Vasculitis

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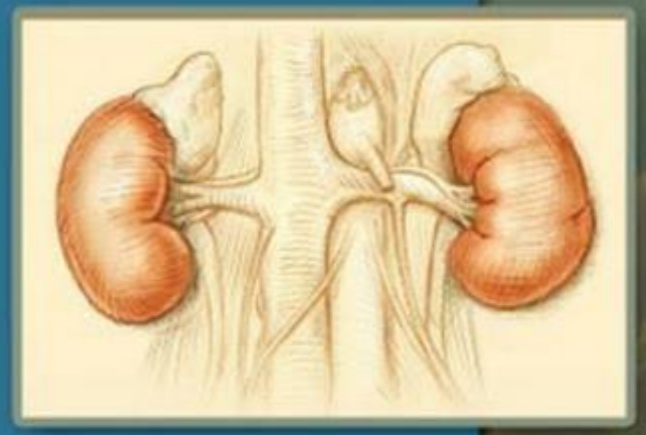
Monash University

Declaration

- Sponsorship for personal educational and university research studies from Servier and Roche
- I sit on no industry boards etc

Declaration of Why I am Doing This Talk

- Not a GN person!
- The legends – Richard Kitching, Grant Luxton, Chen Au Peh – they could not come (Dr Vivian Mah my Reg!!)
- So SPEC (aka Muh Geot) asked me
- I have heard no less that 50!!!! ANCA lectures
- So I said – Right what drives me nuts in my clinic!
- Case of a 78 YO chap that is not so perfect who gets ANCA….
- Case of a 81 YO lady where the ANCA may be back or not….



JÜRGEN FLOEGE
RICHARD J. JOHNSON
JOHN FEEHALLY

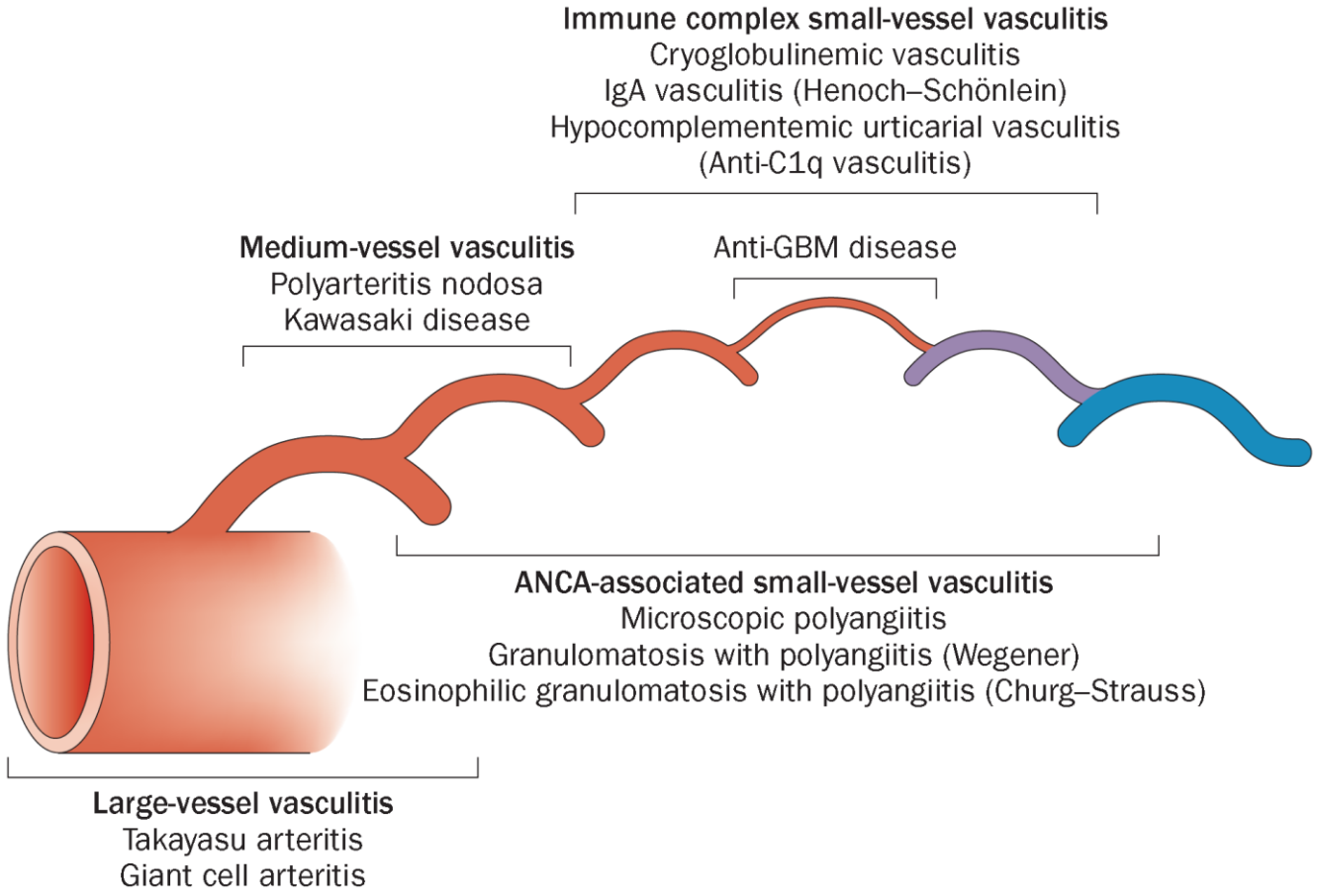
Comprehensive Clinical Nephrology

Fourth Edition

Rapidly Progressive Glomerulonephritis (RPGN)

- Rapidly progressive renal failure
- Hematuria ± rbc casts; RBC dysmorphia
- Oliguria - variable
- Hypertension - unusual
- Proteinuria - variable

Chapel Hill classification



- Kidneys are targets for a variety of systemic vasculitis, especially those that affect small vessels

