Université de Bretagne Occidentale

Centre de Référence des Maladies Auto-Immunes Systémiques Rares du Nord et Nord-Ouest

Effets secondaires des corticoïdes

et comment les éviter (les corticoïdes) dans le traitement des maladies systémiques

Divi Cornec, Rhumatologie CHU Brest

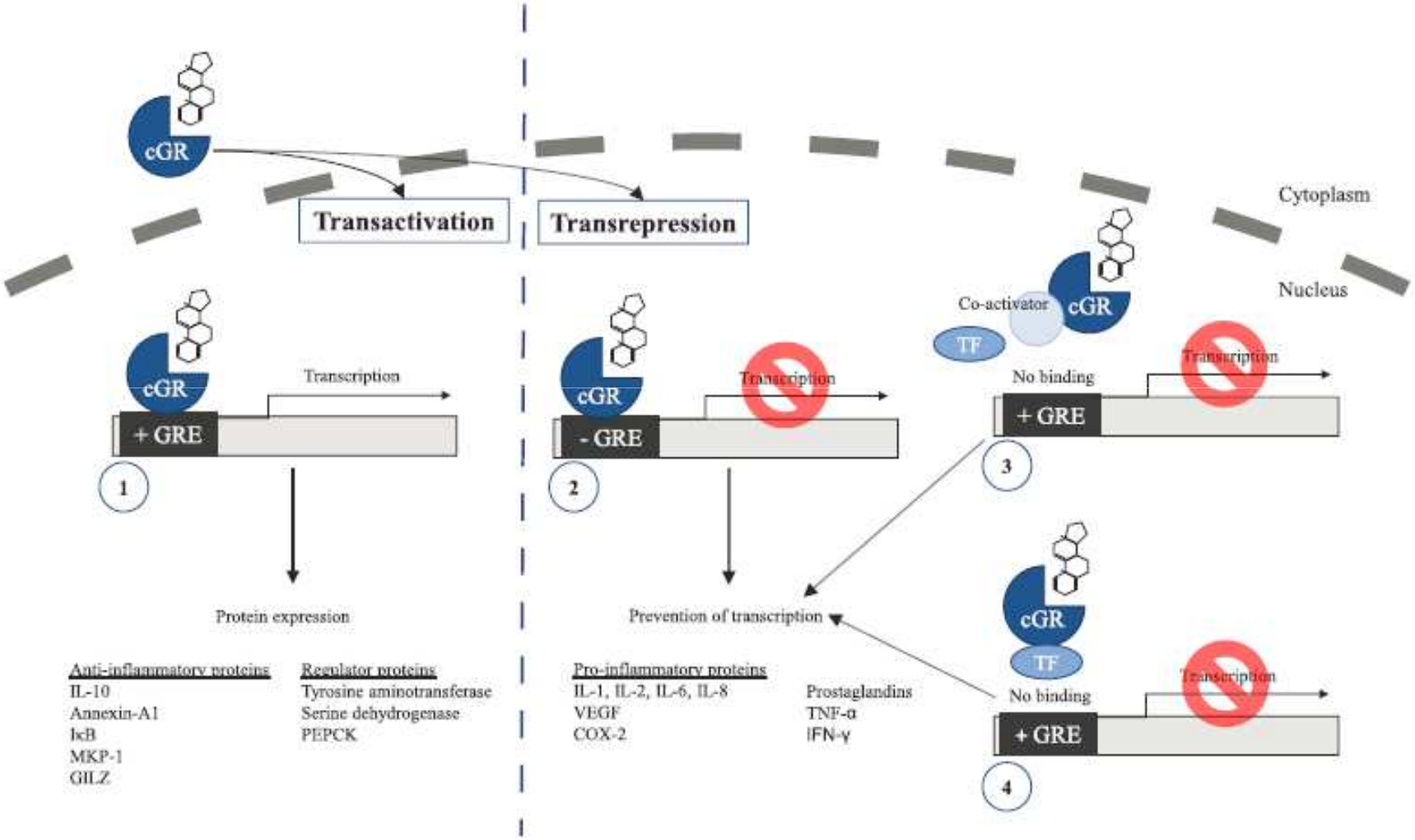
LBAI U1227

CHRU BREST CENTRE HOSPITALIER REGIONAL UNIVERSITAIRE

Agenda

- Effets secondaires des corticoïdes
- Est-ce un vrai problème pour toutes les pathologies ?
- Comment les éviter (les corticoïdes) ?

FIG. 1 Genomic mechanisms of action of glucocorticoids



Buttgereit et al, Rheumatology 2018

TABLE 1 Glucocorticoid-related adverse events according to mechanism of action

Transactivation	Partial transactivation	Transrepression
Arterial hypertension	Osteoporosis	Infections
Diabetes mellitus	Skin atrophy	Hypothalamic–pituitary axis suppression
Glaucoma	Growth retardation	
	Cushingoid appearance	

Buttgereit et al, Rheumatology 2018

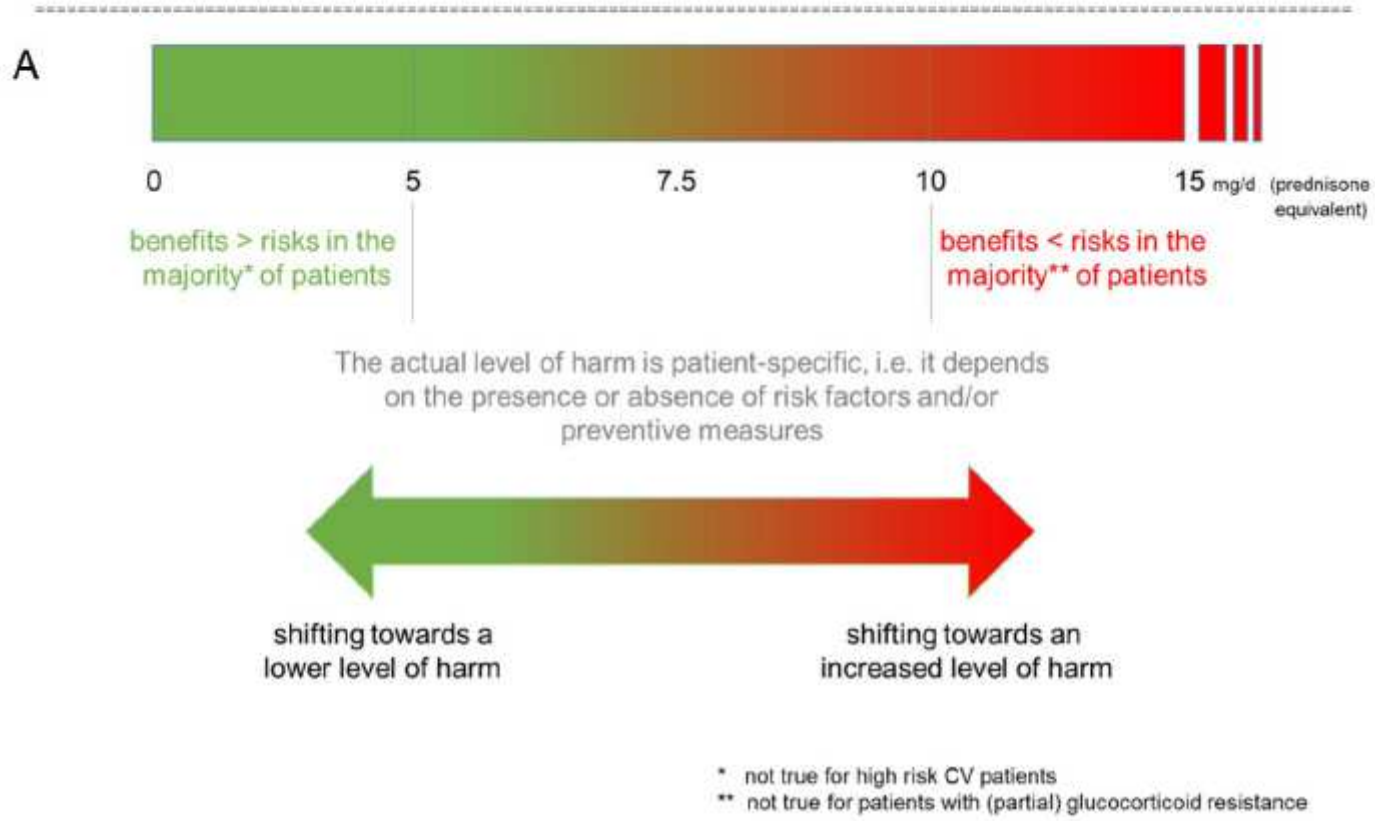
Par exemple dans le Horton

TABLE 2 Incidence of glucocorticoid-related adverse events based on claims data

Adverse event	Events/patient-year[a]	Hazard ratio per 1000 mg[b] increase in cumulative exposure (95% CI)	Percentage increase per 1000 mg[b] increase in cumulative exposure
Any	0.426	1.03 (1.02, 1.05)	3
Cataract	0.158	1.03 (1.02, 1.05)	3
Bone disease	0.156	1.05 (1.03, 1.06)	5
Osteoporosis	0.099	1.05 (1.03, 1.07)	5
Fracture	0.066	1.04 (1.03, 1.06)	4
Hip replacement	0.008	1.04 (0.99, 1.08)	4
Aseptic necrosis of bone	0.004	1.06 (1.01, 1.12)	6
Pneumonia	0.068	1.03 (1.01, 1.04)	3
Glaucoma	0.022	1.05 (1.01, 1.08)	5
Opportunistic infections	0.010	1.04 (1.00, 1.08)	4
Ulcer disease	0.006	1.00 (0.94, 1.06)	0

