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Flash Info sur l'étude ADVOCATE au cours des vascularites à ANCA

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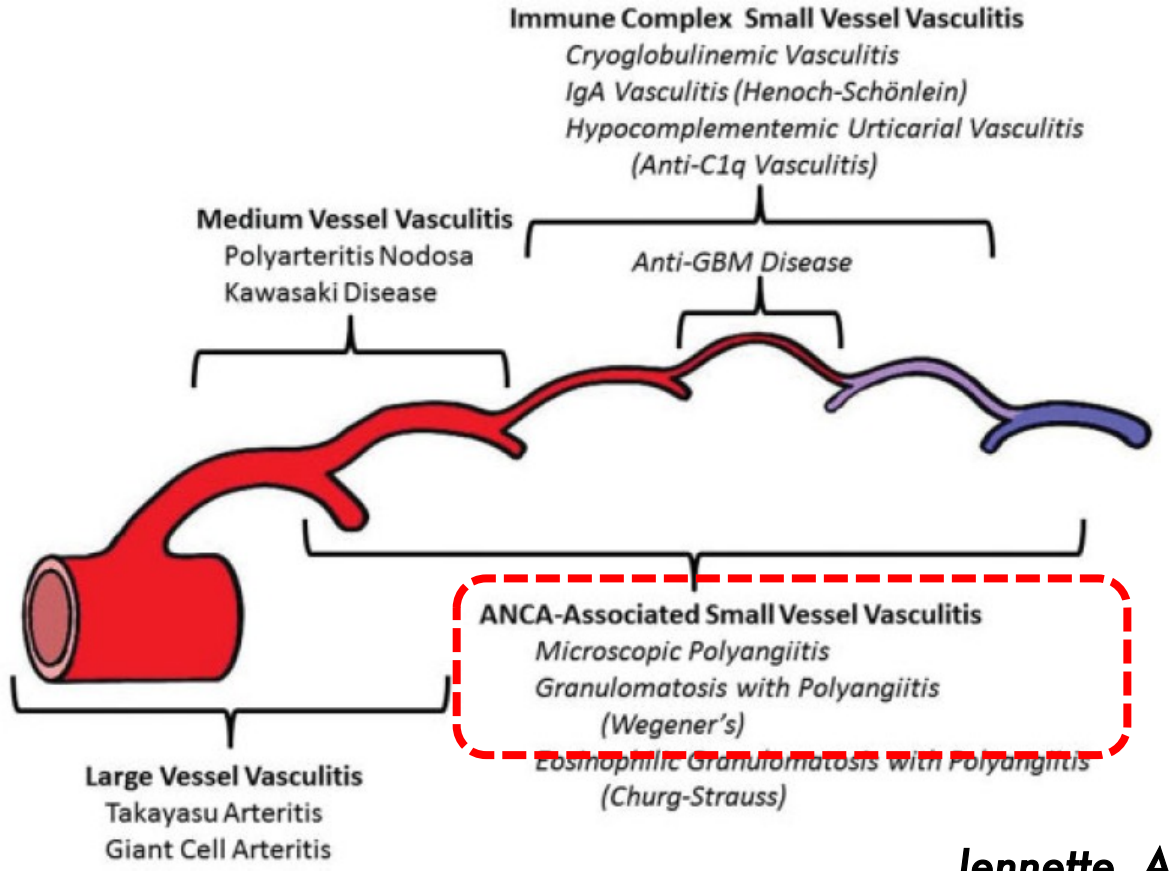
GFEV GROUPE FRANÇAIS D'ÉTUDE DES VASCULARITES

