Actualités thérapeutiques dans l'ACG : de la paillasse au patient

Journée du Centre de Référence des Maladies auto-immunes et auto-inflammatoires rares d'Ile de France de l'Est et de l'Ouest

13 octobre 2023

Maxime Samson

Service de Médecine Interne et Immunologie Clinique, CHU de Dijon

INSERM UMR 1098, TAI-IT, équipe "Immunopathologie et Immunorégulation"

Liens d’intérêt

Symposium, boards, consulting

- ROCHE CHUGAI
- NOVARTIS
- BOEHRINGER
- CSL VIFOR
- GSK
- ARGENX

Invitations à des congrès nationaux et internationaux

- ROCHE CHUGAI
- GSK
- NOVARTIS
- OTSUKA
- CSL VIFOR

Traitement de l'ACG

Corticothérapie

- Prednisone 0,7 à 1 mg/Kg/j
- 15 mg/j à M3, 5 à 10 mg/j à M6
- **sevrage à M12**

47% des patients rechutent

30% des patients rechutent au moins **2 fois**

17% des patients rechutent **≥3 fois**

↑ dose cumulée de CS → EI des CS

→ Epargne en corticoïdes +++

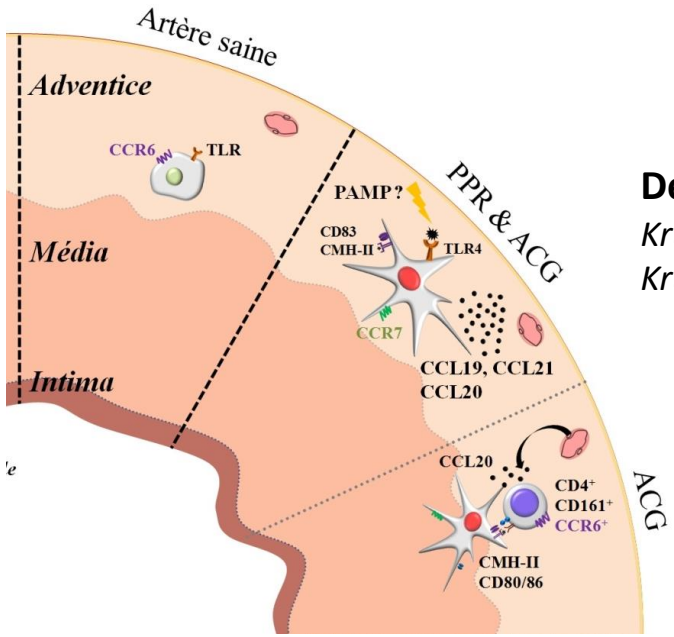
Protocole National de Diagnostic et de Soins

Artérite à Cellules Géantes (Horton)

Actualisation 2023

Mainbourg S etal, Arth Care Res 2020
Dumont A et al, J Rheumatol 2019
Aussedat M et al. Autoimmunuty Rev 2021
Moreel L et al. Bone Joint Spine 2022

Quelles cibles thérapeutiques ?

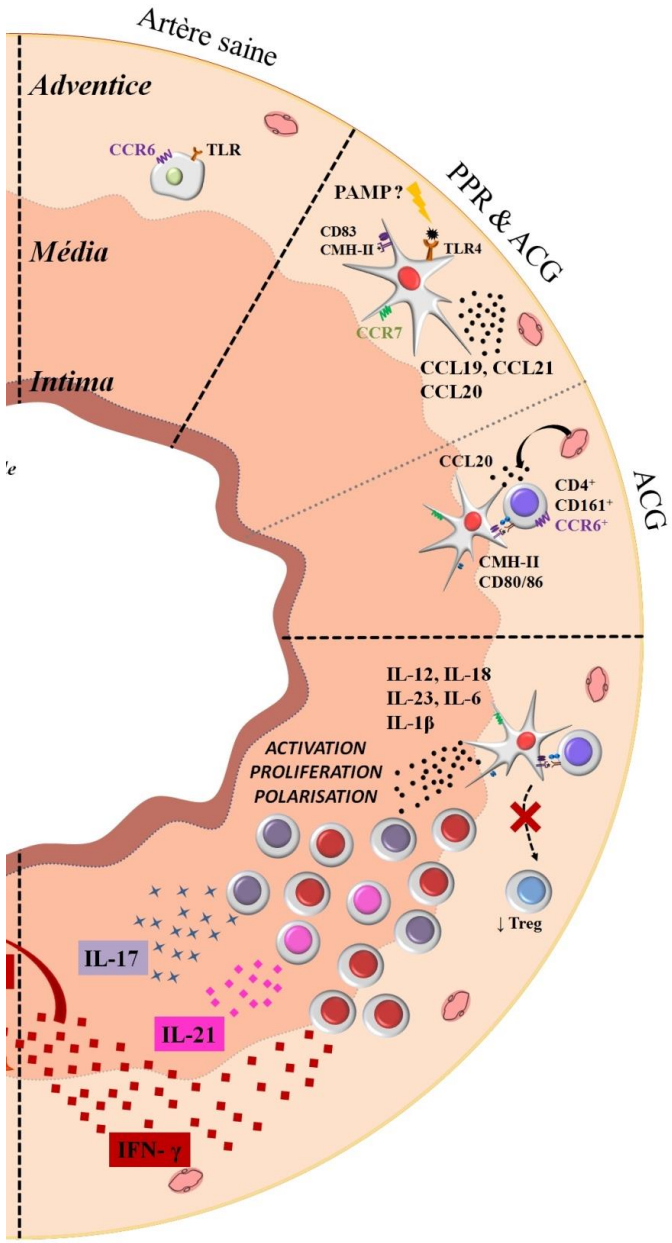


Dendritic cells

Krupa M et al. J Exp Med 2000

Krupa M et al. Am J of Pathol 2002

Quelles cibles thérapeutiques ?



↑ Th17

Deng J et al Circulation 2011
Samson M et al A&R 2012
Terrier B et al A&R 2012

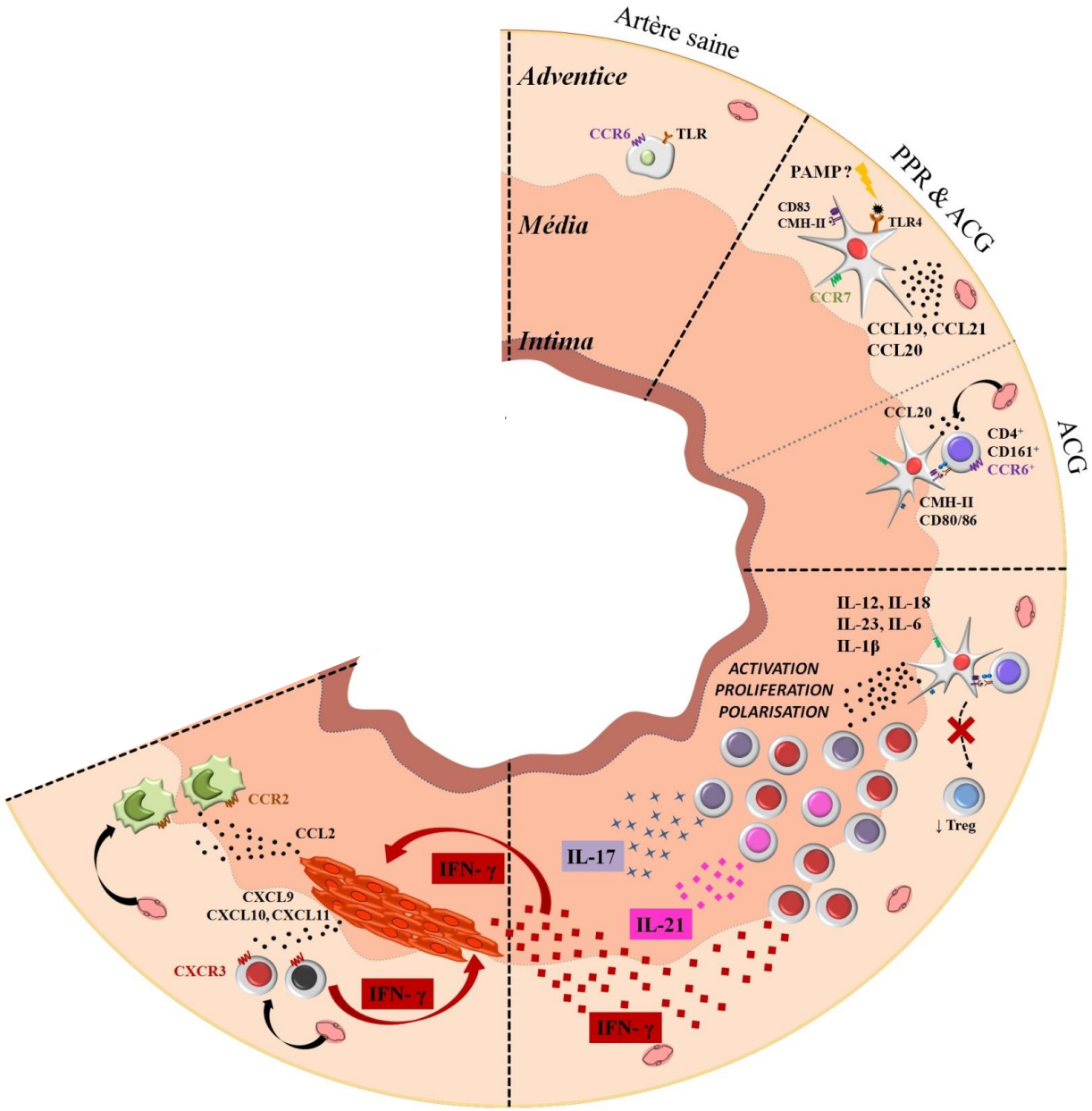
↓ Treg

Miyabe C et al. ARD 2017
Samson M et al CTI 2021

Quelles cibles thérapeutiques ?

Role de l'IFN-γ

Corbera-Bellalta M...Cid MC. ARD 2015

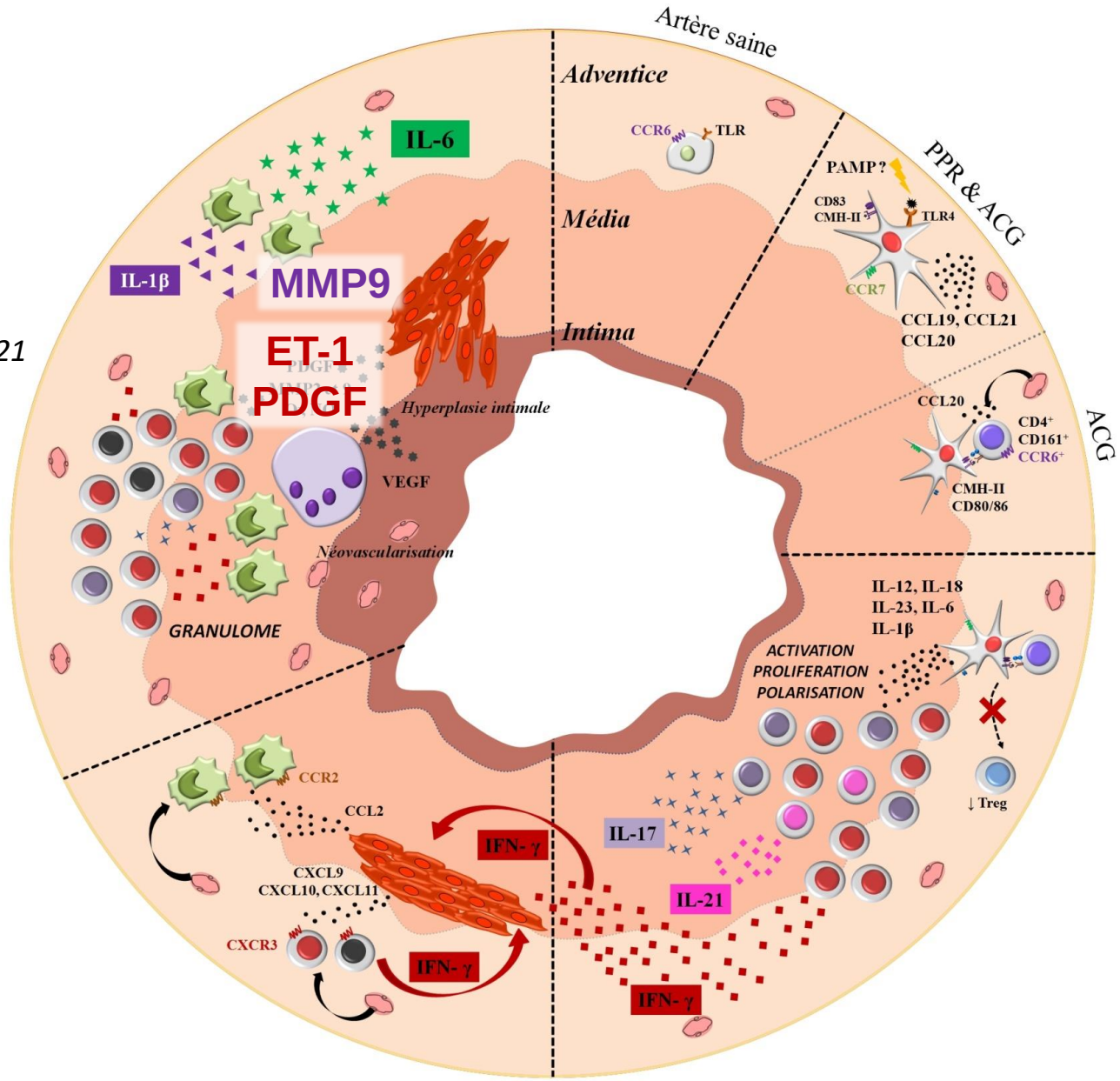


Quelles cibles thérapeutiques ?

