min/1.73 m^2)	
	>30	≤30	>30	≤30
<60	2	1.5	15	12.5
60-70	1.5	1.25	12.5	10
>70	1.25	1	10	7.5

■ RTX
375mg/m2 週1回の合計4回　追加投与なし

※上記のどれを選択するかは治験責任医師の判断

Outcome

Primary outcome

①臨床的寛解 26週時点でのBVAS 0, 直近4週のステロイド投与なし
②持続的寛解 26週と52週時点でそれぞれ寛解しており、52週の直近4週で
　ステロイド投与なし

Secondary outcome

26週までのGlucocorticoid Toxin Index(GTI)によるグルココルチコイド誘発毒性
腎疾患患者でのeGFR,アルブミン尿などのパラメーター変化

※再燃の定義；BVASの少なくともmajor 1項目,minor 3項目,2回連続の受診
　でminor 1or 2項目を満たすこと

statistics

非劣性マージン20%,ステロイド群での寛解率60%と仮定すると、avacopoanのPSLに対する非劣性を示すのに90%のパワーを検出するためには各群のサンプルサイズを150人と仮定

解析；intension to treat, per protocol

characteristic

Characteristic	Avacopan (N = 166)	Prednisone (N = 164)
Age — yr	61.2±14.6	60.5±14.5
Sex — no. (%)		
Male		88 (53.7)
Female		76 (46.3)
Race — no		
White		140 (85.4)
Asian		15 (9.1)
Black		2 (1.2)
Other		7 (4.3)
Body-mass		26.8±5.2
Median du		0.25 (0–212.5)
Vasculitis		
Newly		114 (69.5)
Relapse		50 (30.5)
ANCA statu		
Antipro		70 (42.7)
Antimy		94 (57.3)
Type of vas		
Granul		90 (54.9)
Micros		74 (45.1)
Birmingha		16.2±5.7
Vasculitis		0.7±1.4
Immunosu		
Intrave		107 (65.2)
Intrave		51 (31.1)
Oral cy		6 (3.7)
Organ invo		
Renal		134 (81.7)
Genera		114 (69.5)
Ear, no		69 (42.1)
Chest		71 (43.3)
Nervou		31 (18.9)
Mucou		40 (24.4)
Cutane		23 (14.0)
Cardiov		3 (1.8)
Abdom		1 (0.6)
Glucocorti		
Use of		135 (82.3)
Intr		73 (44.5)
Ora		113 (68.9)
Total p		727.8±787.8
Daily prednisone-equivalent dose — mg		52.0±56.3
Previous immunosuppressant use — no. (%)††		
Cyclophosphamide	4 (2.4)	2 (1.2)
Rituximab	1 (0.6)	4 (2.4)

年齢 60歳
アジア人 15%
再発 30%
PR3陽性 40%, MPO陽性 60%
GPA 55%,MPA 45%
BVAS平均 16
Induction RTX 60%,IVCY 30%,POCY 4%
腎 80%,肺 40%. ENT領域 40%
Screening 期間にステロイド70-80%使用

Outcome

End Point	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Primary end points			
Remission at wk 26 — no. (%)†	120 (72.3)	115 (70.1)	3.4 (–6.0 to 12.8)‡§
Sustained remission at wk 52 — no. (%)¶	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3)‡‖

Primary outcome

①臨床的寛解 26週時点でのBVAS 0, 直近4週のステロイド投与なし
avacopan 120人(72.3%) vs PSL 115人(70.1%) 3.4 95%CI(-6.0-12.8) P=0.001(非劣性)