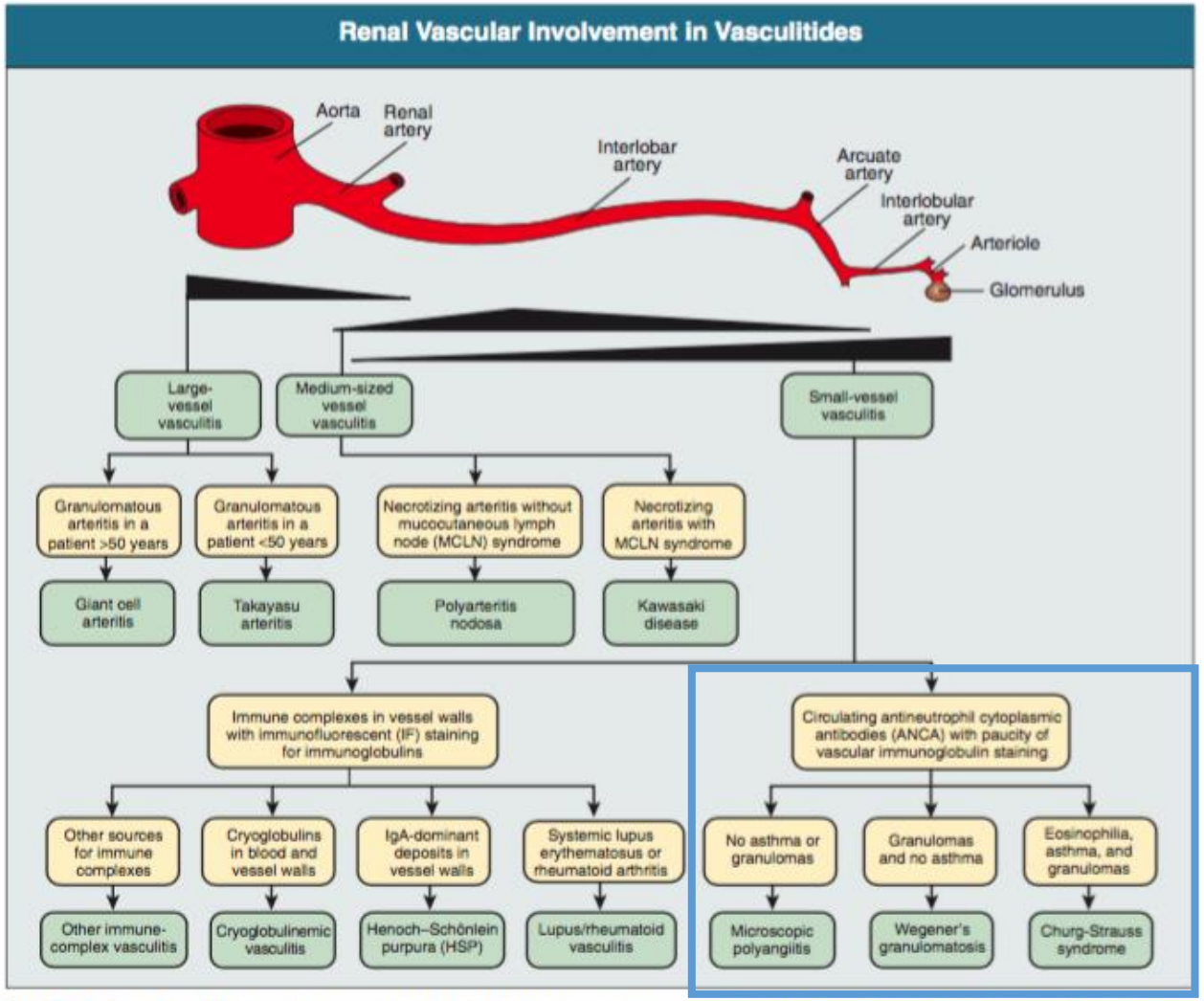


Figure 24.1 Renal vasculitis: the predominant distribution of renal vascular involvement by a variety of vasculitides. The heights of the trapezoids represent the relative frequency of involvement of different portions of the renal vasculature by the three major categories of vasculitis. *(Modified from reference 3.)*

Small vessel vasculitis

- ANCA positive
- **Granulomatous polyangiitis (GPA)**
  - granulomatous inflammation
  - upper and lower respiratory tract involvement
  - anti PR3 (proteinase 3)
- **Microscopic polyangiitis (MPA)**
  - small vessel vasculitis without granulomas
  - anti MPO (myeloperoxidase)

Classification of Antineutrophil Cytoplasmic Autoantibody Vasculitides The Role of ANCA Specificity for MPO or PR3 in Disease Recognition and Prognosis

Lionaki et al. *Arth Rheum* 2012

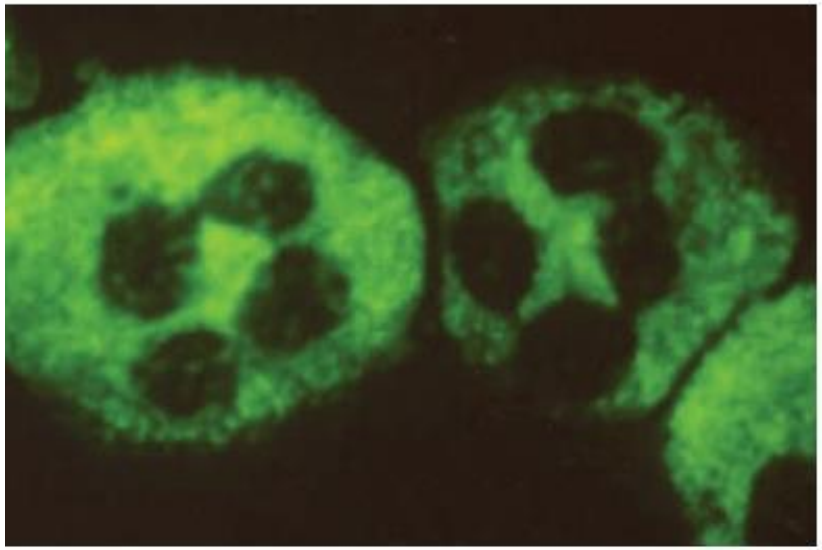
	Treatment resistance	Relapse	ESRD	Death
Chapel Hill				
GPA %	17	60	21	17
MPA %	22	37	30	30
Renal ltd %	30	19	47	33
European %				
GPA %	22	44	28	26
MPA %	25	30	39	31
ANCA spec				
MPO	27	29	37	31
PR3	17	51	26	23