Buttgereit et al, Rheumatology 2018

Prévention des effets secondaires



Strehl et al, Ann Rheum Dis 2016

Prévention des effets secondaires

B

	Factors	References
General	early diagnosis, low disease activity, low cumulative glucocorticoid dosage, healthy life style (especially cessation of smoking, low alcohol consumption), monitoring and treatment of risk factors and co-morbidities	[1] [21] [37]
Glucocorticoid-induced osteoporosis	sufficient vitamin D & calcium intake, exercise, muscle strengthening, prescription on indication: bisphosphonates, osteoanabolic drugs, selective oestrogen receptor modulators	[36] [39] [40] [41] [42]
Infections	screening for infections, vaccination, usage of risk scores before therapy, follow rules of conduct (avoiding infected persons, appropriate wound care, washing hands, good sleep)	[44] [50] [52]
Carbohydrate metabolism	healthy diet, appropriate exercise, weight loss for obese patients, prescription on indication: hydroxychloroquine, diuretics	[58] [59]
Cardiovascular	diet in low saturated fat & calories, physical activity, weight normalization, sodium restriction, follow the EULAR-recommendations for cardiovascular risk management (including medications like statins or angiotensin-converting enzyme inhibitors on indication)	[2] [60] [70] [75] [76] [77]

Strehl et al, Ann Rheum Dis 2016

Fréquence des EI vs incidence chez des sujets *comparables* ? Exemple de la PPR

Table 1. Distribution of current and cumulative prednisone-equivalent glucocorticoid (GC) dosage in patients with polymyalgia rheumatica

	Starting dose	1 year	2 years	5 years	10 years
Current dose, mg/day*					
No.	352	229	130	57	16
Mean ± SD	16.9 ± 7.1	5.9 ± 5.6	6.1 ± 7.6	7.2 ± 9.5	9.1 ± 14.1
Median	15.0	5.0	4.4	5.0	5.0
Quartile 1, quartile 3	15.0, 20.0	2.8, 7.6	2.5, 7.0	3.0, 6.8	3.0, 9.1
Range	5.0–60.0	1.0–60.0	1.0–60.0	1.0–60.0	1.0–60.0
Cumulative dose, grams†					
No.	359	334	302	201	78
Mean ± SD	0.0 ± 0.0	2.9 ± 1.8	4.0 ± 3.5	6.3 ± 9.8	9.4 ± 25.1
Median	0.0	2.7	3.4	3.9	4.2
Quartile 1, quartile 3	0.0, 0.0	1.9, 3.6	2.1, 5.4	2.1, 7.9	1.9, 8.4
Range	0.0–0.1	0.0–21.8	0.0–43.7	0.0–109.4	0.0–218.9

* Among patients on GC at each time point.
† Among all patients being followed, still under observation at each time point, including patients who are no longer on GC therapy.

Shbeeb et al Artritis Care Res 2017

Fréquence des EI vs incidence chez des sujets *comparables* ? Exemple de la PPR

Table 2. Glucocorticoid-related complication rates in patients with polymyalgia rheumatica (PMR) and comparators without PMR*

Complication	Electronic coding, %		No. of events†		Cumulative incidence (95% CI)		
	Agreement‡	Excess events§	Before	After	At 5 years, PMR	At 5 years, non-PMR	HR (95% CI)
Diabetes mellitus	81	18	93/104	38/39	9.5 (5.8–13.1)	11.5 (7.3–15.5)	0.85 (0.54–1.33)
Hypertension	85	13	255/253	42/47	30.4 (20.2–39.2)	33.4 (23.3–42.2)	0.79 (0.52–1.21)
Hyperlipidemia	78	21	276/268	28/30	24.0 (13.6–33.1)	26.6 (16.6–35.4)	1.03 (0.61–1.74)
Cataracts	85	10	203/197	77/66	41.0 (32.1–48.7)	27.3 (19.8–34.2)	1.72 (1.23–2.41)
Hip or femoral neck fracture	99	1	NA	21/25	3.9 (1.8–6.0)	5.1 (2.7–7.4)	0.80 (0.45–1.43)
Symptomatic vertebral fracture	90	3	NA	22/17	3.9 (1.8–6.0)	2.4 (0.7–4.0)	1.27 (0.67–2.39)
Colles fracture	99	3	NA	15/13	2.4 (0.7–4.0)	2.5 (0.8–4.2)	1.11 (0.53–2.33)
Any fracture	90	4	NA	49/49	9.5 (5.8–13.1)	11.5 (7.3–15.5)	0.85 (0.54–1.33)

* 95% CI = 95% confidence interval; HR = hazard ratio; NA = not applicable.
† PMR incidence/non-PMR index date.
‡ Agreement between electronic coding and manual abstraction.
§ Excess events by coding.

Shbeeb et al Artritis Care Res 2017

Comment les réduire (éliminer) dans les maladies systémiques ?

- Utiliser de plus fortes doses… au début : preuves d'efficacité des bolus IV ?
- Utiliser de plus faibles doses, moins longtemps ?
- Ne pas en utiliser du tout ??
- Les remplacer par d'autres traitements ?

Bolus de solumédrol

- Dans quelles pathologies l'efficacité des bolus de solumédrol est-elle suggérée par des études ?
  - La PR
  - Les myosites
  - Le Horton
  - Les vascularites à ANCA
  - Le lupus systémique

Bolus de solumédrol

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  - Le Horton
  - Les vascularites à ANCA
  - Le lupus systémique

Efficacité des bolus IV ?

- Horton
  - 13 patients PBO
  - 14 patients bolus (3*1g)
  - Tous prednisone 40 mg puis décroissance protocolisée
  - Suivi 18 mois

Table 2. Remission rates and median daily dose of prednisone at 36, 52, and 78 weeks according to intervention*

Weeks treated, treatment group	No. of patients with disease in remission and receiving ≤5 mg/day prednisone	Prednisone dosage, median (IQR) mg/day

Table 3. Relapse rates according to intervention group*

	Placebo group		IV GC group	
No. of flares	No. of patients†	Total flares	No. of patients†	Total flares
0	1	0	4	0
1	1	1	2	2
2	2	4	5	10
3	5	15	3	9
4	3	12	0	0
5	1	5	0	0
Total	13	37	14	21

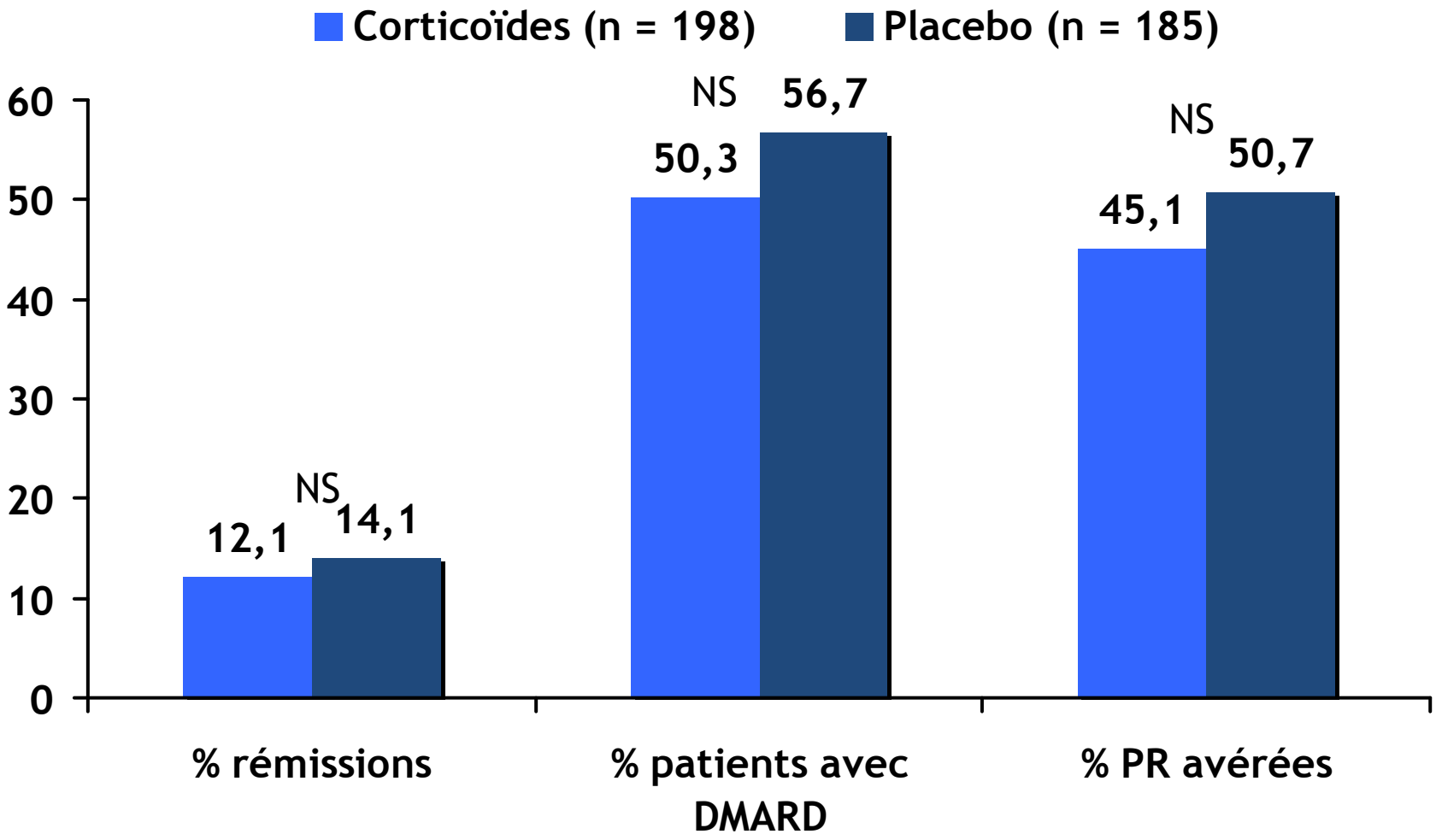
Mazlumzadeh et al, Arthritis Rheum 2006

Polyarthrite indifférenciée et bolus de corticoïde : étude SAVE (Stop Arthritis Very Early)