→非劣性ではあるが有意差ない

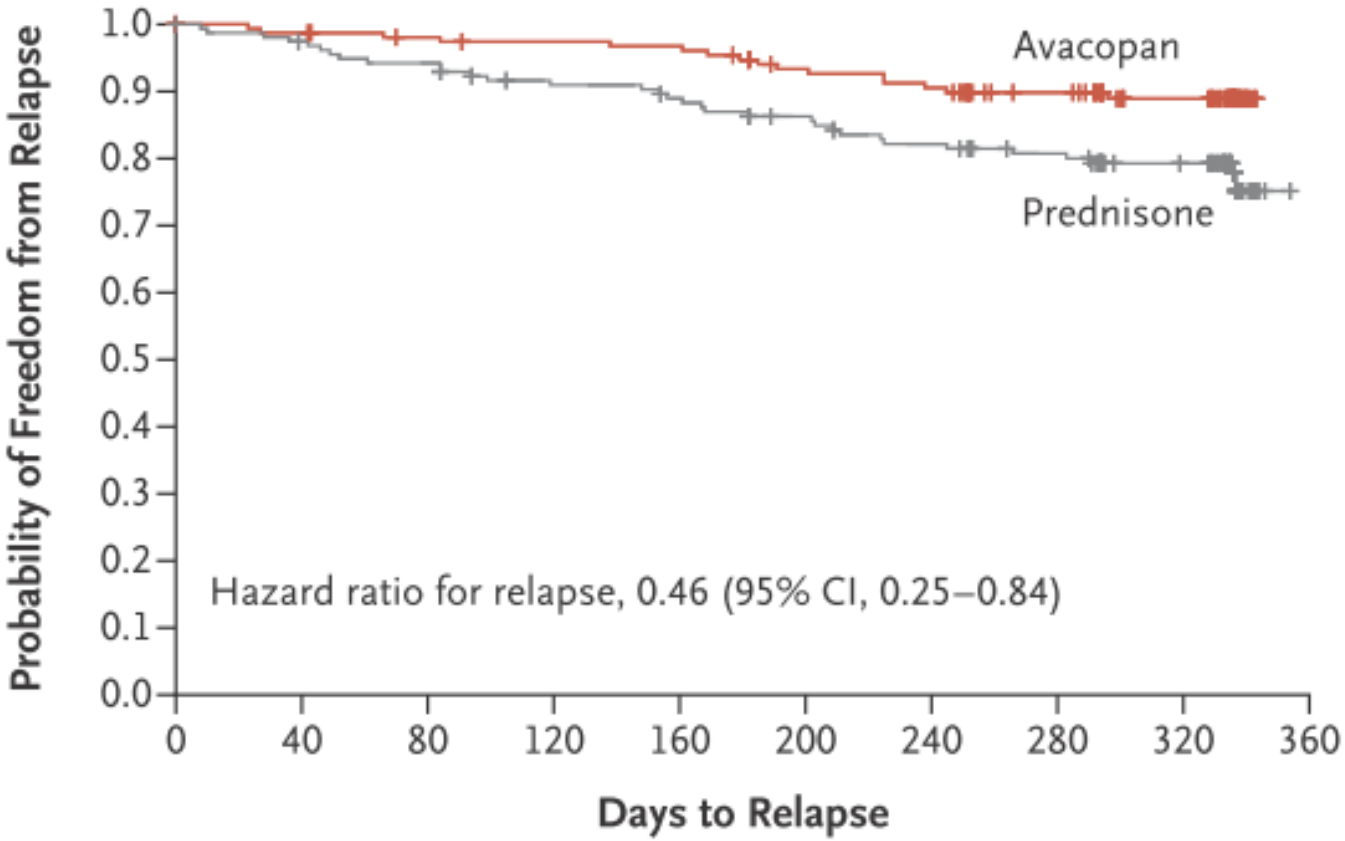
②持続的寛解 26週と52週時点でそれぞれ寛解しており、52週の直近4週でステロイド投与なし
avacopan 109人(65.7%) vs PSL 90人(54.9%) 12.5 95%CI (2.6-22.3)
P=0.001(非劣性), P=0.007(優位性)

