ANCA -Associated Vasculitis

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Melborne 1982:First description of ANCA

SHORT REPORTS

Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology?

Focal and segmental glomerulonephritis occur in mesangial IgA disease and several systemic diseases, but often the aetiology is unknown.[1] We describe eight patients seen over five years with a generalised illness associated with segmental necrotising glomerulonephritis. Clinical findings and the geographic distribution of the cases suggest that infection by a group A arbovirus may have been an aetiological factor.

Patients, methods, and results

The patients were four men and four women aged 28-71 years. All had been ill for several weeks with lethargy, weight loss, arthralgia or myalgia, and anorexia, nausea, vomiting, or diarrhoea. Renal symptoms (haematuria, loin pain, and oedema) were present in five and respiratory symptoms (dyspnoea or haemoptysis) in four. In all cases urine analysis showed

function, but none required chronic haemodialysis or renal transplantation. Recurrent disease occurred in two cases, three and five years after the onset. In both this was associated with reappearance of antineutrophil factor in the serum, and renal biopsy showed active segmental glomerulonephritis on a background of long-standing glomerular scarring. Both patients again responded to treatment with prednisolone and cyclophosphamide.

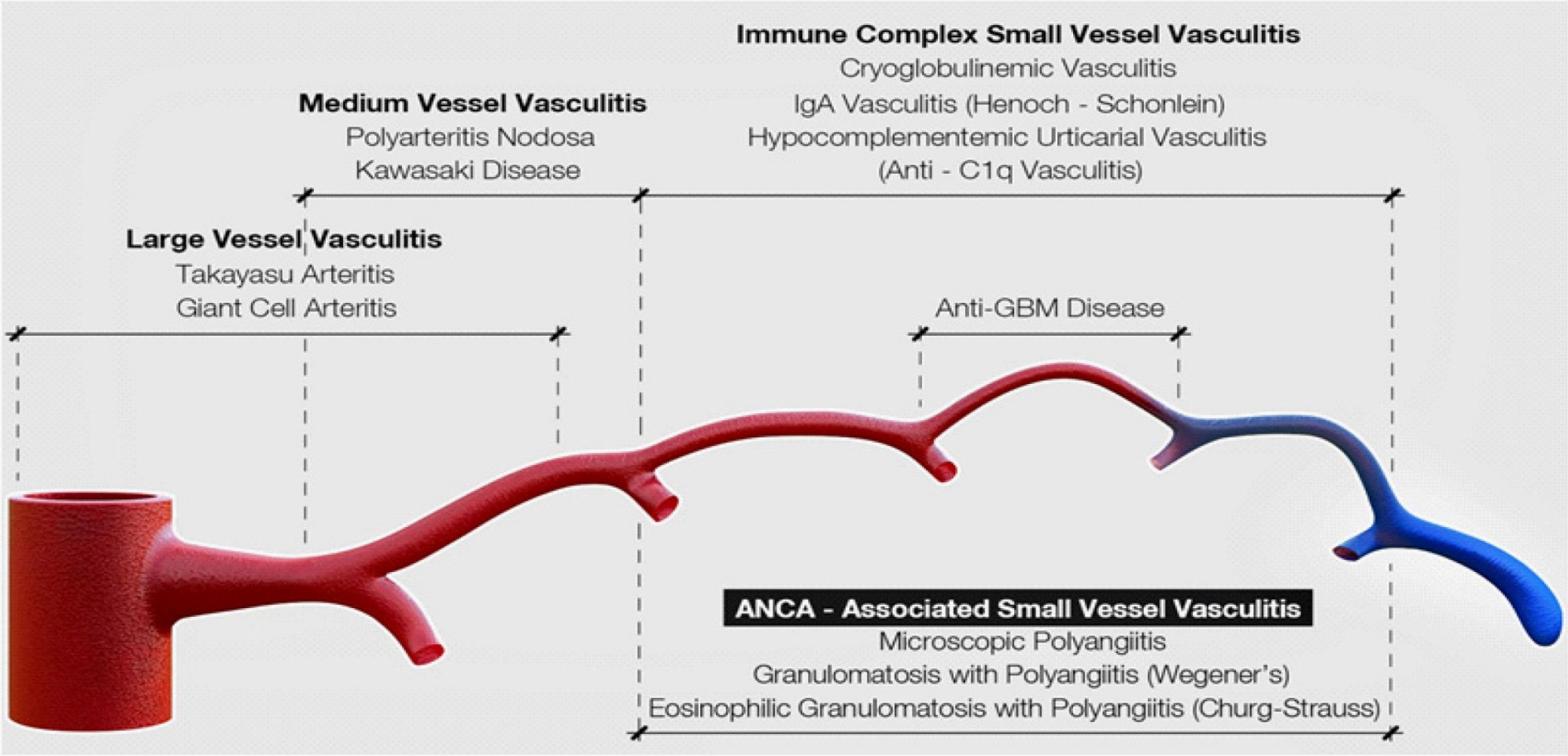
Comment

The glomerular lesions in these cases were morphologically indistinguishable from those in microscopic polyarteritis nodosa.[2] Staining of neutrophil cytoplasm by these patients' sera was a characteristic diagnostic finding; this has not been previously described and has not been seen otherwise in more than 5000 sera examined during the past five years. Because of an unusual rural clustering of the cases, mainly in the Murray River valley, and the prominence of arthralgia and myalgia, this condition may be related to epidemic polyarthritis, which is common in this area[3] and caused by Ross River virus.[4] Serology showed evidence of previous infection by this virus in seven of the eight patients; the prevalence of serum antibodies to this virus in this region is 14·6%.[5]

Further serological investigation using IgM antibody as an index of recent infection is needed to establish a causal role for Ross River

D J DAVIES,1982

Distribution of vessel involvement in vasculitis



Epidemiology

- **Annual incidence** of AAVs :**13 to~20 cases per million** individuals.
- **Prevalence** : **46 to~184** cases per million individuals worldwide.
- **EGPA** is less common than GPA or MPA
  EGPA annual incidence :**0.5-2.0/million** , prevalence of **10-45/** million
- The gender distribution is **fairly similar**.
- Peak incidence occurs in the middle of the **sixth decade** of life .

Genetic Associations in ANCA Associated Vasculitis

- In **anti-PR3 AAV** was associated with :
- *HLA-DP: HLA-DRB1*15, HLA DPB1*0401*
- *PRTN3* (the gene encoding proteinase-3)
- *SERPINA1* (the gene encoding a1-antitrypsin, a circulating inhibitor of PR3)

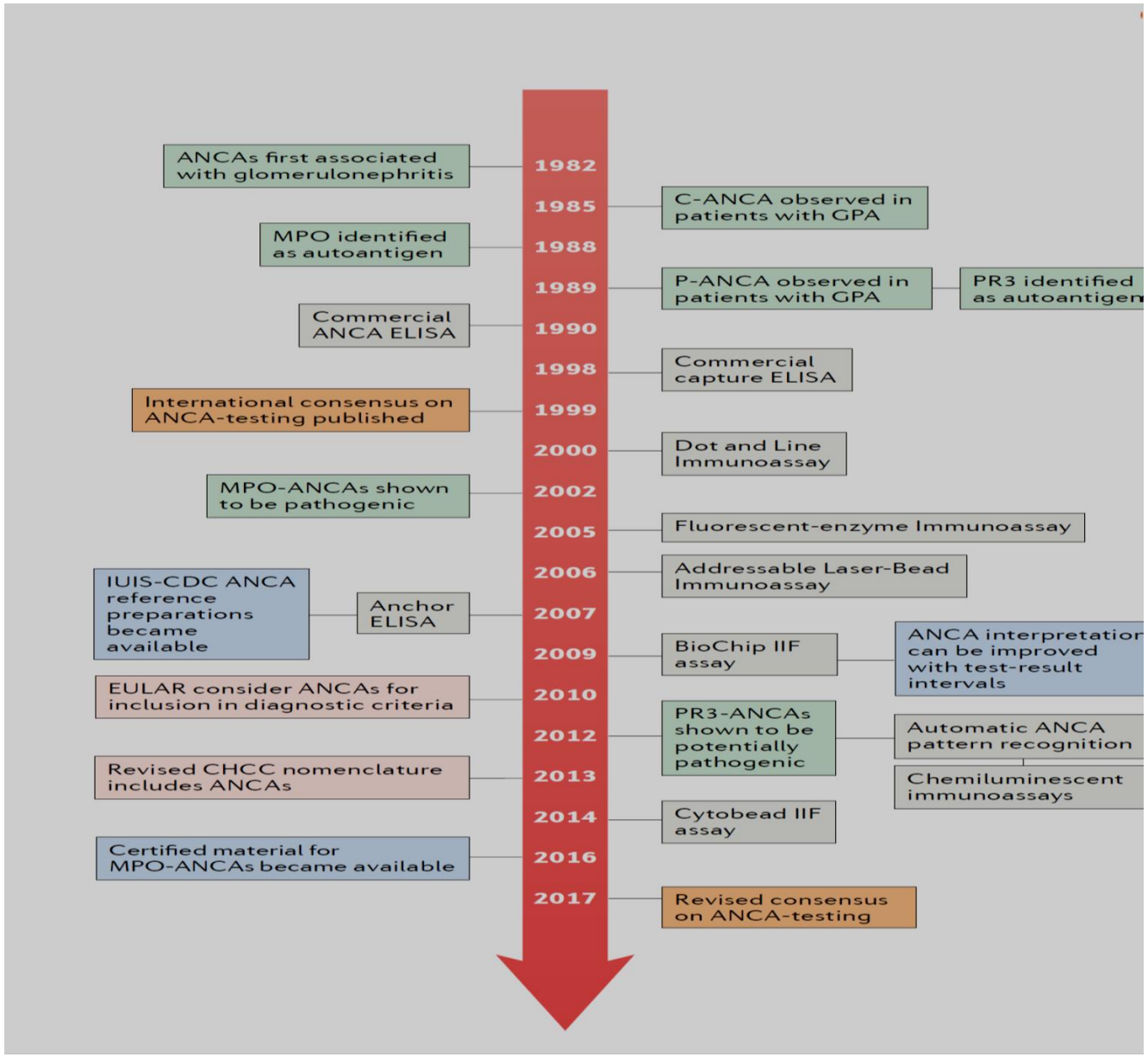
- In **anti-MPO** AAV was associated with:
- *HLA-DQ*