- Etude multicentrique, randomisée en double aveugle
- Arthrites indifférenciées récentes (< 16 semaines d'ancienneté)
- 1 injection IM , soit de 120 mg de méthylprednisolone (n = 198), soit de placebo (n = 185)
- Suivi effectué sur 12 mois
- Critère principal d'évaluation : rémission sans traitement à 1 an

Machold et al, Ann Rheum Dis 2010

Polyarthrite indifférenciée et bolus de corticoïdes - Etude SAVE à 1 an



EULAR 2009 - D'après une communication de KP. Machold - OP-0131
Ann Rheum Dis 2009;68(Suppl3):113

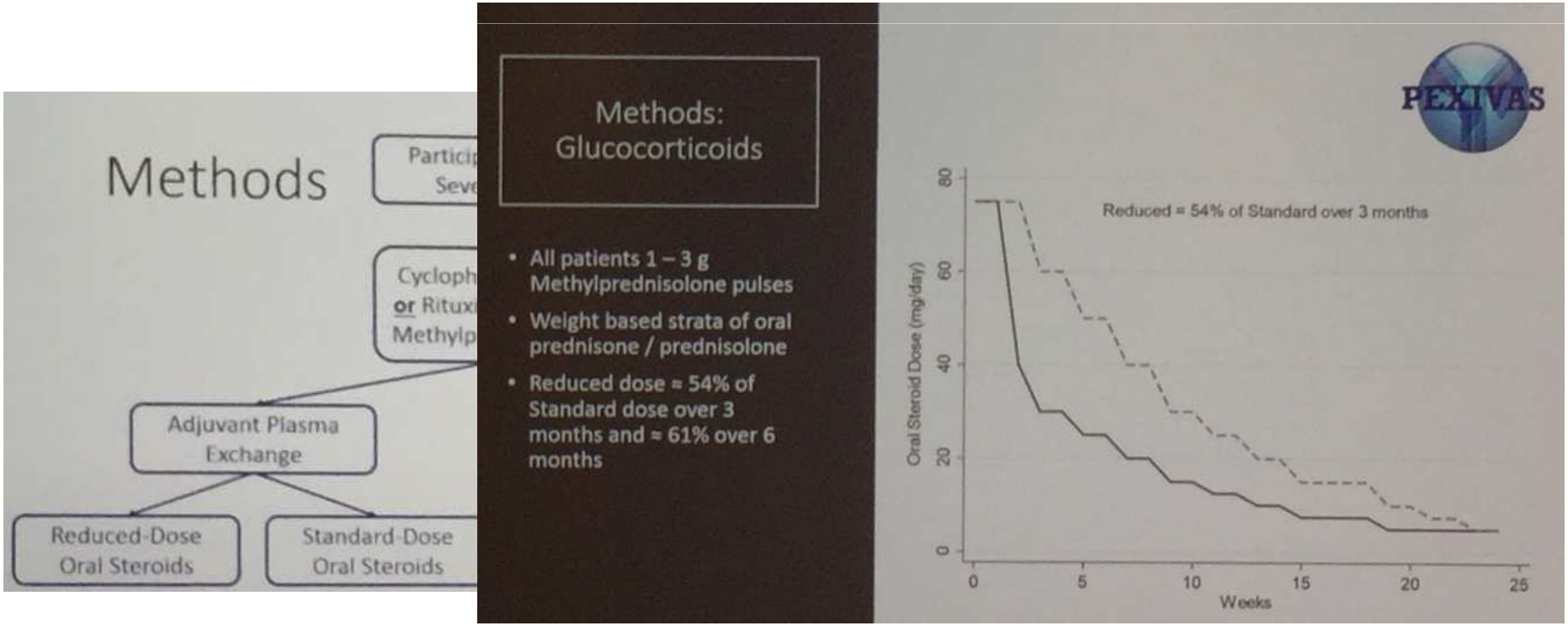
Parmi ces pathologies, lesquelles doivent être traitées par de fortes doses de corticoïdes oraux ?

- *(Par exemple 0,7 à 1 mg/kg 1 mois puis décroissance progressive sur 12 à 18 mois)*

- Vascularite à ANCA sévère
- Lupus avec atteinte rénale
- Artérite à cellule géante
- Dermatomyosite
- Maladie de Still

Diminuer les doses/durée de prednisone ?

- Vascularites associées aux ANCA : PEXIVAS
- > 700 patients avec vascularite sévère
- Double randomisation