Liens d'intérêt

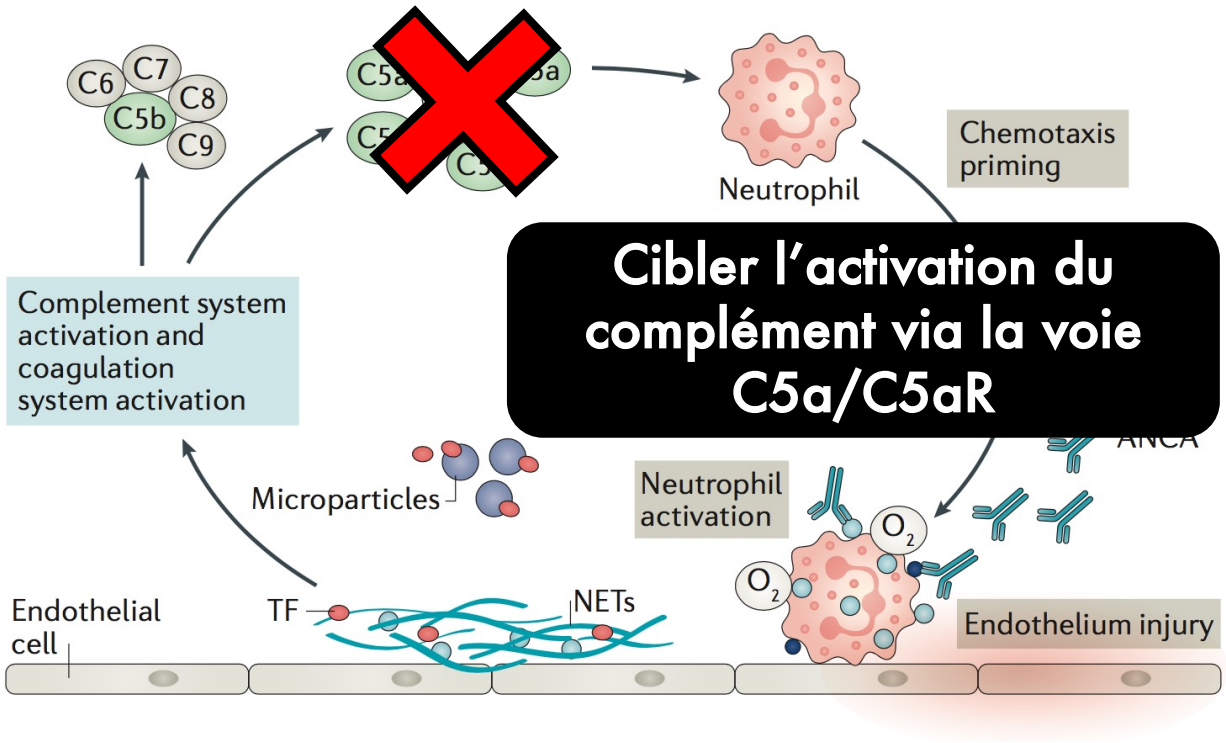
- Boards/consultations : Roche, Chugaï, Vifor, LFB, Grifols, AstraZeneca
- Frais de déplacement/congrès : Roche, LFB, Grifols, Octapharma, GSK, Janssen
- Soutien pour la recherche : Roche, Chugaï, Vifor, LFB, GSK, AstraZeneca, BMS