Environmental Associations and Immunogenicity of ANCA

- **Silica**
- **Bacterial species** Staphylococcus ,Streptococcus
- **Virus species** Parvovirus B-19 ,Epstein-Barr virus ,Ross River Virus
- **Antibiotics:** Cefotaxime ,Minocycline
- **Antithyroid drugs :** Methimazole ,Propylthiouracil
- **Anti-tumor necrosis factor agents :**Adalimumab,Etanercept ,Infliximab
- **Psychoactive agents:** Clozapine ,Thioridazine
- **Miscellaneous drugs :**

Allopurinol ,D-Penicillamine,Hydralazine,Levamisole

Historical landmarks of ANCA-testing in small vessel vasculitis :



Bossuyt,NATURE REVIEWS RHEUMATOLOGY2017

Comparison of the specificity and sensitivity for different ANCA assays

Study population	IIF		Immunoassay	
	C-ANCA	P-ANCA	PR3-ANCA	MPO-ANCA
Specificity in disease controls				
Hagen *et al.* (*n* = 184)	95%	81%	86–89%	91%
Damoiseaux *et al.* (*n* = 924)	97–98%	81–96%	98–99%	96–99%
Sensitivity in 'newly diagnosed' GPA				
Hagen *et al.* (*n* = 97)	64%	21%	65–67%	24%
Damoiseaux *et al.* (*n* = 186)	65–77%	11–15%	77–81%	9–12%
Sensitivity in 'newly diagnosed' MPA				
Hagen *et al.* (*n* = 44)	23%	58%	25–27%	58%
Damoiseaux *et al.* (*n* = 65)	5–6%	85–89%	5–9%	71–88%

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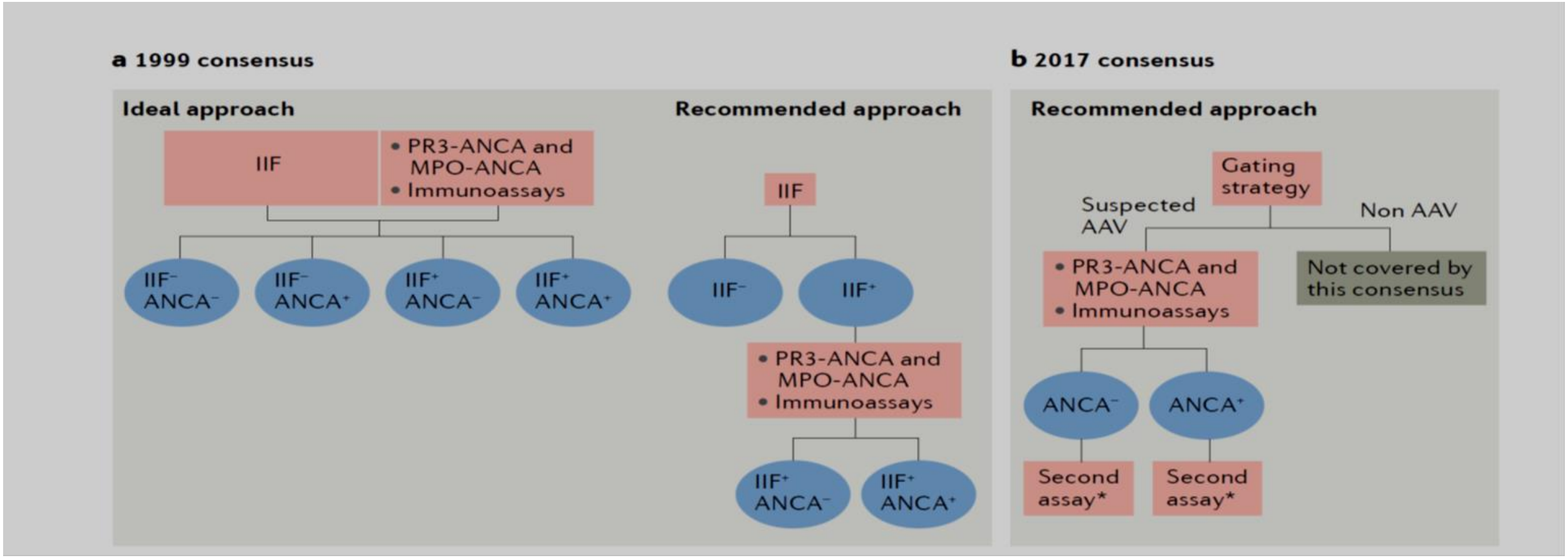
Visual representation of the 1999 recommendations and revised 2017 recommendations.



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Clinical indications for ANCA testing

In order to assure appropriate anti-neutrophil cytoplasmic antibody (ANCA)-test usage to support the diagnosis of ANCA-associated vasculitis (AAV), ANCA should be requested for patients with the following clinical indications.

- Glomerulonephritis, especially rapidly progressive glomerulonephritis
- Pulmonary haemorrhage, especially pulmonary renal syndrome
- Cutaneous vasculitis with systemic features
- Multiple lung nodules
- Chronic destructive disease of the upper airways
- Long-standing sinusitis or otitis
- Subglottic tracheal stenoses
- Mononeuritis multiplex or other peripheral neuropathy
- Retro-orbital mass
- Scleritis

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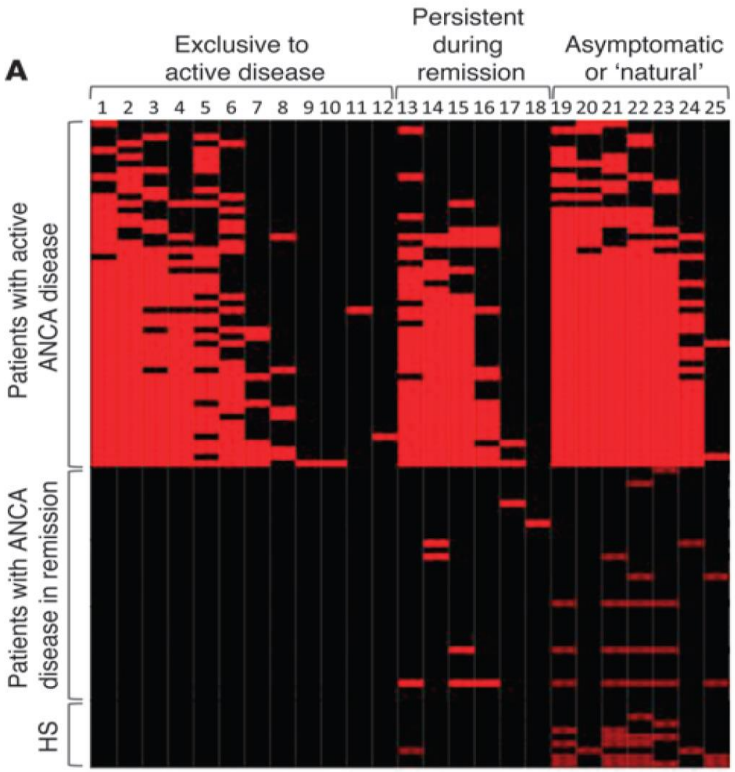
PATHOGENESIS

Research article

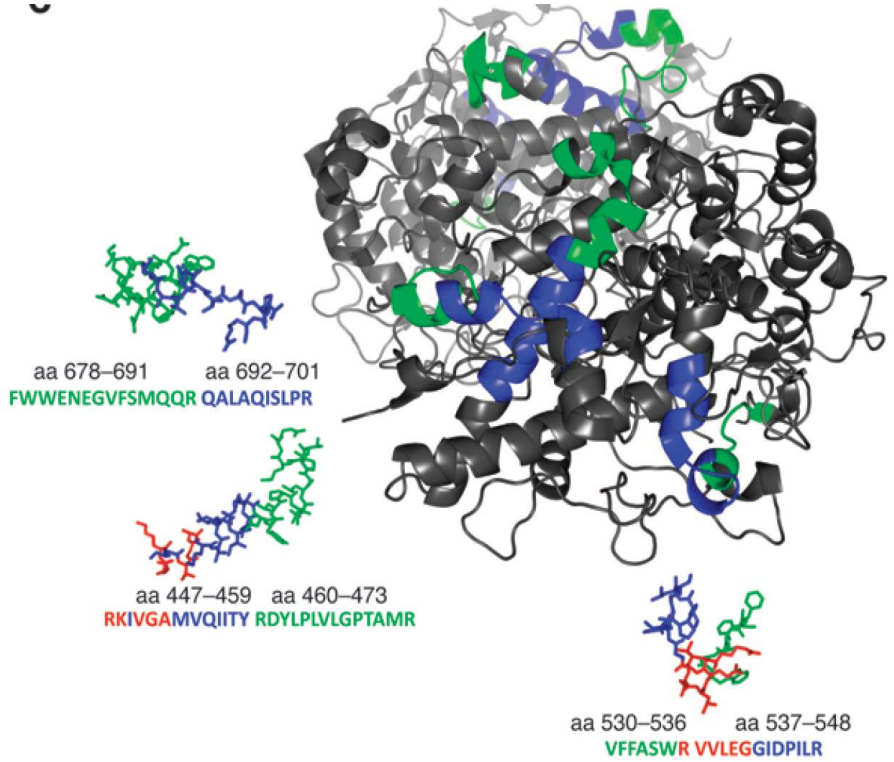
Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis

Aleeza J. Roth,[1] Joshua D. Ooi,[2] Jacob J. Hess,[1] Mirjan M. van Timmeren,[3] Elisabeth A. Berg,[1] Caroline E. Poulton,[1] JulieAnne McGregor,[1] Madelyn Burkart,[1] Susan L. Hogan,[1] Yichun Hu,[1] Witold Winnik,[4] Patrick H. Nachman,[1] Coen A. Stegeman,[3] John Niles,[5] Peter Heeringa,[3] A. Richard Kitching,[2] Stephen Holdsworth,[2] J. Charles Jennette,[1] Gloria A. Preston,[1] and Ronald J. Falk[1]