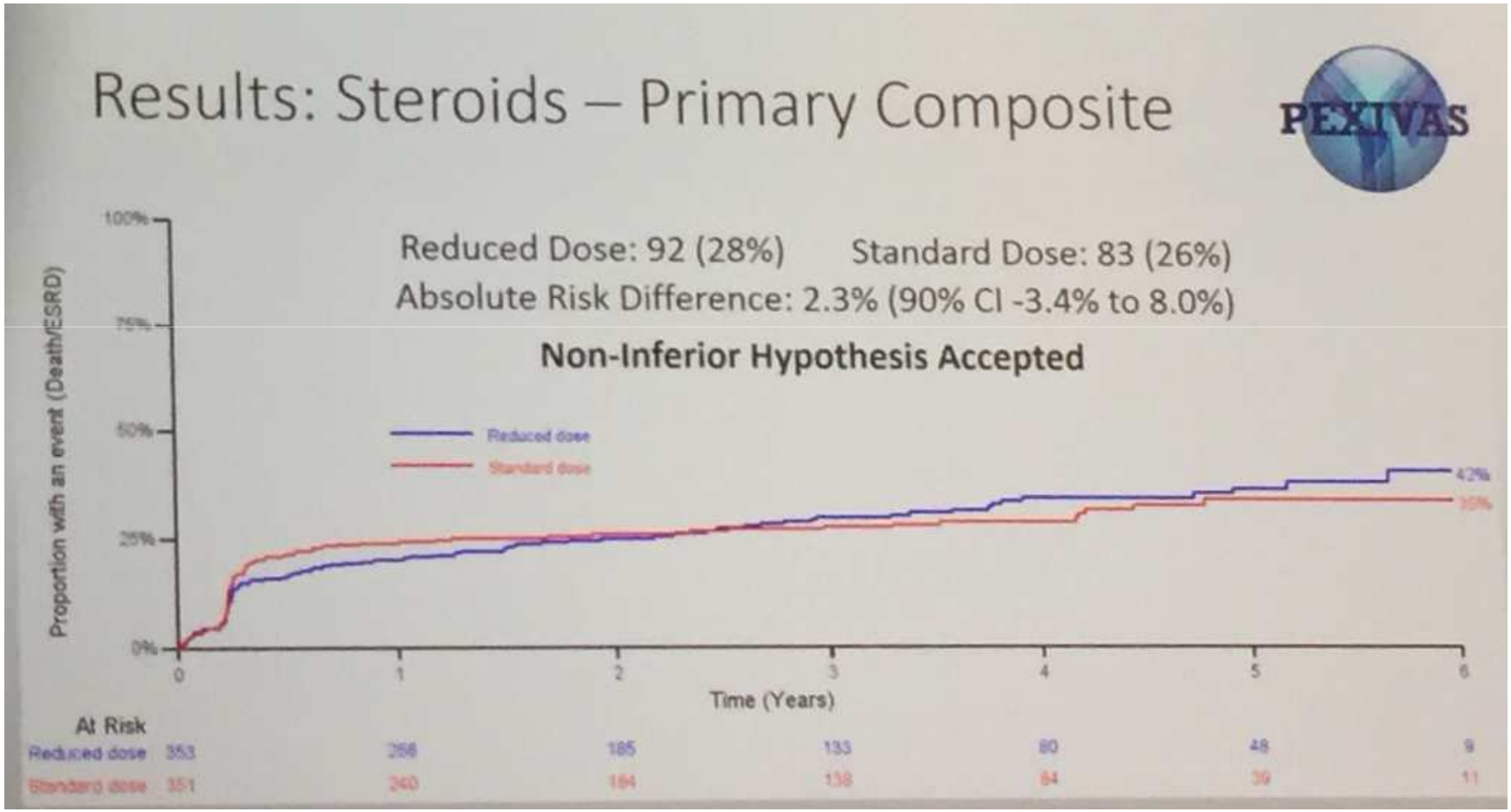


PEXIVAS

Results: Participants

Characteristic	PLEX (n=352)	Control (n=352)	Reduced Dose (n=353)	Standard Dose (n=351)
Mean age, years (SD)	62.8 (14.4)	63.5 (13.7)	63.3 (14.2)	63.1 (13.9)
Female, n (%)	149 (42.3)	158 (44.9)	156 (44.2)	151 (43.0)
Dominant ANCA, n (%)				
PR3+	143 (40.6)	143 (40.6)	143 (40.5)	143 (40.7)
MPO+	209 (59.4)	209 (59.4)	210 (59.5)	208 (59.3)
Lung Hemorrhage, n (%)				
Any	95 (27.0)	96 (27.3)	96 (27.2)	95 (27.0)
Severe	31 (8.8)	30 (8.5)	31 (8.8)	30 (8.5)
Creatinine				
Median (25^{th} - 75^{th})	327 (206 – 491)	335.9 (209 – 495)	320 (190 – 480)	335 (219 – 502)
>500 umol/L, n (%)	101 (28.7)	104 (29.5)	102 (28.9)	103 (29.3)
On Dialysis, n (%)	66 (18.8)	74 (21.0)	67 (19.0)	73 (20.8)
Immunosuppression, n(%)				
IV Cyclophos.	177 (50.3)	177 (50.3)	179 (50.7)	175 (49.9)
Oral Cyclophos.	120 (34.1)	121 (34.3)	120 (34.0)	121 (34.5)
Rituximab	55 (15.6)	54 (15.4)	54 (15.3)	55 (15.6)

PEXIVAS

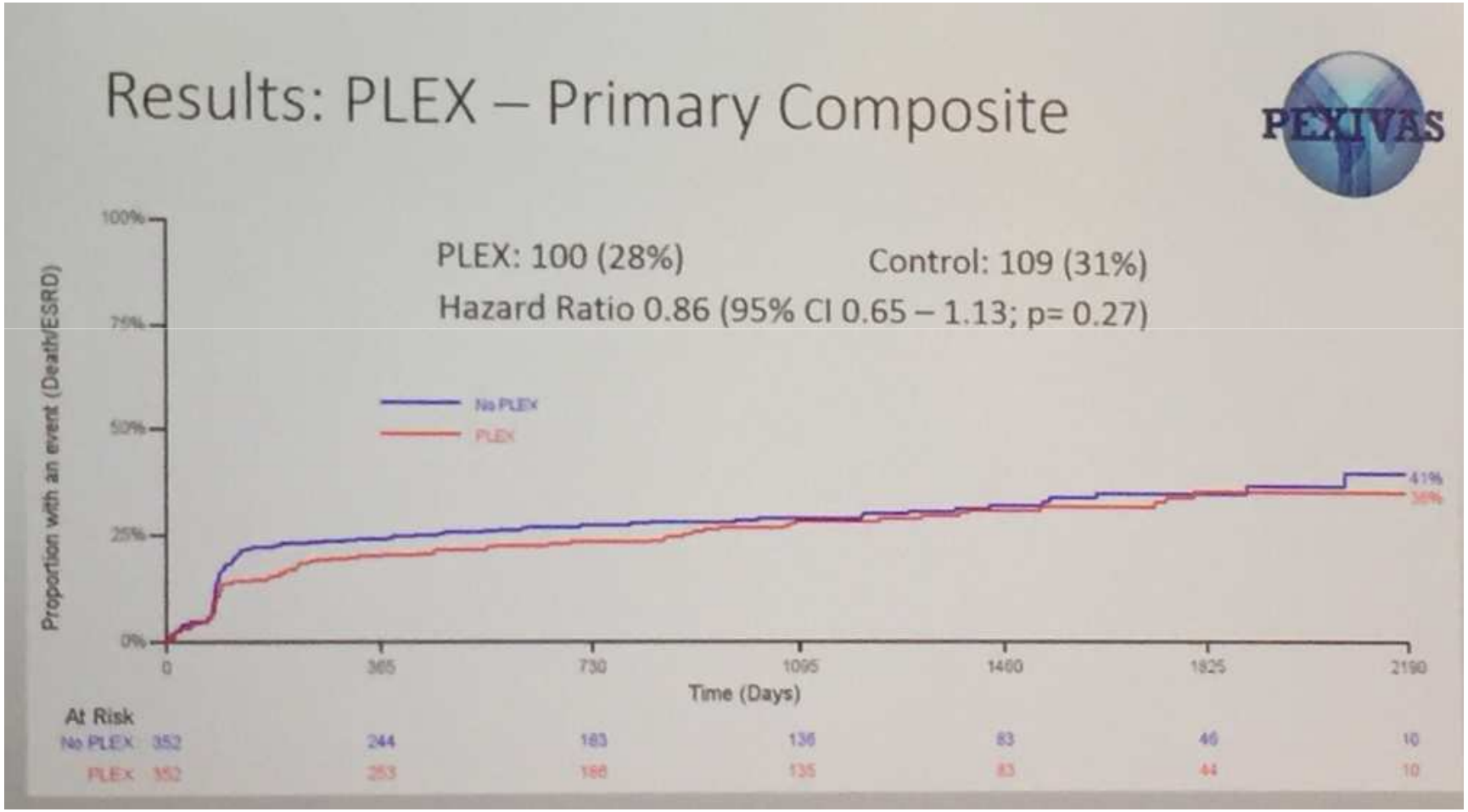

Results: Steroids – Primary Composite
PEXIVAS
Reduced Dose: 92 (28%)
Standard Dose: 83 (26%)
Absolute Risk Difference: 2.3% (90% CI -3.4% to 8.0%)
Non-Inferior Hypothesis Accepted
Proportion with an event (Death/ESRD)
100%
75%
50%
25%
0%
Reduced dose
Standard dose
42%
35%
0
1
2
3
4
5
6
Time (Years)
At Risk
Reduced dose 353 268 185 133 80 48 9
Standard dose 351 240 164 138 84 39 11

PEXIVAS

Results: Steroids – Secondary Outcomes

Outcome	Reduced	Standard	Hazard Ratio (95% CI)	P-value
Death, n (%)	46 (13)	53 (15)	0.78 (0.53 – 1.17)	0.23
ESRD, n (%)	70 (20)	68 (19)	0.96 (0.68 – 1.34)	0.65
Sustained Remission, n (%)	204 (58)	193 (55)	1.04 (0.92 – 1.19)	0.48
SAEs, n (%)	231 (65)	218 (62)	1.05 (0.94 – 1.17)	0.20
			Incidence Rate Ratio (95% CI)	
Year 1 Serious Infections, n (%)	96 (27)	116 (33)	0.70 (0.52 – 0.94)	0.02

PEXIVAS


Results: PLEX – Primary Composite
PEXIVAS
PLEX: 100 (28%)
Control: 109 (31%)
Hazard Ratio 0.86 (95% CI 0.65 – 1.13; p= 0.27)
No PLEX
PLEX
Proportion with an event (Death/ESRD)
100%
75%
50%
25%
0%
41%
0
365
730
1095
1460
1825
2190
Time (Days)
At Risk
No PLEX 352 244 183 136 83 46 10
PLEX 352 253 166 135 83 44 10

Diminuer les doses ?

- L'exemple de GiACTA

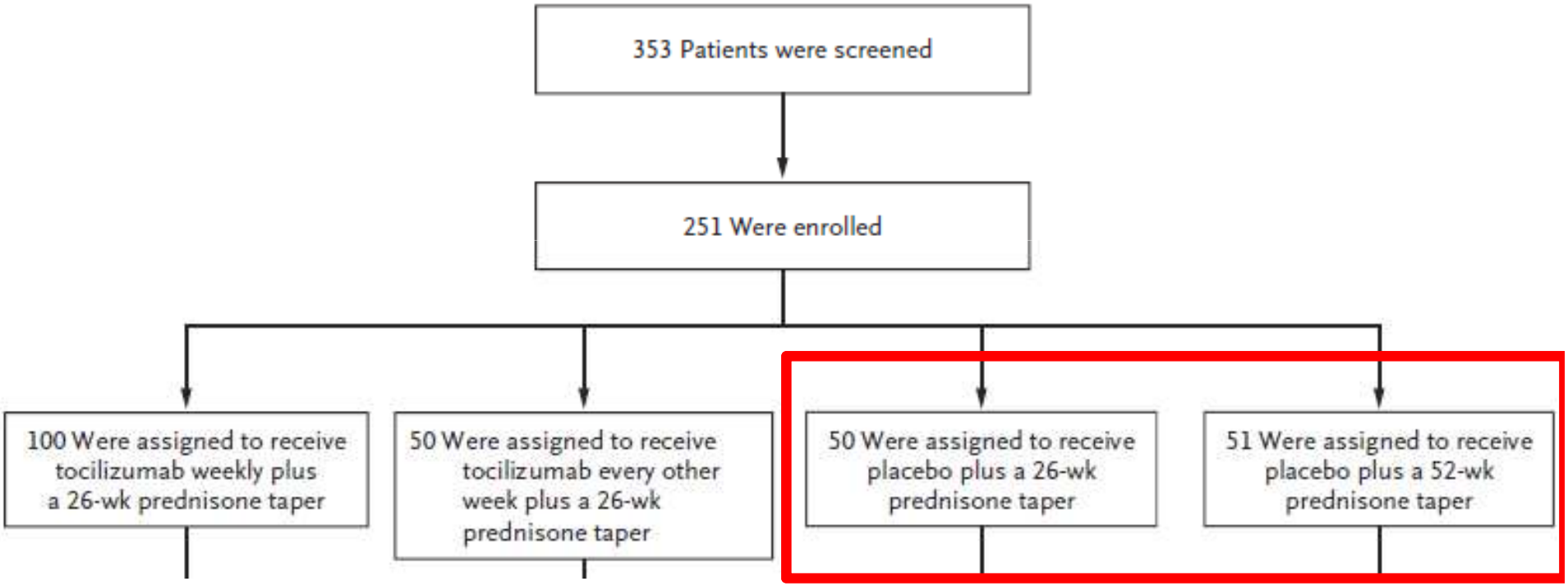
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 27, 2017 VOL. 377 NO. 4