Nomenclature de Chapel Hill 2012



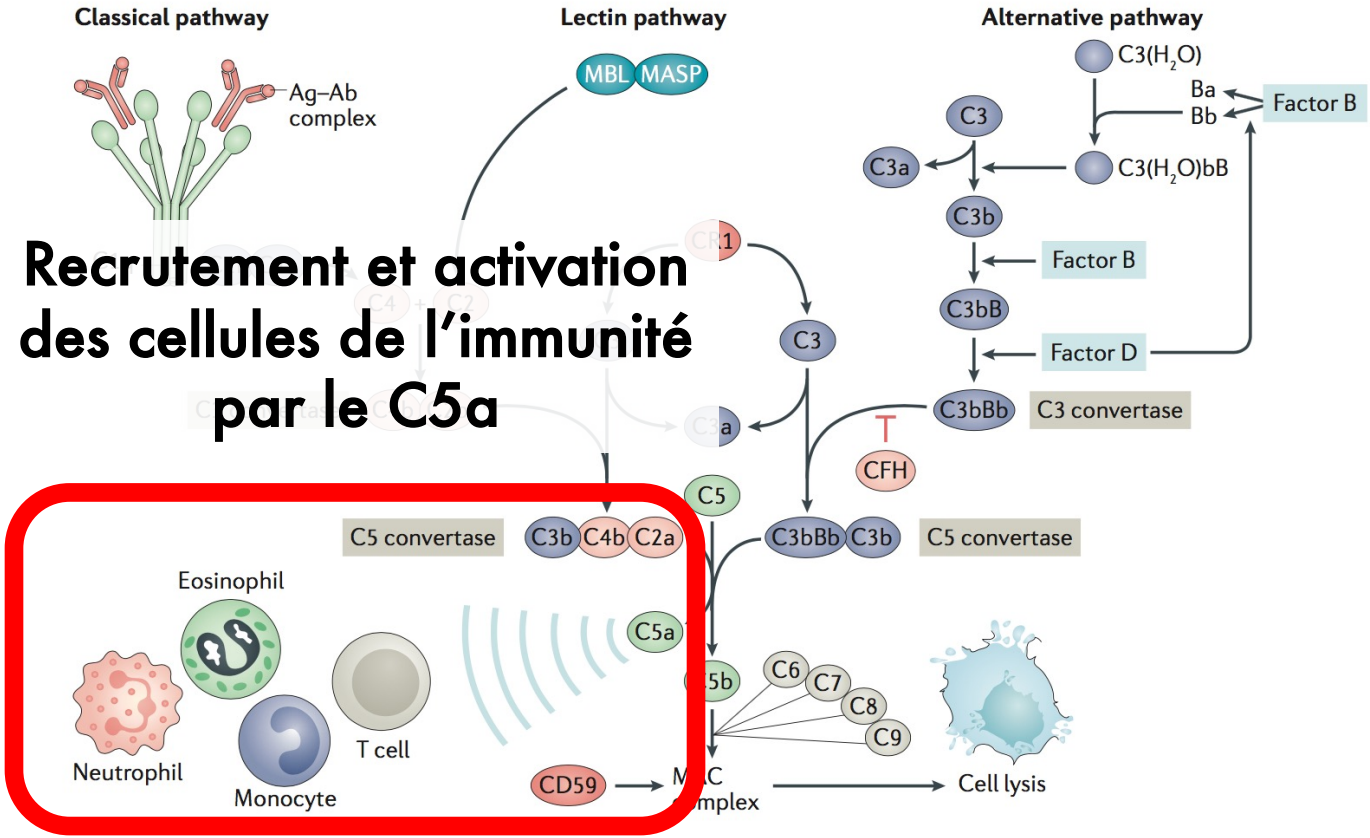
Jennette, Arthritis Rheum, 2013

Physiopathologie des vascularites à ANCA



Chen, Nat Rev Rheumatol, 2017

Voie du complément et du C5a/C5aR



Recrutement et activation des cellules de l'immunité par le C5a

Chen, Nat Rev Rheumatol, 2017

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Avacopan for the Treatment of ANCA-Associated Vasculitis