Usual Talks I Hear

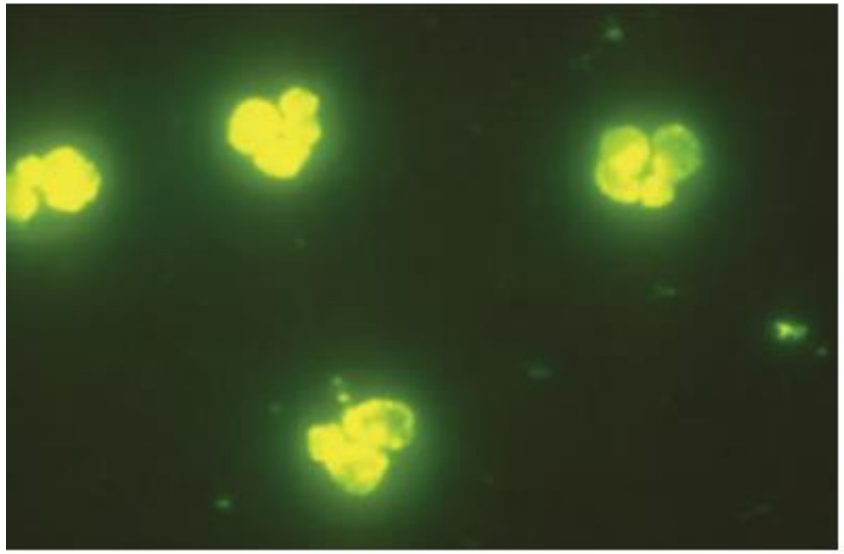
1. the use of ANCAs in diagnosis and management
2. the pathogenesis of vasculitis
3. prognostic factors
4. evidence-based treatment for induction and maintenance

ANCAs

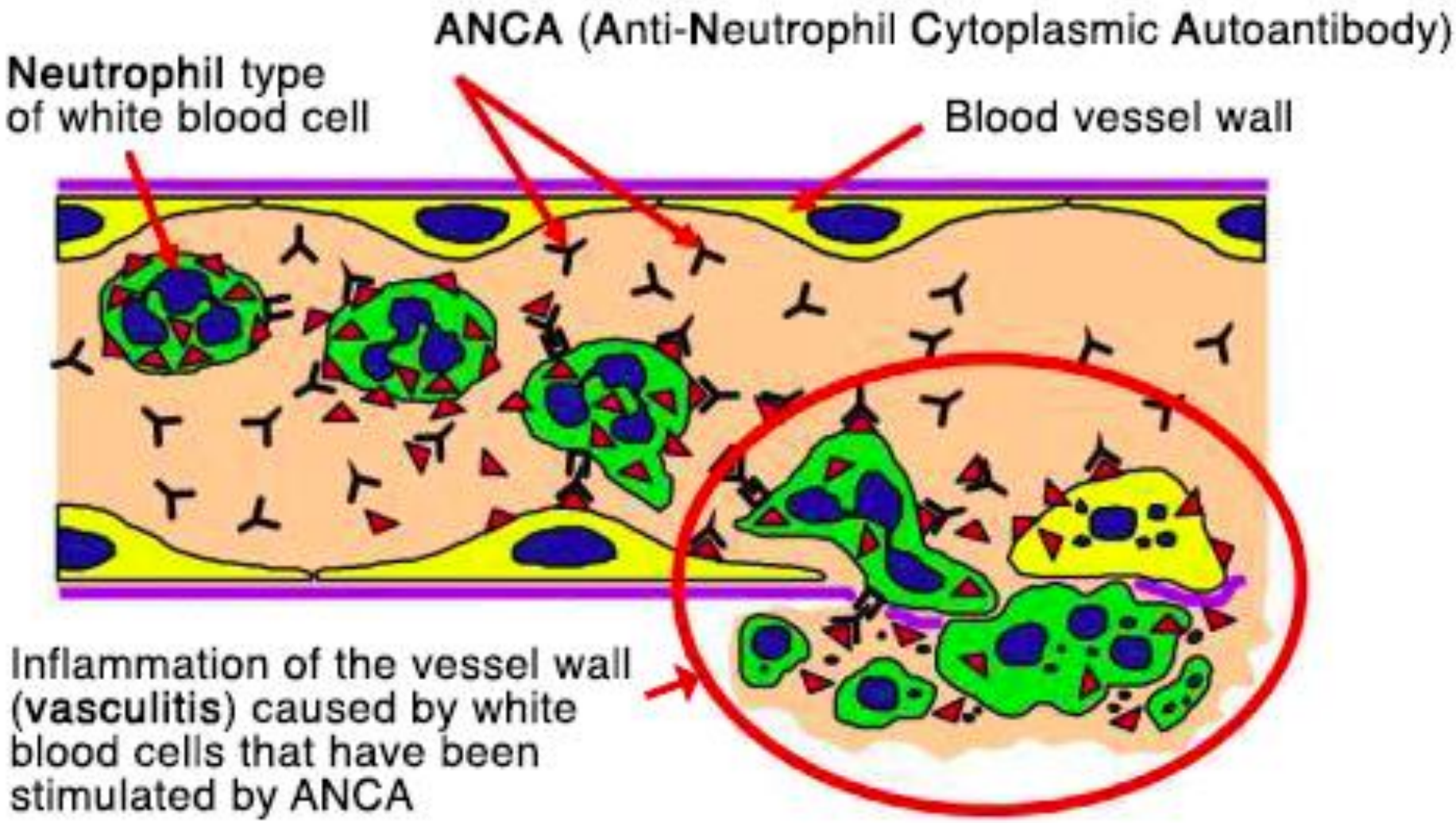
- autoantibodies against components of neutrophil cytoplasmic granules
- immunofluorescence (IIF):
  - c-ANCA (cytoplasmic) and p-ANCA (perinuclear)
- ELISA
  - PR3 (proteinase 3) and MPO (myeloperoxidase)
  - “atypical” ANCAs
  - direct/capture/anchor ELISAs