Trial of Tocilizumab in Giant-Cell Arteritis

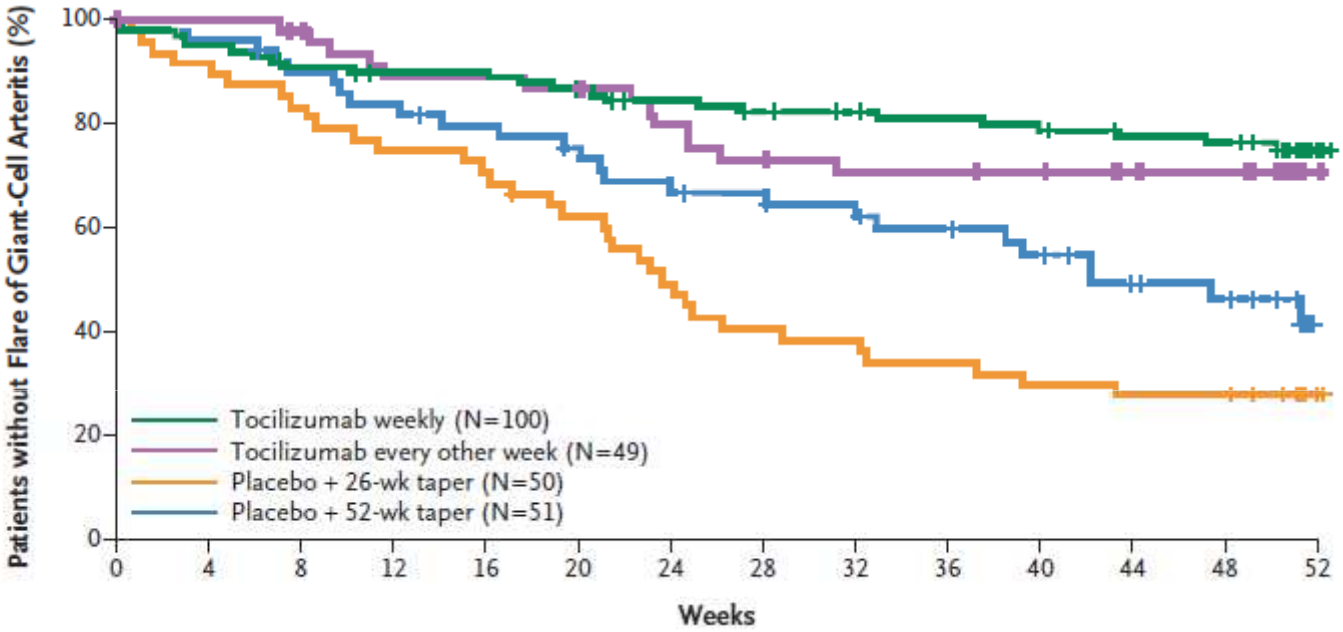
J.H. Stone, K. Tuckwell, S. Dimonaco, M. Klearman, M. Aringer, D. Blockmans, E. Brouwer, M.C. Cid, B. Dasgupta, J. Rech, C. Salvarani, G. Schett, H. Schulze-Koops, R. Spiera, S.H. Unizony, and N. Collinson

Schéma de l'étude



Prednisone 26-Week Taper (n=200)							Prednisone 52-Week Taper (n=50)						
Taper week	**Dose, mg/day**	**5 mg**	**2.5 mg**	**1 mg**	**Placebo**		**Taper week**	**Dose, mg/day**	**5 mg**	**2.5 mg**	**1 mg**	**Placebo**	
1	60	Open-label supplied by sponsor Patient starts at any of these incremental doses				Open-label	1	60	Open-label supplied by sponsor Patient starts at any of these incremental doses				
2	50						2	50					
3	40						3	40					
4	35						4	35					
5	30						5	30					
6	25						6	25					
7	20						7	20					
8	15	3			1		8	17.5	3	1			
9	12.5	2	1		1		9	17.5	3	1			
10	12.5	2	1				10	15	3				
11	10	2			1		11	15	3				
12	9	1		4			12	12.5	2	1		2	
13	8	1		3			13	10	2			2	
14	7	1		2			14	10	2			1	
15	6	1		1			15	10	2				
16	6	1		1			16	10	2				
17	5	1			4		17	9	1		4		
18	5	1			4		18	9	1		4		
19	4			4	1		19	9	1		4		
20	4			4	1		20	9	1		4		
21	3			3	1		21	8	1		3		
22	3			3	1		22	8	1		3		
23	2			2	2		23	8	1		3		
24	2			2	2		24	8	1		3		

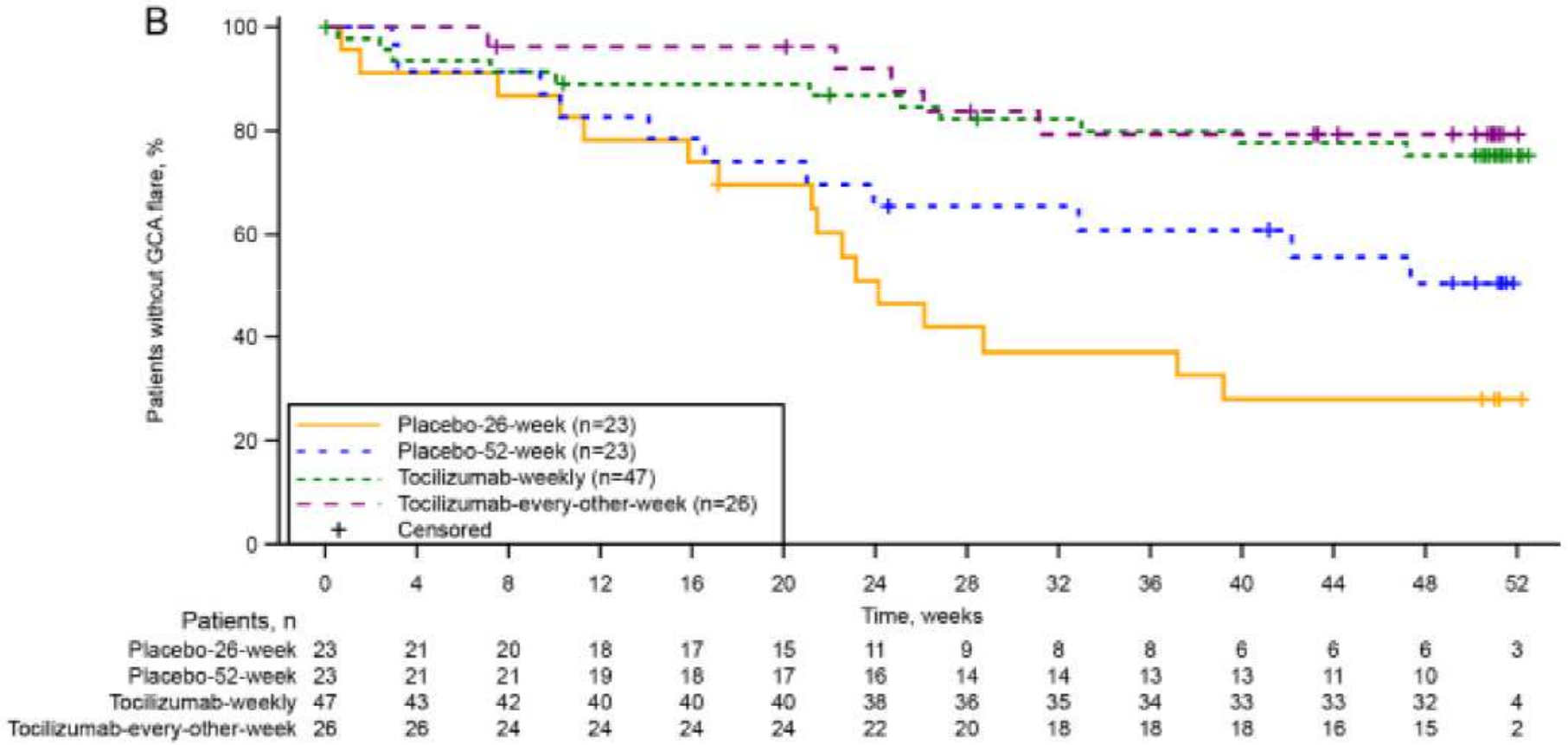
Efficacité



CUMULATIVE PREDNISONE DOSE

The total median cumulative prednisone dose over the 52-week period was 1862 mg (95% CI, 1582 to 1942) in the group that received tocilizumab weekly and 1862 mg (95% CI, 1568 to 2240) in the group that received tocilizumab every other week, as compared with 3296 mg (95% CI, 2730 to 4024) in the placebo group that underwent the 26-week taper and 3818 mg (95% CI, 2818 to 4426) in the placebo group that underwent the 52-week taper