Study of autoantibody epitope specificity within an MPO-ANCA–positive cohort



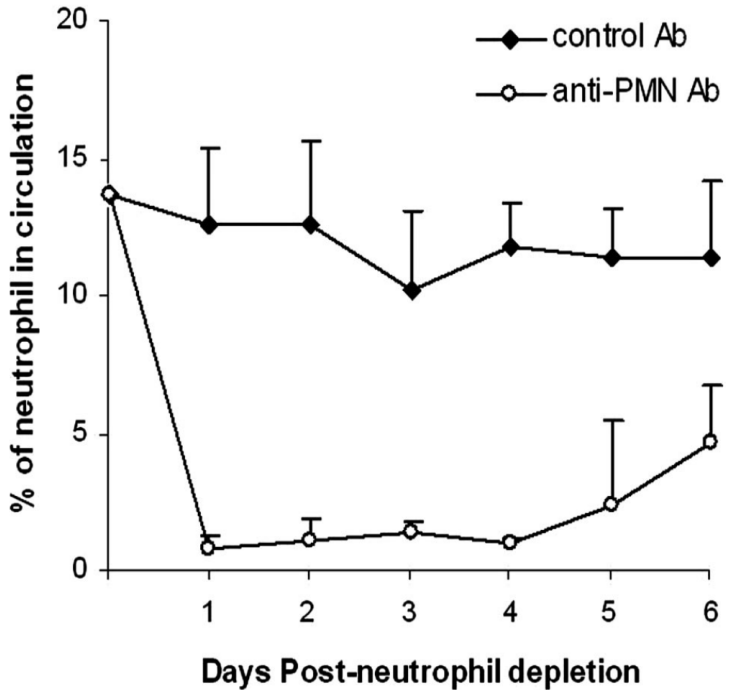
Location of epitopes on the MPO molecule.



Cells and Pathways Involved in AAV Pathogenesis and Regulation of the Immune Response

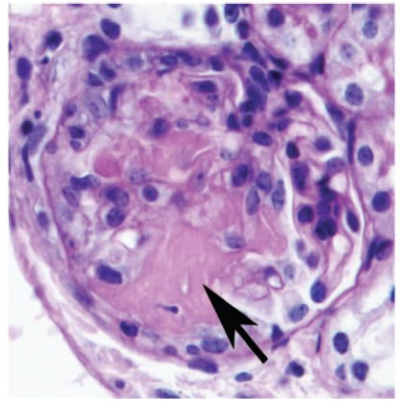
- **Neutrophils in AAV**
- **Lymphocytes in AAV**
- **Complement in AAV**

The Role of Neutrophils in the Induction of Glomerulonephritis by Anti-Myeloperoxidase Antibodies