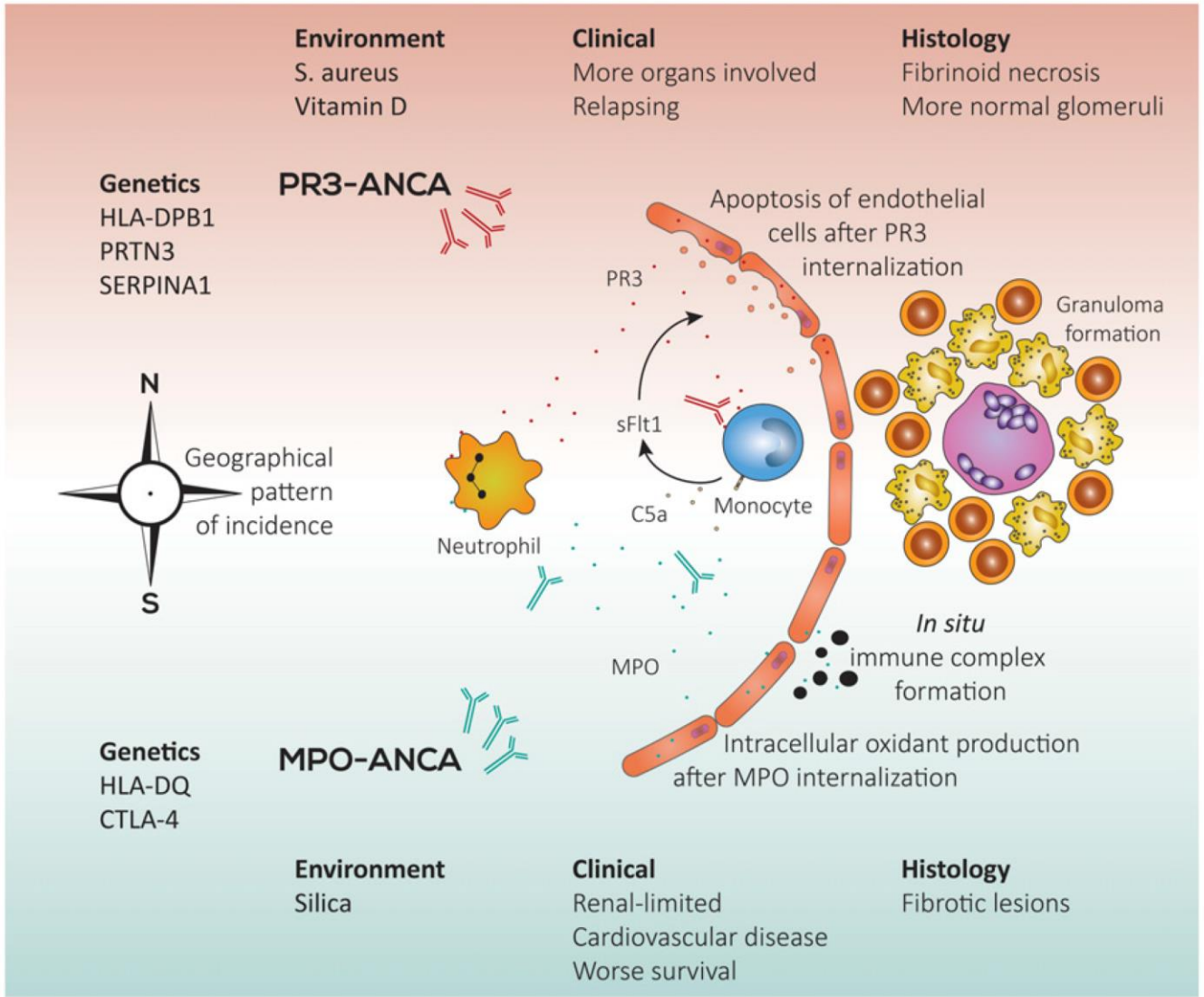
C – ANCA
Usually anti-PR3



P – ANCA
Usually anti-MPO


ANCA (Anti-Neutrophil Cytoplasmic Autoantibody)
Neutrophil type of white blood cell
Blood vessel wall
Inflammation of the vessel wall (vasculitis) caused by white blood cells that have been stimulated by ANCA

PR3 vs MPO


Environment
S. aureus
Vitamin D
Clinical
More organs involved
Relapsing
Histology
Fibrinoid necrosis
More normal glomeruli
Genetics
HLA-DPB1
PRTN3
SERPINA1
PR3-ANCA
Apoptosis of endothelial cells after PR3 internalization
PR3
Granuloma formation
N
S
Geographical pattern of incidence
sFlt1
C5a
Monocyte
Neutrophil
MPO
In situ immune complex formation
Intracellular oxidant production after MPO internalization
Genetics
HLA-DQ
CTLA-4
MPO-ANCA
Environment
Silica
Clinical
Renal-limited
Cardiovascular disease
Worse survival
Histology
Fibrotic lesions

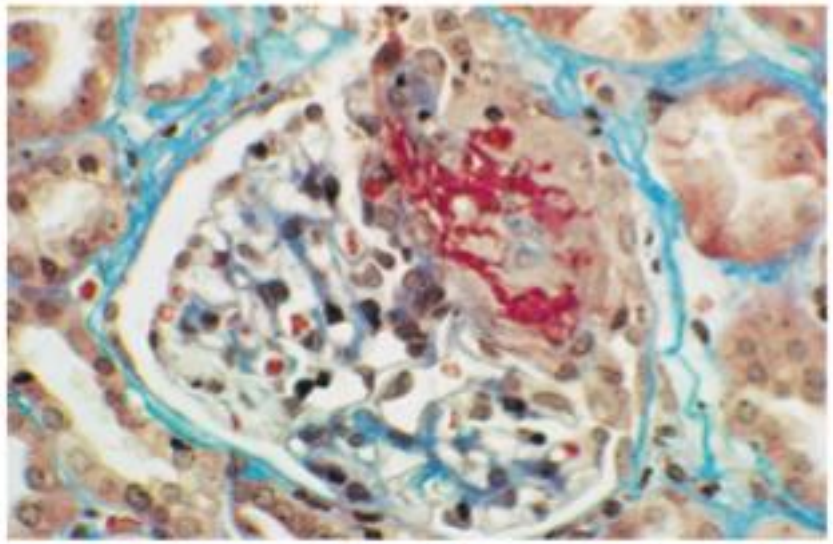


Figure 24.11 Segmental glomerular necrosis and crescent formation in a patient with antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis. The fibrinoid material is red. The uninvolved segments appear normal. (Masson trichrome; original magnification ×150.)