Nouveaux diagnostics (47%)



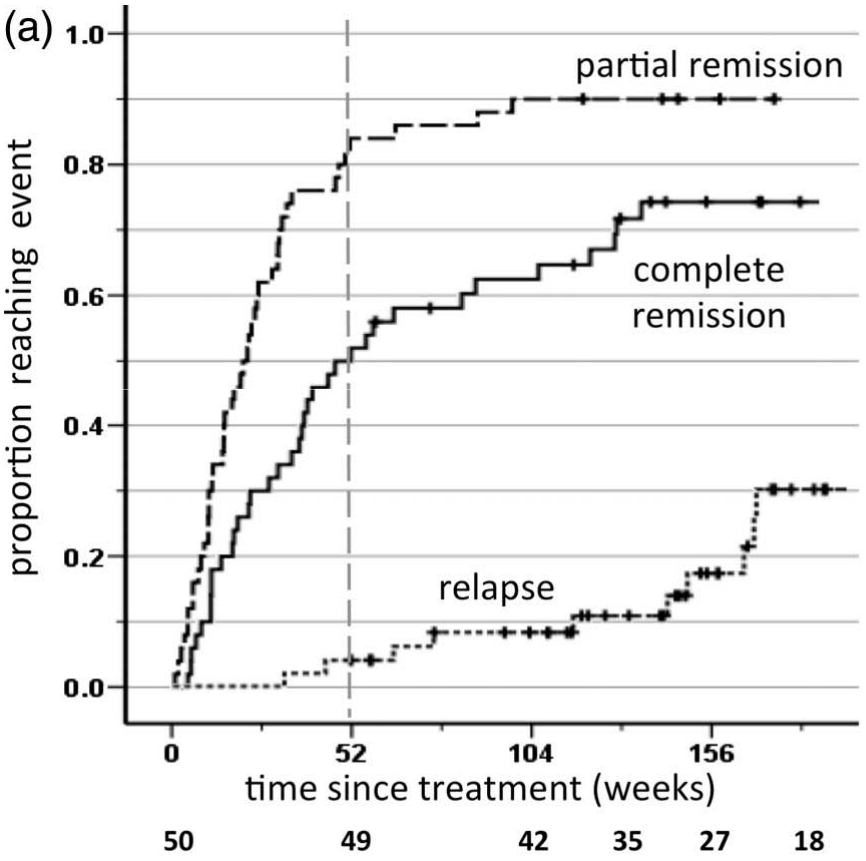
Tolérance

Table 3. Safety over the 52-Week Trial Period.*

Variable	Tocilizumab Weekly (N=100)	Tocilizumab Every Other Week (N=49)	Placebo +26-Wk Taper (N=50)	Placebo +52-Wk Taper (N=51)
Duration in trial — patient-yr	92.9	45.6	47.4	48.1
Patients with ≥1 adverse event — no. (%)	98 (98)	47 (96)	48 (96)	47 (92)
Adverse events				
No. of events	810	432	470	486
Rate per 100 patient-yr (95% CI)	872.0 (813.0–934.2)	948.0 (860.7–1041.7)	990.8 (903.2–1084.5)	1011.2 (923.3–1105.3)
Patients with ≥1 infection — no. (%)				
Any	75 (75)	36 (73)	38 (76)	33 (65)
Serious	7 (7)	2 (4)	2 (4)	6 (12)

Protocoles sans corticoïdes oraux ?

- RITUXILUP
  - Étude ouverte, 50 patients avec atteinte rénale (2006-2010, UK)
  - 2 injections de RTX 1g (+ 500 mg Solumedrol)
  - + MMF
- Définition définie sur critères rénaux
  - fonction rénale et protéinurie



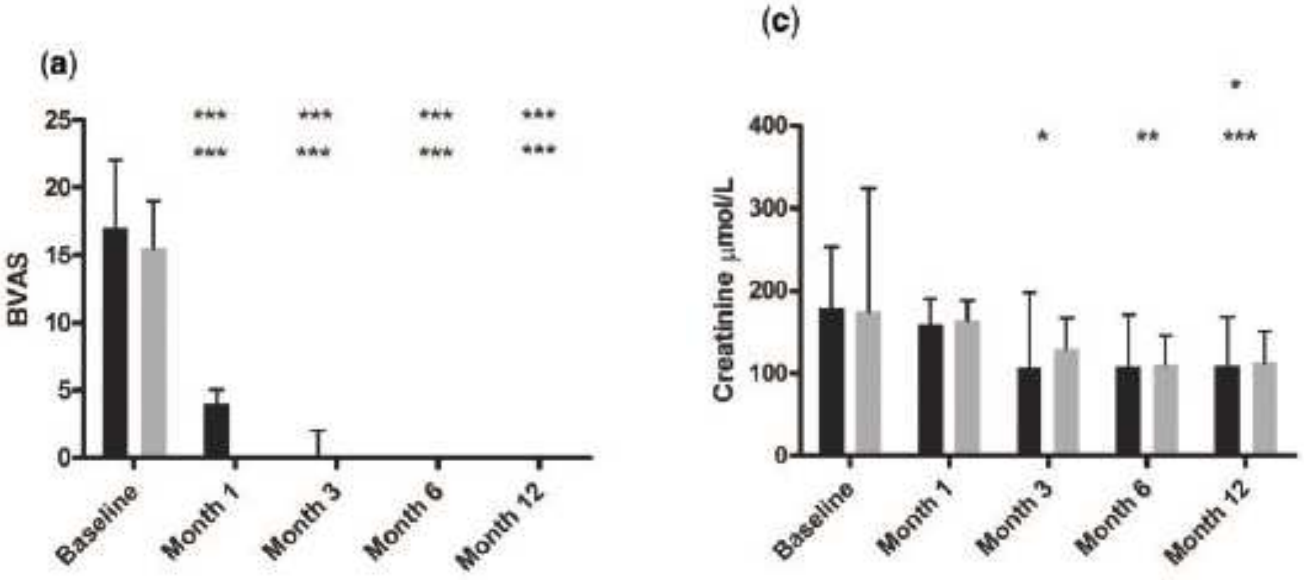
Condon et al, Ann Rheum Dis, 2013

RITUXILUP PHRC 2018

- Traitement d'induction des néphropathies lupiques sévères **sans adjonction de corticoïdes oraux** (CT): étude randomisée ouverte multicentrique comparant un traitement classique par **corticoïdes et mycophenolate mofetil** (MMF) **versus** un traitement par **Rituximab et MMF**
- Nathalie Costedoat, Hôpital Cochin