Monocytes
Jiemy WF et al. CTI 2020
Van Sleen Y et al. Arthritis Rheum 2021
Watanabe R et al Circ Research 2018

LT CD8 et MAIT
Samson M et al. J Autoimm 2016
Ghesquière T…Samson M. J Autoimm 2021

Remodelage
Lozano E et al. ARD 2008
Planas Rigol E et al. ARD 2017
Regent A et al. Autoimm Rev 2017
Ly KH Arthritis Res Ther. 2014
Watanabe R et al Circ Research 2018



Quelles cibles thérapeutiques ?

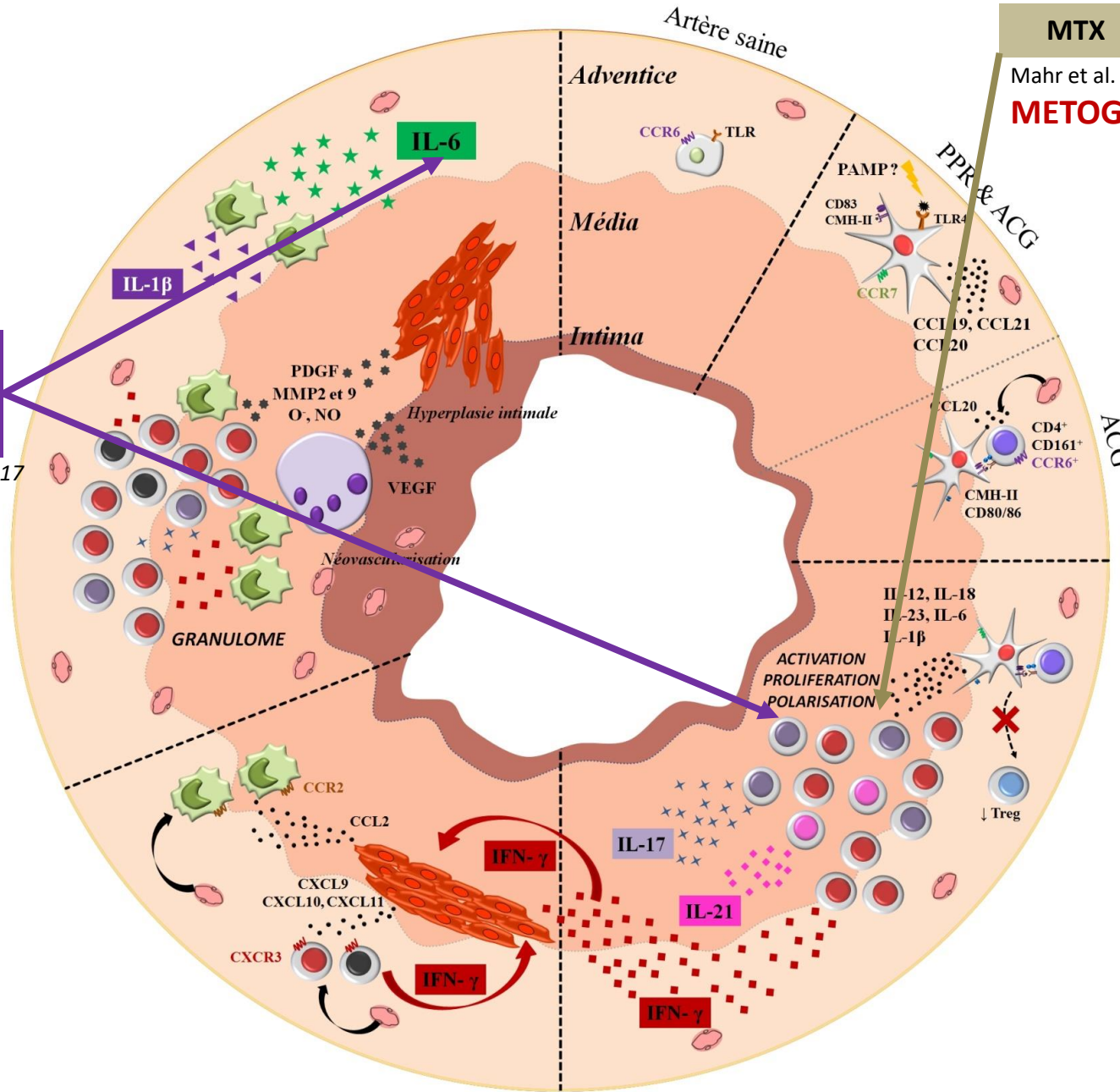
AMM

Anti IL-6R
(tocilizumab)
(sarilumab)

Stone JH et al. NEJM 2017
NCT03600805

MTX

Mahr et al. A&R 2007
METOGIA



Quelles cibles thérapeutiques ?

AMM

IL-1RA (*anakinra*)

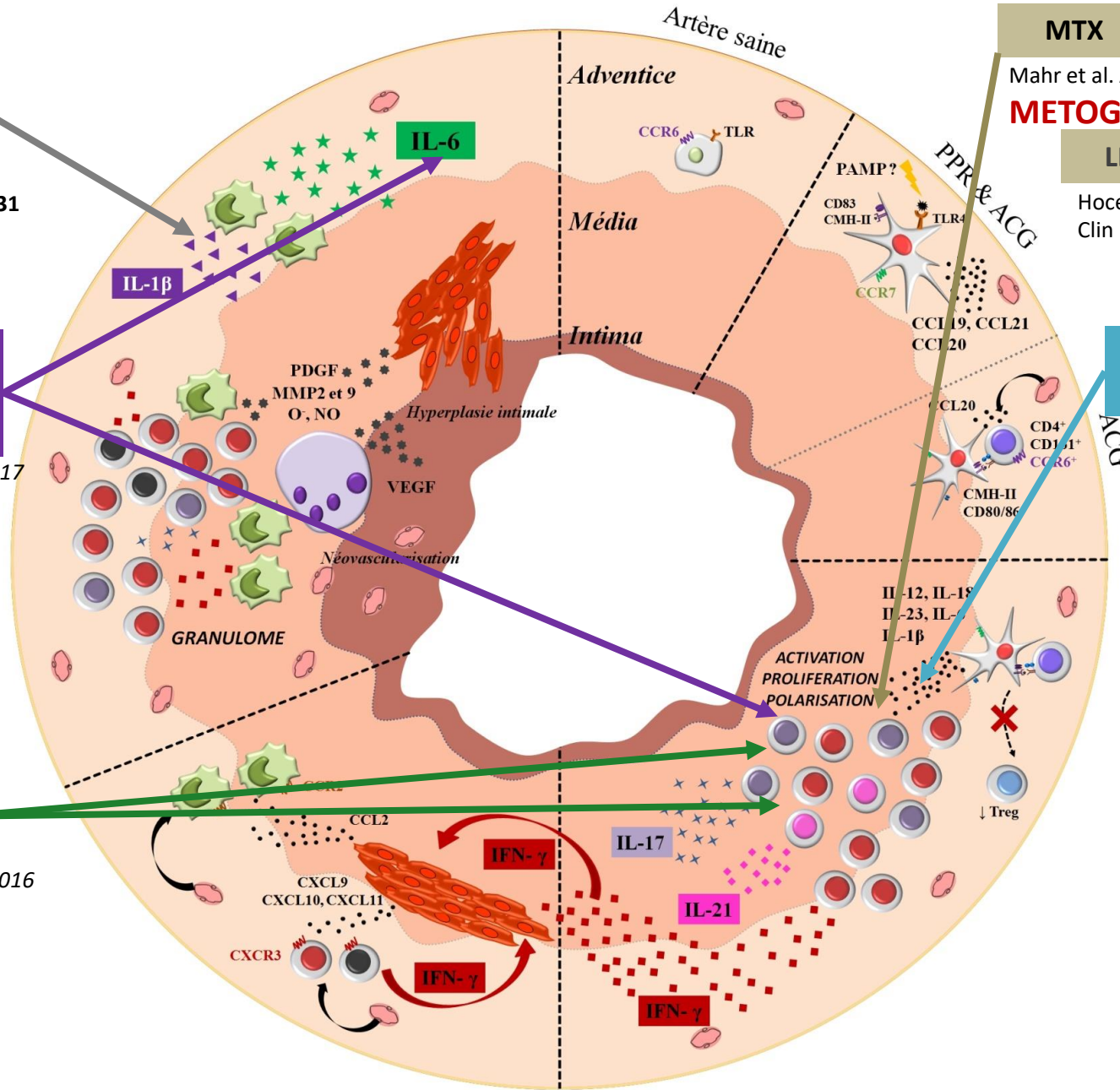
Ly K et al. BJS 2014
PHRC-I : NCT02902731

Anti IL-6R (**tocilizumab**) (*sarilumab*)

Stone JH et al. NEJM 2017
NCT03600805

Anti IL-12/IL-23 (*ustekinumab*)