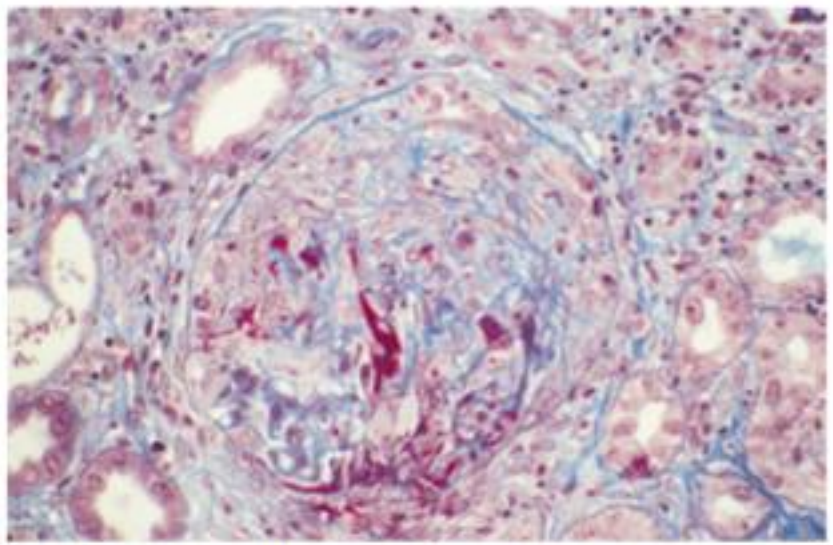


Figure 24.12 Global glomerular necrosis and circumferential crescent formation in a glomerulus from a patient with antineutrophil cytoplasmic antibody (ANCA)–associated small-vessel vasculitis. (Masson trichrome; original magnification ×150.)

Floege et al. Comprehensive clinical nephrology, 4th edition, 2010


¡EL HIPOPOTAMO DIABLO!
INSANEPICTURES.COM

Prognosis

- 20% two year survival pre-cyclophosphamide
- 80% five year survival today
- meta-analysis of 10 studies with 3338 patients: mortality 2.7 X general population (Tan 2017)
- 9X increased mortality in first year especially in first 6 months (infection)
- 15-38% progress to ESKD at years
- venous thrombosis, CV disease, CVA ↑

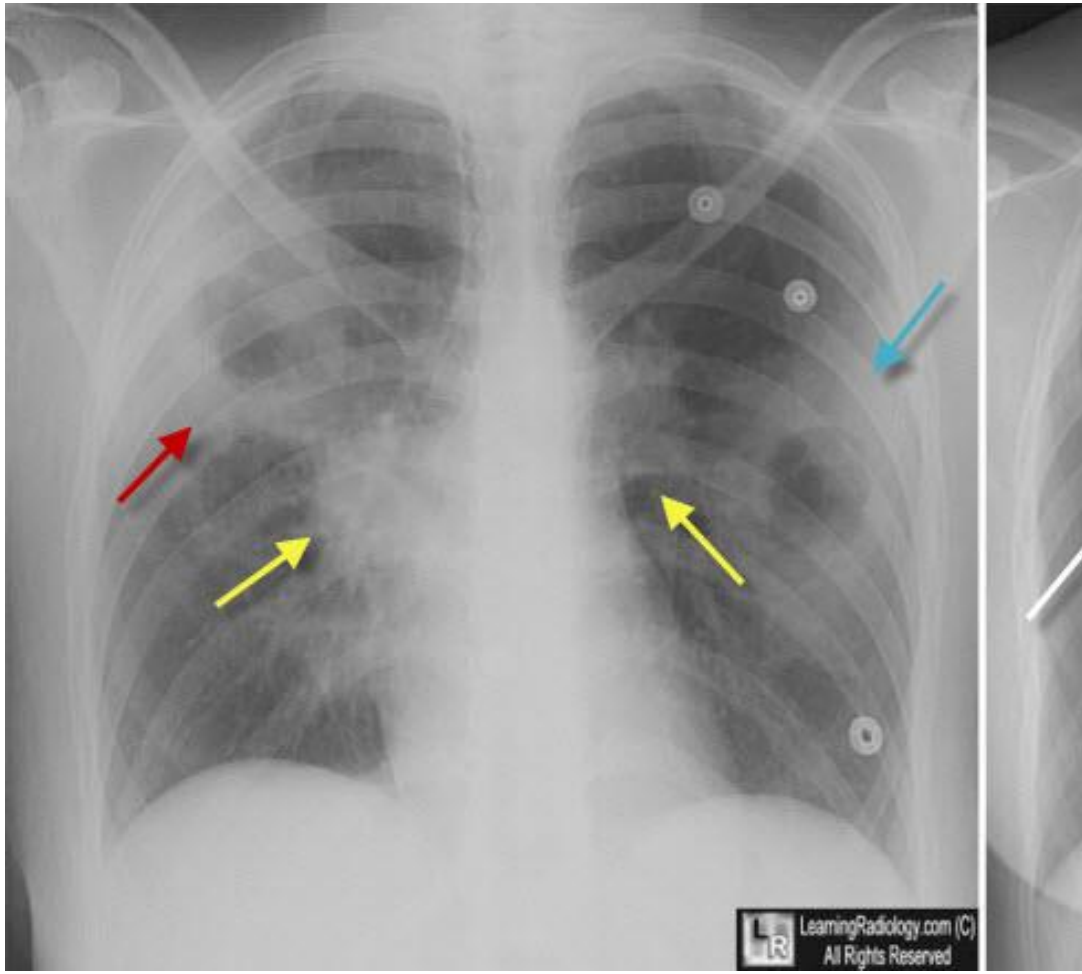
INDUCTION TREATMENT

Case 1

- I was on a Gen Medical Ward and Mr XO (Greek) presented unwell with a PUO
- Told both UTI and Pneumonia in setting of man from Home with wife needing IV Antibiotics
- He has IHD (one NSTEMI, and CVS risks of Htn, Hyper lipidaemia, past smoker)
- He had COAD by RFTs (30 yr pack history)
- He had Bad OA and did use a 4 pronged stick
- Wife and him survived at home (he cared for her – she was much sicker and had some dementia)
- Great GP! – had an ACAS, ACP and was ready to pop him and wife into care in future (little family input)