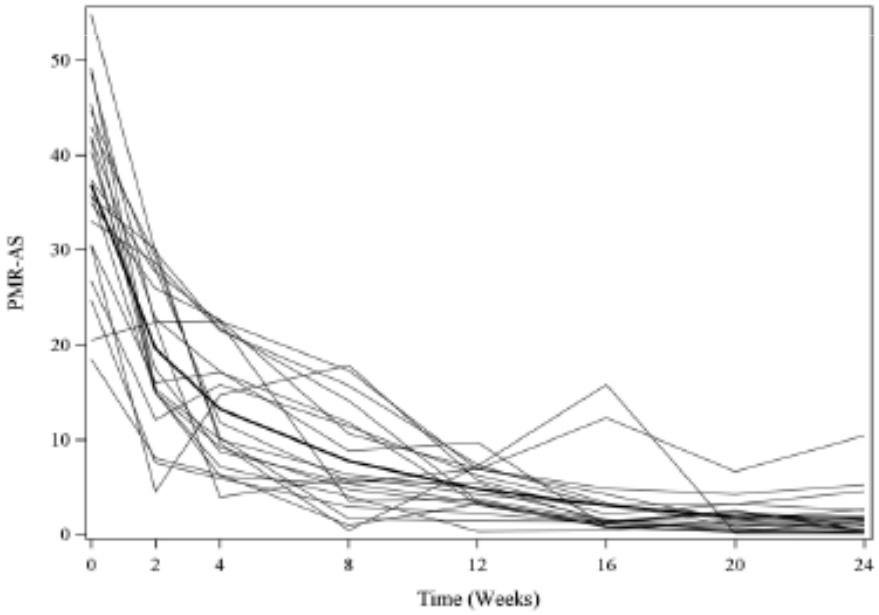
Vascularites à ANCA

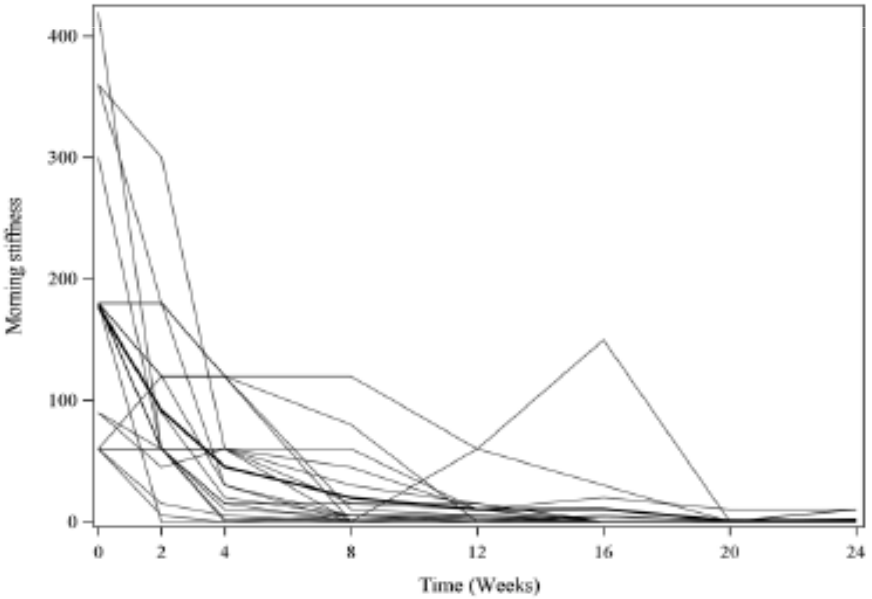
- Étude ouverte 49 patients (Londres et Dublin)
- Rituximab + 6 Endoxan IV +/- 1 bolus solumedrol + prednisone 1 à 2 semaines



Pepper et al, Rheumatology 2018

Traiter la PPR sans corticoïdes ?

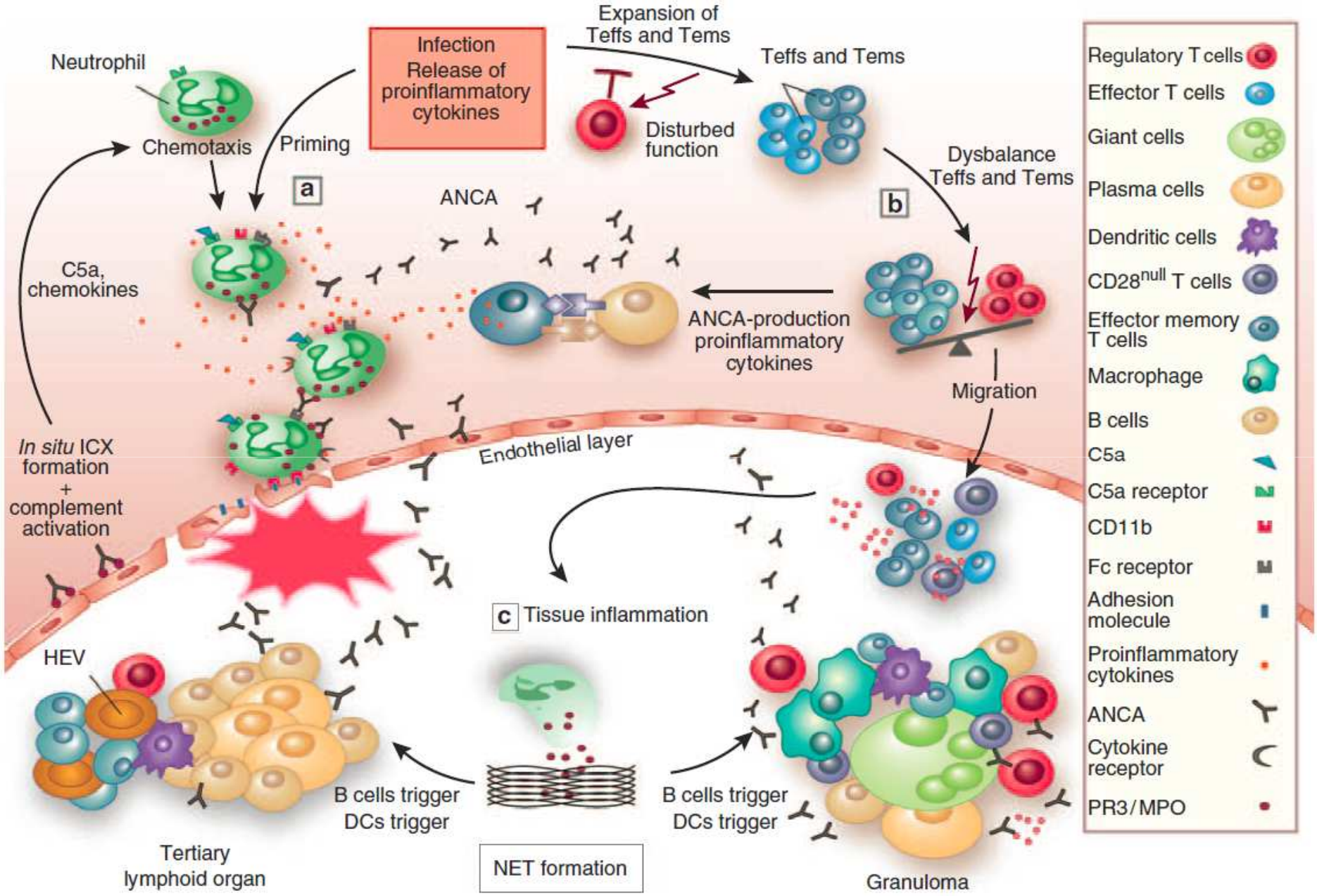




Devauchelle-Pensec et al, Ann Rheum Dis 2016

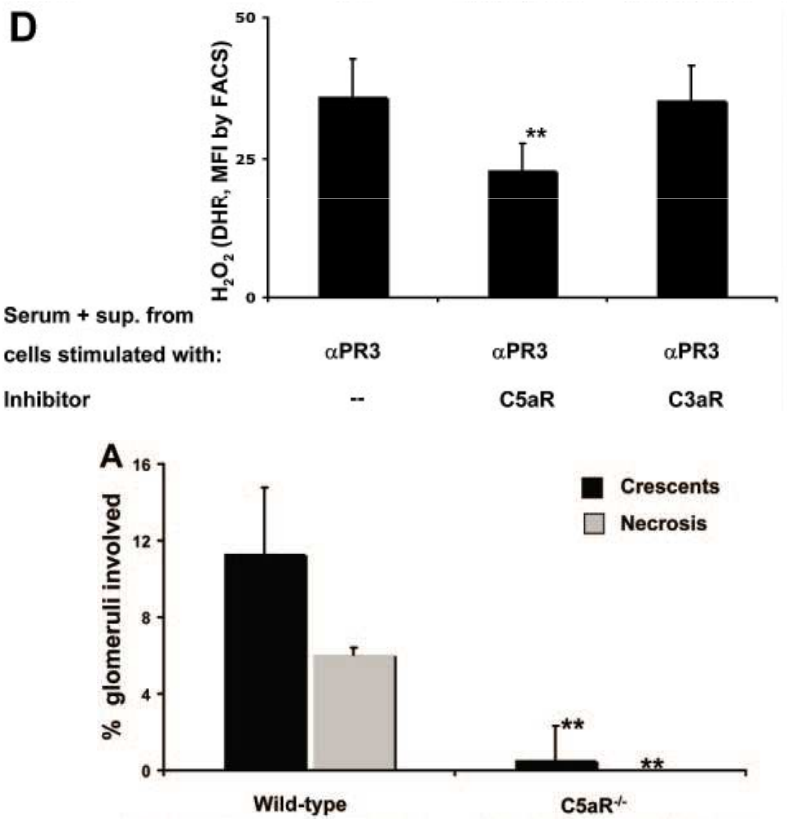
Des alternatives aux corticoïdes ?

Avacopan : bloquer le récepteur au C5a pour une révolution dans le traitement des vascularites à ANCA ?


Neutrophil
Chemotaxis
Priming
Infection
Release of proinflammatory cytokines
Expansion of Teffs and Tems
Teffs and Tems
Disturbed function
Dysbalance Teffs and Tems
a
b
ANCA
C5a, chemokines
ANCA-production proinflammatory cytokines
Migration
In situ ICX formation + complement activation
Endothelial layer
c Tissue inflammation
HEV
Tertiary lymphoid organ
B cells trigger DCs trigger
NET formation
B cells trigger DCs trigger
Granuloma
Regulatory T cells
Effector T cells
Giant cells
Plasma cells
Dendritic cells
CD28null T cells
Effector memory T cells
Macrophage
B cells
C5a
C5a receptor
CD11b
Fc receptor
Adhesion molecule
Proinflammatory cytokines
ANCA
Cytokine receptor
PR3/MPO

Bloquer le C5a-R ?