Conway R et al. ARD 2016
Etude UGCA
Etude ULTRA



MTX

Mahr et al. A&R 2007

METOGIA

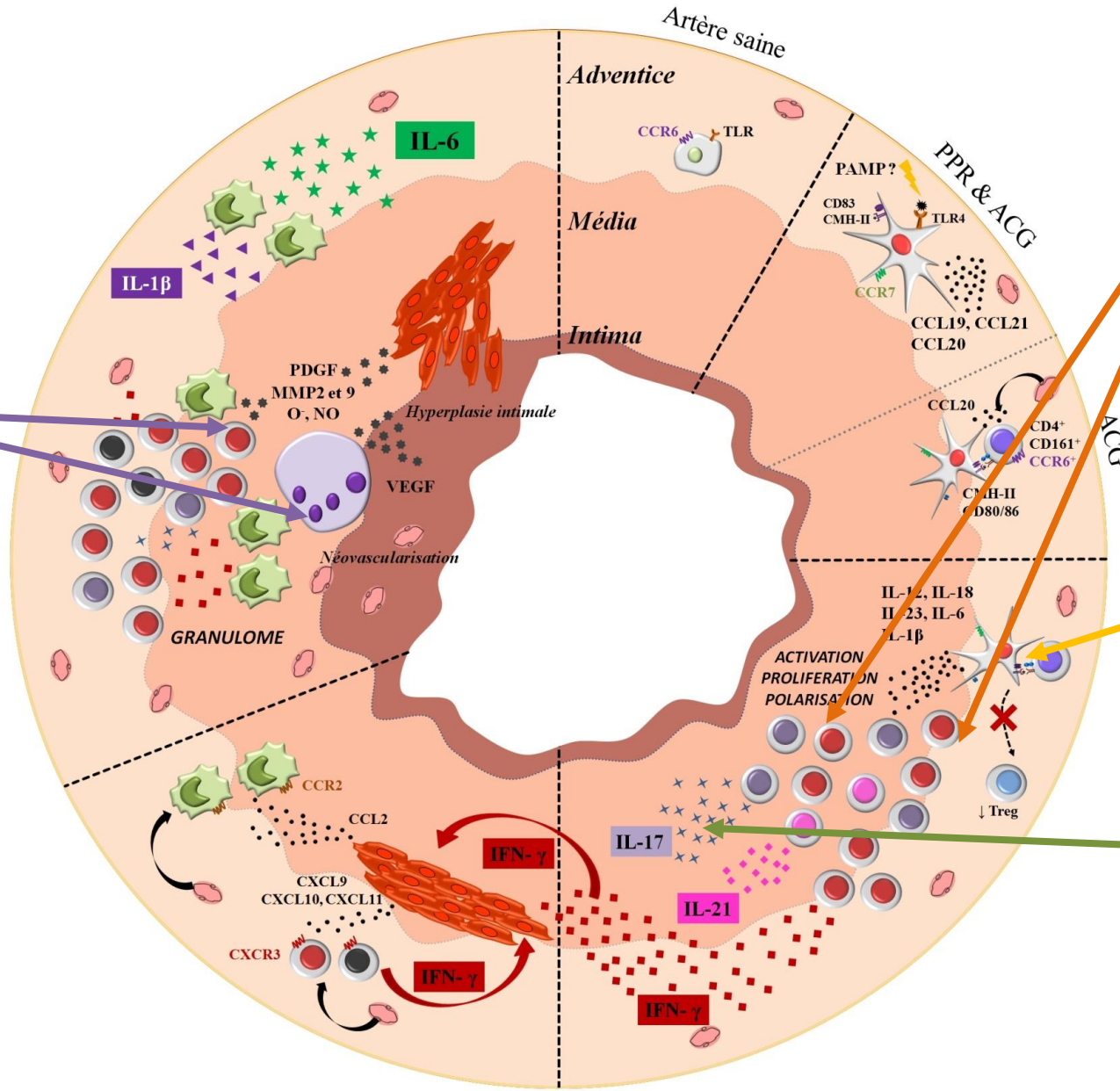
LEF

Hocevar A et al.
Clin Rheum 2019

Anti p19 (*guselkumab*)

THEIA study

Quelles cibles thérapeutiques ?



anti-GM-CSF (*mavrilimumab*)

JAKi

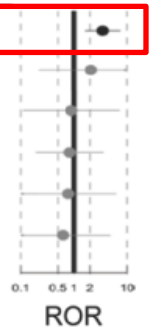
CTLA4-Ig (*abatacept*)

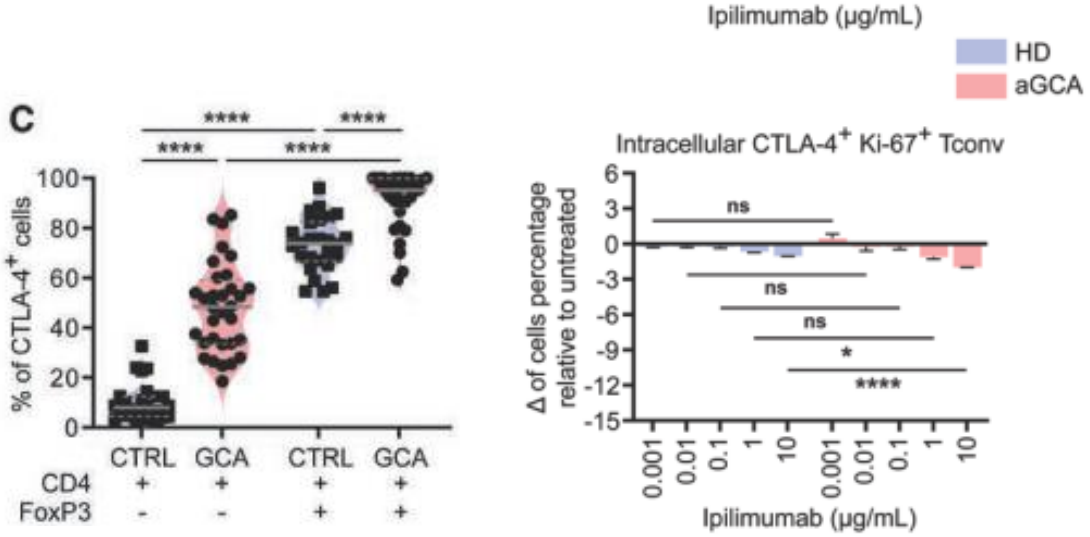
Anti IL-17 (*secukinumab*)

Implication de CTLA4

VigiBase

Reaction	Monotherapy		ROR [95% CI] of αCTLA-4 vs. αPD-(L)1
	αCTLA-4	αPD-(L)1	
Giant cell arteritis	10	18	3.48 [1.61;7.55]
Renal vasculitis	1	3	2.09 [0.22;20.09]
Retinal vasculitis	1	7	0.90 [0.11;7.28]
ANCA-associated vasculitis	2	15	0.84 [0.19;3.66]
Aortitis	1	8	0.78 [0.10;6.27]
Central nervous system vasculitis	1	10	0.63 [0.08;4.90]





Treg très sensibles à la déplétion par ipilimumab

Régnier P et al Circulation Research 2023

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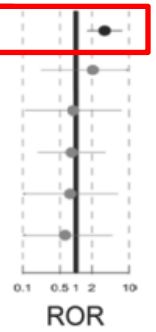
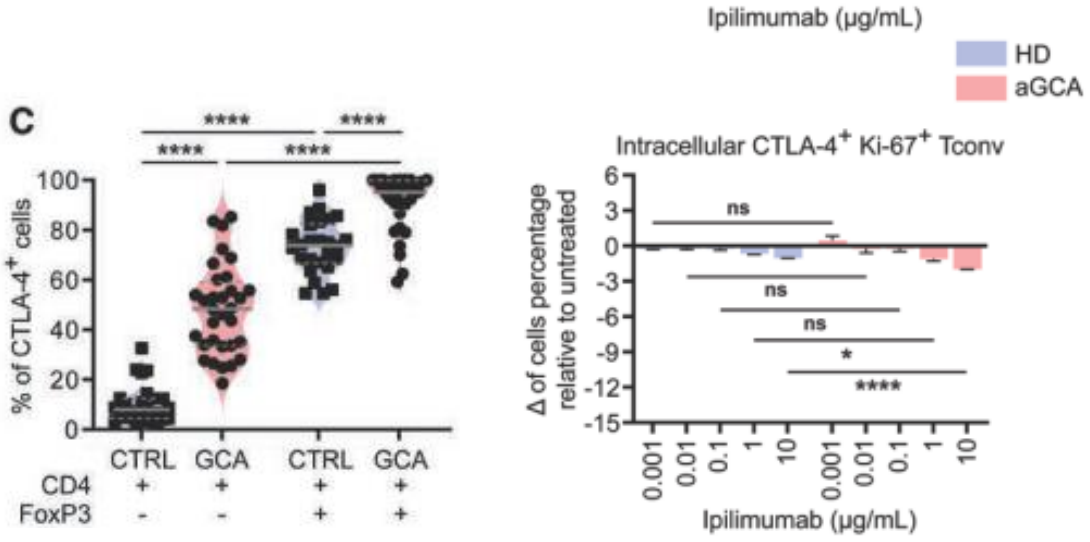
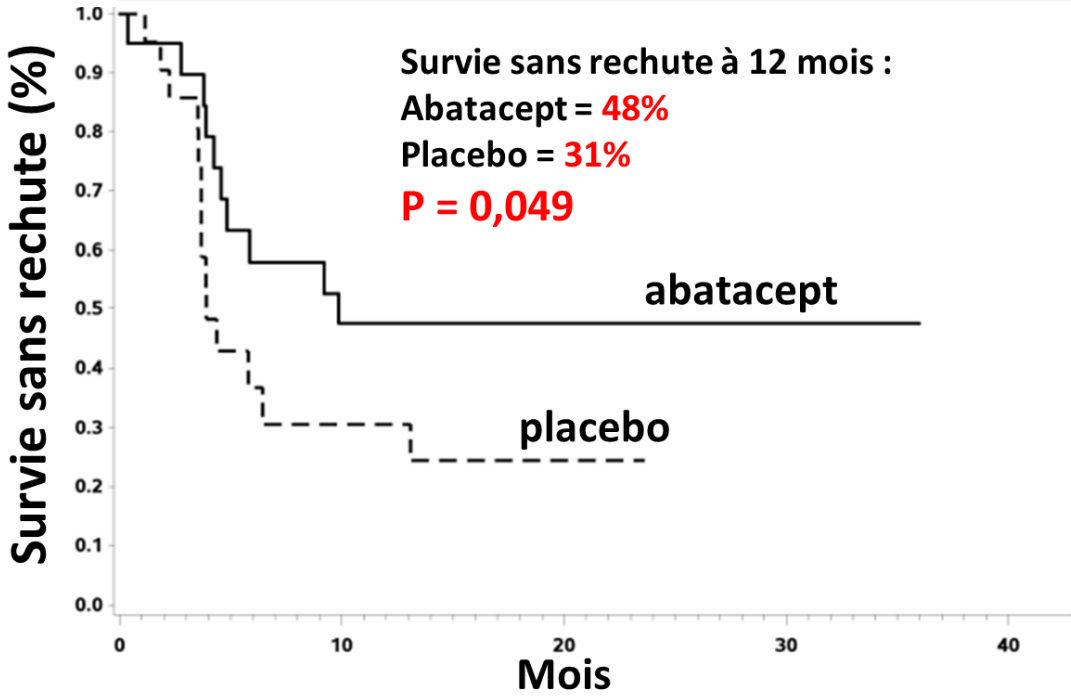




Treg très sensibles à la déplétion par ipilimumab

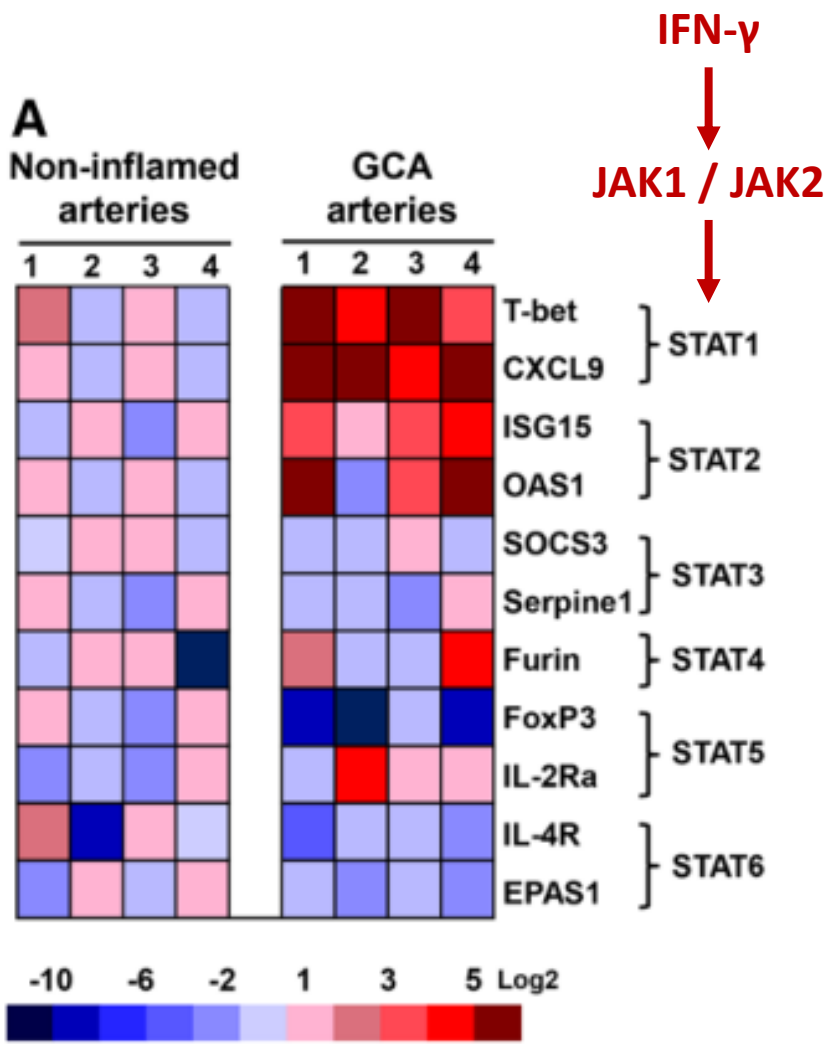
41 patients (44% rechuteurs)