Case 1 Continued

- Bloods – Elevated WCC 15, Crp 130
- Unfortunately Cr 170umol/l Ur 25mmol/l
- Urine was unusual –
  - WCC 100
  - RCC >1000!
  - No Bacteria
- CXR was Even More Unusual



Further History and Investigations

- Lovely story of being unwell with a flu on/off for months
- Some arthritis flares
- Some URTI’s requiring Abs
- ANCA Positive
- PR3 120!
- Renal Biopsy GPA

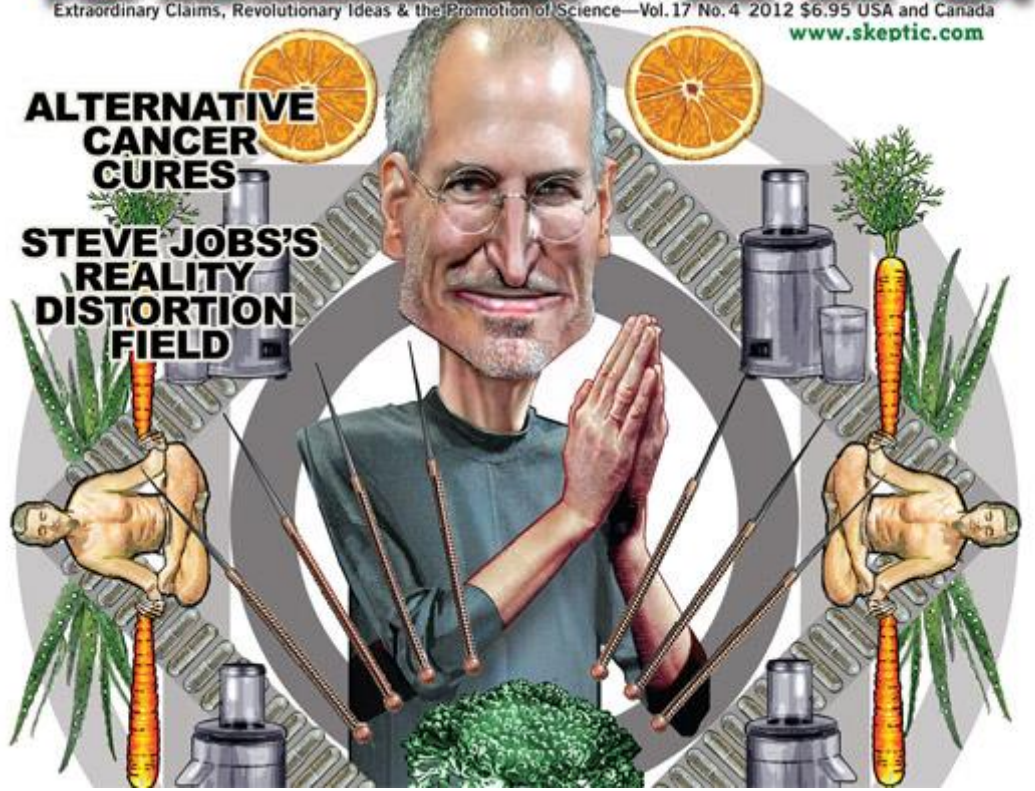

Pragmatist

True Believers

ALTERNATIVE CANCER CURES • WAS JESUS MARRIED? • PHYSICS & FREE WILL

SKEPTIC

Extraordinary Claims, Revolutionary Ideas & the Promotion of Science—Vol. 17 No. 4 2012 $6.95 USA and Canada
www.skeptic.com



Treatments

Cyclophosphamide

- Seminal studies conducted at the National Institutes of Health in Bethesda [1-3]
  - During 1970s and 1980s
  - Reported 5-year survival of 80%

- Toxicities of this regimen limit its long-term use
  - Urological and hematological toxicities
  - Osteoporosis
  - Infections

[1] Fauci AS, Wolff SM. Wegener's granulomatosis: studies in eighteen patients and a review of the literature. Medicine 1973; 52: 535–561
[2] Fauci AS, Haynes BF, Katz P et al. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 1983; 98: 76–85
[3] Hoffman GS, Kerr GS, Leavitt RY et al. Wegener granulomatosis: an analy- sis of 158 patients. Ann Intern Med 1992; 116: 488–498

Standard induction immunosuppression

- **cyclophosphamide** –oral or pulse (IV)
- **steroids** – oral +/- IV
- continue till remission (usually 3 – 6 months)

Induction immunosuppression

- **cyclophosphamide**
  - oral or pulse (IV)
  - pulse lower cumulative dose 8g vs 16g
  - similar remission rate but higher rate of relapse 20% vs 40% (NDT 2001, CYCLOPS Annals Int Med 2009)
  - more neutropaenia and infection with oral
  - cancer risk associated with >36g

Induction immunosuppression

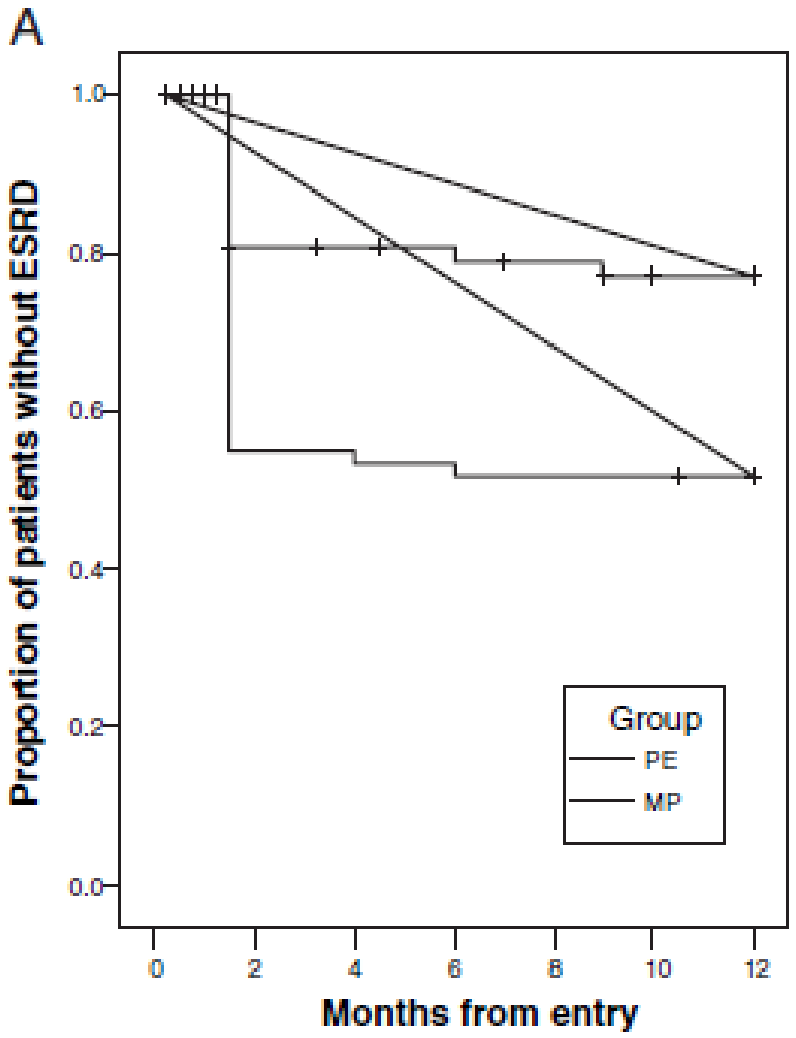
- **steroids**
  - IV pulse methylprednisolone x 3
  - oral prednisolone 1mg/kg
  - taper to 10-20mg by 3 months

