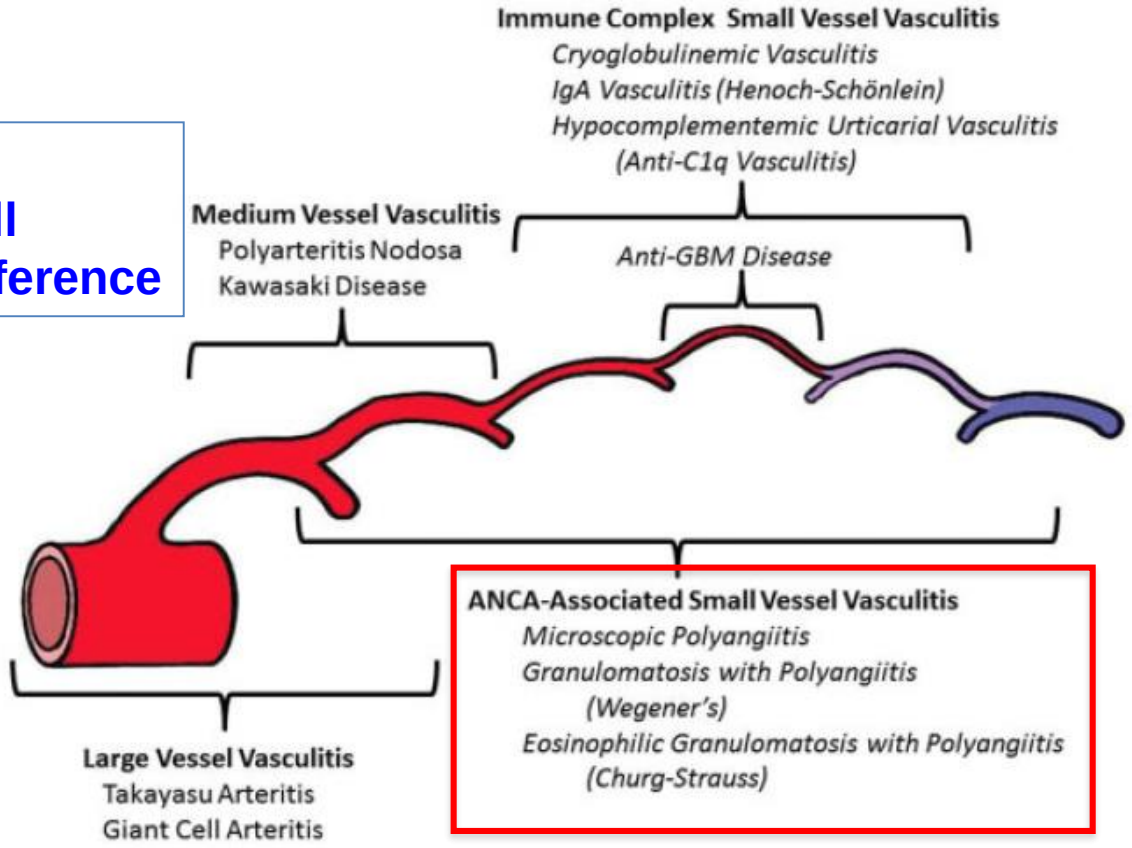
# Vascularites à ANCA : quelles nouveautés en 2018 ?

**Alexandre Karras**

# Introduction

Une nouvelle nomenclature

**2012**
**Chapel Hill**
**Consensus Conference**




**= MPA**
**= GPA**
**= EGPA**

# Vascularites pauci-immunes = ANCA

## Granulomatose avec polyangéïte (GPA) ex-Wegener

-cANCA anti-PR3

-granulomes histo

-atteintes prédominantes :
- ORL +++, OPH
- pulmonaire (nodules)
- rénale ++

-Risque accru de rechutes

## Polyangéïte Microscopique (MPA)

-pANCA antiMPO (70%)
cANCA antiPR3

-atteintes prédominantes :
- rénale +++
- pulmonaire (fibrose++)
- neuro

-Formes “rampantes”, peu symptomatiques

## Granulomatose Eosinophilique avec polyangéïte (EGPA) ex-Churg&Strauss

-ANCA neg (50%)
ou pANCA antiMPO

-atteintes prédominantes :
- pulmonaire (asthme)
- ORL
- cardiaques
- neurologiques

-Cortico-dépendance +++

# Introduction

## Une nouvelle séparation nosologique ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Genetically Distinct Subsets within ANCA-Associated Vasculitis

N ENGL J MED 367;3 NEJM.ORG JULY 19, 2012

Association génétique avec les polymorphismes

antiPR3 : HLA-DP, α1antitrypsine, protéinase 3
antiMPO : HLA-DQ

**Table 2. Associations of SNPs and ANCA–Associated Vasculitis, According to Clinical and ANCA Subgroups.***

| Chromosome | Locus | SNP | Overall Analysis of Combined Cohort (N=2267 Case Patients, 6858 Controls) | | GPA vs. MPA (N=1683 vs. 489) | | Proteinase 3 vs. Myeloperoxidase (N=1521 vs. 556) | |
|---|---|---|---|---|---|---|---|---|
| | | | odds ratio | P value | odds ratio | P value | odds ratio | P value |
| 6 | *HLA–DP* | rs3117242 | 3.67 | $1.5\times10^{-71}$ | 3.49 | $1.9\times10^{-27}$ | 5.10 | $2.5\times10^{-46}$ |
| 6 | *HLA–DQ* | rs5000634 | 0.80 | $2.9\times10^{-9}$ | 1.17 | $9.0\times10^{-2}$ | 1.28 | $8.2\times10^{-3}$ |
| 6 | *ARHGAP18* | rs1705767 | 0.80 | $6.2\times10^{-7}$ | 0.92 | $9.2\times10^{-1}$ | 0.90 | $7.2\times10^{-1}$ |
| 14 | *SERPINA1* | rs7151526 | 0.59 | $2.4\times10^{-9}$ | 0.74 | $1.7\times10^{-1}$ | 0.64 | $1.1\times10^{-2}$ |
| 19 | *PRTN3* | rs62132295 | 0.83 | $6.6\times10^{-4}$ | 0.81 | $3.9\times10^{-2}$ | 0.67 | $6.9\times10^{-6}$ |
| X | *MOSPD2* | rs6628825 | 0.79 | $9.7\times10^{-6}$ | 0.91 | $5.1\times10^{-1}$ | 0.79 | $8.3\times10^{-2}$ |

La spécificité antigénique (anti-PR3/MPO) différencie mieux les patients que le phénotype clinique (GPA/MPA)

# Traitement de la VAA :


| Traitement d'attaque | Traitement d'entretien |
| --- | --- |
| 3-6 mois | >18 mois |

# 2009 Guidelines

**Table 1 | Disease categories as defined by the European League Against Rheumatism[124]**

| Disease category | Definition |
|---|---|
| Localized | Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms |
| Early systemic | Any, without organ- or life-threatening disease |
| Generalized | Organ-threatening disease, if renal involvement: serum creatinine <5.6 mg/dl |
| Severe | Vital organ failure, if renal involvement: serum creatinine >5.6 mg/dl |
| Refractory | Disease progression despite therapy with cyclophosphamide and steroids |

**Table 2 | Recommendations for therapy of AAV by the European League Against Rheumatism[124]**

| Disease category | Recommended therapy | Grade of recommendation[a] | Level of evidence[b] |
|---|---|---|---|
| *Remission induction* | | | |
| Early systemic/localized disease | Methotrexate+steroids | B | 1B |
| Generalized disease | Cyclophosphamide (i.v. or oral)+steroids | A | $1A^{WG/MPA}$ $1B^{CSS}$ |
| Severe disease with renal failure | Adjunct: plasma exchange | A | 1B |
| *Maintenance therapy* | | | |
| Low-dose steroids + | Azathioprine | A | 1B |
| | Leflunomide | B | 1B |
| | Methotrexate | B | 2B |

Abbreviations: ANCA-associated vasculitis; CSS, Churg-Strauss syndrome; i.v., intravenous; MPA, microscopic polyangiitis; RCT, randomized controlled trial; WG, Wegener's granulomatosis.

[a]Grade of recommendation: A, based on at least evidence level 1A/B; B, based on at least level 2 evidence or extrapolated recommendations from level 1 evidence.

[b]Levels of evidence: 1A, evidence from meta-analysis of RCT; 1B, from at least one RCT; 2B, from at least one type of quasi-experimental study.

Mukthyar C, Guillevin L, Ann Rheum Dis 2009

# 2017 Guidelines

## EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

M Yates,[1,2] R A Watts,[2,3] I M Bajema,[4] M C Cid,[5] B Crestani,[6] T Hauser,[7] B Hellmich,[8] J U Holle,[9] M Laudien,[10] M A Little,[11] R A Luqmani,[12] A Mahr,[13] P A Merkel,[14] J Mills,[15] J Mooney,[1] M Segelmark,[16,17] V Tesar,[18] K Westman,[19] A Vaglio,[20] N Yalçındağ,[21] D R Jayne,[22] C Mukhtyar[1]

| Statement | Level of evidence | Grade of recommendation |
|---|---|---|
| 1. We recommend that patients with AAV are managed in close collaboration with, or at, centres of expertise. | 3 | C |
| 2. A positive biopsy is strongly supportive of a diagnosis of vasculitis and we recommend biopsies to assist in establishing a new diagnosis and for further evaluation for patients suspected of having relapsing vasculitis. | 3 | C |
| 3. For remission-induction of new-onset organ-threatening or life-threatening AAV we recommend treatment with a combination of glucocorticoids and either cyclophosphamide OR rituximab. | 1 for GPA/MPA, 3 for EGPA | A for GPA/MPA, C for EGPA |
| 4. For remission-induction of non-organ-threatening AAV we recommend treatment with a combination of glucocorticoids and either methotrexate or mycophenolate mofetil*. | 1B | B for MTX, C for MMF |
| 5. For a major relapse of organ-threatening or life-threatening disease in AAV we recommend treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR rituximab. | 1 for GPA/MPA, 3 for EGPA and CYC, 4 for EGPA and RTX | A for GPA/MPA, C for EGPA and CYC, C for EGPA and RTX |
| 6. (i) Plasma exchange should be considered for patients with AAV and a serum creatine level of ≥500 μmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease. | 1B | B |
| 6. (ii) Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage. | 3 | C |
| 7. For remission-maintenance of AAV we recommend treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate or mycophenolate mofetil*. | 1B for GPA/MPA<br>3 for EGPA and AZA | A for GPA/MPA, C for EGPA and AZA |
| 8. We recommend that remission-maintenance therapy for AAV be continued for at least 24 months following induction of sustained remission. | 4 | D |
| 9. For patients with AAV refractory to remission-induction therapy we recommend switching from cyclophosphamide to rituximab or from rituximab to cyclophosphamide. These patients should be managed in close conjunction with, or referred to, an expert centre for further evaluation and potential enrolment in clinical trials. | 3 | C |

# Rituximab en traitement d'attaque

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 15, 2010 VOL. 363 NO. 3

## Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rachel B. Jones, M.R.C.P., M.D., Jan Willem Cohen Tervaert, M.D., Ph.D., Thomas Hauser, M.D., Raashid Luqmani, D.M., F.R.C.P., F.R.C.P.(E.), Matthew D. Morgan, M.R.C.P., Ph.D., Chen Au Peh, F.R.A.C.P., Ph.D., Caroline O. Savage, Ph.D., F.R.C.P., F.Med.Sci., Mårten Segelmark, M.D., Ph.D., Vladimir Tesar, M.D., Ph.D., Pieter van Paassen, M.D., Ph.D., Dorothy Walsh, B.S.C.N., Michael Walsh, M.D., F.R.C.P.(C.), Kerstin Westman, M.D., Ph.D., and David R.W. Jayne, M.D., F.R.C.P., for the European Vasculitis Study Group

Essai RITUXVAS

Essai RAVE

NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., and Ulrich Specks, M.D., for the RAVE–ITN Research Group*