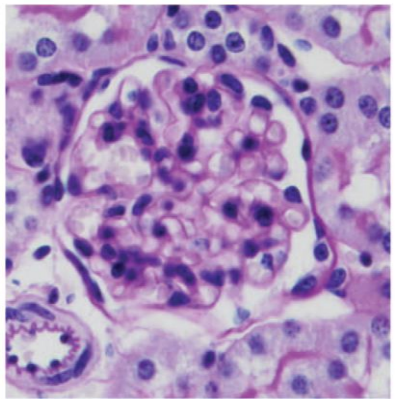
Xiao H et al ,Amj 2005

Anti MPO IgG REcipients



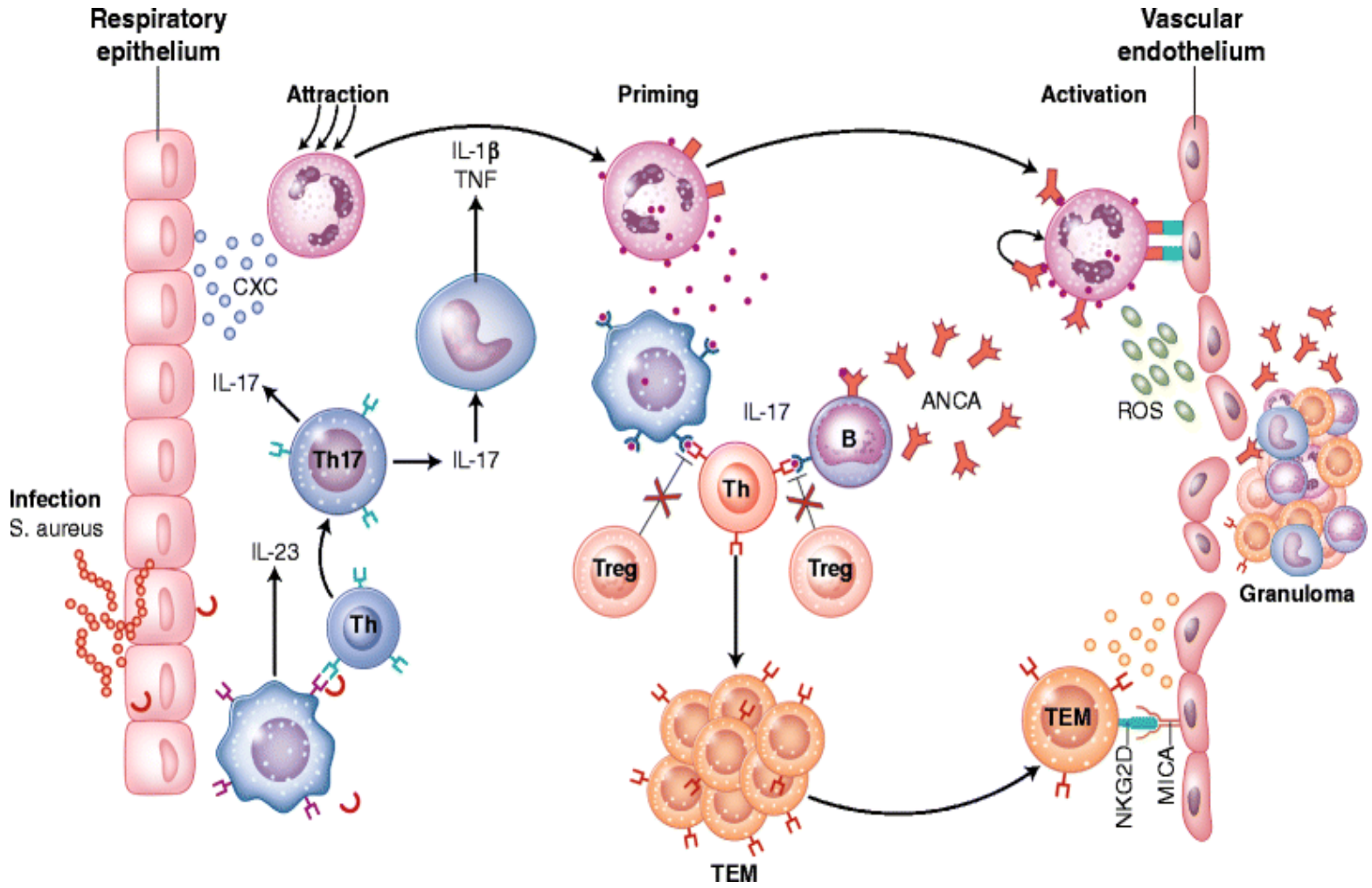
Crescent 11%
Segmental nec 6%

Neutrophil depleted anti MPOIgG recipients



Crescent 0%
Segmental nec 0%

Lymphocytes in AAV

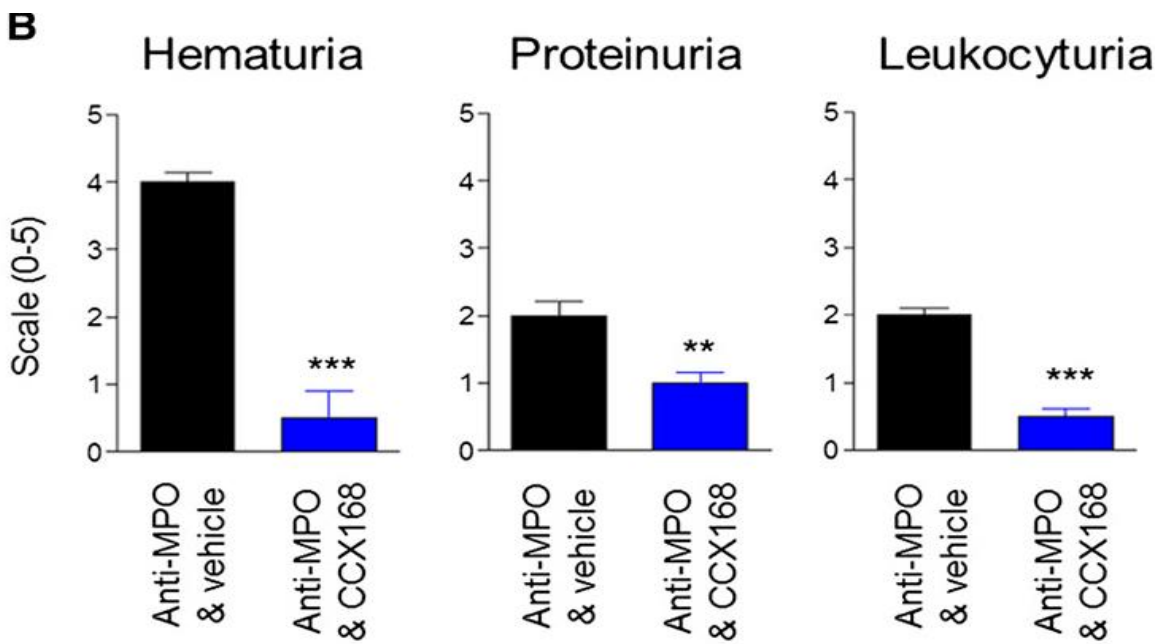


BRIEF COMMUNICATION www.jasn.org

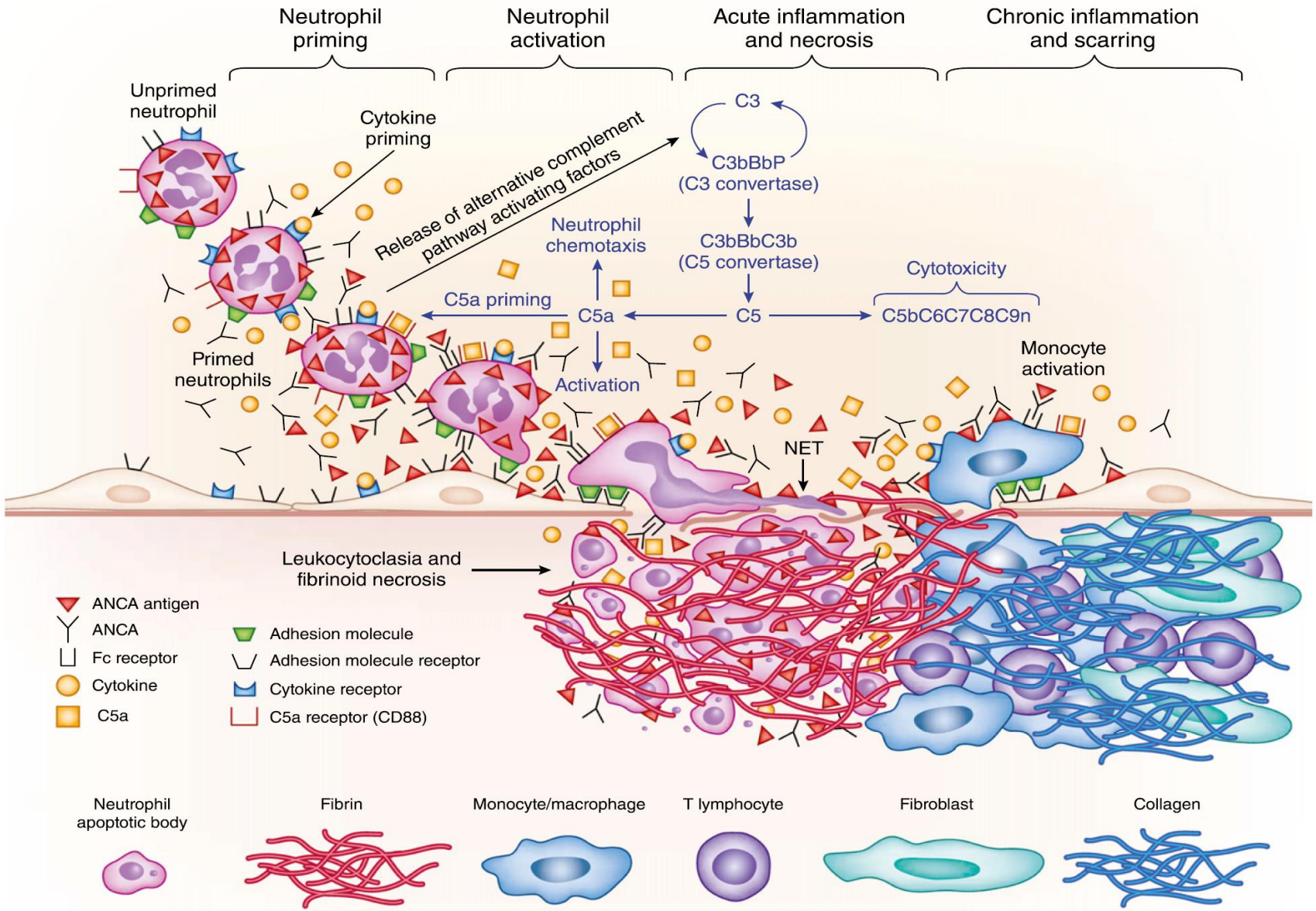
C5a Receptor (CD88) Blockade Protects against MPO-ANCA GN

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*†

Crescent 30% to 3%



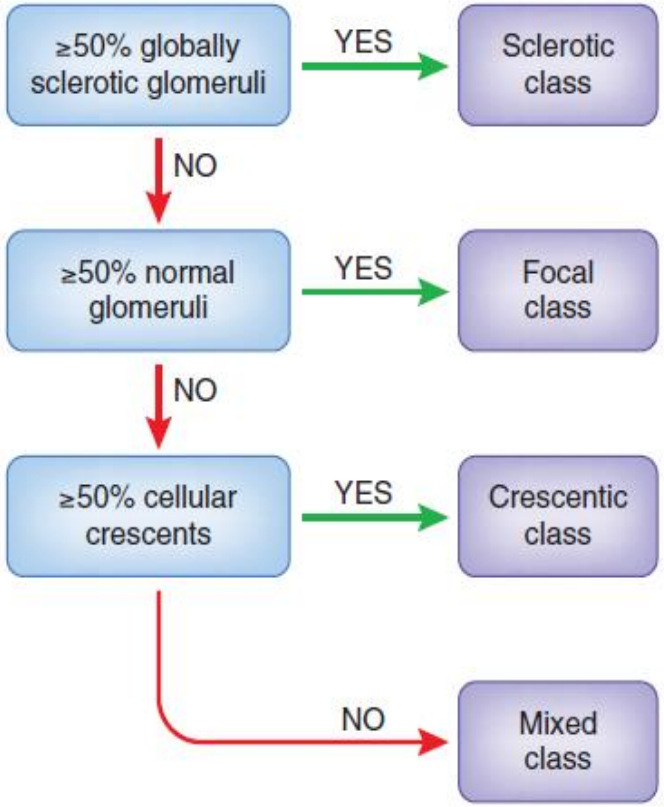
J Am Soc Nephrol 2014


Neutrophil priming
Neutrophil activation
Acute inflammation and necrosis
Chronic inflammation and scarring
Unprimed neutrophil
Cytokine priming
Release of alternative complement pathway activating factors
C3
C3bBbP (C3 convertase)
C3bBbC3b (C5 convertase)
Neutrophil chemotaxis
Cytotoxicity
C5a priming
C5a
C5
C5bC6C7C8C9n
Primed neutrophils
Activation
Monocyte activation
NET
Leukocytoclasia and fibrinoid necrosis
ANCA antigen
ANCA
Fc receptor
Cytokine
C5a
Adhesion molecule
Adhesion molecule receptor
Cytokine receptor
C5a receptor (CD88)
Neutrophil apoptotic body
Fibrin
Monocyte/macrophage
T lymphocyte
Fibroblast
Collagen

The ACR/EULAR 2017 Provisional Classification Criteria for GPA

Items	Score
Score for the ACR/EULAR 2017 provisional classification criteria for GPA	Sum≥5
Bloody nasal discharge, ulcers, crusting or sinonasal congestion	3
Nasal polyps	-4
Hearing loss or reduction	1
Cartilaginous involvement	2
Red or painful eyes	1
C-ANCA or PR3-ANCA	5
Eosinophil count ≥1 ($\times 10^9$/L)	-3
Nodule, mass or cavitation on chest imaging	2
Granuloma on biopsy	3

Classification schema for ANCA-associated GN



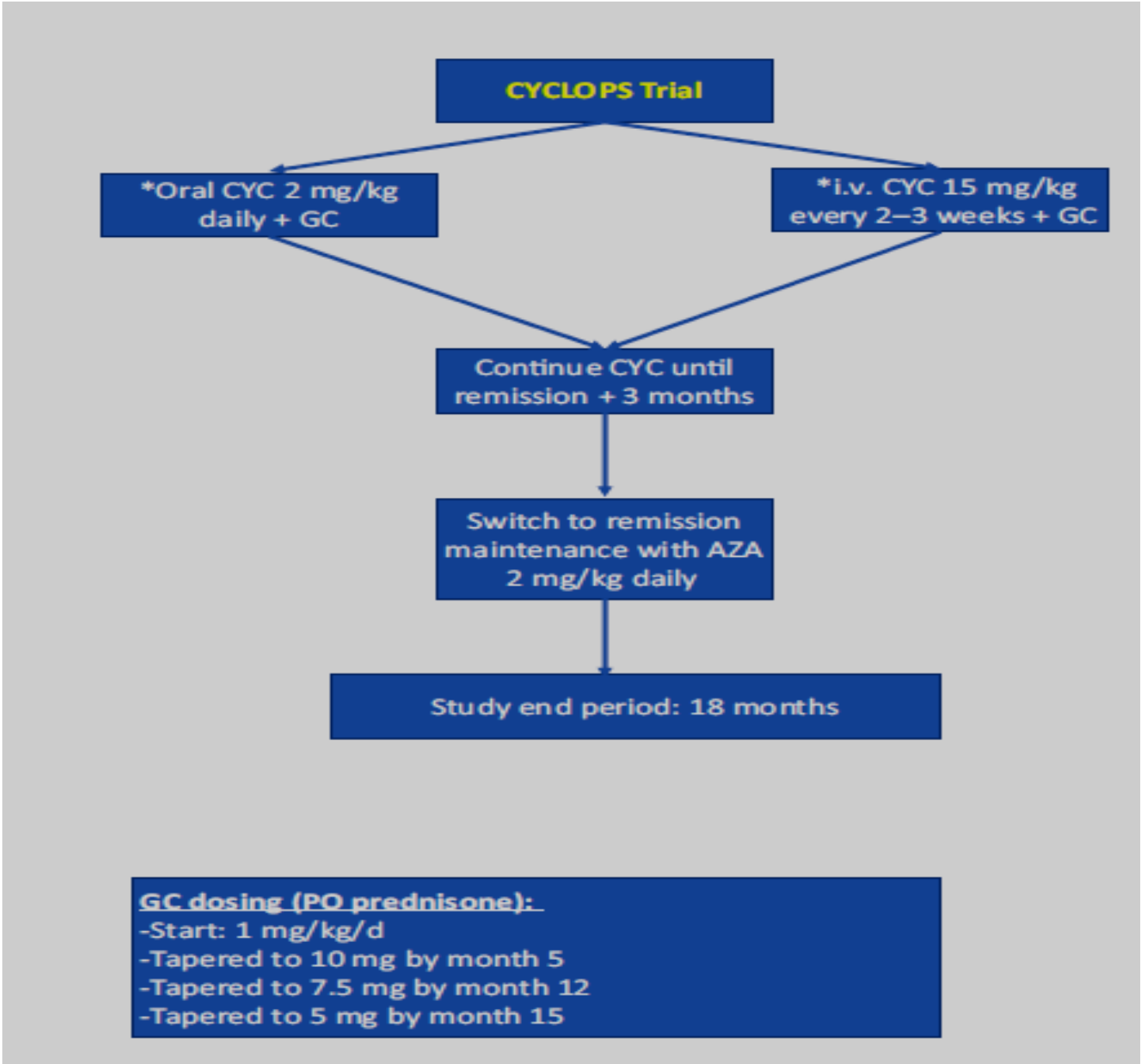
Class	Inclusion Criteria[a]
Focal	≥50% normal glomeruli
Crescentic	≥50% glomeruli with cellular crescents
Mixed	<50% normal, <50% crescentic, <50% globally sclerotic glomeruli
Sclerotic	≥50% globally sclerotic glomeruli