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Design de l'étude ADVOCATE

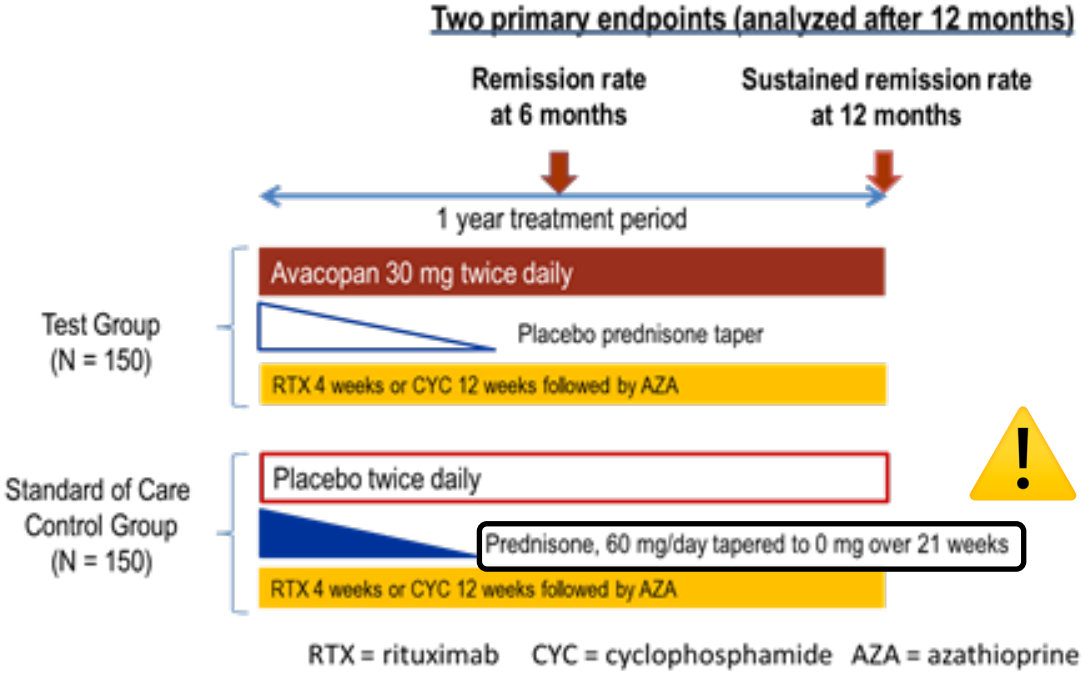
Etude de phase 3, internationale, randomisée contre placebo (1:1), en double aveugle comparant le CCX168/Avacopan (30 mg x 2/j *pendant 52 sem.*) et la prednisone (*pendant 20 sem.*), 331 patients inclus

Critères d'inclusion :

- GPA/PAM
- ANCA-PR3/MPO positifs
- Maladie nouvelle/rechute
- DFGe >15 ml/min

Critères de jugement:

- Rémission à S26 sans GCs
- Maintien rémission à M12 sans GCs



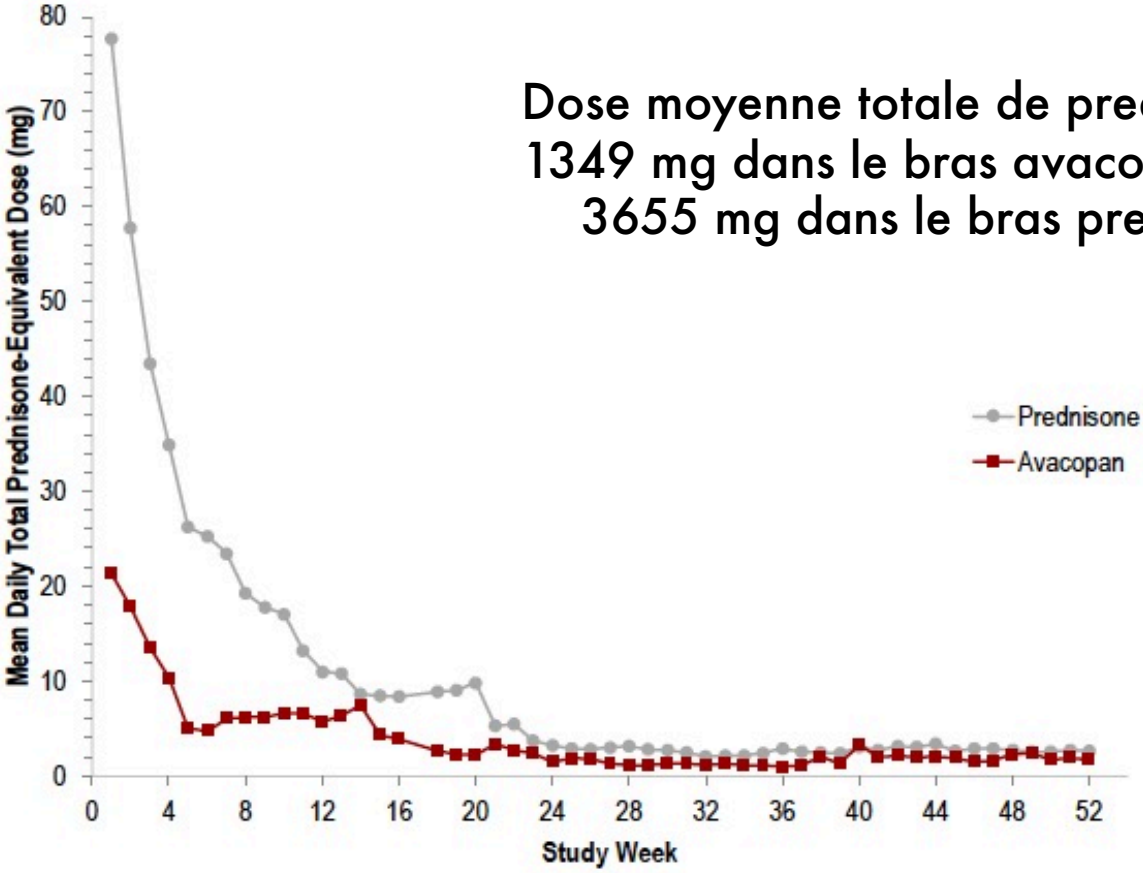
Population de l'étude ADVOCATE

Characteristic	Avacopan (N=166)	Prednisone (N=164)
Age — yr	61.2±14.6	60.5±14.5
Sex — no. (%)		
Male	98 (59.0)	88 (53.7)
Female	68 (41.0)	76 (46.3)
Race — no. (%)†		
White	138 (83.1)	140 (85.4)
Asian	17 (10.2)	15 (9.1)
Black	3 (1.8)	2 (1.2)
Other	8 (4.8)	7 (4.3)
Body-mass index‡	26.7±6.0	26.8±5.2
Median duration of ANCA-associated vasculitis (range) — mo	0.23 (0–362.3)	0.25 (0–212.5)
Vasculitis disease status — no. (%)		
Newly diagnosed	115 (69.3)	114 (69.5)
Relapsed	51 (30.7)	50 (30.5)
ANCA status — no. (%)		
Antiproteinase 3 positive	72 (43.4)	70 (42.7)
Antimyeloperoxidase positive	94 (56.6)	94 (57.3)
Type of vasculitis — no. (%)		
Granulomatosis with polyangiitis	91 (54.8)	90 (54.9)
Microscopic polyangiitis	75 (45.2)	74 (45.1)
Birmingham Vasculitis Activity Score§	16.3±5.9	16.2±5.7
Vasculitis Damage Index¶	0.7±1.5	0.7±1.4
Immunosuppressant induction treatment — no. (%)		
Intravenous rituximab	107 (64.5)	107 (65.2)
Intravenous cyclophosphamide	51 (30.7)	51 (31.1)
Oral cyclophosphamide	8 (4.8)	6 (3.7)