# Rituximab en traitement d'attaque

## Essai RAVE

- Essai prospectif multicentrique américain
- 197 patients WG/MPA de novo ou en rechute
- Randomisation (1:1)
  - RTX (375mg/m² x4) +cort, sans entretien
  - CYC PO (M3), entretien AZA + cort
- Atteinte rénale : 66%
- Evaluation M6
- Critère Iaire : rémission sans cort

| | RTX (n=99) | CYC (n=98) |
|---|---|---|
| Critère Iaire | 64% | 53% |
| Rechutes | 11 | 14 |

Non infériorité
Pas de supériorité

Stone, NEJM 2010

# Rituximab en traitement d'attaque

## Essai RAVE

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- Atteinte rénale : 66%
- Evaluation M6
- Critère Iaire : rémission sans cort

**ATTENTION :**

Les formes rénales sévères (creat>350) ou avec hémorragie intra-alvéolaire sévère étaient EXCLUES du protocole

Le risque infectieux à court terme n'est pas inférieur avec le RTX vs le CYC

| | RTX (n=99) | CYC (n=98) |
|---|---|---|
| Critère Iaire | 64% | 53% |
| Rechutes | 11 | 14 |
| Négativation ANCA | 47% | 24% |
| Critère Iaire (ss-gp pts rechute) | 67% | 42% |

Non infériorité
Pas de supériorité

P<0.05

P<0.05

Stone, NEJM 2010

# Rituximab en traitement d'entretien

## Etude MAINRITSAN

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 6, 2014 VOL. 371 NO. 19

### Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

Groupe Français d'Etude des Vascularites

# Rituximab en traitement d'entretien

## Etude MAINRITSAN

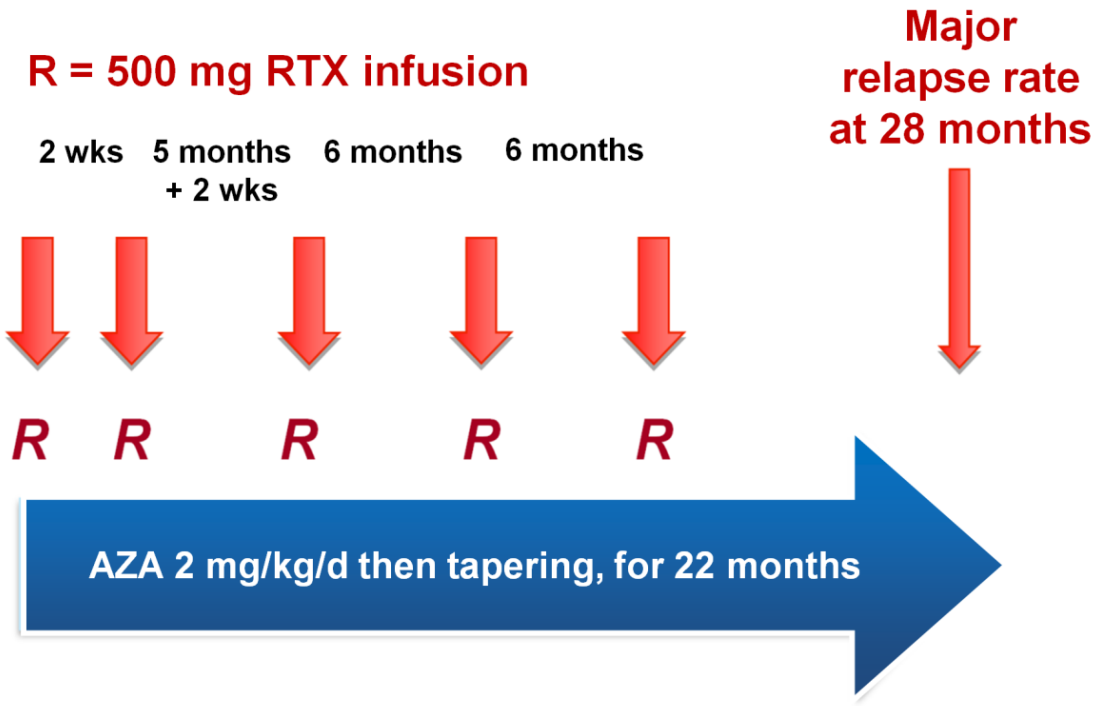
***Induction therapy***

1 g x 3 i.v. methylprednisolone

Prednisone (1 mg/kg/day)
then 20 mg/d at 3 months
then 10 mg/d at 6 months

CYC i.v.
0.6 g/m2 x 3 then 0.7 g/m2 x 3

***Maintenance therapy***



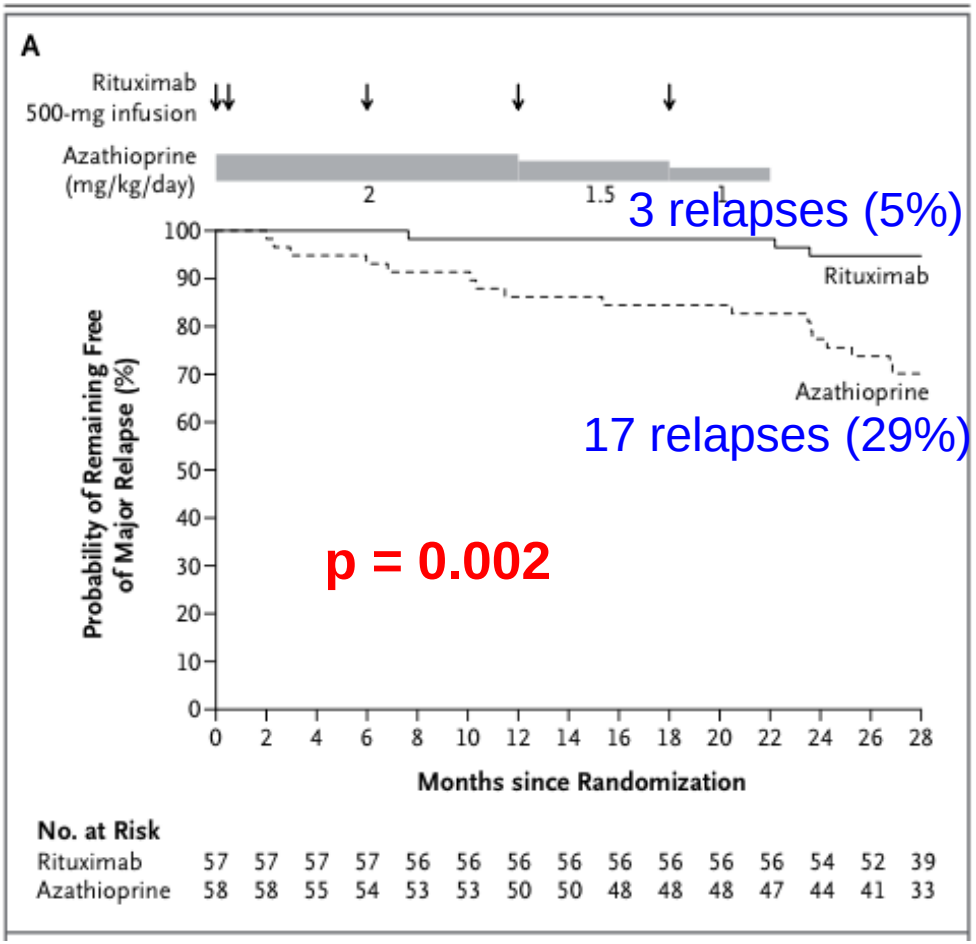
# Rituximab en traitement d'entretien

## Etude MAINRITSAN

- 117 patients
- 66 hommes (56.4%) et 51 femmes (43.6%), âge 55±13 ans
- 80 patients GPA, 24 MPA and 5 vascularites rénales isolées
- Manifestations initiales :

  ORL 88 (77.2%), pulmonaires 69 (60.5%), rénales 82 (71.9%)
- Créat à l'inclusion : 195±171 (AZA) vs 175±196 (RTX)
- Randomisation des patients
  - ✓ 59 sous AZA ( 47 poussées initiales et 12 rechutes)
  - ✓ 58 sous Rituximab ( 46 poussées initiales et 12 rechutes)

# Rituximab en traitement d'entretien




| Severe Adverse Event | Azathioprine Group (N=58) | Rituximab Group (N=57) |
|---|---|---|
| | *no. of events* | |
| Infection | 8 | 11 |
| Bronchitis | 0 | 3 |
| Tuberculosis | 0 | 1 |
| Pneumonia with respiratory distress | 1 | 2 |
| *Pneumocystis jiroveci* pneumonia | 0 | 1 |
| Bacterial endocarditis | 1 | 0 |
| Atypical mycobacterial infection | 1 | 0 |
| Prostatitis | 1 | 0 |
| Herpes zoster infection | 1 | 1 |
| Cholecystitis | 1† | 0 |
| Septicemia | 1‡ | 0 |
| Esophageal candidiasis | 0 | 1 |
| Infectious diarrhea | 1§ | 2¶ |
| Cancer | 2 | 1 |
| Pancreas | 1‡ | 0 |
| Prostate | 0 | 1 |
| Basocellular carcinoma | 1 | 0 |
| Hematologic event | 9 | 1 |
| Anemia | 1 | 0 |
| Leukopenia | 6 | 0 |
| Lymphopenia | 1 | 1 |
| Thrombocytopenia | 1 | 0 |
| Other‖ | 25 | 26 |

**Maintenance therapy with « low-dose » rituximab prevents relapse in AAV**

# Echanges plasmatiques dans la VAA ?

## Etude MEPEX

CLINICAL RESEARCH www.jasn.org

### Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis

David R.W. Jayne,* Gill Gaskin,† Niels Rasmussen,‡ Daniel Abramowicz,§ Franco Ferrario,‖ Loic Guillevin,¶ Eduardo Mirapeix,** Caroline O.S. Savage,†† Renato A. Sinico,‖ Coen A. Stegeman,‡‡ Kerstin W. Westman,§§ Fokko J. van der Woude,‖‖ Robert A.F. de Lind van Wijngaarden,¶¶ and Charles D. Pusey; on behalf of the European Vasculitis Study Group†

European Vasculitis Society EUVAS

Jayne, JASN 2007

# Echanges plasmatiques dans la VAA ?

## Etude MEPEX

- 137 patients WG/MPA avec **atteinte rénale sévère (creat >500)**
- Les deux groupes reçoivent :
  - CYC PO 2.5 mg/kg/j J0-M3 puis 1.5 mg/kg M4-M6, relais AZA
  - Cort : 1 mg/kg/j dès J1
- Randomisation :

vs
- **Echanges plasmatiques (60 ml/kg x7 en 2 semaines)**
- **Solumédrol IV (1000 x3)**

- Critères d'évaluation :
  - Primaire : % de patients vivants, hors dialyse (et creat <500) à M3
  - Secondaires : survie patients, fonction rénale, effets secondaires