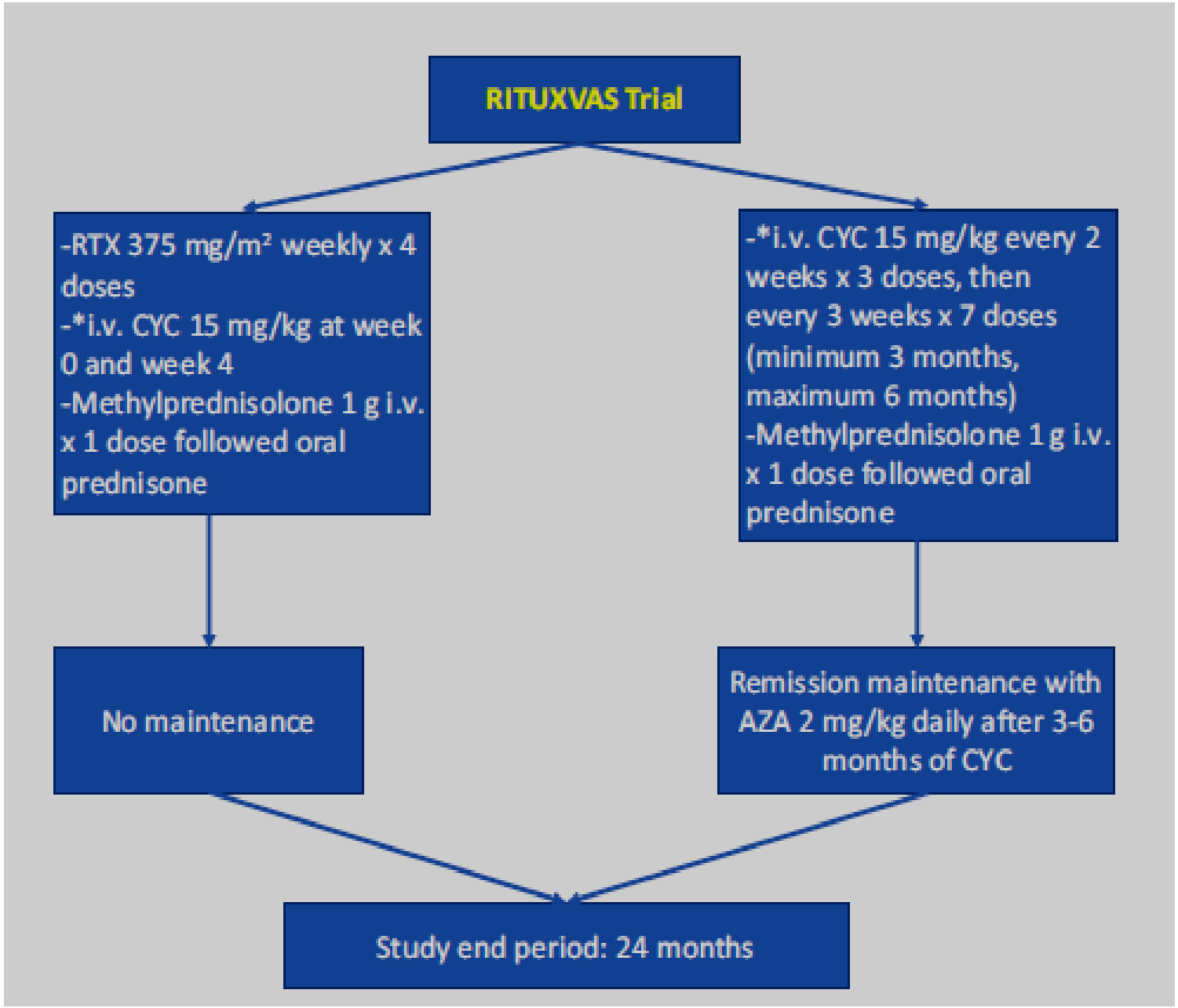
[a]Pauci-immune staining pattern on immunofluorescence microscopy (IM) and ≥1 glomerulus with necrotizing or crescentic glomerulonephritis on light microscopy (LM) are required for inclusion in all four classes. See Figure 1 for hierarchical structure.

TREATMENTS

Trial (*n*)	Inclusion criteria	Treatment groups (dose)	Primary end-points	Outcome
Induction of remission				
NORAM (100)	New diagnosis of GPA or MPA, and creatinine < 150 μmol/L	Methotrexate (0.3 mg/kg once weekly) *vs* daily oral cyclophosphamide	Remission Time to relapse	Methotrexate not inferior to cyclophosphamide Time to relapse shorter with methotrexate
CYCLOPS (149)	New diagnosis of GPA, MPA, or relapse with renal involvement, creatinine 150-500 μmol/L	Intravenous pulse cyclophosphamide (15 mg/kg) *vs* daily oral cyclophosphamide (2 mg/kg)	Remission Time to relapse	Pulse cyclophosphamide not inferior to oral cyclophosphamide Less leucopenia and trend towards more relapses with pulse cyclophosphamide
RITUXVAS (44)	New diagnosis of AAV and severe renal involvement	Rituximab (four 375 mg/m² infusions) plus two intravenous pulses of cyclophosphamide, *vs* intravenous pulse cyclophosphamide only	Sustained remission	Rituximab not inferior to pulse cyclophosphamide
RAVE (198)	New or relapsing GPA or MPA	Rituximab (4 × 375 mg/m² infusions) *vs* daily oral cyclophosphamide	Complete remission and cessation of glucocorticoids at 6 mo	Rituximab not inferior to oral cyclophosphamide Rituximab better in patients with relapse than after first diagnosis
MEPEX (137)	New diagnosis of GPA or MPA and creatinine > 500 μmol/L	Plasma exchange and oral cyclophosphamide *vs* 3 × intravenous methylprednisolone pulse and oral cyclophosphamide	Renal survival at 3 mo	Better renal survival with plasma exchange 24% risk reduction for ESRD with plasma exchange
MYCYC (140)	New diagnosis of GPA, MPA and major organ involvement	Mycophenolate mofetil (2-3 g daily) *vs* intravenous pulse cyclophosphamide (15 mg/kg)	Remission at 6 mo Relapse	Preliminary data: noninferiority not proven for mycophenolate mofetil *vs* pulse cyclophosphamide
CORTAGE (104)	New diagnosis of MPA, GPA, EGPA, PAN and age > 65 yr	Rapid glucocorticoid tapering and reduced-dose intravenous pulse cyclophosphamide (500 mg) *vs* standard intravenous pulse cyclophosphamide (500 mg/m²)	Severe adverse events	Preliminary data: less severe adverse events with reduced immunosuppression, no difference in remission and relapse rates

Maintenance of remission				
CYCAZAREM (144)	GPA, MPA or relapse and renal or vital organ involvement	Oral azathioprine (2 mg/kg) *vs* oral cyclophosphamide (1.5 mg/kg daily)	Relapse Adverse events	No difference in relapse
IMPROVE (165)	New diagnosis of GPA or MPA	Oral mycophenolate mofetil (2 g daily) *vs* oral azathioprine (2 mg/kg)	Time without relapse Adverse events	More relapses with mycophenolate mofetil than azathioprine, trend towards more adverse events with azathioprine
WEGENT (126)	GPA or MPA and renal or multiorgan involvement	Methotrexate (0.3 mg/kg once weekly) *vs* azathioprine (2 mg/kg)	Adverse events with consecutive treatment cessation or death	No difference between groups in primary end point and relapses
LEM (54)	Generalized GPA and creatinine < 1.3 mg/dL	Leflunomide (30 mg daily) *vs* methotrexate (up to 20 mg per week)	Relapse	More relapses with methotrexate than leflunomide, trend towards more adverse events with leflunomide
WGET (174)	GPA and BVAS > 3	Etanercept and methotrexate or cyclophosphamide *vs* placebo and methotrexate or cyclophosphamide	Sustained remission for > 6 mo	No benefit with etanercept, more cancers in etanercept group


CYCLOPS Trial
*Oral CYC 2 mg/kg daily + GC
*i.v. CYC 15 mg/kg every 2–3 weeks + GC
Continue CYC until remission + 3 months
Switch to remission maintenance with AZA 2 mg/kg daily
Study end period: 18 months
GC dosing (PO prednisone):
-Start: 1 mg/kg/d
-Tapered to 10 mg by month 5
-Tapered to 7.5 mg by month 12
-Tapered to 5 mg by month 15


RITUXVAS Trial
-RTX 375 mg/m² weekly x 4 doses
-*i.v. CYC 15 mg/kg at week 0 and week 4
-Methylprednisolone 1 g i.v. x 1 dose followed oral prednisone
-*i.v. CYC 15 mg/kg every 2 weeks x 3 doses, then every 3 weeks x 7 doses (minimum 3 months, maximum 6 months)
-Methylprednisolone 1 g i.v. x 1 dose followed oral prednisone
No maintenance
Remission maintenance with AZA 2 mg/kg daily after 3-6 months of CYC
Study end period: 24 months