➔ **Essai de phase 3 : ABAGART**
(NCT04474847) ; n=78 patients

Langford CA et al. Arthritis Rheum 2017
Régnier P et al Circulation Research 2023

Voie JAK STAT



NSG

Tofacitinib (*ex vivo*)

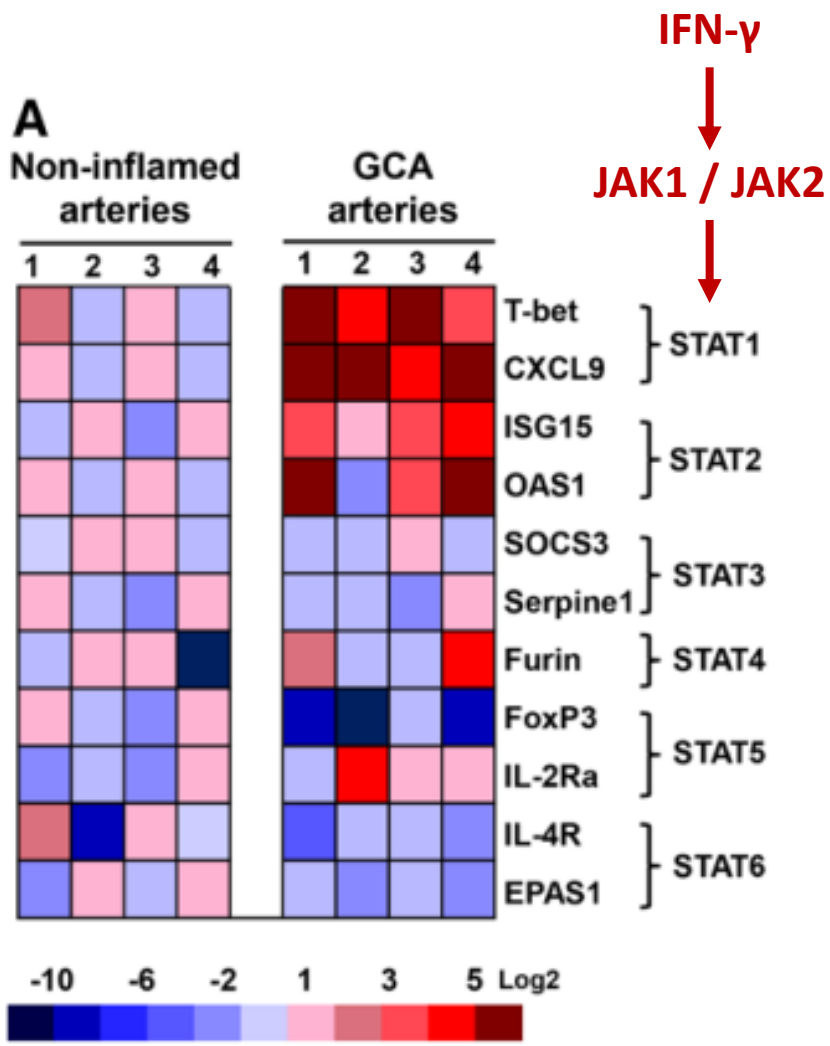
↓ Th1 & vascular inflammation

↓ neoangiogenesis

↓ intimal hyperplasia

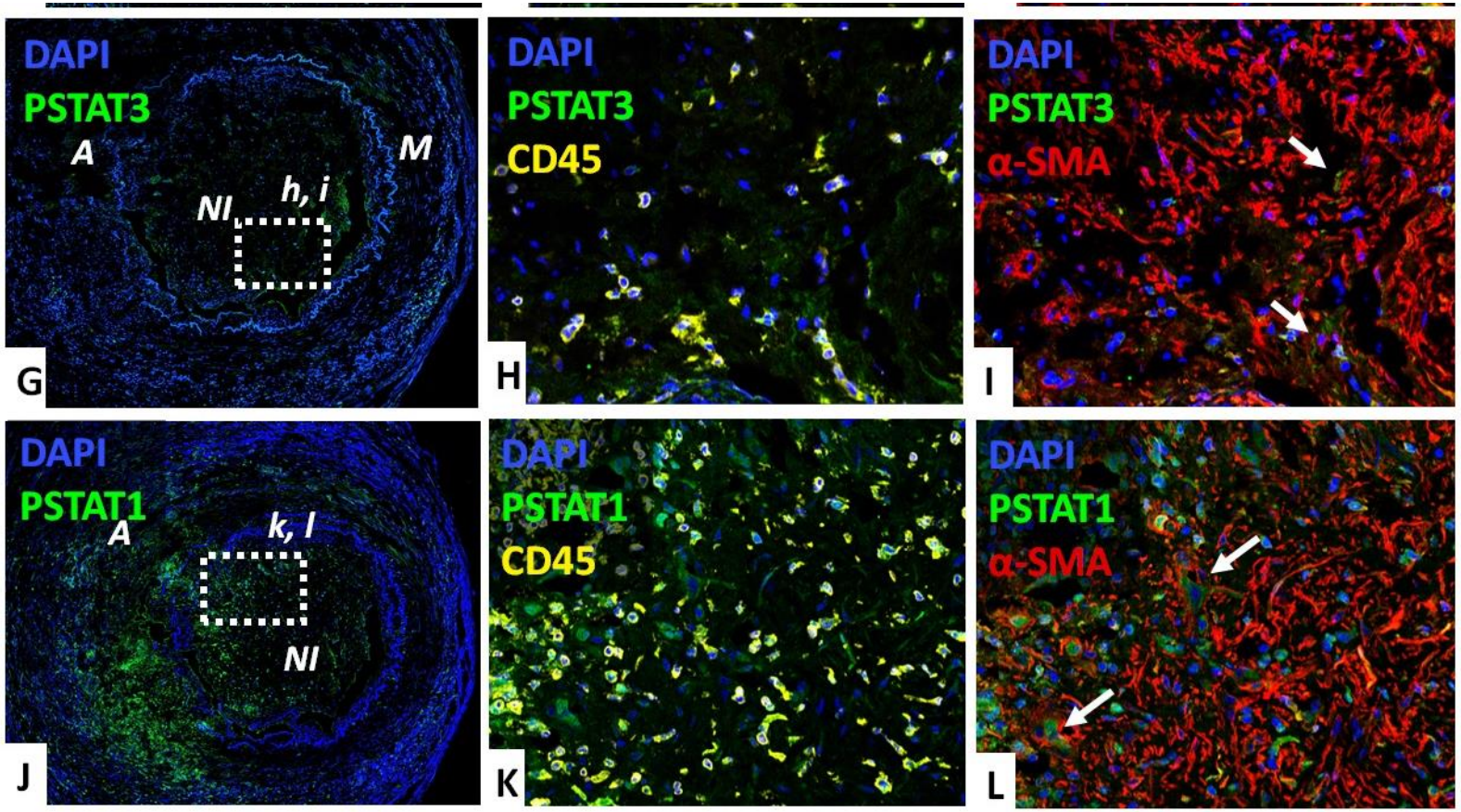
Zhang H et al. Circulation 2017

Voie JAK STAT



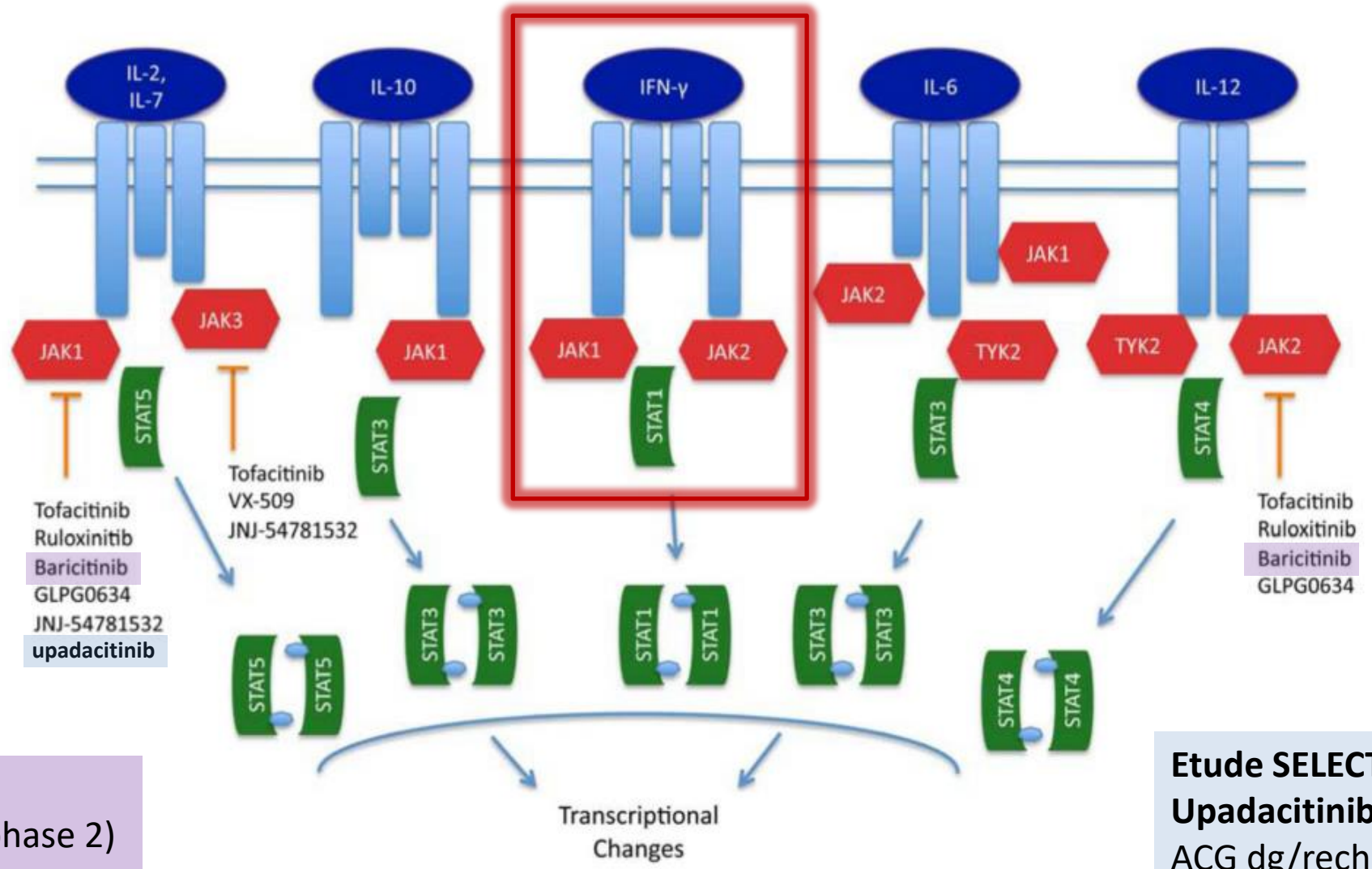
Zhang H et al. Circulation 2017

pSTAT1 > pSTAT3



Greigert H…, Bonnotte B, Samson M. In revision

Inhibiteurs de JAK



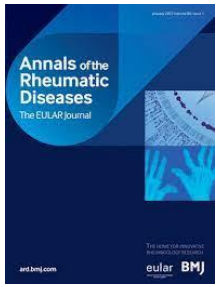
Baricitinib
Etude pilote (phase 2)
ACG en rechute
(NCT030226504)

Etude SELECT-GCA (phase 3)
Upadacitinib (Abbvie)
ACG dg/rechute
N=420 patients (NCT03725202)