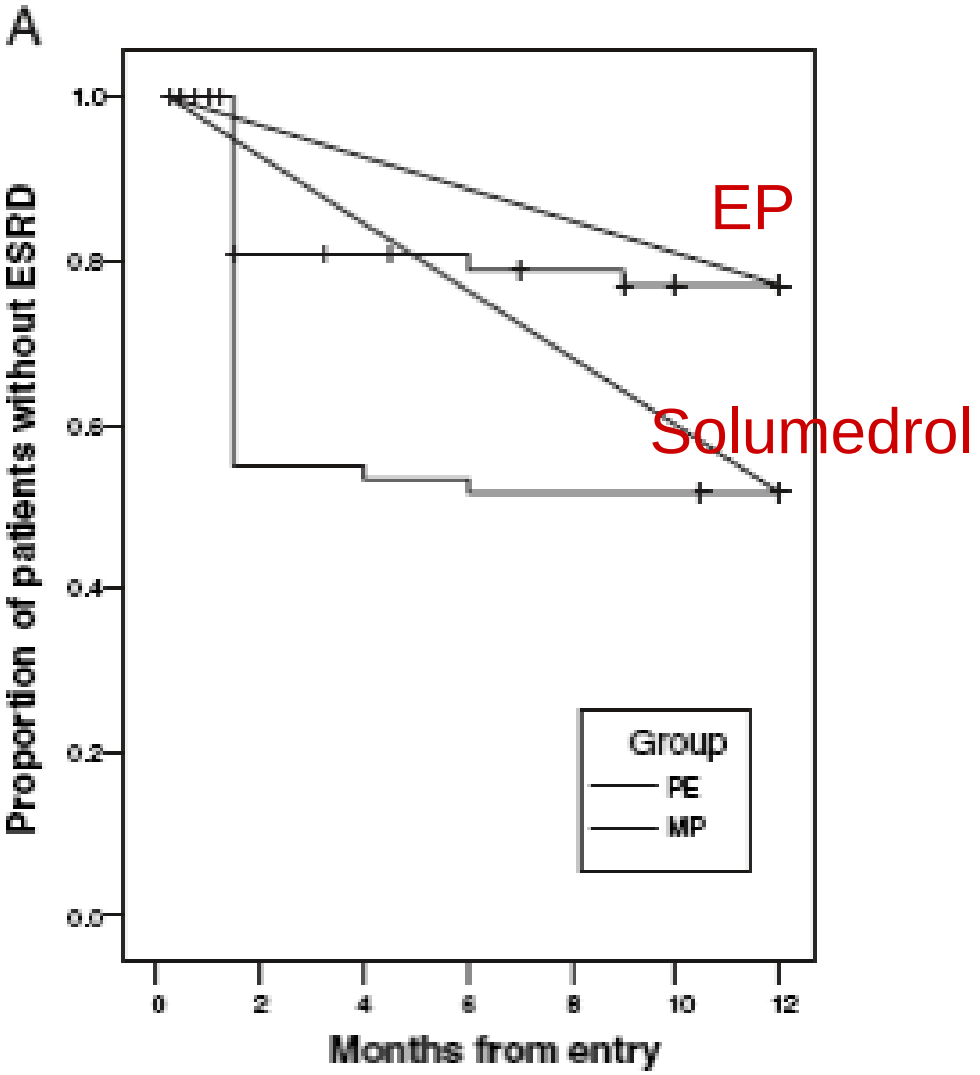
Jayne, JASN 2007

# Echanges plasmatiques dans la VAA ?

## Etude MEPEX

- 137 patients WG/MPA avec **atteinte rénale sévère (creat >500)**
- Les deux groupes reçoivent :
  - CYC PO 2.5 mg/kg/j
  - Cort : 1 mg/kg/j dès J1
- Randomisation :
  - vs **-Echanges plasmatiques**
  - **-Solumédrol IV (1000 x3)**

Le risque de d'IRT est réduit de 24% dans le gp EP




Jayne, JASN 2007

# Echanges plasmatiques dans la VAA ?

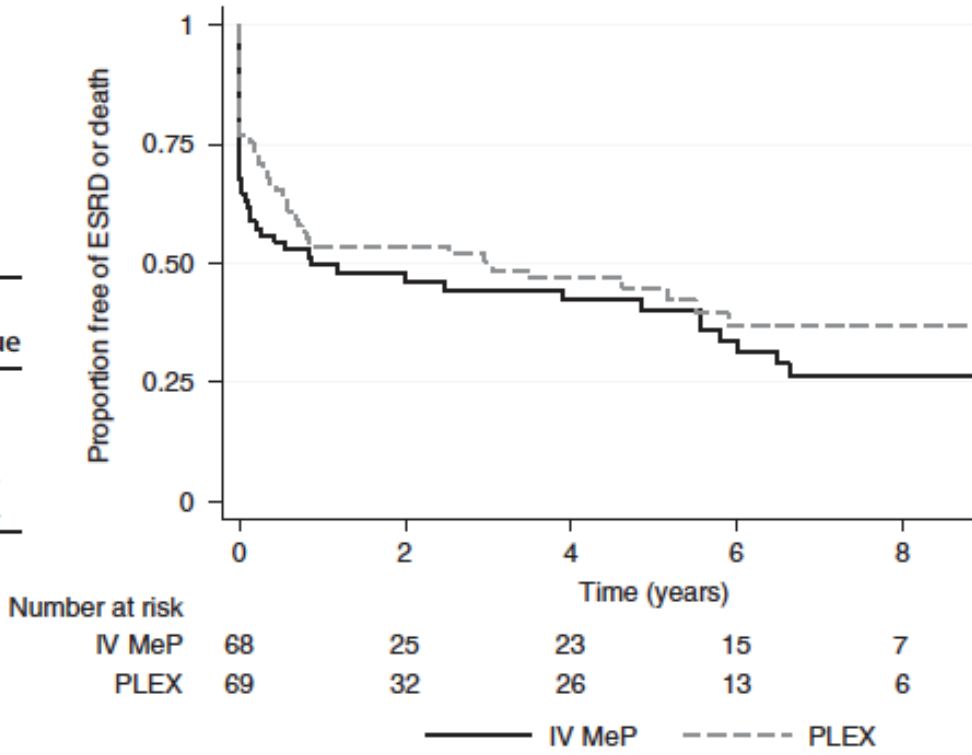
## Etude MEPEX

Quid à long terme ?

Suivi moyen 3.9 années

**Table 3 | Long-term primary and secondary outcomes by treatment group**

| Outcome | IV MeP, $n = 68$ (%) | PLEX, $n = 69$ (%) | HR (95% CI) | *P*-value |
|---|---|---|---|---|
| Death or ESRD | 46 (68) | 40 (58) | 0.81 (0.53–1.23) | 0.32 |
| Death | 35 (51) | 35 (51) | 1.08 (0.67–1.73) | 0.75 |
| ESRD[a] | 33 (49) | 23 (33) | 0.64 (0.40–1.05) | 0.08 |
| Relapse[a] | 16 (21) | 10 (14) | 0.56 (0.26–1.21) | 0.14 |




Mortalité très élevée+++
(dose de CYC non adaptée au DFG)

Walsh, Kidney Int 2013

Intérêt des EP dans les stades plus précoces ? => Etude PEXIVAS

# Individualisation du traitement ?

## Iatrogénicité au cours de la vascularite à ANCA

**Table 3** Causes of death within and after the first year of follow-up, respectivel

| Cause of death | <1 Year | | >1 Year | |
|---|---|---|---|---|
| | Primary cause | Contributing factor | Primary cause | Contributing factor |
| Active vasculitis | 11 (18.6) | 17 (28.8) | 6 (8.1) | 7 (9.5) |
| Pulmonary haemorrhage | 6 | | 2 | |
| Infection | 28 (47.5) | 31 (52.5) | 15 (20.3) | 23 (31.1) |
| Pneumonia | 15 | | 8 | |
| Sepsis | 8 | | 7 | |
| CMV | 2 | | | |
| PCP | 3 | | | |
| Cardiovascular | 9 (15.3) | 11 (18.6) | 19 (25.7) | 21 (28.4) |
| Myocardial infarction | 2 | | 4 | |
| Cerebrovascular accident | 2 | | 2 | |
| Pulmonary embolus | 2 | | | |
| Sudden death | 1 | | 3 | |
| Malignancy | 0 (0) | | 16 (21.6) | 18 (24.3) |
| Solid organ | | | 12 | |
| Haematological | | | 4 | |

N=535
Suivi med 5.2 ans
25% de mortalité
FdR de mortalité :
- age >60
- DFG <15

Flossmann, Ann Rheum Dis 2011

# Individualisation du traitement ?

## Réduction de l'immunosuppression chez le sujet âgé

### Etude CORTAGE :

VAA de novo, âge >65 ans,

- Gp A : CYC 500 mg/m2 x6
  décroissance standard des stéroïdes
  entretien par AZA
- Gp B : CYC 500 mg x6
  diminution rapide des stéroïdes
  entretien par AZA

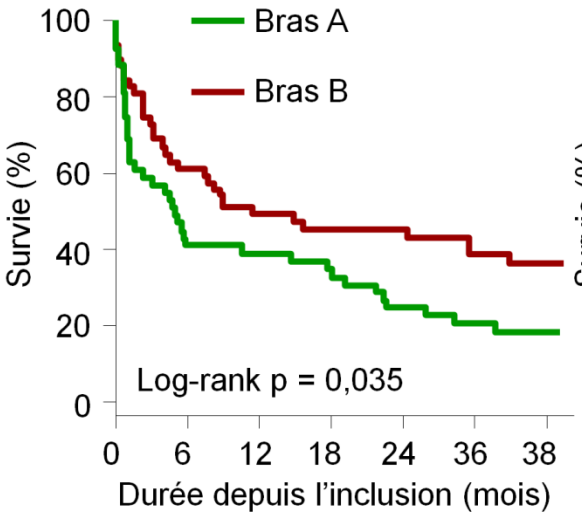
108 patients inclus, age moyen 75 ans, suivi 3 ans

Pagnoux, Arthr Rheum 2015

# Individualisation du traitement ?

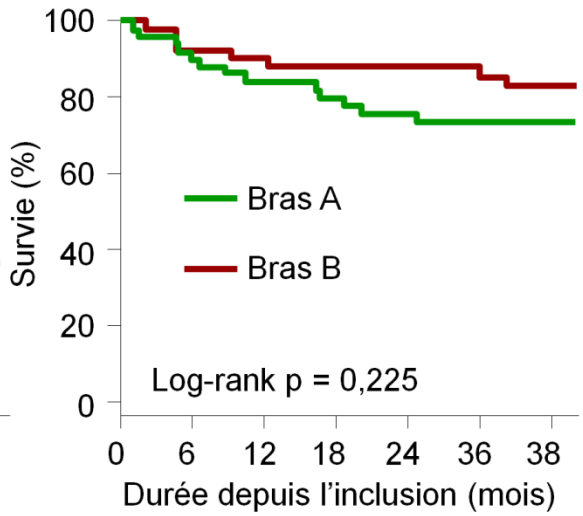
## Réduction de l'immunosuppression chez le sujet âgé

***Effets indésirables sévères***



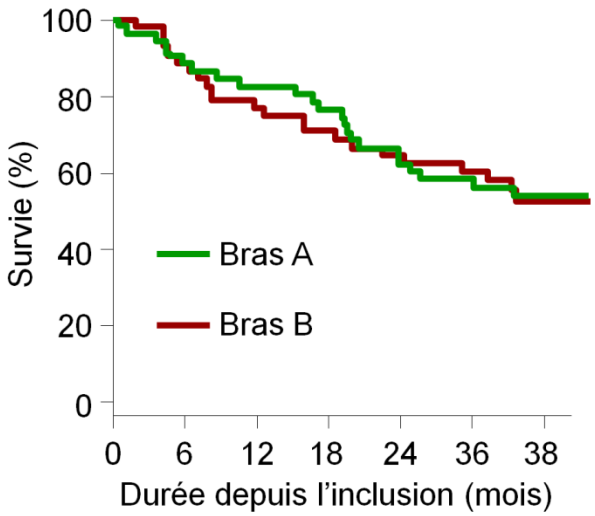

**Bras A : 80,8 % versus**
**Bras B : 62,5 %**

***Décès***




**Bras A : 13 décès versus**
**Bras B : 8 décès**

***Sans rechute à 3 ans***




**Bras A : 54,2 % versus**
**Bras B : 53,2 %**

**Meilleure tolérance d'un traitement allégé avec dose fixe de CYC à 500 mg et moindre dose cumulée de corticoïdes, sans baisse d'efficacité**