GC dosing (PO prednisone) following the 1 g i.v. Methylprednisolone dose:

-Start: 1 mg/kg/d

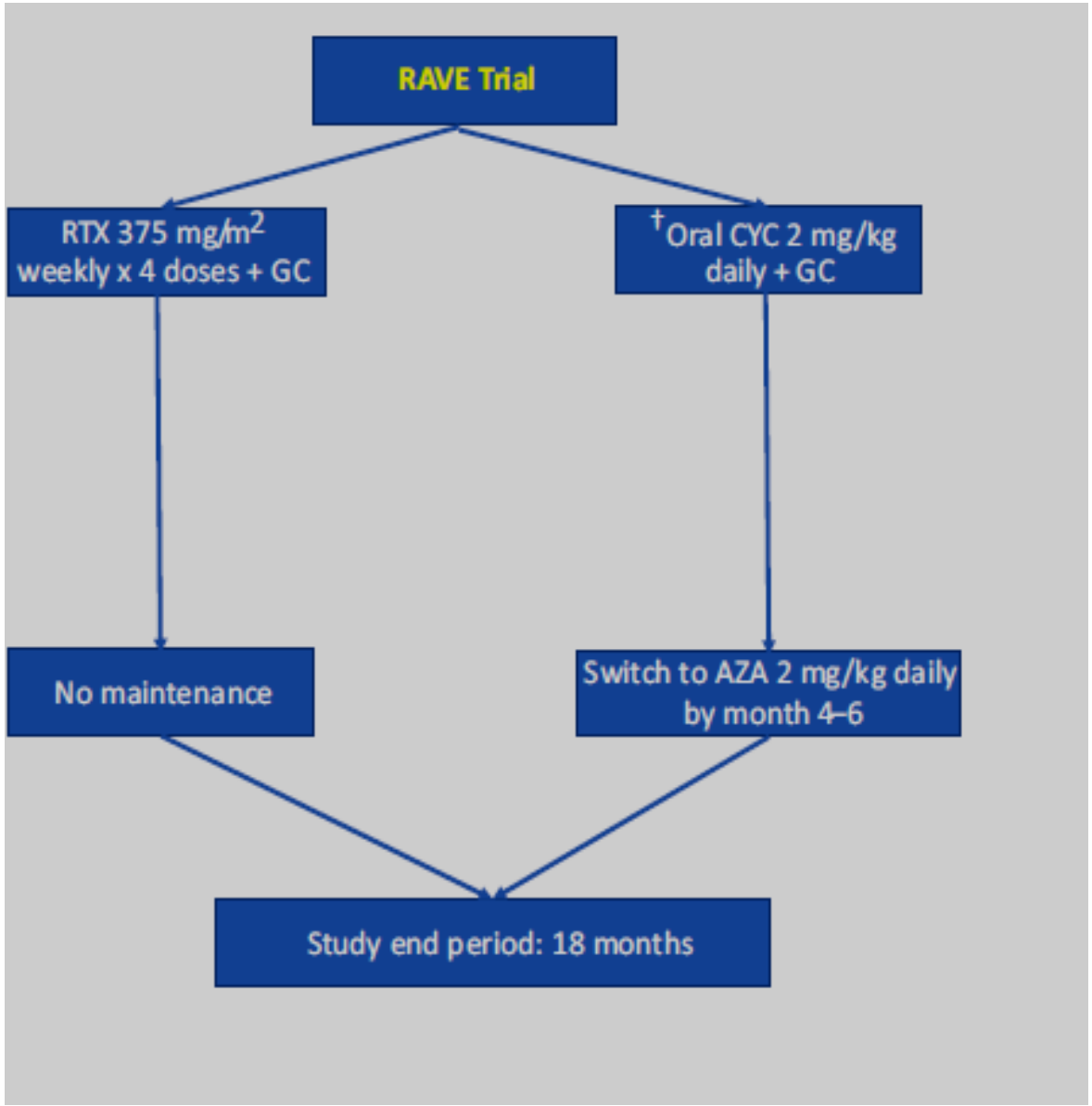
-Tapered to 12.5 mg by month 3

-Month 4: 10 mg

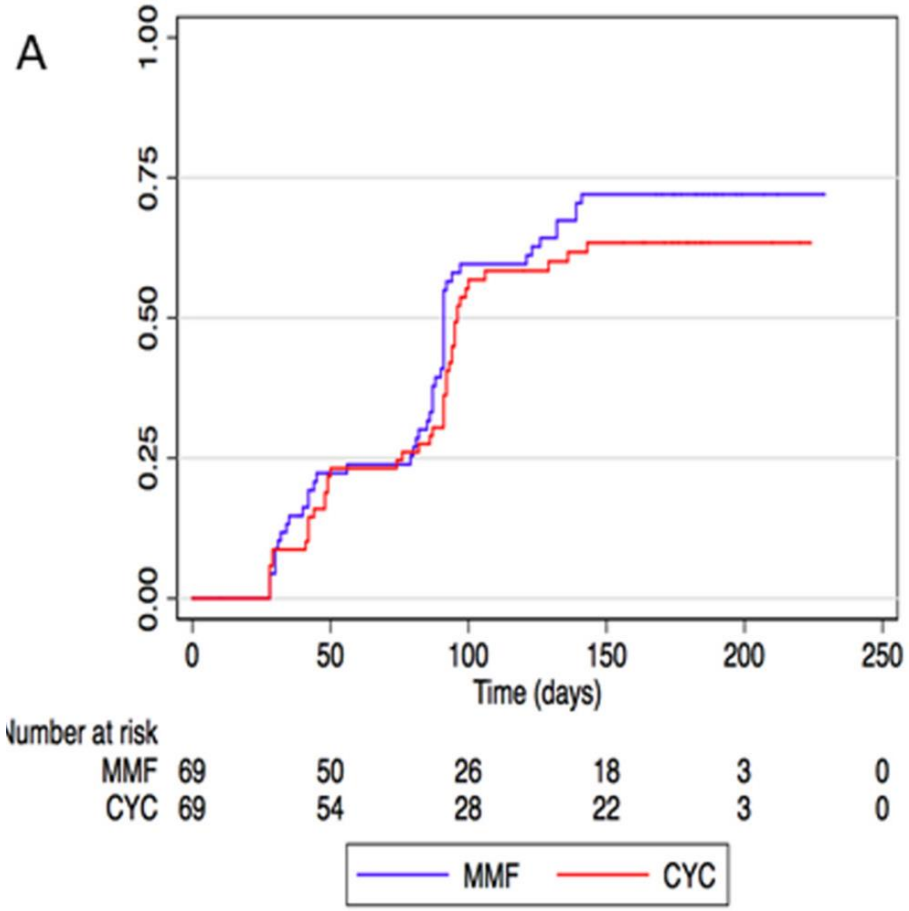
-Month 5: 7.5 mg

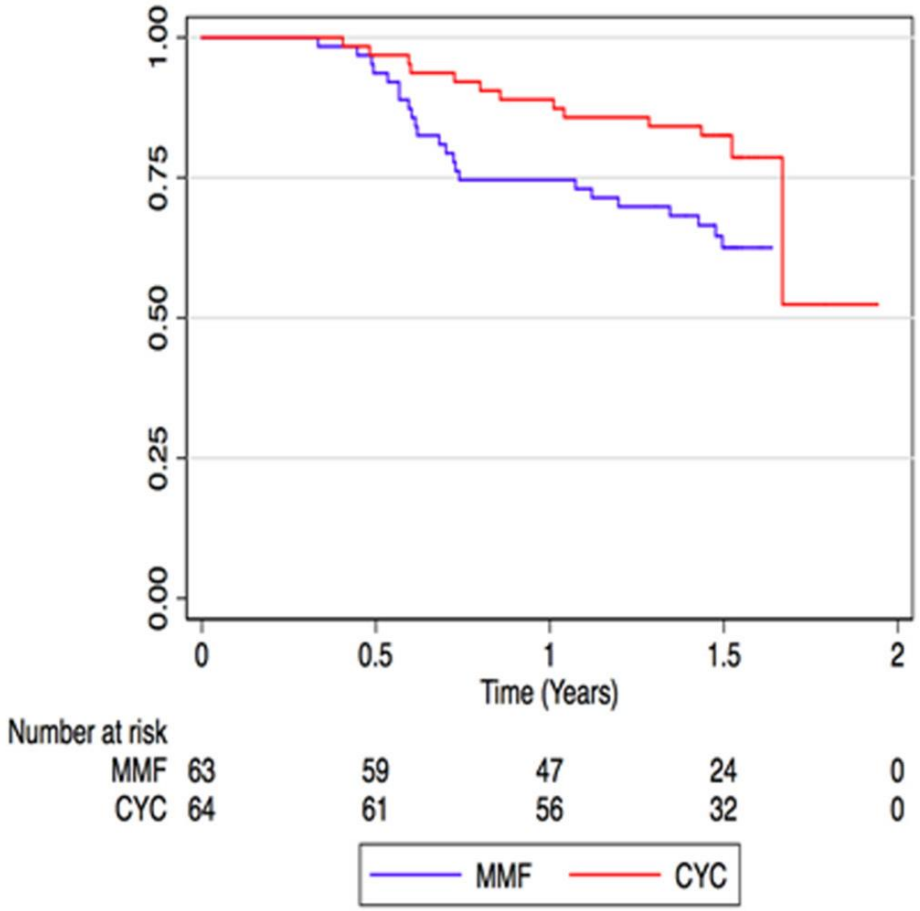
-Month 6: 5 mg

-Month 18 to 24: reduce from 5 mg to 2.5 mg



Remission and relapse in MYCYC Study





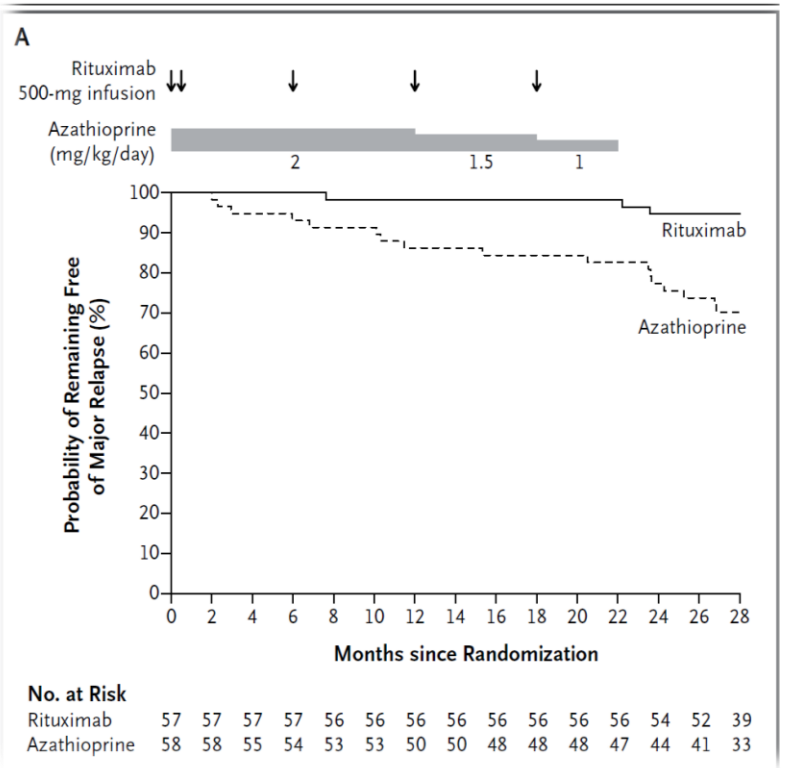
The NEW ENGLAND JOURNAL of MEDICINE

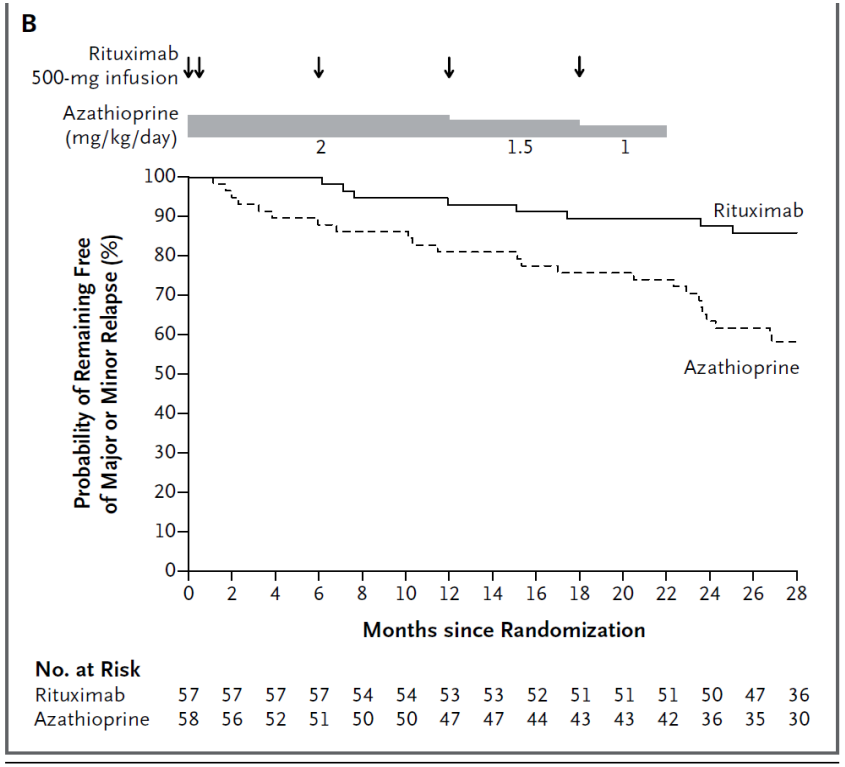
ESTABLISHED IN 1812 NOVEMBER 6, 2014 VOL. 371 NO. 19

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*

115 patients
58 (AZA)
57(RTX)
28mo F/u

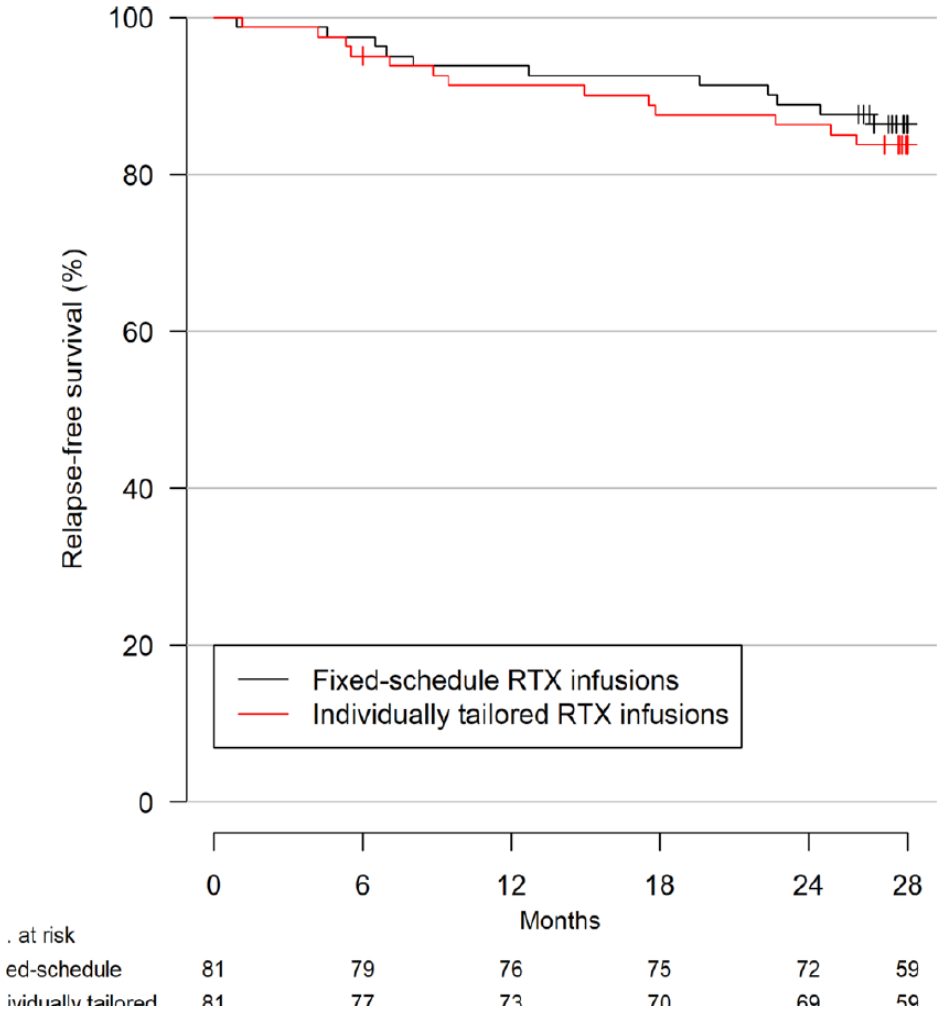




MAINRITSAN2

- rituximab at randomization:
- 1.ANCA and CD19+ B lymphocytes were assessed every 3 mo.

2.The control group received the MAINRITSAN trial.



Charles P, et al. Ann Rheum Dis 2018

Features of the compared guidelines

- BSR/BHPR 2014
- EULAR/ERA-EDTA 2015
- CANVAS 2016
- SBR 2017

D Geetha et al.KI report 2018

SEVER DISEASE

CYC

Common view

- **CYC**
- with high-dose steroids for first-line induction is universally recommended
- **GC &CYC therapy should be continued for 3-6 mo**.
- switched to a less toxic maintenance therapy when remission is achieved.
- Dosing adjustments should be
- made for age and renal function (BSR, CanVasc, SBR)

Difference

- **SBR and CanVasc**: Either **oral or i.v**. pulsed CYC.
- **BSR** and **EULAR**: Favor **i.v. pulsed CYC**
- Dosing BSR, SBR: Standard 15 mg/kg, max 1.2 g (SBR)
- 1.5 g (BSR) per pulse, first 3 pulses at 2-wk intervals, then every 3 wks for total of 3-6 mos
- **EULAR**: not specified, but refers to CYCLOPS trial, which is same as the preceding.

RTX

Common view

- All 4 guidelines recommend **RTX with high-dose steroids for first-line** induction in patients in whom CYC is **contraindicated** or **not preferred.**

Difference

- ***First line RTX:***