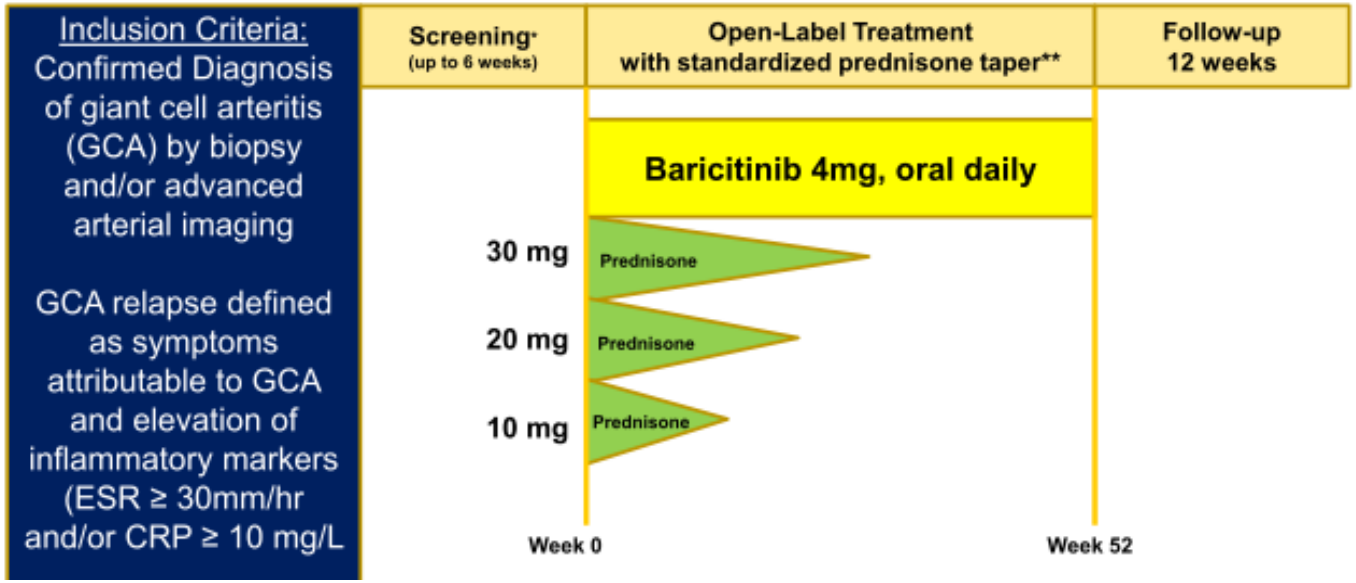
Boland BS et al. Gastroenterol Clin North Am. 2015

Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study

Matthew J Koster ,[1] Cynthia S Crowson ,[2] Rachel E Giblon,[2] Jane M Jaquith,[1] Ali Duarte-García ,[1] Eric L Matteson ,[1] Cornelia M Weyand,[1] Kenneth J Warrington[1]



ARD 2022



15 ACG en rechute

11 F et 4 H
Médiane : 1 rechute (range: 1 – 3)
Durée médiane d'évolution de la maladie : 9 mois (IQR 7-21 mois)

13/15 vaccinés contre le VZV +++

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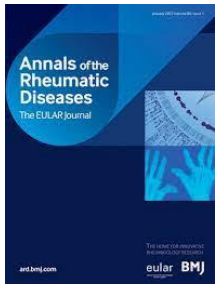
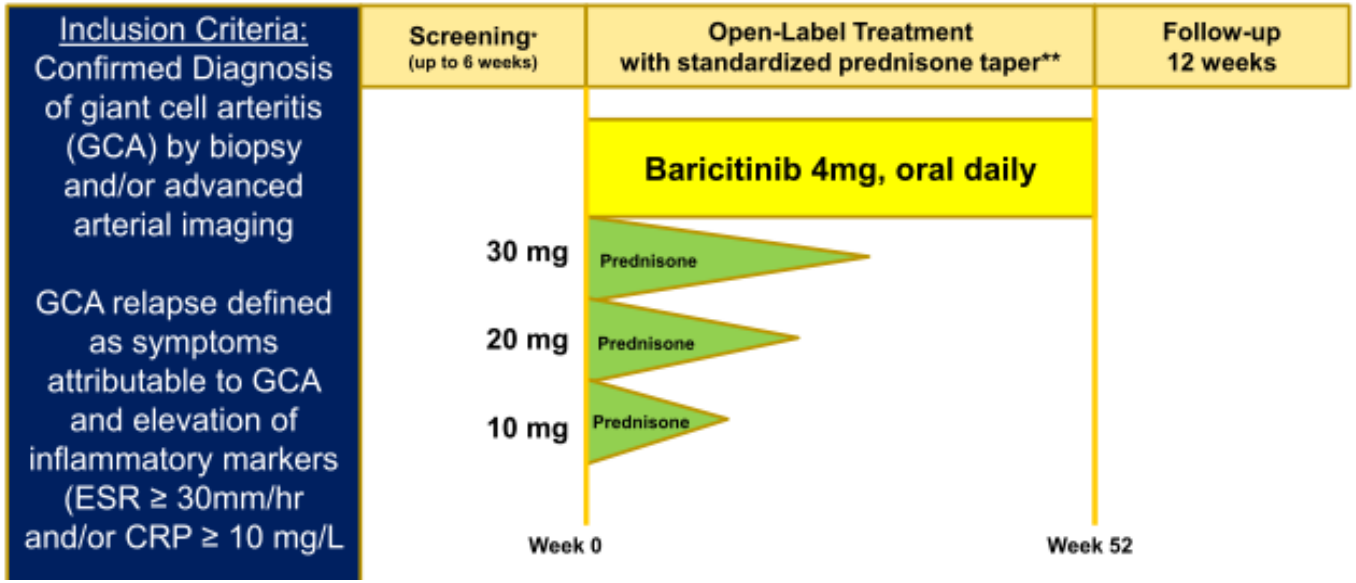


ARD 2022



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13/15 vaccinés contre le VZV +++

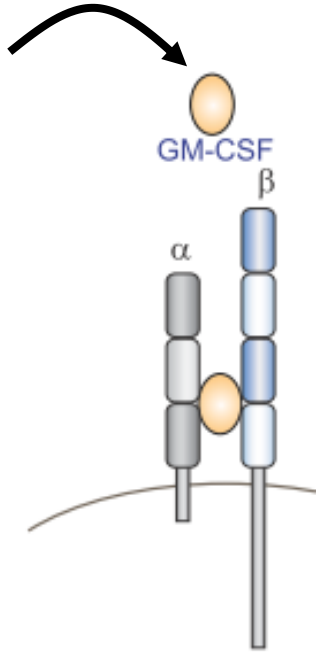
Diminution rapide + sevrage des CS chez 13/14 patients avec maintien en rémission

4/14 (29%) ont rechuté dans les 12 semaines après l'arrêt du baricitinib

- **5 infections** nécessitant des ATB
- 1 arrêt de ttt pour thrombopénie
- 2 COVID-19 sans gravité
- **1 zona**

GM-CSF au cours de l'ACG

Macrophages
Lymphocytes T
Myofibroblastes



Macrophages
Myofibroblastes

=

JAK2

STAT5

Corbera-Bellalta M et al. ARD 2022

GM-CSF au cours de l'ACG

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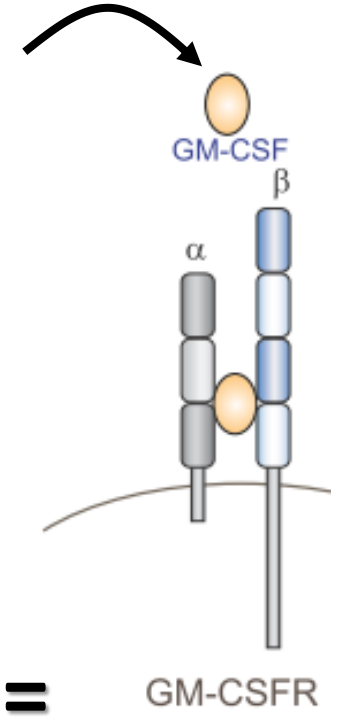
Lymphocytes T
Myofibroblastes



Macrophages
Myofibroblastes

=

JAK2

STAT5

GCA-TAB

Pas de traitement
mavrilimumab (anti-GM-CSF Rα)

5 jours

- **surnageant**
- **RT-PCR (TRIZOL)**
- **confocale**

Effet du GM-CSF:

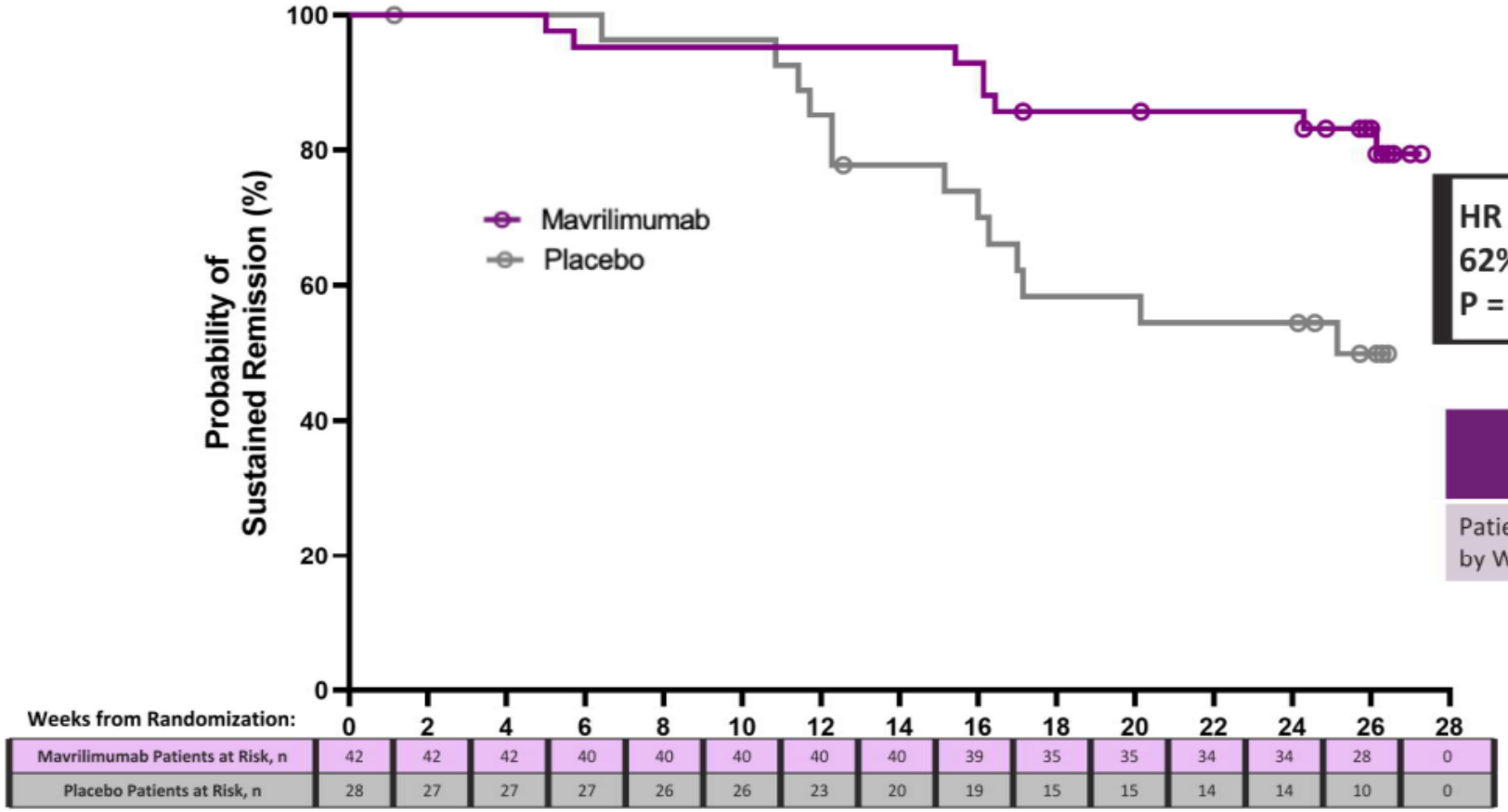
- **Macrophages** :
  - ↑ IL-1β, IL-6, TNF-α
  - ↑ CD83 et HLA-DR
- **↑ Th1**
- **↑ angiogenèse**
- **↑ destruction paroi** (MMP9/TIMP1 ratio)