Pagnoux, Arthr Rheum 2015

# Individualisation du traitement ?

## Adaptation des doses de rituximab aux biomarqueurs

**Essai MAINRITSAN 2**

2 modalités d'administration du RTX en traitement d'entretien

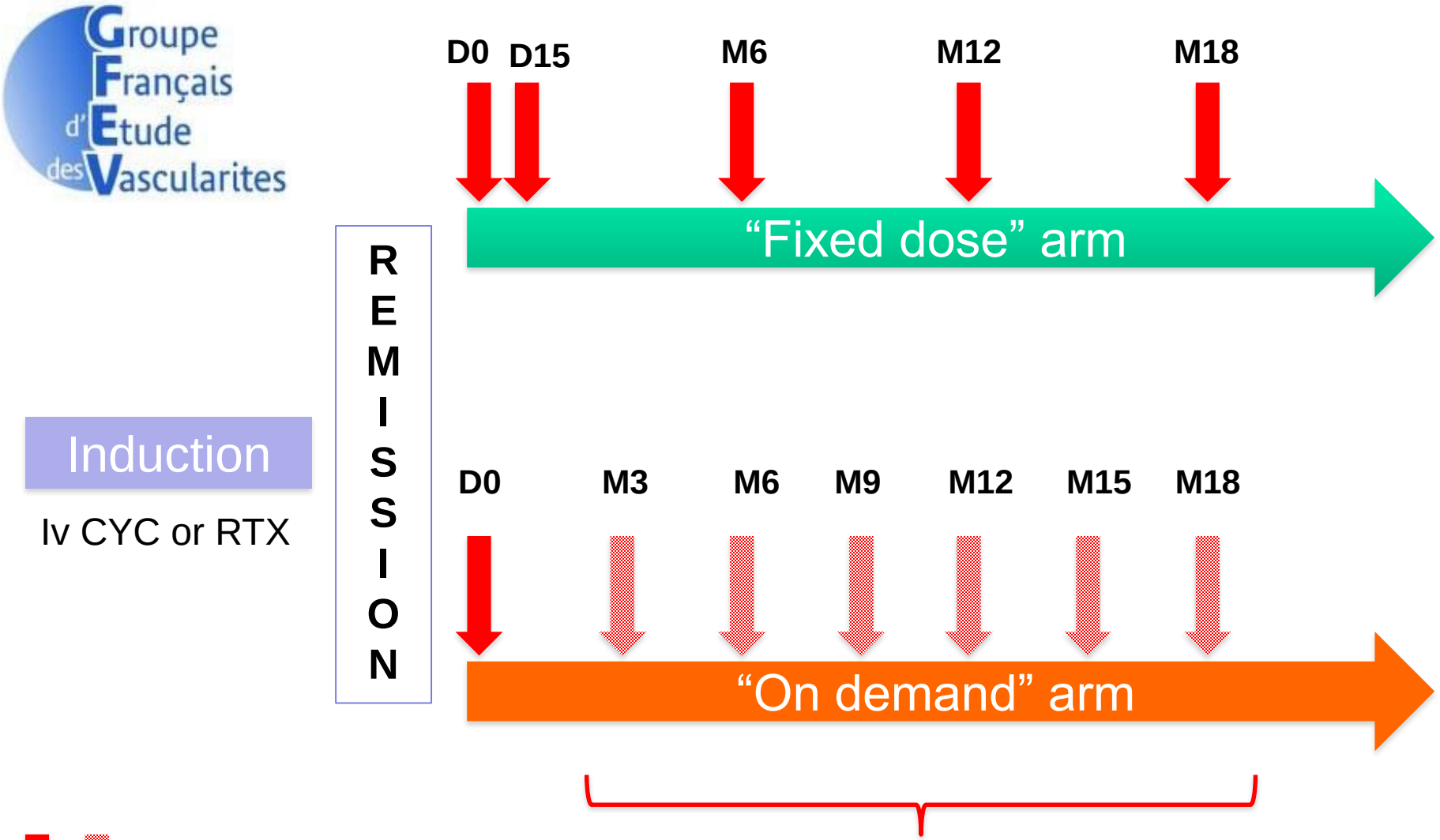
Systématique /6 mois

vs

Tous les 3 mois max, selon déplétion B et/ou taux d'ANCA

Charles P, submitted

# MAINRITSAN 2 – study design




Charles P, submitted

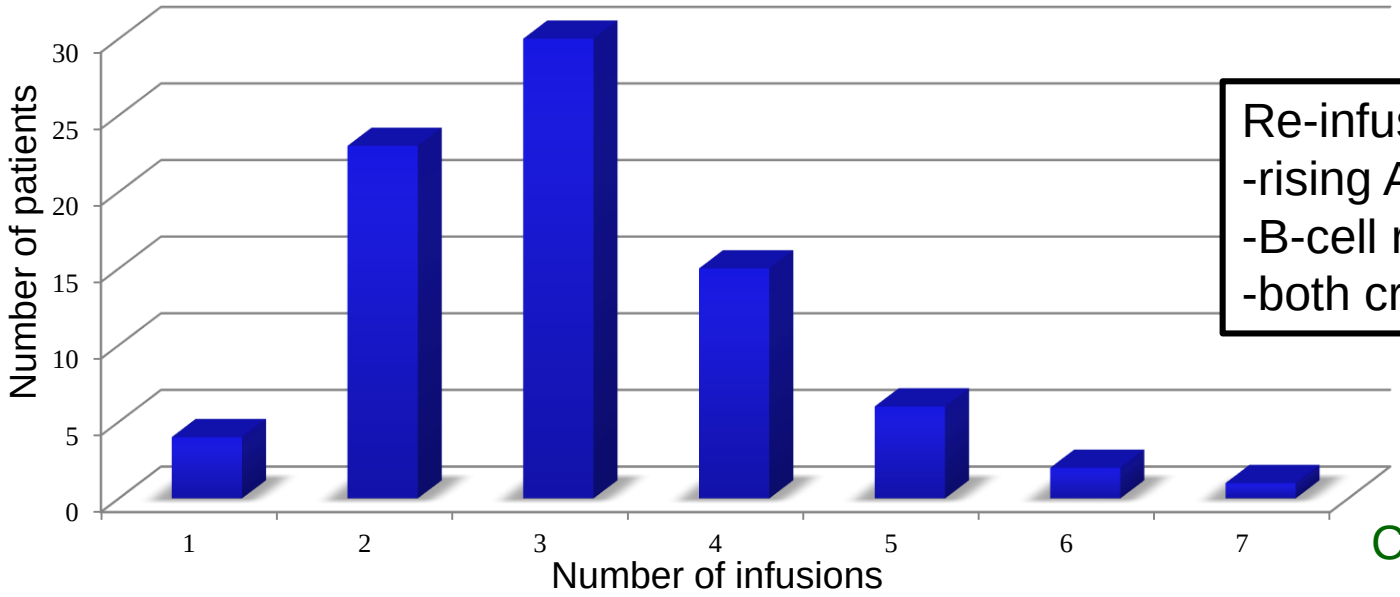
# MAINRITSAN 2 – results

162 patients included in the study

Induction regimen : ivCYC 62%, RTX : 38%
Study population : GPA (72%) / MPA (28%)
Newly diagnosed AAV : 64%

Number of infusions /18 months :

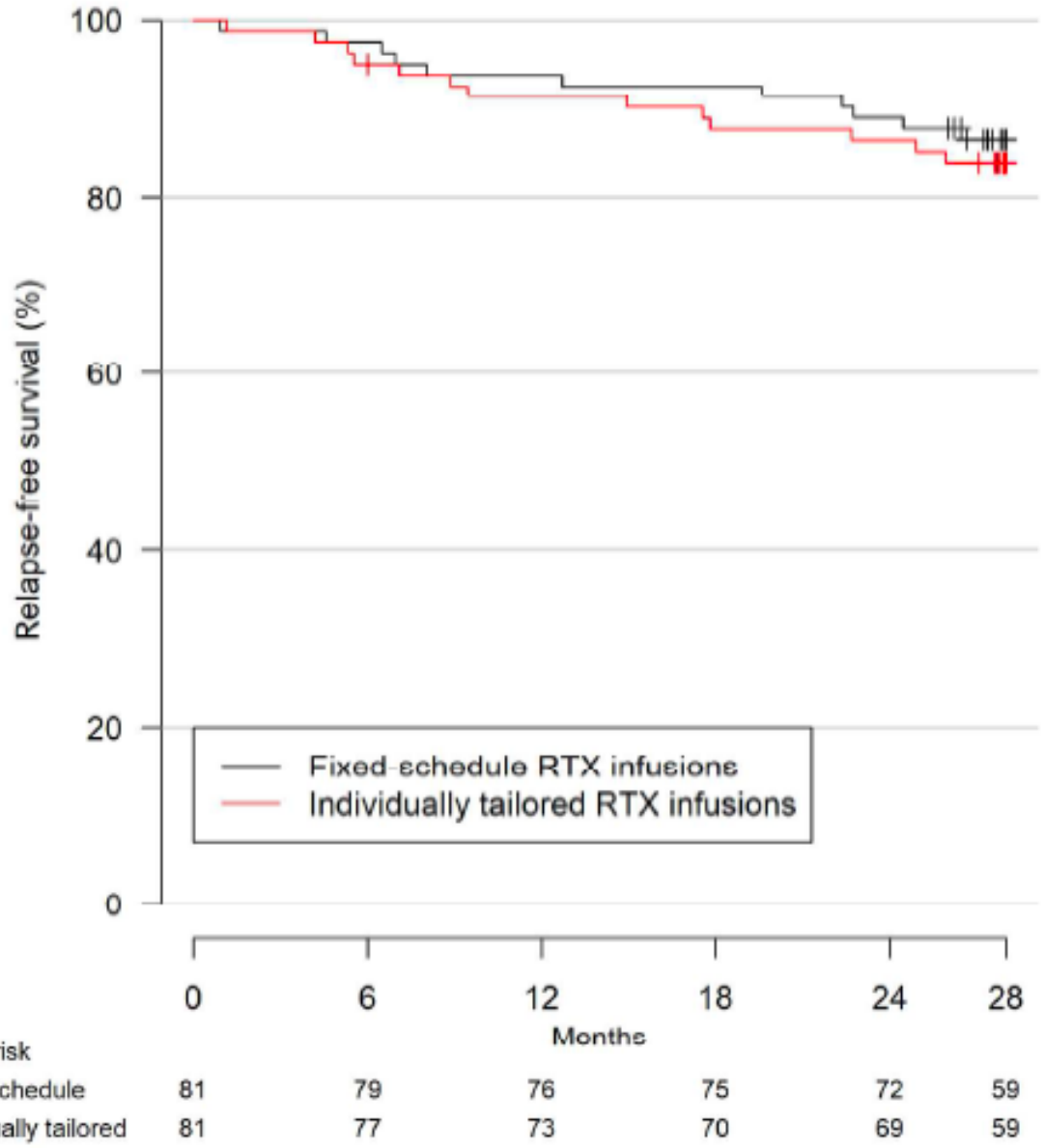
| | tailored-infusion | vs. | fixed-schedule |
|---|---|---|---|
| | n=248 | | n=381 |
| median (IQR) | 3 (2-4) | | 5 (5-5) |




Re-infusions for :
-rising ANCA titers (13%)
-B-cell repopulation (51%)
-both criteria (36%)