- **BSR and EULAR**: recommend RTX first-line in general for all AAV patients.
- **EULAR** notes that the data are weakest among patients with EGPA.
- ***Dosing:***
- **SBR:** rituximab should be given at **375 mg/m2 weekly for 4 wks**, or in 2 infusions 2 wks apart at a dose **of 1 g**.
- **BSR and CanVasc**: recommend 375 mg/m2 weekly for 4 wks

GC dosing

Common view

- Every patient should receive systemic GCs.
- In severe disease, patient may be started first on i.v. pulse methylprednisolone.

Difference

- ***Oral GC dosing and schedule***:
- **BSR**: start oral prednisolone at 1.0 mg/kg per day (max, 60 mg/d), tapered to 15 mg per day at 12 wks.
- **SBR**: start prednisone at 0.5-1.0 mg/kg per day (max, 80 mg/d) for 14 wks, taper by 10 mg for 24 wks until 20 mg/d, then reduce by 2.55.0 mg every 2 -4 wks until full withdrawal.
- **CanVasc**: start prednisone equivalent at 1.0 mg/kg per day (max, 60-80 mg/d) for 1 mo, then gradually tapered
- **EULAR**: 1.0 mg/kg per day (max, 80 mg/d)
- ***i.v. pulse methylprednisolone dosing***:
- **BSR**: 200-500 mg/d before or with first 2 doses of CYC
- **CanVasc**: 500-1000 mg/d for 1-3 days
- **SBR**: 500-1000 mg/d or 15 mg/kg per day for 1-3 days
- **EULAR**: not specified

IVig

- **SBR**: **infection** and persistent disease
- disease **refractory to GC ,CYC**, or
- **contraindications to CYC or RTX**

- **CanVasc**:
- **refractory disease**,
- **pregnant women** in whom **other immunosuppressants are contraindicated**
- and those with **current severe infection or**
- **recurrent severe infections**

- **EULAR**: **refractory setting**

Others agents

Common view

- **Etanercept should not be used to treat AAV**.
- **other TNF-a inhibitors have limited evidence** (BSR, CanVasc, SBR)

Difference

- **BSR, CanVasc**: Possible experimental options for **refractory disease** include **mepolizumab** for patients with **EGPA**, **alemtuzumab** (anti-CD52).
- **BSR**: other experimental options include **gusperimus** and **leflunomide**.