Corbera-Bellalta M et al. ARD 2022

Mavrilimumab au cours de l'ACG

Randomisé, contrôlé, double aveugle
70 patients (50% de rechutes)
Prednisone + placebo **26 semaines**
Vs Prednisone + mavrilimumab 150 mg/2sem **26 semaines**

CRP, VS et imagerie **= pas d'aveugle**
Comité d'adjudication en aveugle
Rechute = signes cliniques ET CRP>10 mg/L

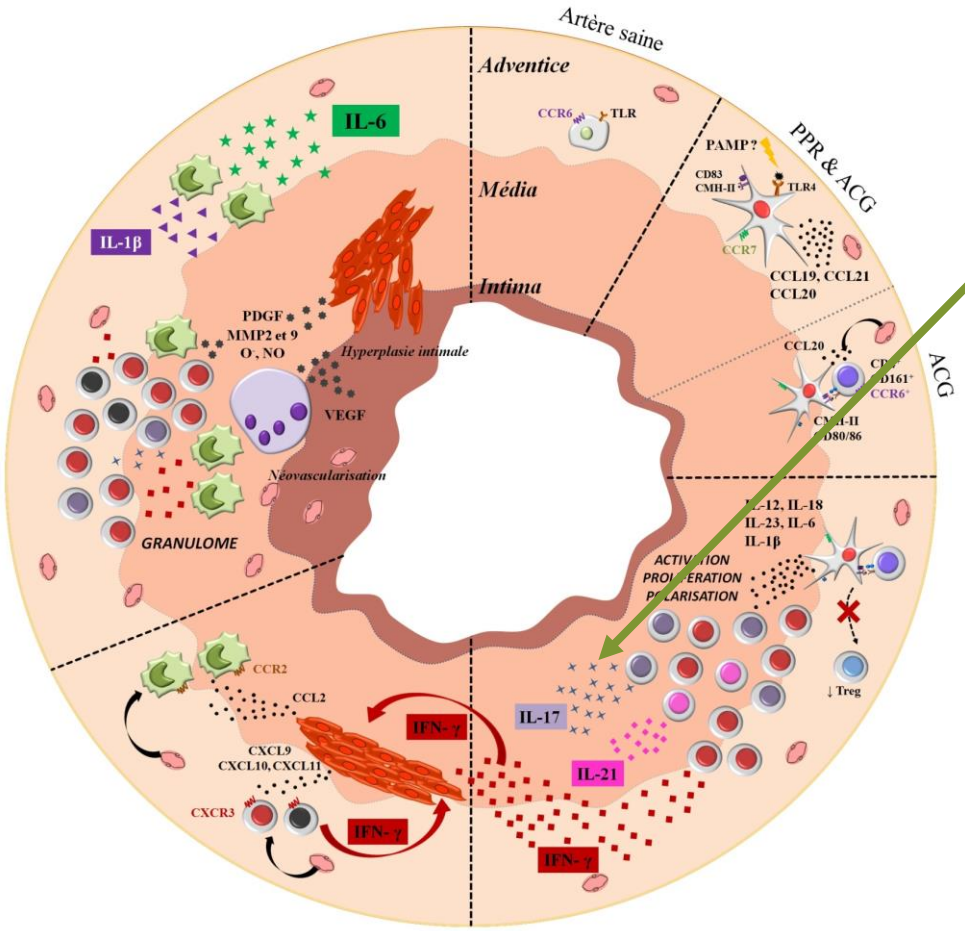


HR (95% CI) 0.38 (0.15, 0.92)
62% Risk Reduction
P = 0.0263

	Mavrilimumab (N=42)	Placebo (N=28)
Patients with Flare by Week 26, n (%)	8 (19)	13 (46.4)

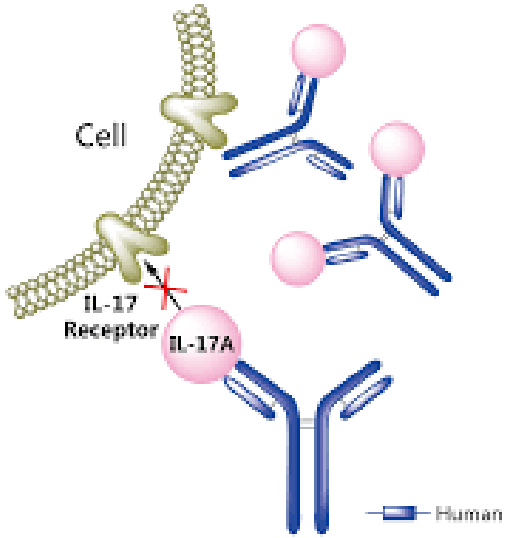
Cid MC et al. ARD 2022

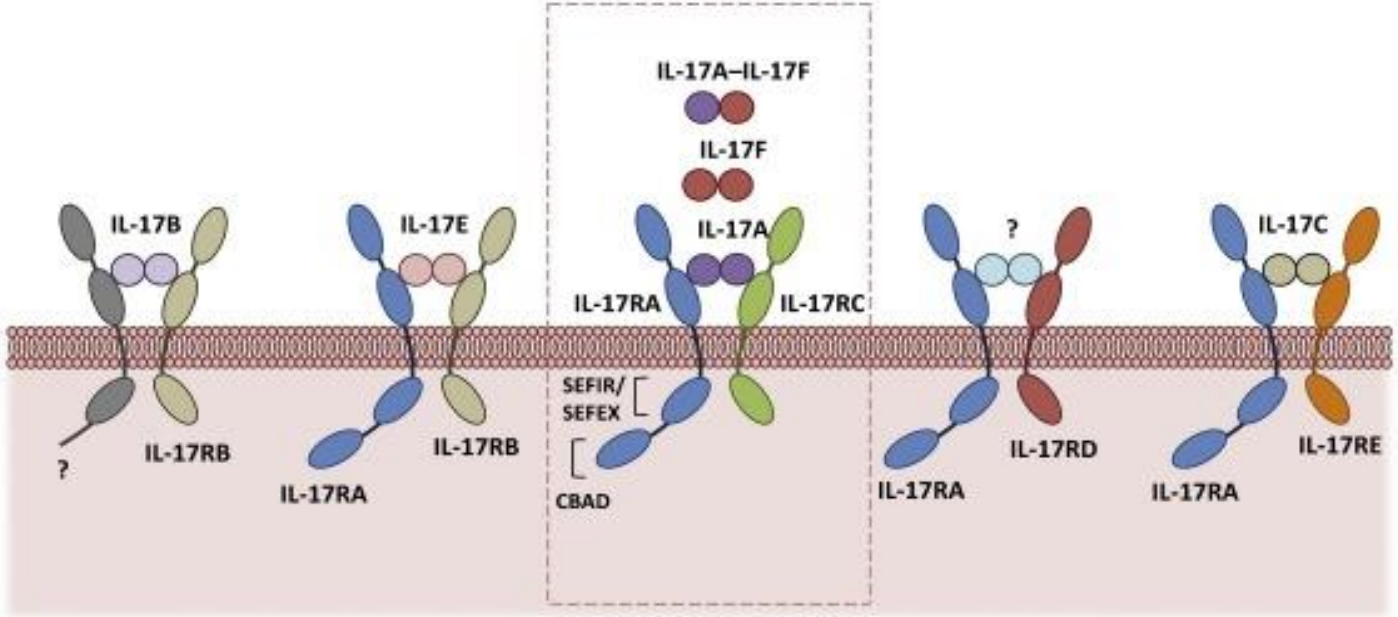
Secukinumab



Anti IL-17A
(*secukinumab*)

TitAIN : NCT04930094
GCAPTAIN : NCT04930094



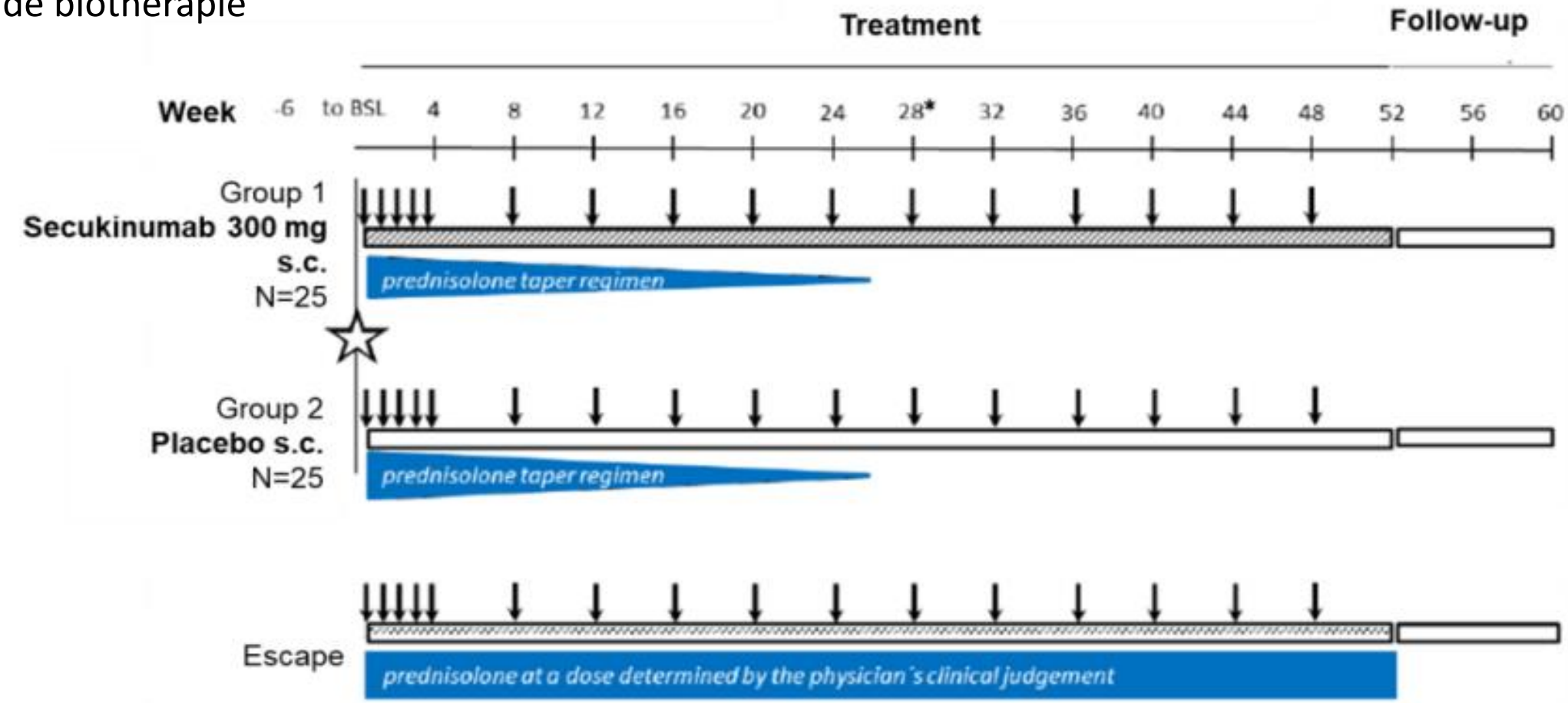


Trends in Immunology

Secukinumab

Critères d'inclusion :

- ACG active (diagnostic ou rechute)
- patients naïfs de biothérapie



Venhoff N et al. Lancet Rheumatol 2023

Secukinumab

	Secukinumab group (n=27)	Placebo group (n=25)	Total (n=52)
Age, years	77 (71–80)	71 (63–76)	75 (69–79)
Sex			
Female, n (%)	17 (63%)	18 (72%)	35 (67%)
Male, n (%)	10 (37%)	7 (28%)	17 (33%)
Race, n (%)			
White	27 (100%)	25 (100%)	52 (100%)
Giant cell arteritis diagnosis, n (%)			
New onset giant cell arteritis	23 (85%)	19 (76%)	42 (81%)
Relapsing giant cell arteritis	4 (15%)	6 (24%)	10 (19%)
Time since diagnosis of giant cell arteritis, months	1·0 (0·6–1·3)	0·8 (0·7–1·4)	0·9 (0·6–1·4)
Time since first giant cell arteritis symptom, months	3·0 (1·7–8·4)	4·4 (1·6–10·5)	3·1 (1·7–9·5)
Baseline coadministered prednisolone treatment category, n (%)			
≥40 mg/day	19 (70%)	14 (56%)	33 (63%)
<40 mg/day	8 (30%)	11 (44%)	19 (37%)

Data are median (IQR) or n (%).