→avacopan群に有意差あり

52週でのper protocol解析

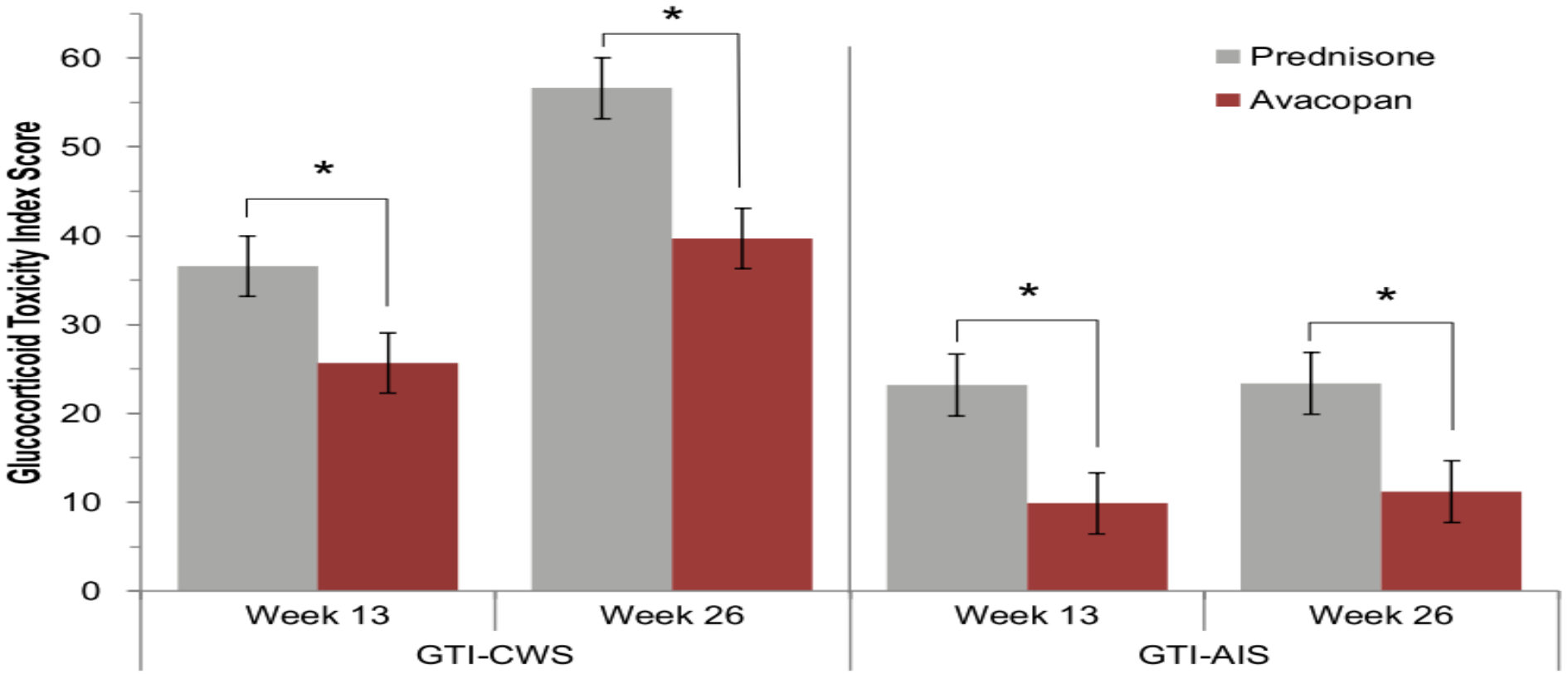
	Prednisone (N=164)	Avacopan (N=166)
All Patients*	90 / 164 (54.9%)	109 / 166 (65.7%)
Disease Status		
Newly diagnosed patients	66 / 114 (57.9%)	70 / 115 (60.9%)
Relapsing disease	24 / 50 (48.0%)	39 / 51 (76.5%)
ANCA Type		
Anti-proteinase 3 positive	40 / 70 (57.1%)	43 / 72 (59.7%)
Anti-myeloperoxidase positive	50 / 94 (53.2%)	66 / 94 (70.2%)
Background Treatment		
Cyclophosphamide	30 / 57 (52.6%)	33 / 59 (55.9%)
Rituximab	60 / 107 (56.1%)	76 / 107 (71.0%)
Type of ANCA-Associated Vasculitis		
Granulomatosis with polyangiitis	52 / 90 (57.8%)	56 / 91 (61.5%)
Microscopic polyangiitis	38 / 74 (51.4%)	53 / 75 (70.7%)

MPO陽性のMPAにはAvacopan群で寛解率が高い傾向にある



No. at Risk										
Avacopan	158	153	149	146	145	133	129	115	92	0
Prednisone	157	151	146	137	133	126	119	111	90	0