Population de l'étude ADVOCATE

Characteristic	Avacopan (N=166)	Prednisone (N=164)
Organ involvement — no. (%)‖		
Renal	134 (80.7)	134 (81.7)
General	111 (66.9)	114 (69.5)
Ear, nose, and throat	75 (45.2)	69 (42.1)
Chest	71 (42.8)	71 (43.3)
Nervous system	38 (22.9)	31 (18.9)
Mucous membranes or eyes	26 (15.7)	40 (24.4)
Cutaneous	24 (14.5)	23 (14.0)
Cardiovascular	6 (3.6)	3 (1.8)
Abdominal	4 (2.4)	1 (0.6)
Glucocorticoid use during screening period		
Use of any glucocorticoids — no. (%)	125 (75.3)	135 (82.3)
Intravenous use	63 (38.0)	73 (44.5)
Oral use	99 (59.6)	113 (68.9)
Total prednisone-equivalent dose — mg**	654.0±744.4	727.8±787.8
Daily prednisone-equivalent dose — mg**	46.7±53.2	52.0±56.3

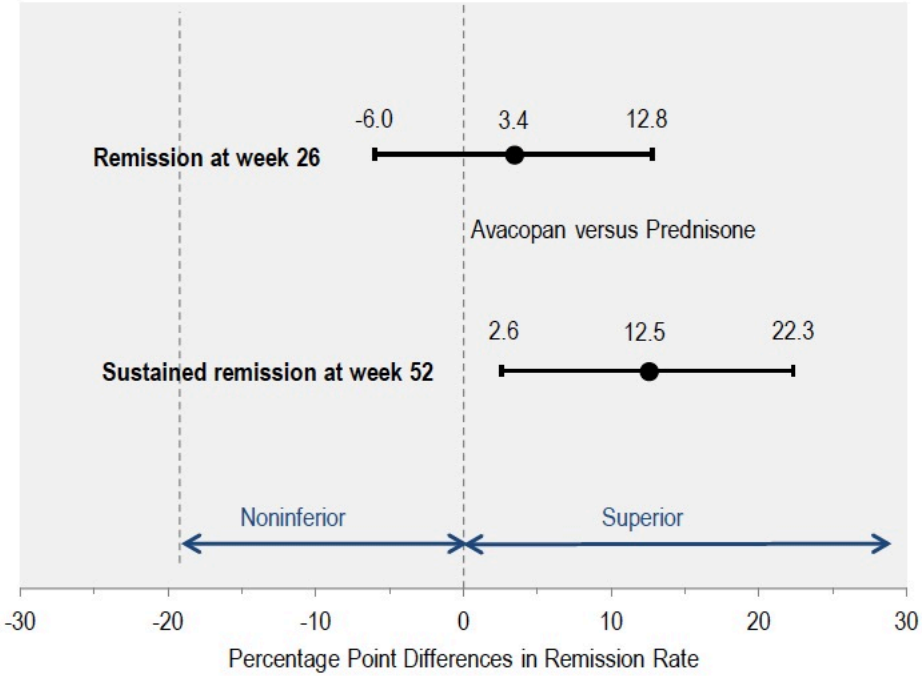
Dose moyenne de glucocorticoïdes



Dose moyenne totale de prednisone de 1349 mg dans le bras avacopan versus 3655 mg dans le bras prednisone

Critère de jugement principal

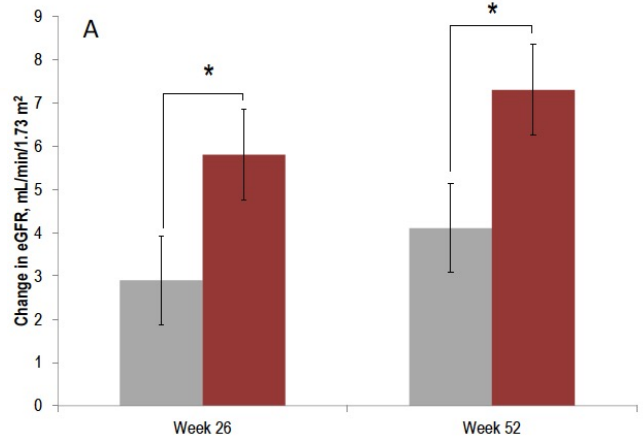
End Point	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Primary end points			
Remission at wk 26 — no. (%)†	120 (72.3)	115 (70.1)	3.4 (–6.0 to 12.8)‡§
Sustained remission at wk 52 — no. (%)¶	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3)‡‖