Charles P, submitted

# MAINRITSAN 2 – results




86.4%
83.8% p=0.58

**CONCLUSIONS :**

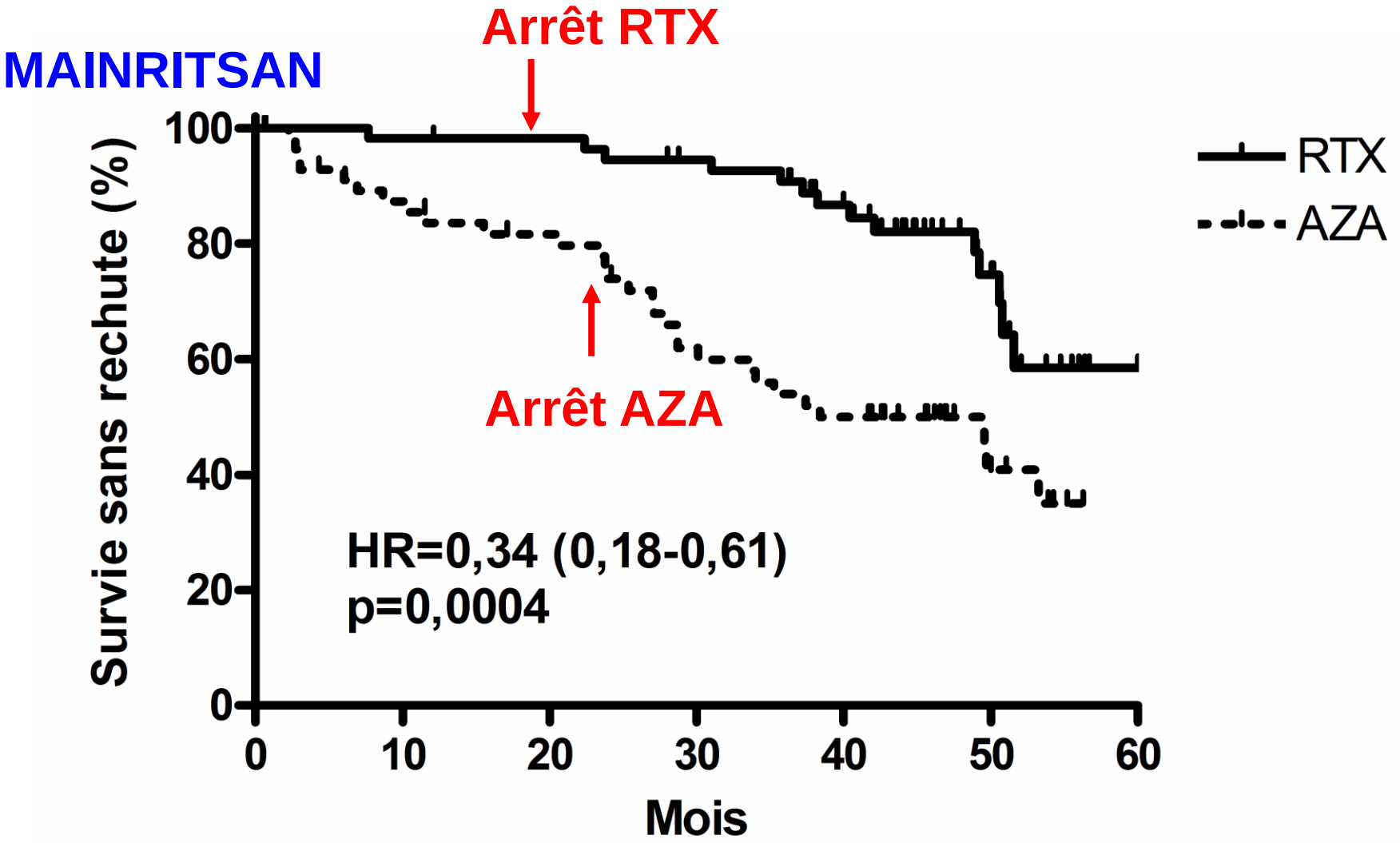
AAV relapse rate for patients treated with individually tailored or fixed-schedule rituximab-infusion regimens did not differ significantly.

Those benefitting from personalized care received fewer infusions and lower total rituximab doses

Charles P, submitted

# Individualisation du traitement ?

## Quelle durée de traitement d'entretien ?



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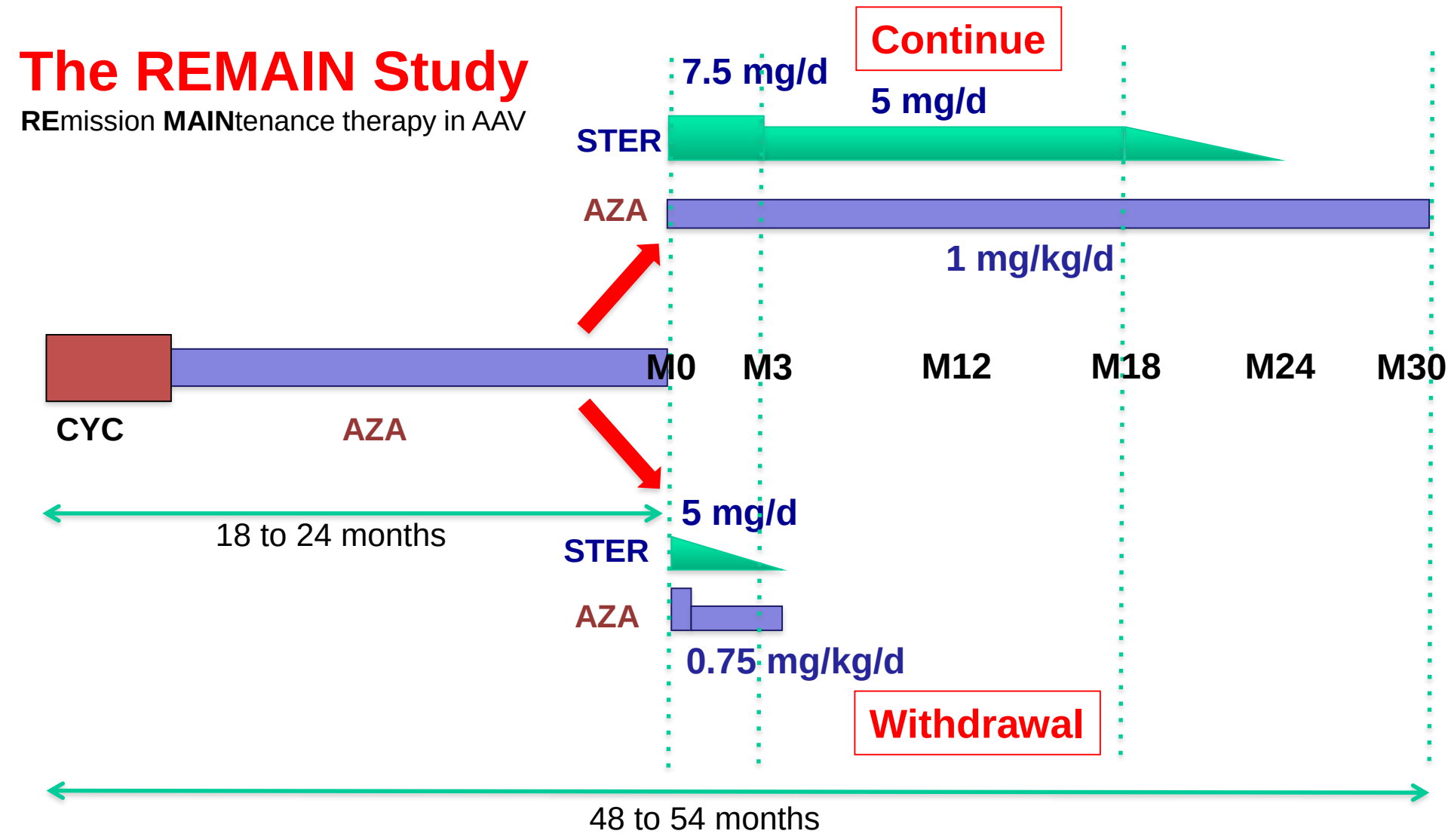

# Individualisation du traitement ?

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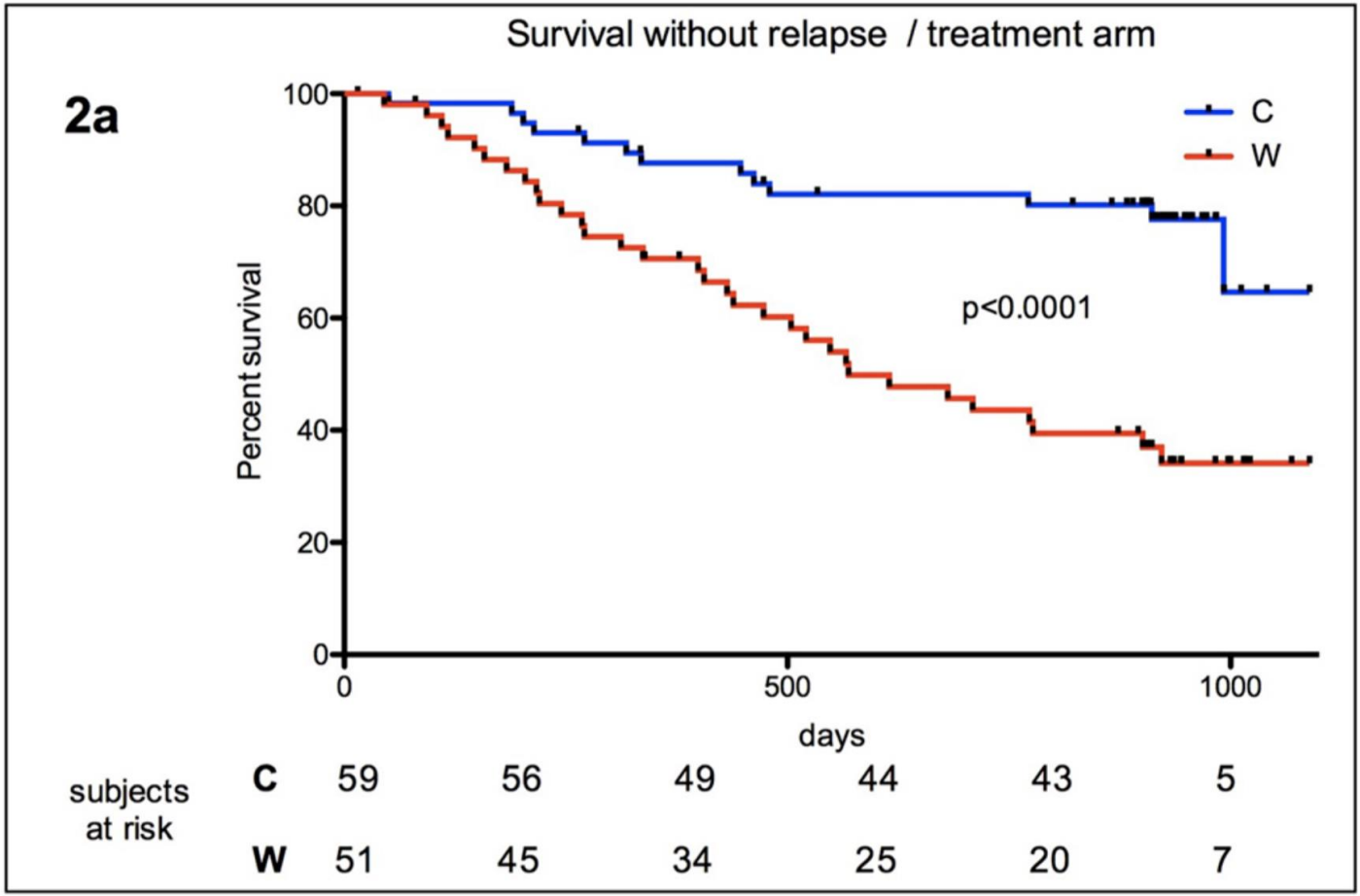
## The REMAIN Study

**RE**mission **MAIN**tenance therapy in AAV

Karras et al, Ann Rheum Dis 2017



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**The REMAIN Study**

**RE**mission **MAIN**tenance therapy in AAV

Karras et al, Ann Rheum Dis 2017

**Table 3** Risk factors associated with AAV relapse

| | Subgroup | Relapse risk | p Value | OR (95% CI) |
|---|---|---|---|---|
| Treatment arm | W | 32/51 (63%) | <0.0001 | 5.96 (2.58 to 13.77) |
| | C | 13/59 (22%) | | |
| ANCA specificity at diagnosis | PR3 | 28/57 (49%) | 0.13 | 1.82 (0.83 to 3.98) |
| | MPO | 17/49 (35%) | | |
| ANCA testing at randomisation | Positive | 30/58 (51%) | 0.017 | 2.57 (1.16 to 5.68) |
| | Negative | 15/51 (29%) | | |
| Disease | MPA | 22/58 (38%) | 0.5 | 0.77 (0.36 to 1.65) |
| | GPA | 23/52 (44%) | | |