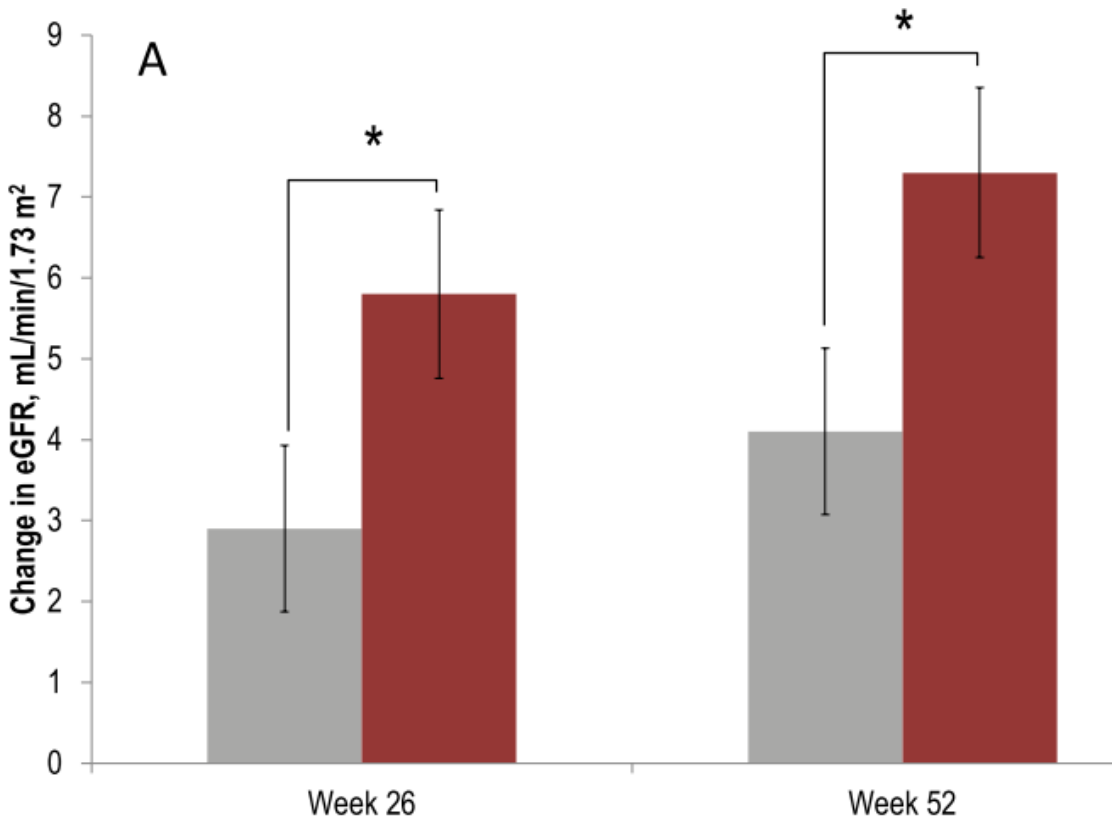
Avacopan群の方が寛解維持率が高い

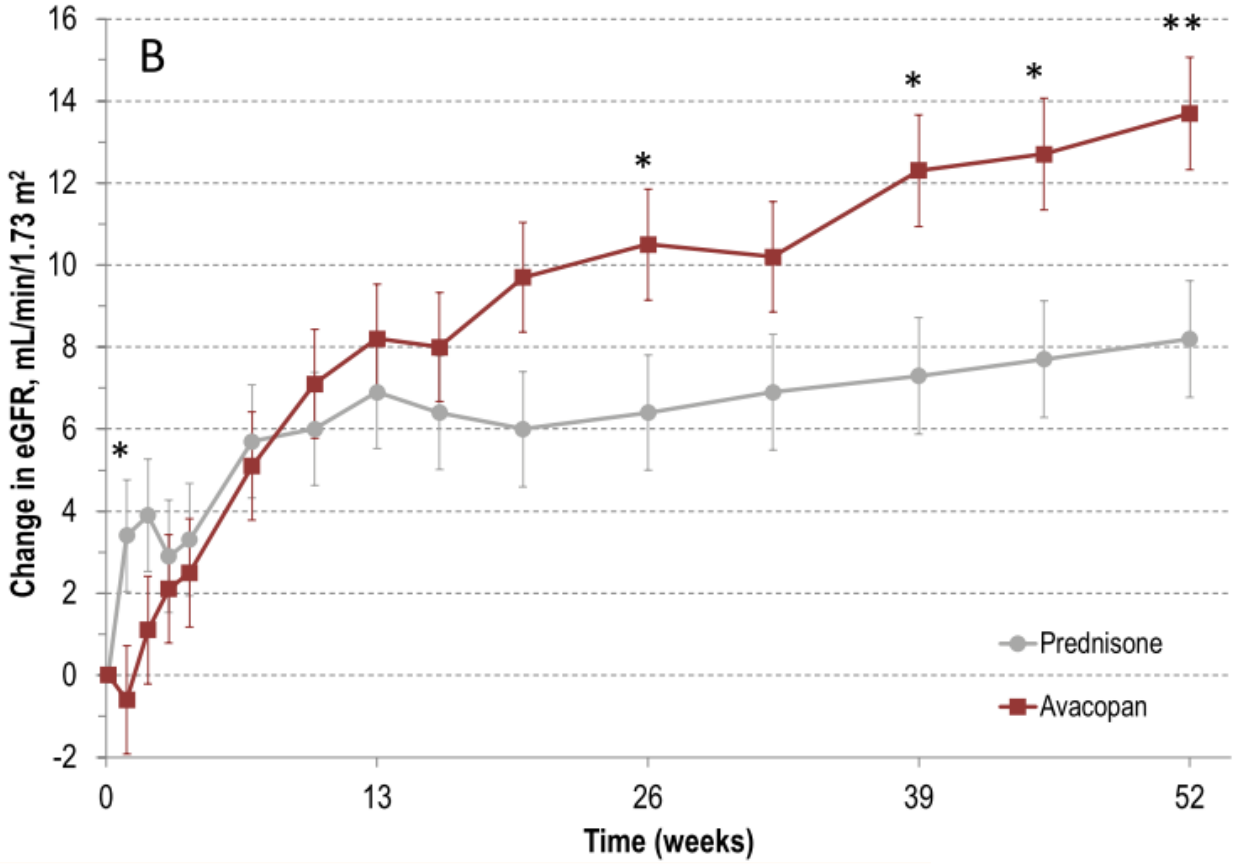


GTI-CWS**			
Wk 13			
Patients evaluated	160	161	
Least-squares mean	25.7±3.4	36.6±3.4	−11.0 (−19.7 to −2.2)
Wk 26			
Patients evaluated	154	153	
Least-squares mean	39.7±3.4	56.6±3.4	−16.8 (−25.6 to −8.0)
GTI-AIS††			
Wk 13			
Patients evaluated	160	161	
Least-squares mean	11.2±3.3	23.4±3.3	−12.1 (−21.1 to −3.2)

ステロイド毒性はAvacopan群の方が低い

eGFRの改善率はAvacopan群で優位





eGFR — ml/min/1.73 m²‡‡			
Baseline			
Patients evaluated	131	134	
Mean	44.6±2.4	45.6±2.4	
Change from baseline to wk 26			
Patients evaluated	121	127	
Least-squares mean	5.8±1.0	2.9±1.0	2.9 (0.1 to 5.8)
Change from baseline to wk 52			
Patients evaluated	119	125	
Least-squares mean	7.3±1.0	4.1±1.0	3.2 (0.3 to 6.1)