  - unclear benefit of pulse IV steroid and how quickly to taper prednisolone (PEXIVAS)

Plasma exchange

- MEPEX:
  - PX vs IV methylpred in addition to oral Cyclo and oral P
  - more renal recovery at 3 and 12 months with PX though no difference at 4 years
- meta-analysis of 387 patients in 9 trials showed RR 0.64 for dialysis dependence with PX though not mortality

Plasma exchange improves renal recovery (MEPEX)



JASN 2007

PEXIVAS

- 704 patients with severe vasculitis (pulmonary haemorrhage and/or renal disease (GN and GFR <50)
- standard immunosuppression (CYC or RTX)
- plasma exchange or no plasma exchange
- standard or reduced dose of steroid
- results…

Treatments

- Several alternative approaches to decrease the cumulative exposure to cyclophosphamide
- Reduce cyclophosphamide use by replacing with less toxic immunosuppressant once remission is achieved
  - CYCAZAREM trial [1]
    - Cyclophosphamide vs azathioprine for early remission phase of vasculitis
    - Prospective randomized trial
    - Confirmed concept of stage remission induction and maintenance therapy

[1] Jayne et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003; 349: 36–44

Treatments

Other treatment options:

- IVIg
  - No cyclophosphamide-sparing effect demonstrated in both refractory or relapsing disease [1,2]
- Mycophenolate mofetil (MMF)
  - Pilot study and small randomized controlled trial suggested MMF may replace cyclophosphamide in non-severe MPA [3,4]

[1] Crickx E, Machelart I, Lazaro E et al. Intravenous Immunoglobulin as an Immunomodulating Agent in Antineutrophil Cytoplasmic Antibody- Associated Vasculitides: A French Nationwide Study of Ninety-Two Patients. Arthritis Rheumatol 2016; 68: 702–712
[2] Jayne DR, Chapel H, Adu D et al. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. QJM 2000; 93: 433–439
[3] Silva F, Specks U, Kalra S et al. Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moder- ate renal involvement–a prospective, open-label pilot trial. Clin J Am Soc Nephrol 2010; 5: 445–453
[4] Hu W, Liu C, Xie H et al. Mycophenolate mofetil versus cyclophosphamide for inducing remission of ANCA vasculitis with moderate renal involve- ment. Nephrol Dial Transpl 2008; 23: 1307–1312

Alternative induction

- methotrexate
  - early systemic disease, creatinine < 150mmol/L (NORAM, 2005)
  - less effective than Cyclo for more extensive disease, more relapses
- biologicals
  - rituximab (NEJM 2010)

Treatments

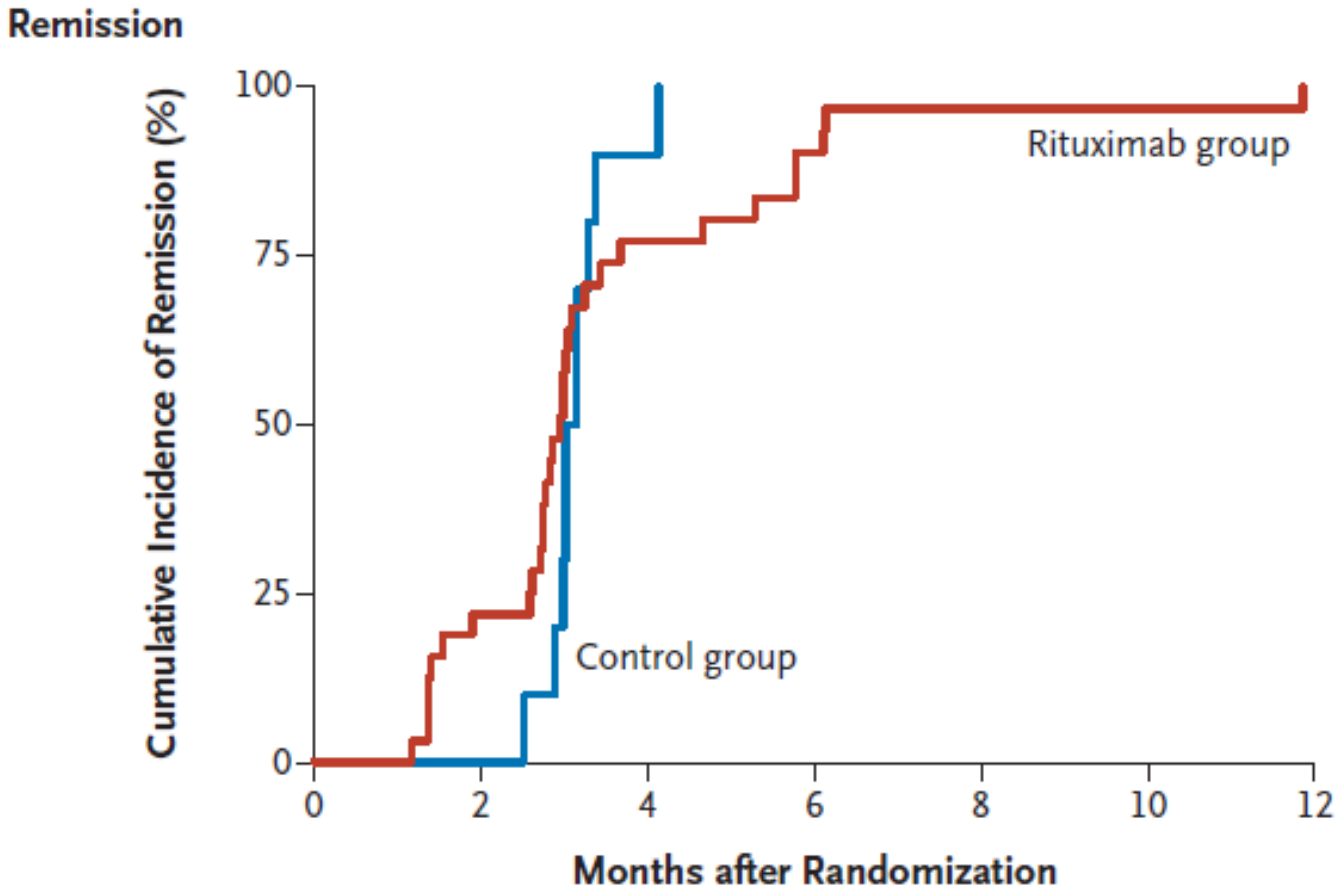
- RITUXVAS trial [1,2]
  - Randomized trial of rituximab vs cyclophosphamide in ANCA-associated vasculitis
  - Included a patient cohort with significantly higher average age and more severe renal disease