# Individualisation du traitement ?

## Quelle durée de traitement d'entretien ?

### The REMAIN Study

**RE**mission **MAIN**tenance therapy in AAV

18 vs 48 months of AZA maintenance therapy

### The MAINRITSAN3 Study

18 vs 48 months of RTX maintenance therapy

En cours…

# How we treat renal AAV in HEGP

- Induction of remission :

CYCLOPHOSPHAMIDE IF
First flare of AAV
Severe renal disease (sCreat >40 mg/l) or severe IAH

With dose reduction in elderly patients

RITUXIMAB IF
Relapsing AAV
Young patients
High cumulative CYC dose
Past history of cancer

PLASMA EXCHANGE IF
Severe renal disease (sCreat >500) or severe IAH

STEROIDS
Rapid tapering if age >65

- Maintenance of remission :

RITUXIMAB (off-label)
All new patients
500 mg/6 months
-for 18 months if MPO and negative ANCA at M18
-for 48 months if PR3 or positive ANCA at M18

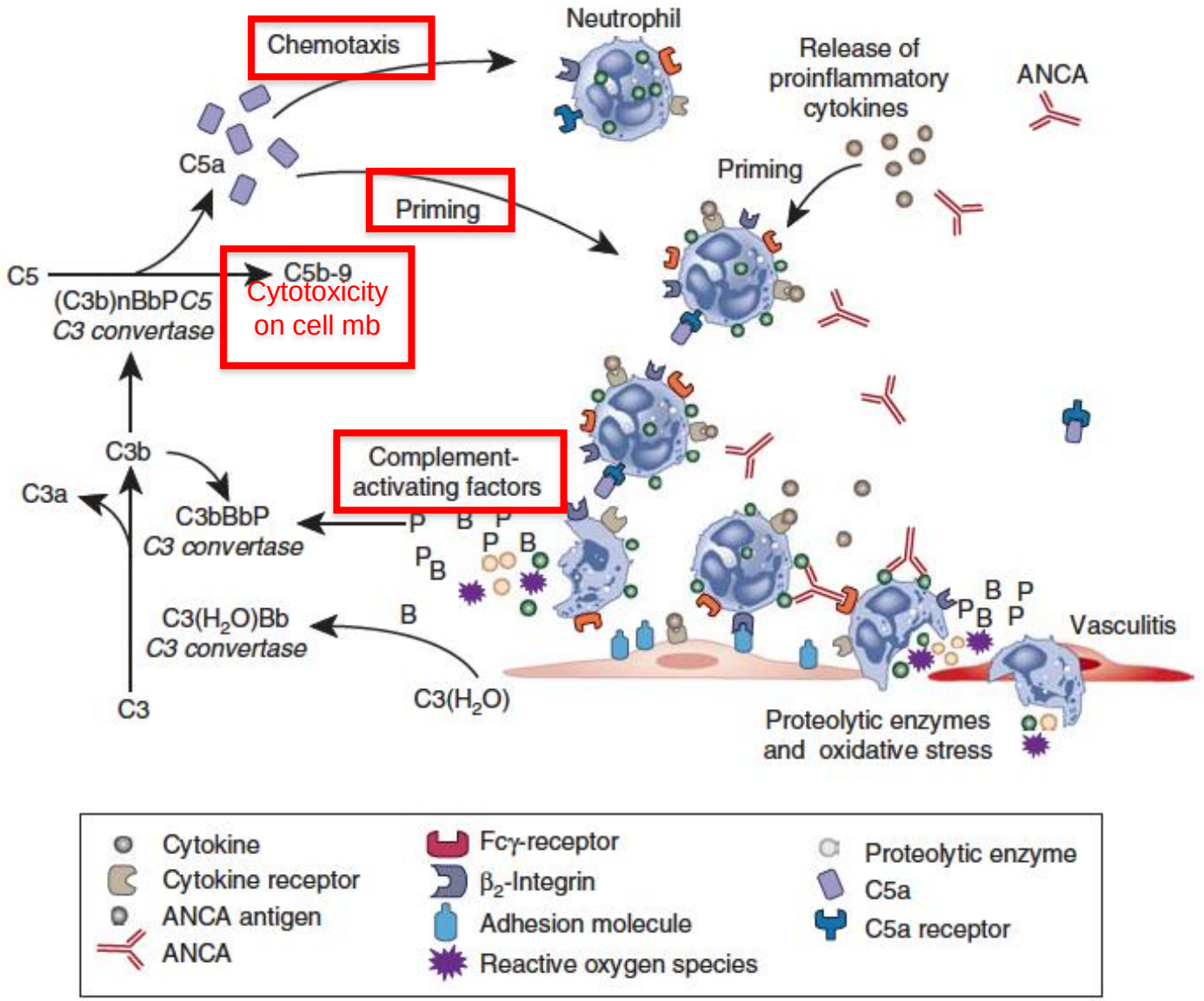
STEROIDS
Stop at M12, if possible

# Les prochains défis

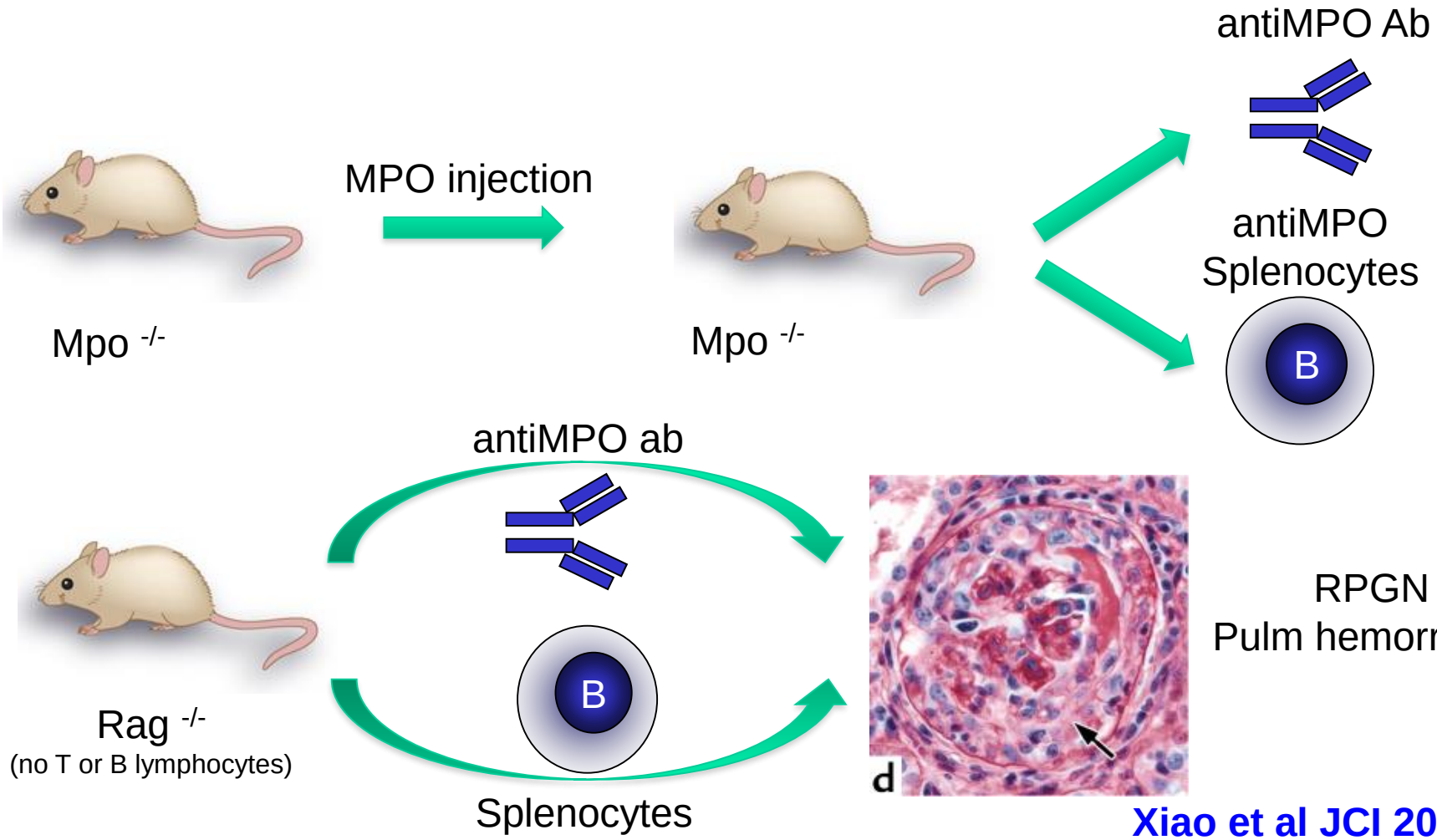
Arrêt précoce des corticoïdes grâce à l'utilisation de nouveaux immunosuppresseurs ?

Blocage du complément ?

# A role for complement in AAV ?



# The animal model of antiMPO AAV




Xiao et al JCI 2002

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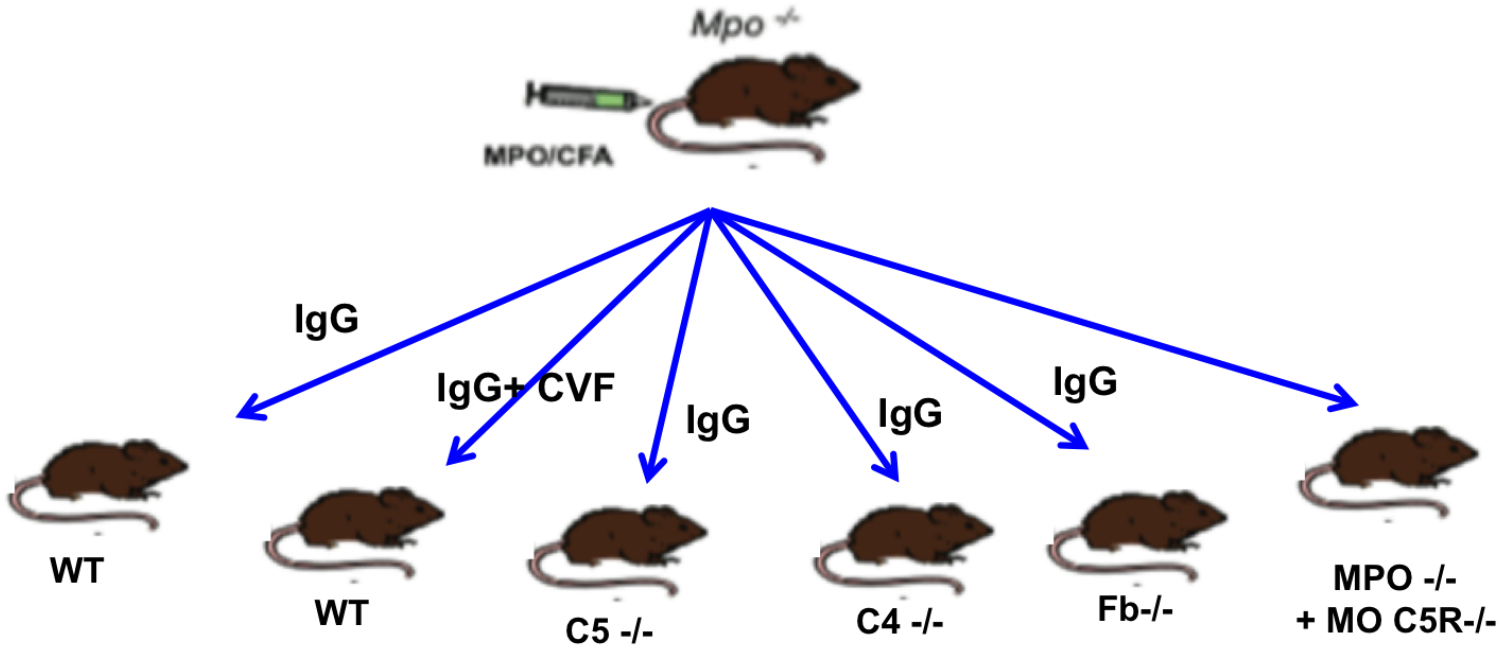



| | | | | | | |
|---|---|---|---|---|---|---|
| % croissants | 11% | 0 | 0 | 18% | 0 | 0.5 |
| % nécrose | 5% | 0 | 0 | 9% | 0 | 0 |