Table 1: **Demographics and baseline characteristics in the full analysis set**

Venhoff N et al. Lancet Rheumatol 2023

Secukinumab

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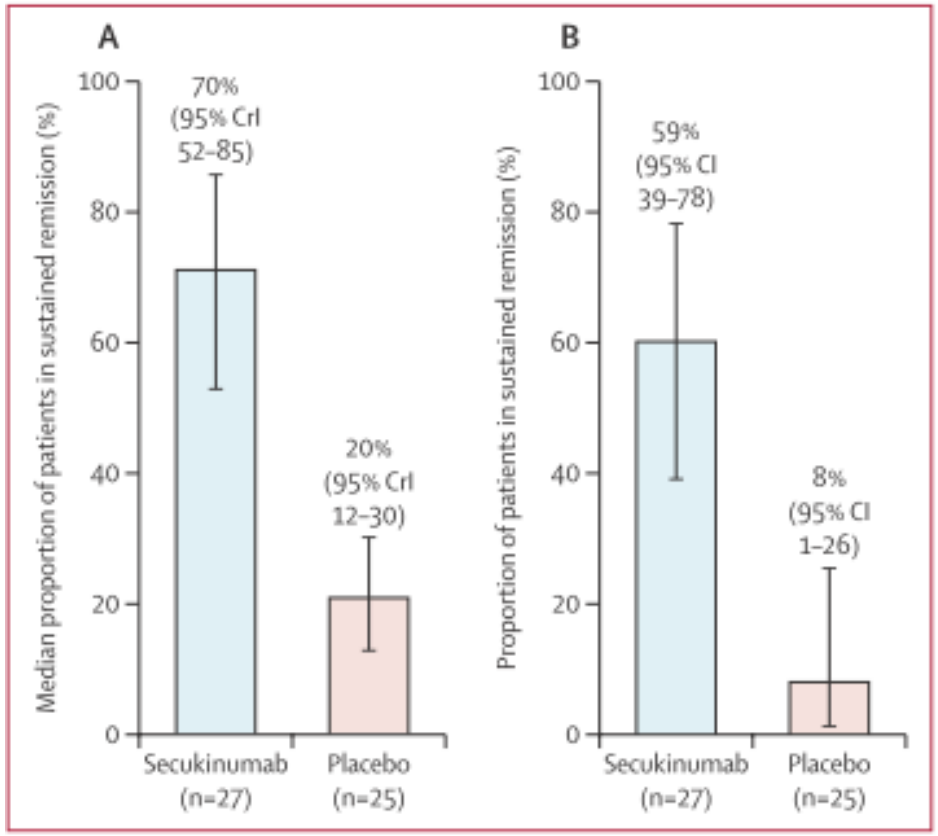
S28 **S52**



Secukinumab > placebo

…mais les patients du groupe placebo ne recevaient plus de traitement après M6

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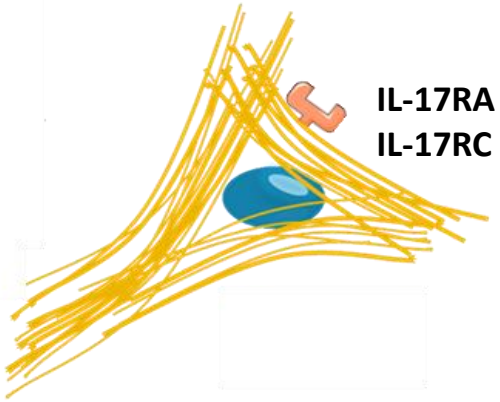
Tolérance

	Secukinumab group (n=27)	Placebo group (n=25)	Total (n=52)
Any adverse event	27 (100%)	24 (96%)	51 (98%)
Adverse events suspected to be related to study treatment	16 (59%)	14 (56%)	30 (58%)
Adverse events leading to study treatment discontinuation	2 (7%)	2 (8%)	4 (8%)
Adverse events leading to study dose adjustment or interruption	1 (4%)	5 (20%)	6 (12%)
Any serious adverse event	6 (22%)	11 (44%)	17 (33%)
Fatal serious adverse events	1 (4%)	1 (4%)	2 (4%)
Most frequent adverse events by preferred term			
Hypertension	6 (22%)	8 (32%)	14 (27%)
Nasopharyngitis	5 (19%)	5 (20%)	10 (19%)
Headache	4 (15%)	3 (12%)	7 (13%)
Urinary tract infections	4 (15%)	2 (8%)	6 (12%)
Oral candidiasis	4 (15%)	1 (4%)	5 (10%)
Muscle spasms	4 (15%)	1 (4%)	5 (10%)
Arthralgia	3 (11%)	3 (12%)	6 (12%)
Osteoarthritis	3 (11%)	2 (8%)	5 (10%)
Bursitis	3 (11%)	1 (4%)	4 (8%)
Fall	3 (11%)	1 (4%)	4 (8%)
Dizziness	3 (11%)	1 (4%)	4 (8%)
Peripheral oedema	2 (7%)	4 (16%)	6 (12%)
Haematoma	2 (7%)	3 (12%)	5 (10%)
Back pain	0	5 (20%)	5 (10%)
Selected adverse events of special interest			
Infections	20 (74%)	16 (64%)	36 (69%)
Serious infections	2 (7%)	1 (4%)	3 (6%)
Hypersensitivity	6 (22%)	3 (12%)	9 (17%)
Malignancy	0	2 (8%)	2 (4%)
Major adverse cardiovascular events	1 (4%)	0	1 (2%)
Interactions with live vaccines	0	1 (4%)	1 (2%)

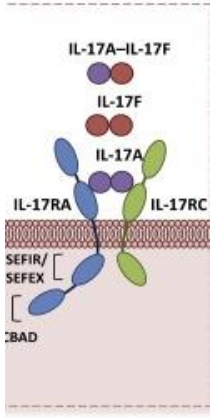
- **aucune candidose invasive**
- **3 infections sévères :**
  - 2 patients (7%) du groupe SCK (une arthrite septique et un érysipèle)
  - 1 patient (4%) du groupe PLA (infection urinaire)
- **2 décès :**
  - 1 chute à domicile et insuffisance cardiaque (SCK)
  - 1 détresse respiratoire (PLA)

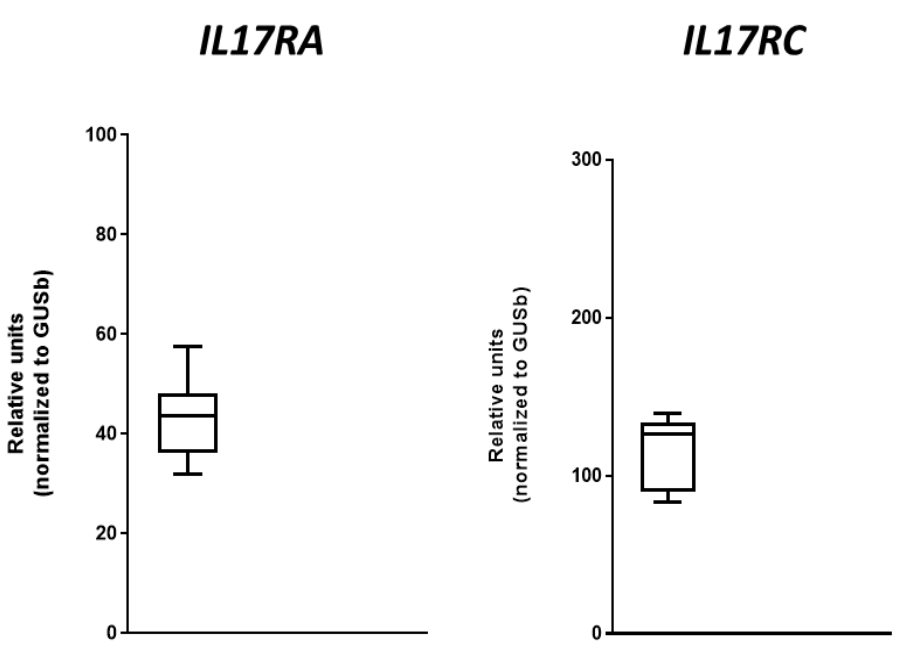
Venhoff N et al. Lancet Rheumatol 2023

Les MF expriment IL-17RA et IL-17RC



IL-17RA
IL-17RC





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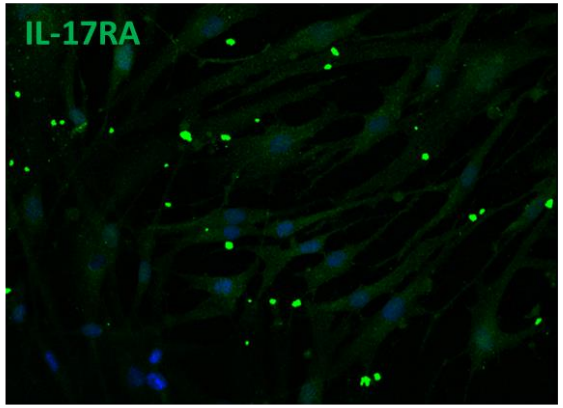
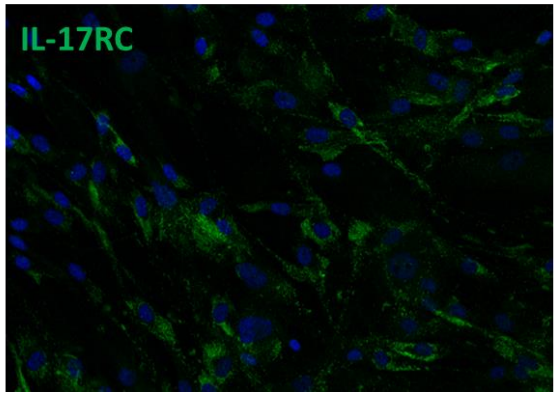
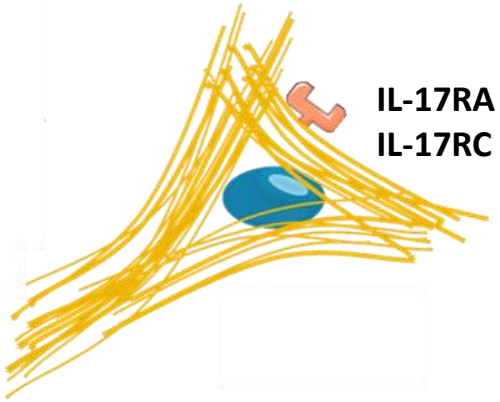
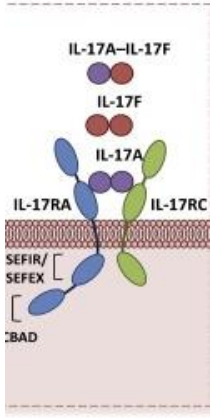