PSL使用量

	Prednisone (N=164)	Avacopan (N=166)
Any Oral or IV Use (mg)*		
n (%)	164 (100.0%)	145 (87.3%)
total dose, mean ± SD	3654.5 ± 1709.83	1348.9 ± 2040.29
daily dose, mean ± SD	11.8 ± 8.96	4.4 ± 6.65
Oral Prednisone Study Medication (mg)		
n (%)	164 (100.0%)	Not applicable
total dose, mean ± SD	2389.2 ± 624.31	Not applicable
daily dose, mean ± SD	7.8 ± 6.11	Not applicable
Oral, Other Than Prednisone Study Medication (mg)†		
n (%)	115 (70.1%)	112 (67.5%)
total dose, mean ± SD	885.8 ± 1329.08	868.1 ± 1501.08
daily dose, mean ± SD	2.6 ± 3.97	2.8 ± 4.61
Any IV Use (mg)		
n		)
to		79
d		

Avacopna群でもPSLは87%で使用されている
総使用量はPSL群の1/3程度

Safety

重篤な有害事象(血管炎の悪化を除く)は、
PSL群がAvacopan群にに比べて**33%**多かった

PSL群は死亡、生命を脅かす有害事象、感染症の発症が多かった

死亡例
Avacopan群 2人(血管炎の悪化に起因,肺炎)
PSL群 4人(真菌感染,感染性胸水,心筋梗塞、原因不明)