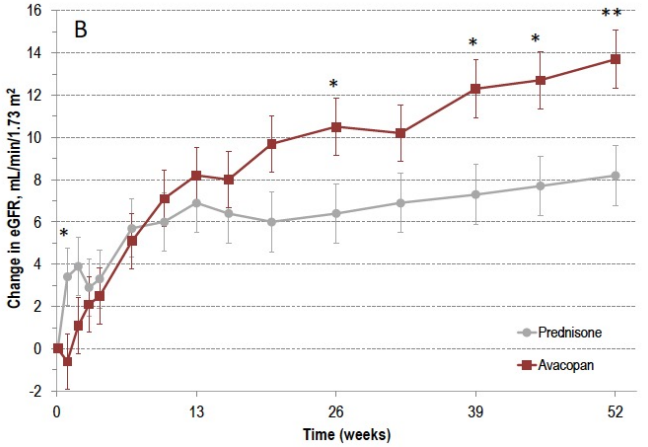


Essai de non-infériorité de l'avacopan pour le critère de jugement à S26, avec une marge de non-infériorité de -20% et un taux de rémission sous prednisone de 60%

Critères de jugement secondaires

End Point	Avacopan (N=166)	Prednisone (N=164)	Difference (95% CI)
Secondary end points			
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)
Urinary albumin:creatinine ratio‖‖			
Baseline			
Patients evaluated	125	128	
Geometric mean (range)	433 (20–6461)	312 (11–5367)	
Percent change from baseline to wk 4			
Patients evaluated	121	124	
Least-squares mean ±SE	−40±10	0±9	−40 (−53 to −22)
Percent change from baseline to wk 52			
Patients evaluated	109	114	
Least-squares mean	−74±10	−77±10	12 (−14 to 45)





Tolérance

Effets indésirables graves (hors vascularite) chez 37,3% Des patients dans le bras avacopan et 39,0% dans le bras prednisone

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)
Any infection		
No. of patients (%)	113 (68.1)	124 (75.6)
No. of events	233	291
Any serious infection¶		
No. of patients (%)	22 (13.3)	25 (15.2)
No. of events	25	31
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)
Any adverse event potentially related to glucocorticoids — no. (%)**	110 (66.3)	132 (80.5)
Cardiovascular	72 (43.4)	85 (51.8)
Infectious	22 (13.3)	25 (15.2)
Gastrointestinal	3 (1.8)	4 (2.4)
Psychological	27 (16.3)	39 (23.8)
Endocrine or metabolic	23 (13.9)	48 (29.3)
Dermatologic	14 (8.4)	28 (17.1)
Musculoskeletal	19 (11.4)	21 (12.8)
Ophthalmologic	7 (4.2)	12 (7.3)

CONCLUSIONS

In this trial involving patients with ANCA-associated vasculitis, avacopan was noninferior but not superior to prednisone taper with respect to remission at week 26 and was superior to prednisone taper with respect to sustained remission at week 52. All the patients received cyclophosphamide or rituximab. The safety and clinical effects of avacopan beyond 52 weeks were not addressed in the trial.

Discussion

Forces

Mécanisme d'action d'innovant issu de la connaissance de la physiopathologie et de modèles pré-cliniques

Première molécule *challengeant* les corticoïdes = révolution thérapeutique

Effet rapide sur les paramètres rénaux +++

Limites

Temps d'exposition à l'avacopan (52 semaines) > corticoïdes (20 semaines)

Traitement d'induction par rituximab sans possibilité de faire de rituximab d'entretien (risque accru de rechute)

Quasi aucune différence dans l'exposition aux glucocorticoïdes après la 20ème semaine