- 2009



J Am Soc Nephrol 20: 289–298, 2009

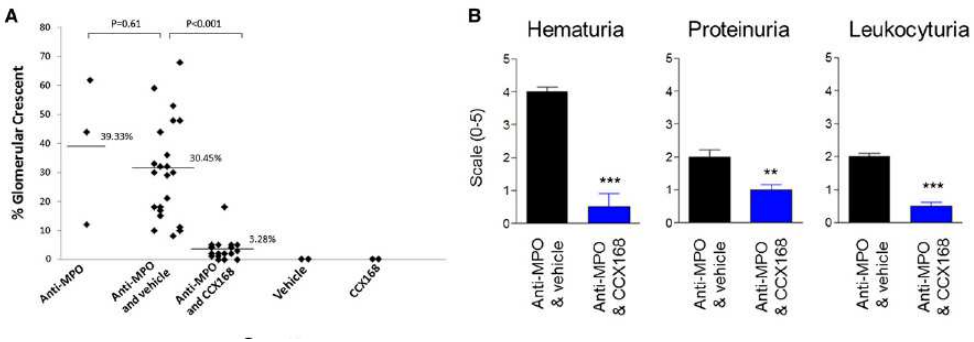
- 2014

BRIEF COMMUNICATION www.jasn.org

C5a Receptor (CD88) Blockade Protects against MPO-ANCA GN

Hong Xiao,*† Daniel J. Dairaghi,‡ Jay P. Powers,‡ Linda S. Ertl, ‡ Trageen Baumgart,‡ Yu Wang,‡ Lisa C. Seitz,‡ Mark E.T. Penfold,‡ Lin Gan,§ Peiqi Hu,*† Bao Lu,§ Norma P. Gerard,‖ Craig Gerard,‖ Thomas J. Schall,‡ Juan C. Jaen,‡ Ronald J. Falk,*† and J. Charles Jennette*†

*Department of Pathology and Laboratory Medicine and †UNC Kidney Center, University of North Carolina, Chapel Hill, North Carolina; ‡ChemoCentryx, Inc., Mountain View, California; §Department of Ophthalmology, University of Rochester, Rochester, New York; and ‖Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts



J Am Soc Nephrol 25: 225–231, 2014

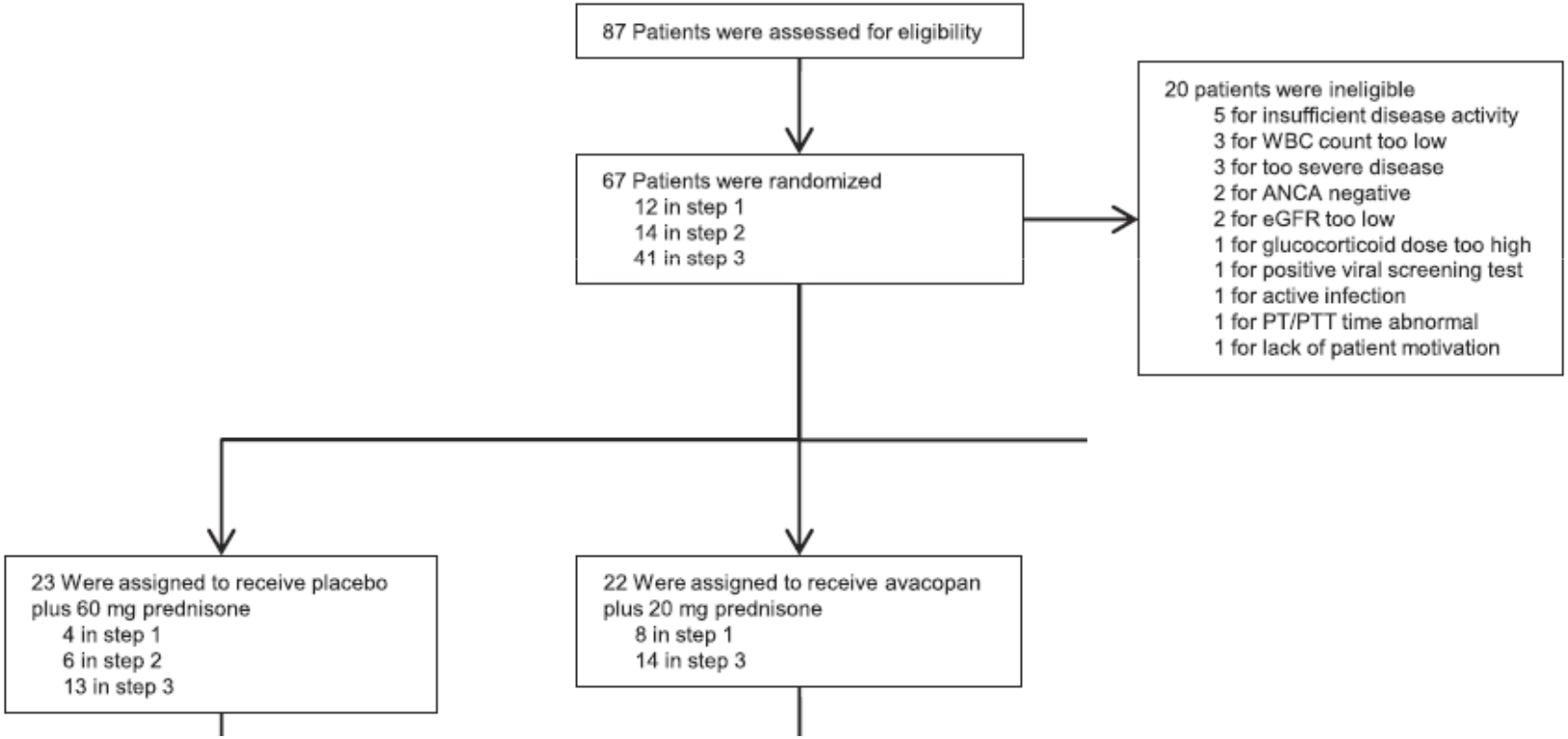
Avacopan – étude CLEAR

- Et en 2017…

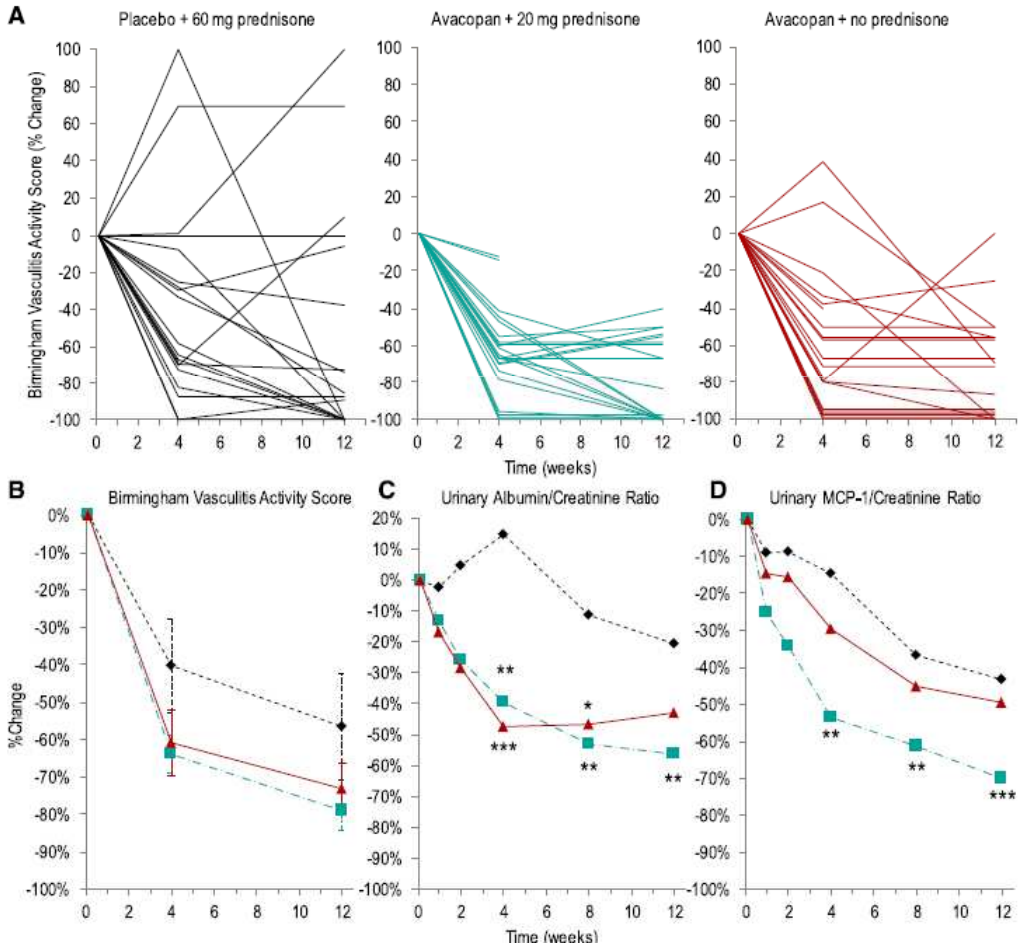
Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

David R.W. Jayne,* Annette N. Bruchfeld,† Lorraine Harper,‡ Matthias Schaier,§ Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶ Michel Jadoul,** István Szombati,†† Vladimír Tesař,‡‡ Mårten Segelmark,§§ Antonia Potarca,‖‖ Thomas J. Schall,‖‖ and Pirow Bekker,‖‖ for the CLEAR Study Group

Avacopan – étude CLEAR



Avacopan – étude CLEAR



Avacopan – la suite

- Etude ADVOCATE
- 331 patients – étude globale
- Avacopan vs prednisone, double placebo
- Inclusions terminées juin 2018
- Résultats fin 2019…

Conclusions

- Doses, durée, voie d'administration des corticoïdes… c'est de la poésie !
- Effets secondaires fréquents et graves
- Possibilité d'utiliser des doses cumulées plus faibles dans la plupart des maladies
- Nécessité de développer des alternatives