- Complement depletion by CVF (cobra venom factor), C5 or factorB délétion, or absence of C5R prevent RPGN
- C5 and C5aR are necessary for AAV pathogenesis

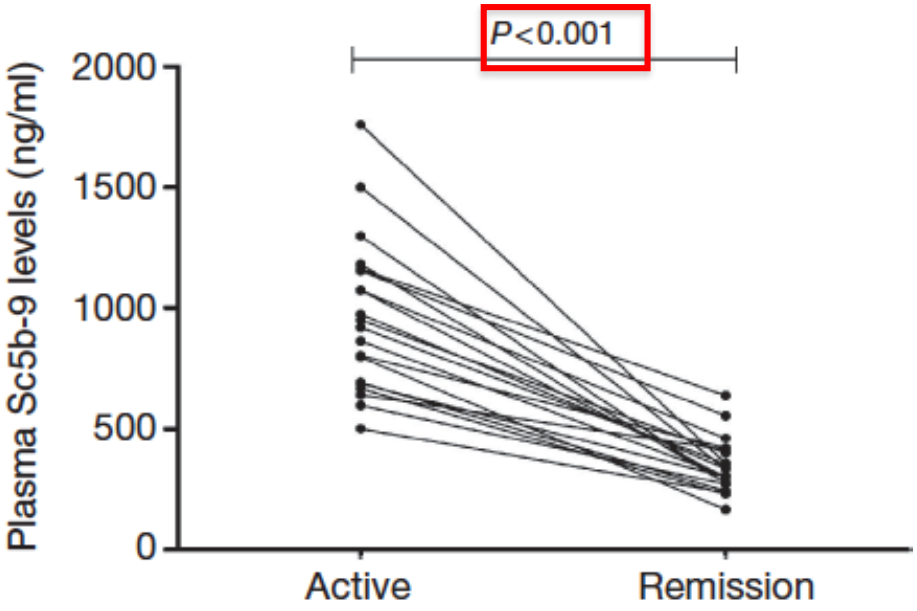
Xiao et al JCI 2002

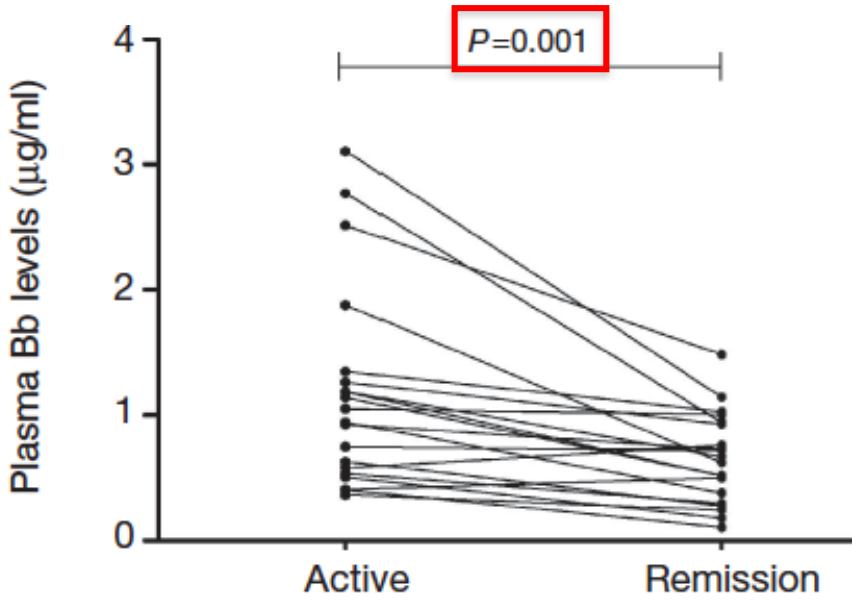
# Evidence for complement activation in human AAV ?

**Circulating complement activation in patients with anti-neutrophil cytoplasmic antibody–associated vasculitis**

*Kidney International* (2012) **83**, 129–137

Shen-Ju Gou[1,3], Jun Yuan[1,2,3], Min Chen[1], Feng Yu' and Ming-Hui Zhao'



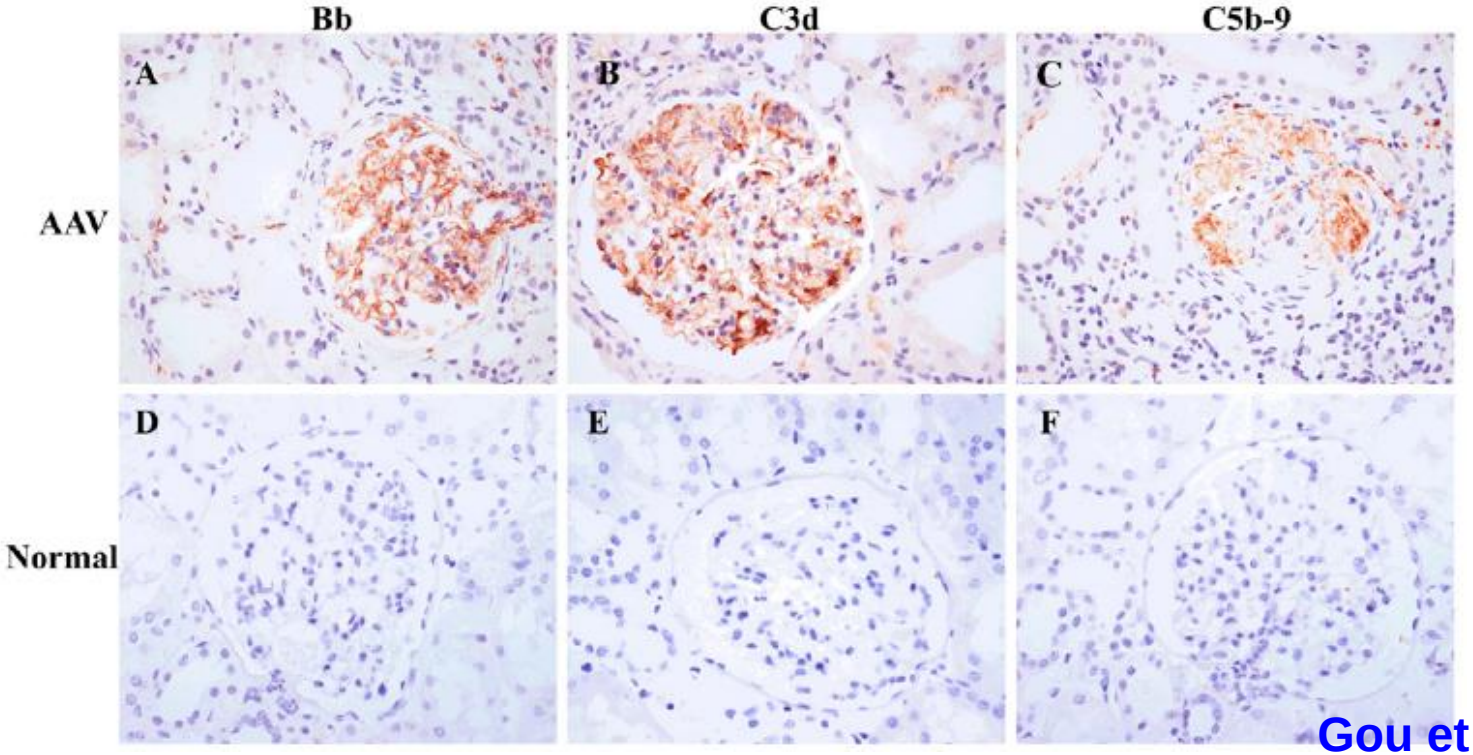




**Gou et al Kidney In**

# Evidence for complement activation in human AAV ?

## Alternative Complement Pathway Activation Products in Urine and Kidneys of Patients with ANCA-Associated GN

*Shen-Ju Gou, Jun Yuan, Chen Wang, Ming-Hui Zhao, and Min Chen*




Gou et al CJASN 2013

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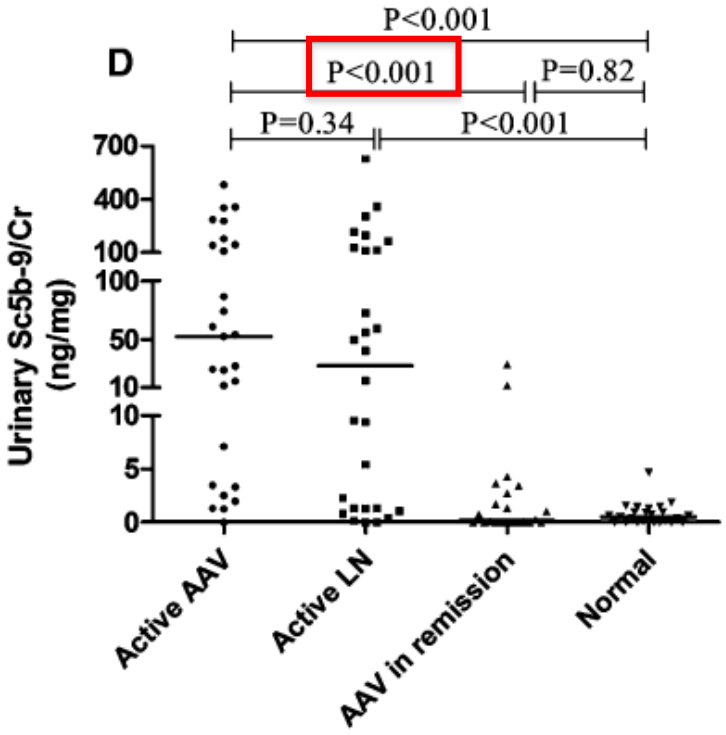


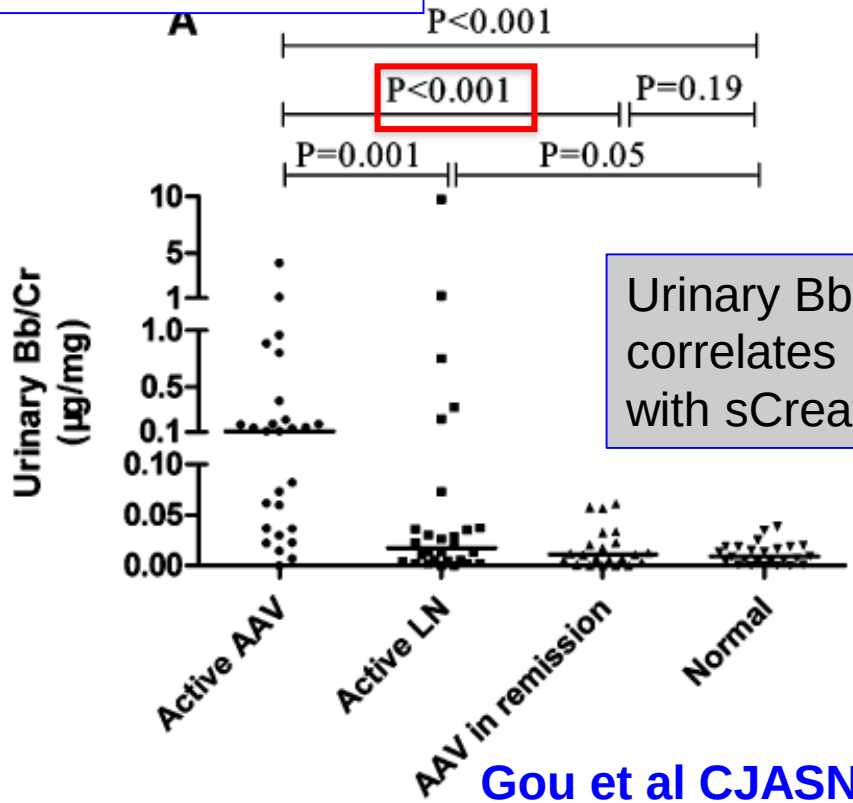


Urinary Bb levels correlates with sCreatinine

**Gou et al CJASN 2013**

# Les prochains défis

## Arrêt précoce des corticoïdes grâce à l'utilisation de nouveaux immunosuppresseurs ?

CLINICAL RESEARCH www.jasn.org

**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

Etude CLEAR (Phase 2) :