Refractory Disease

- **Patients who received CYC**:
- **BSR and EULAR**: all refractory patients with **severe disease** who have failed CYC should receive RTX.
- **CanVasc**: Severe GPA/MPA patients in whom CYC failed should receive RTX.
- **Patients who received RTX:**
- **EULAR:** refractory patients who received RTX should now receive CYC.
- **Other strategies** include adjunct i.v. Ig and
- switching from **pulsed to oral CYC** (when RTX is unavailable/cannot be administered). **(EULAR**).

Recommendations for use of plasma exchange in induction therapy ofAAV

- **1.RPGN:**
- CanVasc: adjuvant if a patient is refractory to high dose GC + CYC/RTX.
- BSR, SBR, and EULAR recommend consideration of plasma exchange for RPGN with serum Cr greater than w500 mmol/l (5.7 mg/dl).
- **2.Diffuse alveolar hemorrhage :**
- adjuvant when patients are in this setting and refractory to standard GC CYC/RTX (all 4 guidelines)

Kidney International Reports (2018)

Maintenance

- Agent:
- **BSR**: **AZA or MTX** with **GC. LEF or MMF** may be alternatives**. RTX** is also an option.
- **CanVasc**: **AZA or MTX**, initially in combination **with low-dose GC. LEF and MMF** are secondline alternatives. RTX is also an option particularly in PR3-ANCA-positive GPA.
- **EULAR**: Patients with GPA/MPA should receive **low-dose GC** and **AZA, RTX, MTX, or MMF**
- those with **EGPA** should receive **AZA**.
- **LEF** is a second-line option.
- **TMP/ SMX** can be considered as adjuvant therapy.

Maintenance Duration

- Duration of immunosuppressant agent in general:
- BSR, EULAR: **24 mos after duration**.
- CanVasc: **18 mos,** but no clear evidence.
- Duration of immunosuppressant agent for **PR3-ANCA patients:**
- **BSR: up to 5 yrs**
- **EULAR:** evidence still pending, **but 36 mos**
- Duration **of GCs**:
- BSR: patients in **remission after 1 yr** can begin to taper GCs. After GCs are withdrawn, the other immunosuppressive agent can be tapered **after 6 mos.**
- - CanVasc: no clear evidence for GC duration

Relaps

Common view

- **severe relapse** : GC CYC or RTX

(BSR, CanVasc, EULAR).

- **Non severe relapse :**
- may be managed with increasing the dosage of GC in addition to optimizing current immunosuppressant agent
- (BSR, CanVasc, EULAR).

Difference

- **Severe relapse**
- **BSR: Severe** relapse should be treated **with GC CYC or RTX**. If the patient is trying a second round of GC , CYC, the dose of GC should be increased; addition **of i.v. methylprednisolone and PLEX** can be considered.
- **CanVasc**: Patients who already tried **GC CYC** should receive RTX.
- **EULAR**: In general, due to the cumulative toxicity of CYC, RTX is recommended over CYC in relapsing disease

Prophylaxis Against Pneumocystis jirovecci

- All 4 guidelines recommend prophylaxis for Pneumocysti jirovecci in AAV patients receiving induction therapy with CYC or RTX.

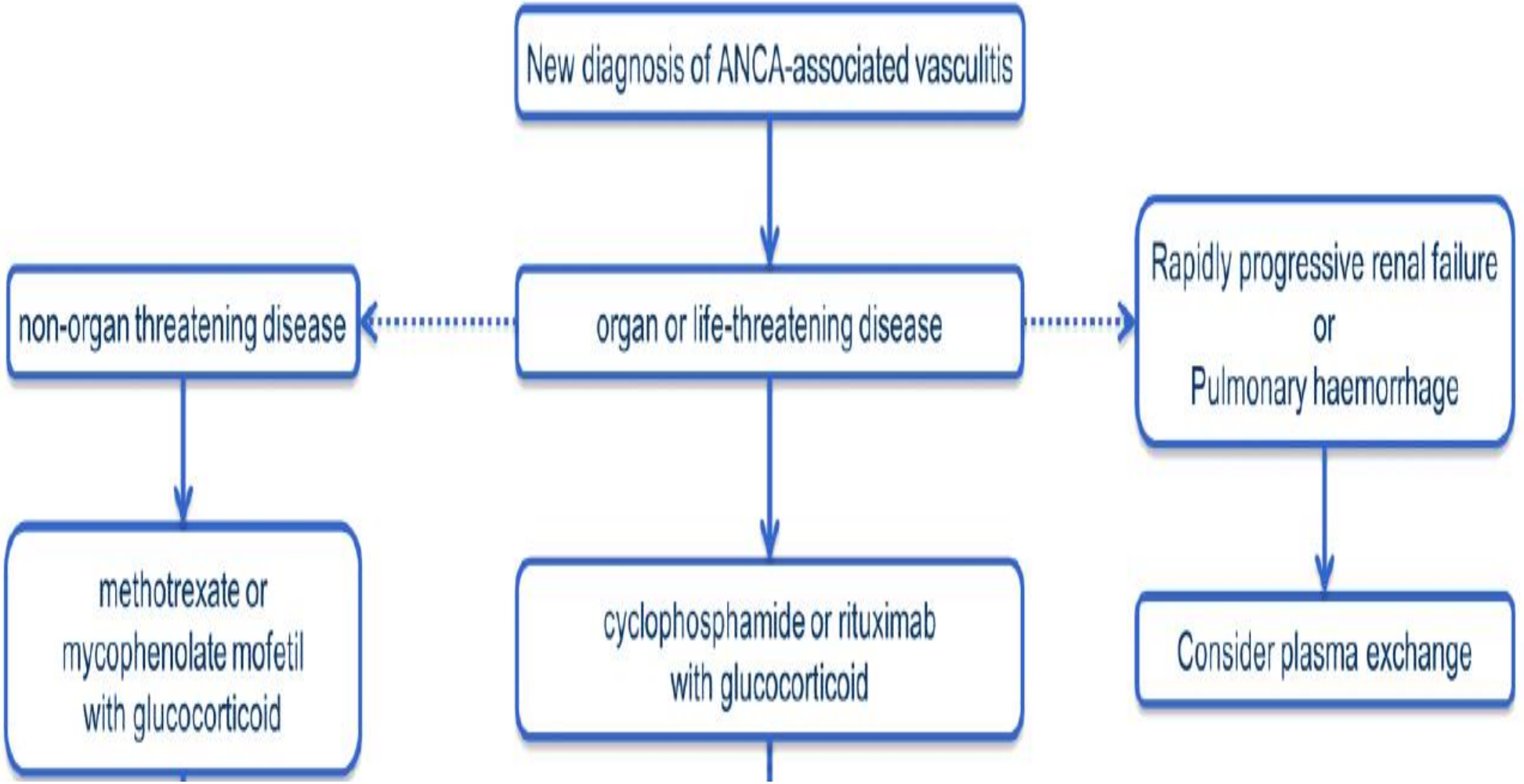
- The recommended first-line prophylaxis by all guidelines in the absence of allergy is **TMP/SMX at a dose of 400/80** mg daily or 800/160 mg 3 times a week.

Frequency of Disease Assessment

- **BSR/BHP R**recommends:

- **monthly** during remission **induction**, **every 3 months** during initial remission **maintenanc**e treatment, thereafter **every 6 months**, and then **annually**

- **CanVasc:** is monthly during remission induction and **every 3 months** for **2 years** while on remission maintenance therapy, and **annually** thereafter.


New diagnosis of ANCA-associated vasculitis
non-organ threatening disease
organ or life-threatening disease
Rapidly progressive renal failure
or
Pulmonary haemorrhage
methotrexate or
mycophenolate mofetil
with glucocorticoid
cyclophosphamide or rituximab
with glucocorticoid
Consider plasma exchange

EULAR 2017

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

- 67 patients
- 22 Placebo+Avacopan
- 22 Prednisolon (20mg)+Avacopan
- 23 High Dose Prednisolon(60mg)
- ***C5a receptor inhibition with avacopan was effective in replacing high-dose glucocorticoids in treating vasculitis***.

Jane et al,J Am Soc Nephrol 2017

Possible tailored regimens of remission induction treatmen in patients with AAV

	Non-severe AAV	Severe AAV
Proteinase-3 ANCA	Methotrexate* or rituximab	Rituximab† or cyclophosphamide
MPO-ANCA	Methotrexate* or MMF or rituximab	Cyclophosphamide or rituximab† or MMF†
ANCA-negative	Methotrexate* or cyclophosphamide	Cyclophosphamide

Immunosuppressive medications should be used in combination with glucocorticoids (at least 40 mg daily of prednisone in non-severe AAV and at least 60 mg daily of prednisone in severe AAV).
*Only in patients with estimated glomerular filtration rate >30 mL/min/1.73 m^2.

Ann Rheum Dis Month 2019

Serum biomarkers

- **anti-LAMP-2 antibodies are present in 80–90% of untreated patients, including PR3-ANCA negative and MPO-ANCA negative**
- Pllasminogen
- Moesine
- NET
- Leucocytes: Breg,CD25+ Treg
- Monocytes
- Complements:c3a,c5a,c5b-9
- MCP1
- Calprotectin
- NGAL


با تشکر از توجه شما