Table 3. Safety Results.*

Event	Avacopan (N=166)	Prednisone (N=164)
Any adverse event		
No. of patients (%)	164 (98.8)	161 (98.2)
No. of events	1779	2139
		41 (25.0)
		94
		14 (8.5)
		22
		4 (2.4)
No. of patients (%)	70 (42.2)	74 (45.1)
No. of events	116	166
Any serious event related to vasculitis worsening§		
No. of patients (%)	17 (10.2)	23 (14.0)
No. of events	18	36
Any serious event not related to vasculitis worsening		
No. of patients (%)	62 (37.3)	64 (39.0)
No. of events	98	130
Discontinuation of trial medication due to adverse event — no. (%)	26 (15.7)	29 (17.7)
Any infection		
Any serious opportunistic infection — no. (%)	6 (3.6)	11 (6.7)
Death due to infection — no. (%)	1 (0.6)	2 (1.2)
Life-threatening infection — no. (%)	1 (0.6)	2 (1.2)
Serious adverse event of abnormality on liver-function testing — no. (%)	9 (5.4)	6 (3.7)
		132 (80.5)
		85 (51.8)
		25 (15.2)
		4 (2.4)
		39 (23.8)
		48 (29.3)
		28 (17.1)
		21 (12.8)
		12 (7.3)
		131 (79.9)
Any serious adverse event potentially related to prednisone as assessed by the investigators — no. (%)	11 (6.6)	24 (14.6)

Safety

Table 3. Safety Results.*

Event	Avacopan (N=166)	Prednisone (N=164)
Any adverse event		
No. of patients (%)	164 (98.8)	161 (98.2)
No. of events	1779	2139
Severe adverse event*		
No.		41 (25.0)
No.		94
Life-th		
No.		14 (8.5)
No.		22
Death		4 (2.4)
Any serious adverse event‡		
No. of patients (%)	70 (42.2)	74 (45.1)
No. of events	116	166
Any se		
No.		23 (14.0)
No.		36
Any se		
No. of patients (%)	62 (37.3)	64 (39.0)
No. of events	98	130
Discontinuation of trial medication due to adverse event — no. (%)	26 (15.7)	29 (17.7)
Any infection		
Ophthalmologic		
Any adverse event potentially related to glucocorticoids as assessed by the investigators — no. (%)	107 (64.5)	131 (79.9)
Any serious adverse event potentially related to prednisone as assessed by the investigators — no. (%)	11 (6.6)	24 (14.6)

肝機能障害
Avacopam群 5.4% vs PSL群 3.7%

莢膜を持つ髄膜炎菌の感染は見られなかった

Table S11. All Serious Infections by Treatment Group

	Prednisone (N=164)	Avacopan (N=166)
Any serious infection*	25 (15.2%)	22 (13.3%)
Pneumonia†	9 (5.5%)	9 (5.4%)
Urinary tract infection	2 (1.2%)	3 (1.8%)

Safety

Table 3. Safety Results.*

Event	Avacopan (N=166)	Prednisone (N=164)
Any adverse event		
No. of patients (%)	164 (98.8)	161 (98.2)
No. of events	1779	2139
Severe adverse event†		
No. of patients (%)	39 (23.5)	41 (25.0)
No. of events	71	94
Life-threatening adverse event		
No. of patients (%)	8 (4.8)	14 (8.5)
No. of events	8	22
Death — no. (%)	2 (1.2)	4 (2.4)
Any serious adverse event‡		
No. of patients (%)	70 (42.2)	74 (45.1)
No. of events	116	166
Any serious event related to vasculitis worsening§		
No. of patients (%)	17 (10.2)	23 (14.0)
No. of events	18	36
Any serious event not related to vasculitis worsening		
No. of patients (%)	62 (37.3)	64 (39.0)
No. of events	98	130
Discontinuation of trial medication due to adverse event — no. (%)	26 (15.7)	29 (17.7)

患者数を見ると両群で有害事象の割合はあんまり差はない

discussion

- PSL群で副作用が多く、有害事象も多かった
- 莢膜を持つ細菌の感染症の発生はなかった
- 肝機能障害がAvacopan群で多い
- Avacopan群もPSLを使用していたが、PSL群の1/3程度
- Avacopan群でのeGFRやアルブミン尿の改善は、
  Avacopanが腎機能に有益な結果をもたらす可能性を示した
- AAVの新規と再燃を同等に扱っており患者間での異質性がある