CCX168 (avacopan) : antagoniste oral du C5aR

N=67 patients en double aveugle

Gp A : placebo+EDX+cort dose standard

Gp B : CCX168+EDX+ cort dose faible

Gp C : CCX168+EDX+placebo (pas de corticoïdes)

Jayne, JASN 2017

# Les prochains défis

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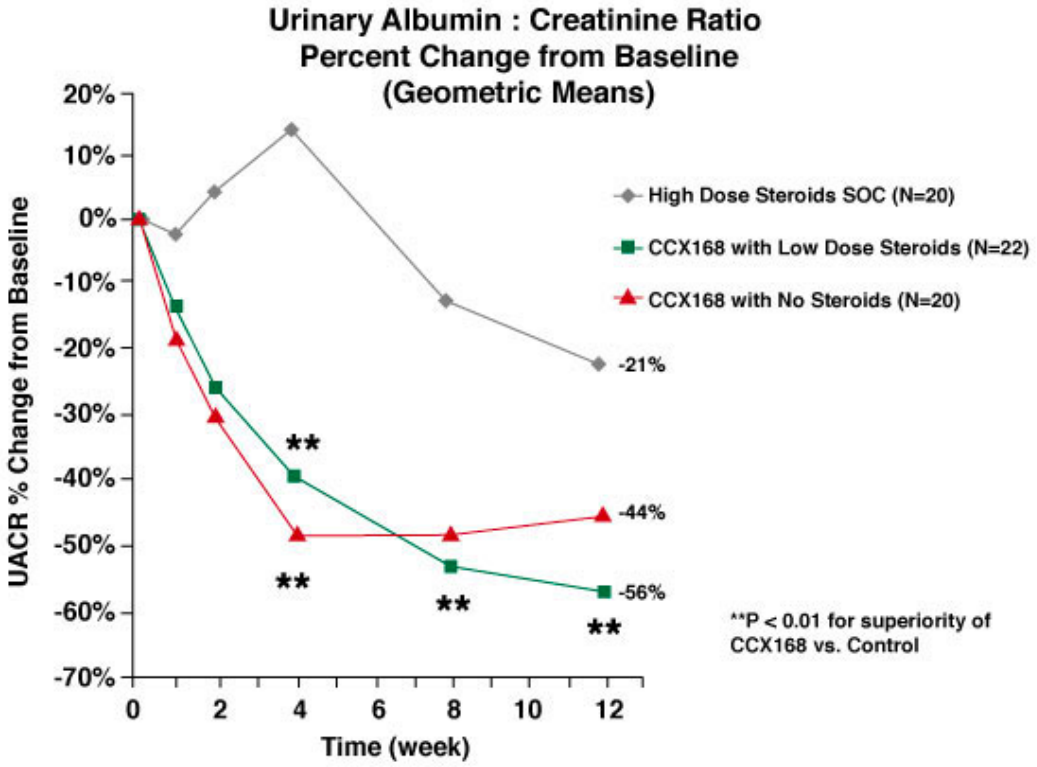
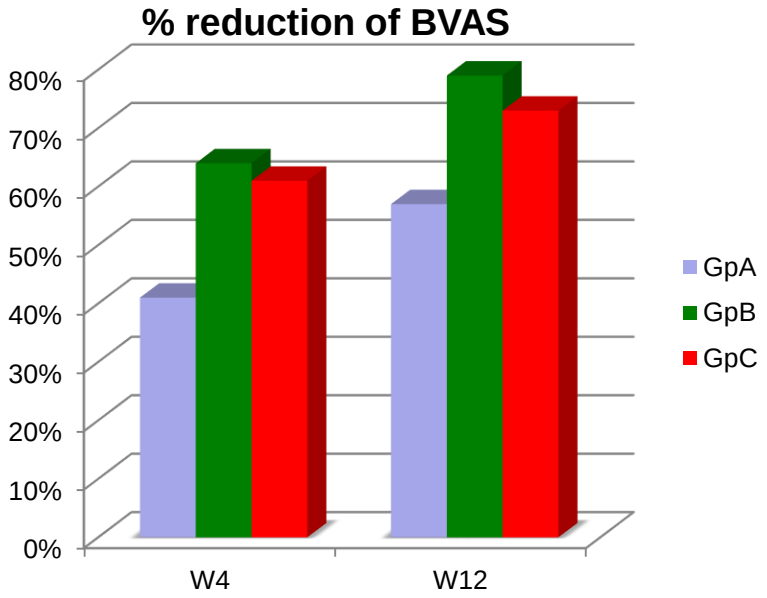



Jayne, JASN 2017

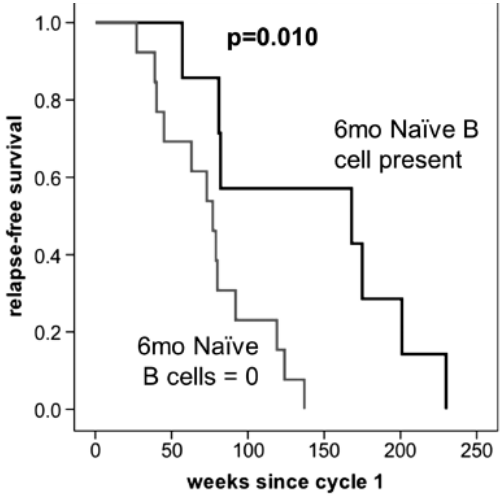
# Les prochains défis

## Identification de nouveaux biomarqueurs prédisant la rechute ?

### Sous-populations lymphocytaires

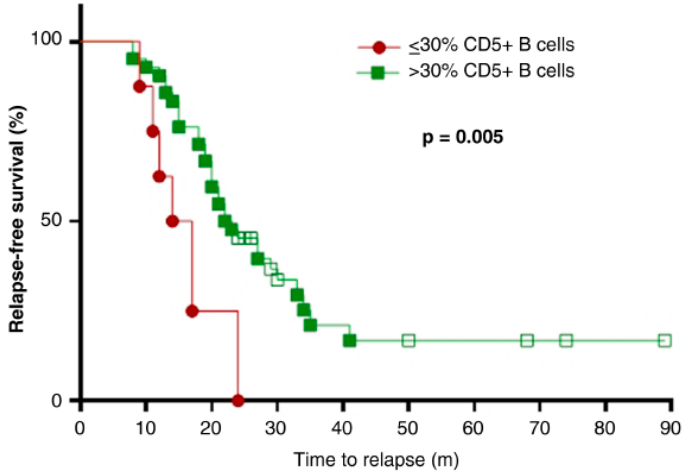
**Lymphocytes B naïf (CD19+CD27-)**
-Déficit dans la VAA active
-Ré-apparition à M6 = protection/rechute

Md Yusof, ARD 2015




**Lymphocytes B reg (CD19+CD5+)**
-Déficit dans la VAA active
-Ré-apparition à M6 = protection/rechute

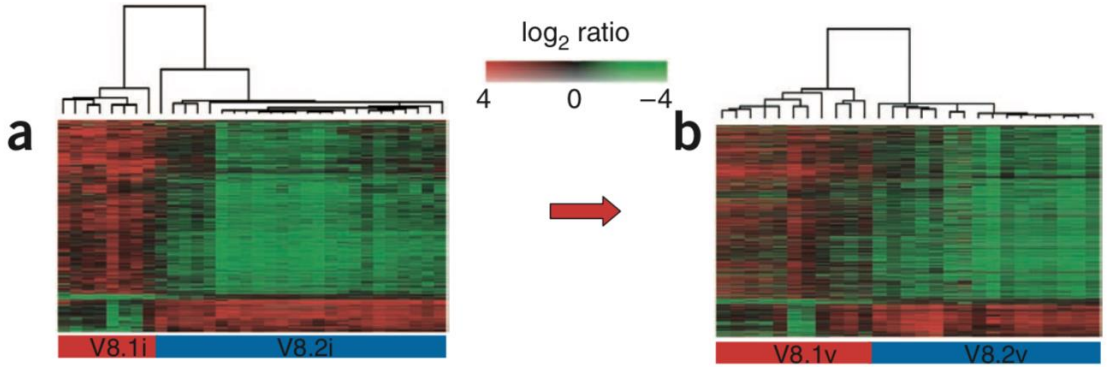
Bunch, ARD 2015

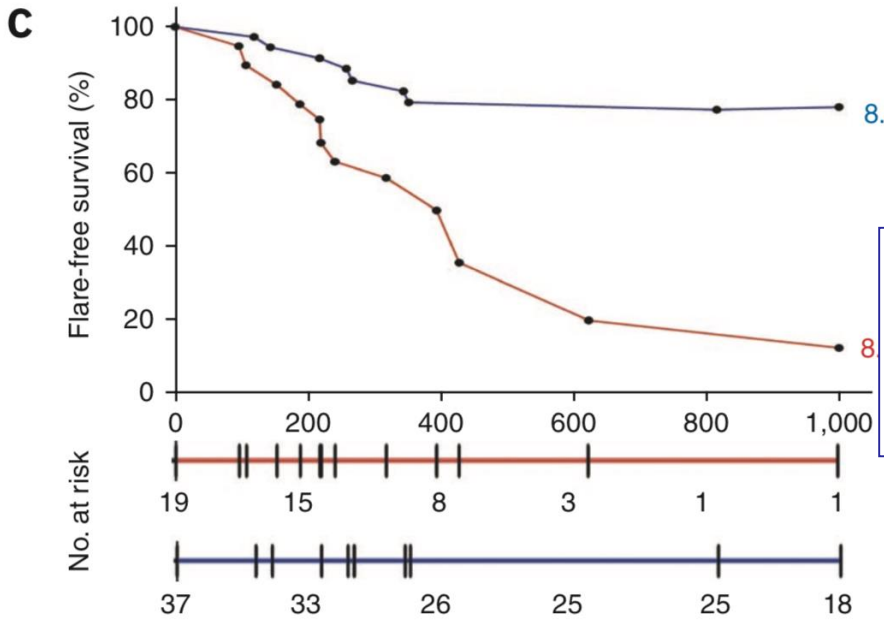


# Les prochains défis

## Identification de nouveaux biomarqueurs prédisant la rechute ?

### Transcriptome lymphocytaire




A CD8$^+$ T cell transcription signature predicts prognosis in autoimmune disease

Eoin F McKinney[1,2], Paul A Lyons[1,2], Edward J Carr[1,2], Jane L Hollis[2], David R W Jayne[2], Lisa C Willcocks[1,2], Maria Koukoulaki[1,2], Alvis Brazma[3], Vojislav Jovanovic[4], D Michael Kemeny[4], Andrew J Pollard[5], Paul A MacAry[4], Afzal N Chaudhry[2] & Kenneth G C Smith[1,2]

VOLUME 16 | NUMBER 5 | MAY 2010 NATURE MEDICINE

# CONCLUSIONS

- Différencier les patients selon spécificité des ANCA (PR3/MPO)
- Privilégier RTX
  - ✓ En traitement d'attaque si forme à rechutes, ATCD cancer, sujet jeune…
  - ✓ En traitement d'entretien
- Limiter EDX et corticoïdes si sujet âgé
- Poursuivre le traitement d'entretien (>18 mois) si risque élevée de rechute (persistance ANCA, PR3)
- Tenter d'arrêter précocément les corticoïdes en utilisant de nouveaux immunosuppresseurs (avacopan ?)
- Définir le rôle des échanges plasmatiques (résultats PEXIVAS…)

# Remerciements

Loic Guillevin, Luc Mouthon, Christian Pagnoux, Benjamin Terrier (Cochin)
David Jayne, Thomas Hiemstra, Rachel Jones (Cambridge)
Tous les collaborateurs français du GFEV

Les centaines de patients inclus dans les protocoles thérapeutiques