Greigert H et al. In preparation

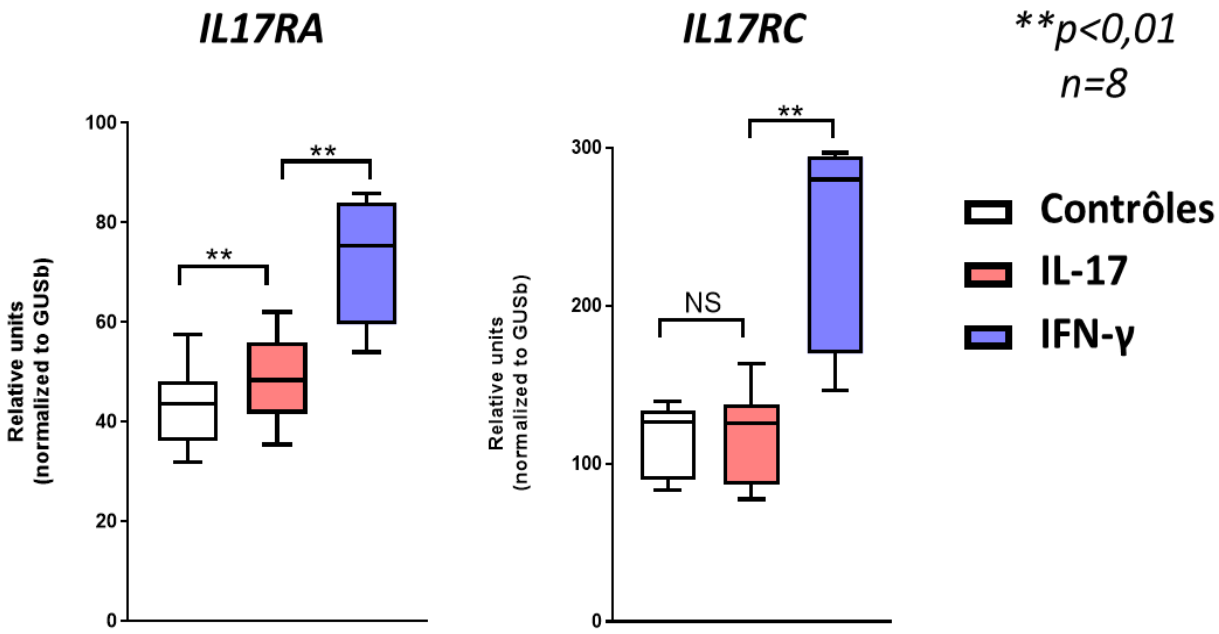
n=3

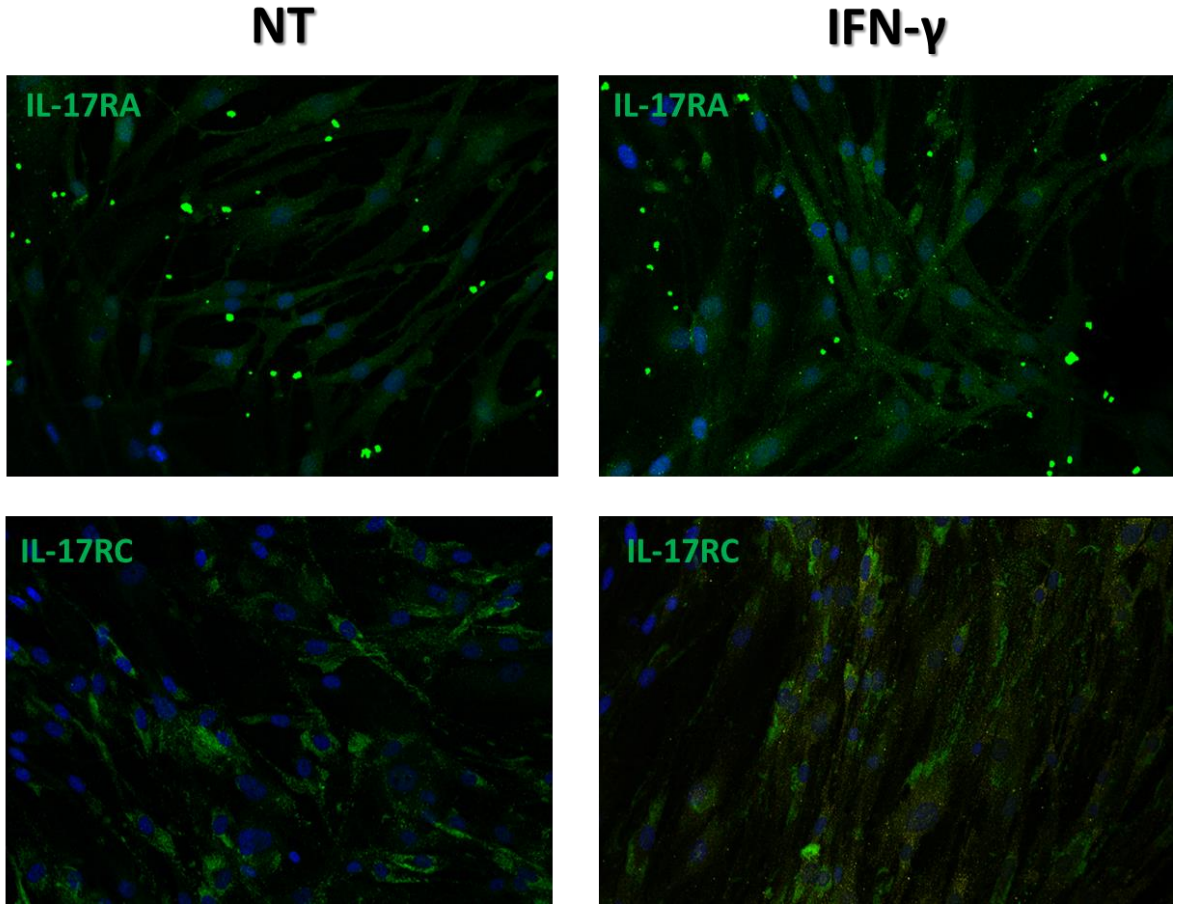




Les MF expriment IL-17RA et IL-17RC

L'expression de IL-17RA et IL-17RC augmente après traitement par IFN-γ





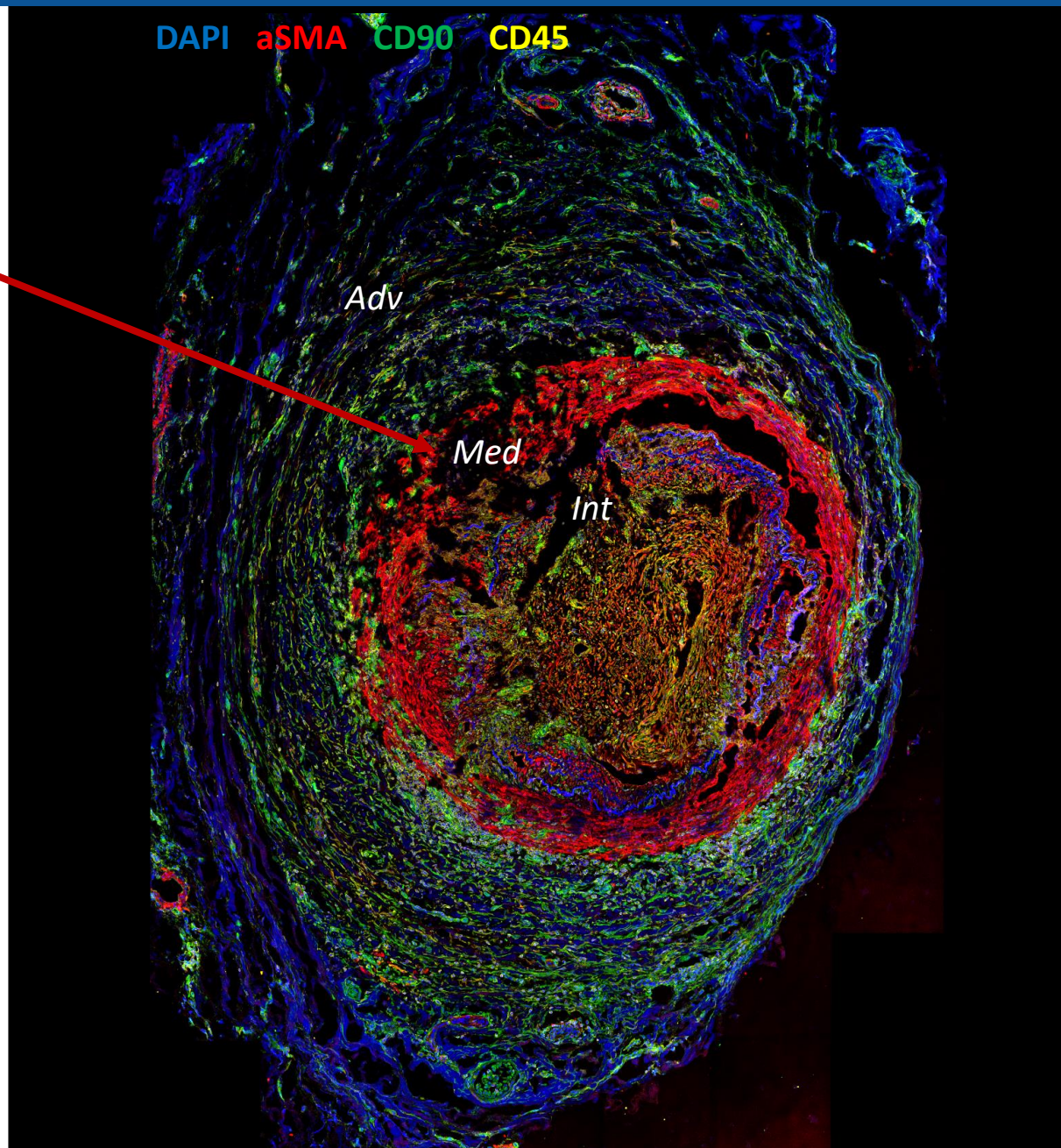
n=3

Greigert H et al. In preparation

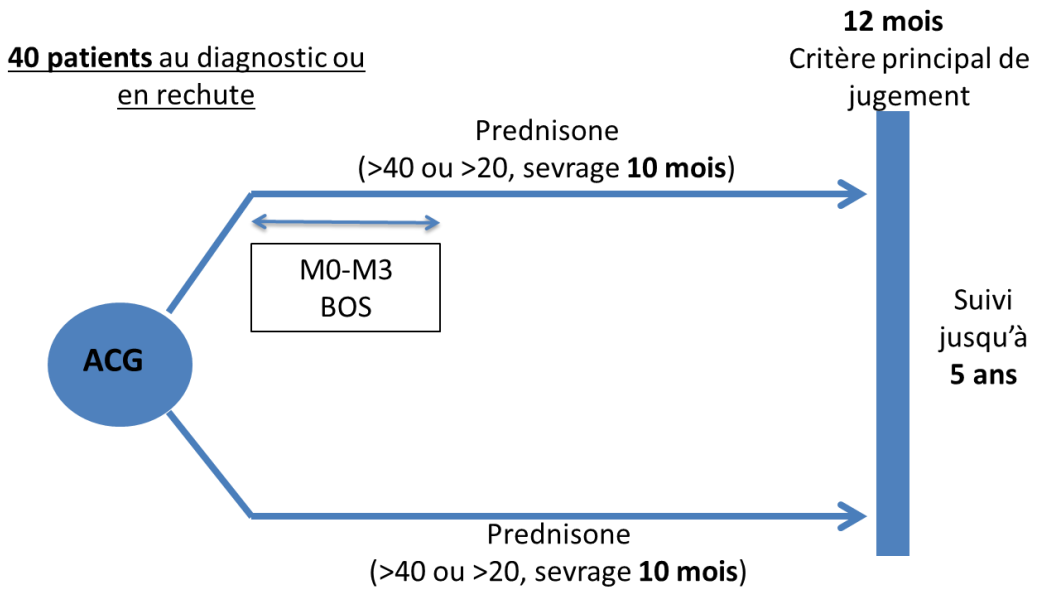
« *Unmet need* » = remodelage vasculaire

Inhibition de la voie de l'endothéline-1

Lozano E et al. ARD 2010
Regent A et al. Autoimm rev 2017
Planas E et al ARD 2017



BOSICART – PHRC 2019



Conclusion

Corticoïdes = pierre angulaire du traitement

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Traitements d'épargne reconnus : tocilizumab, MTX → METOGiA

Conclusion

Corticoïdes = pierre angulaire du traitement

Traitements d'épargne reconnus : tocilizumab, MTX → METOGiA

Cibles thérapeutiques d'avenir :

- **Anti-IL-17**
- **JAKi :** puissant mais !!! Tolérance !!!
- **CTLA4-Ig et anti-GM-CSF :** en attente de la phase 3

Merci pour votre attention