[1] Jones RB, Tervaert JW, Hauser T et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010; 363: 211–220
[2] Jones RB, Furuta S, Tervaert JW et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. Ann Rheum Dis 2015; 74: 1178–1182

Rituximab: RITUXIVAS (NEJM 2010)

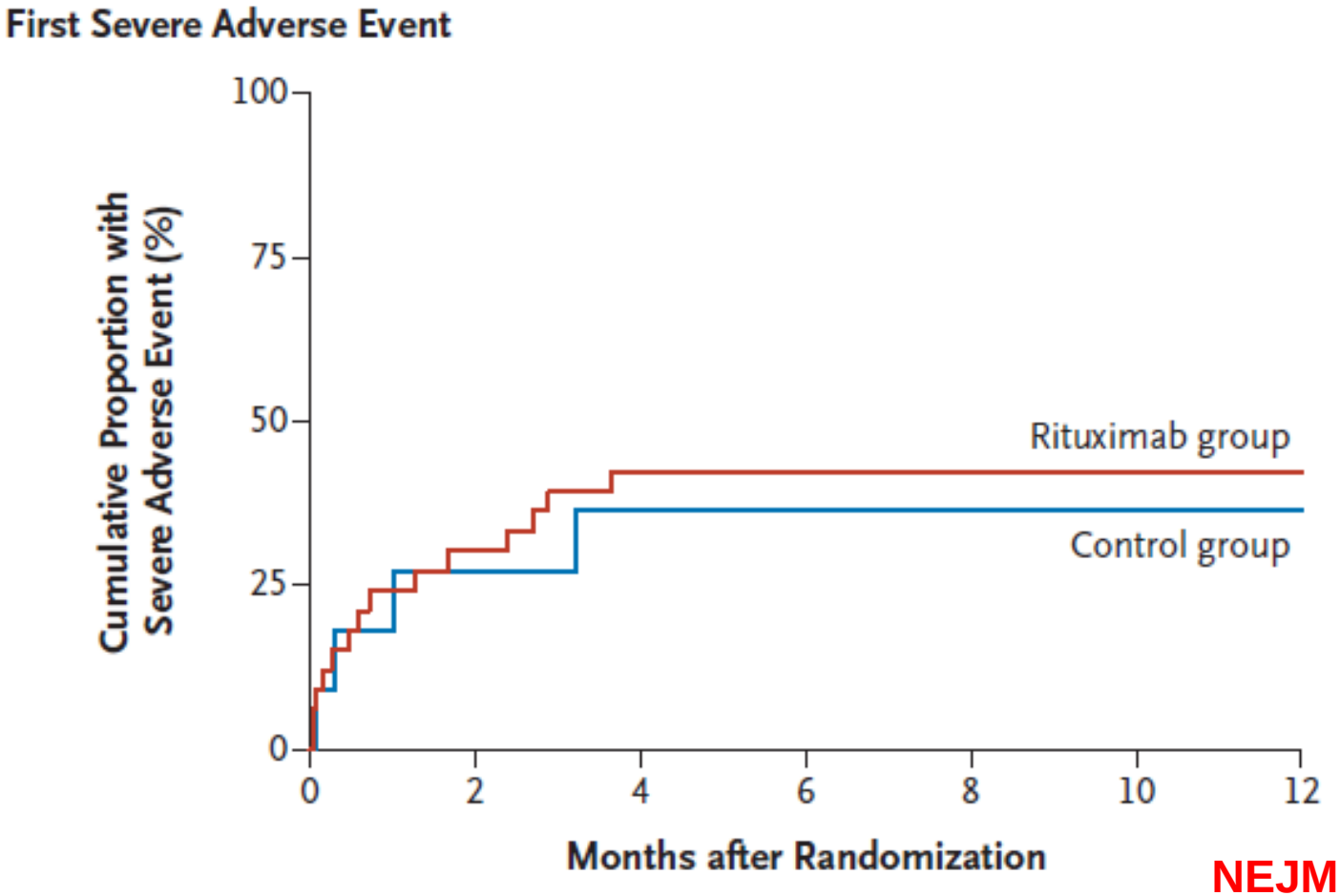
- newly diagnosed patients
- control: IV cyclophosphamide for 3 – 6 months then azathioprine for
- active: IV cyclophosphamide X2 and rituximab 375mg/m2 weekly X4
- non-inferiority: sustained response 82% control vs 76% active
- no difference in adverse event rate with respiratory tract infection common with rituximab

IV CYC vs rituximab (RITUXIVAS)



NEJM 2010

IV CYC vs rituximab (RITUXIVAS)



NEJM 2010

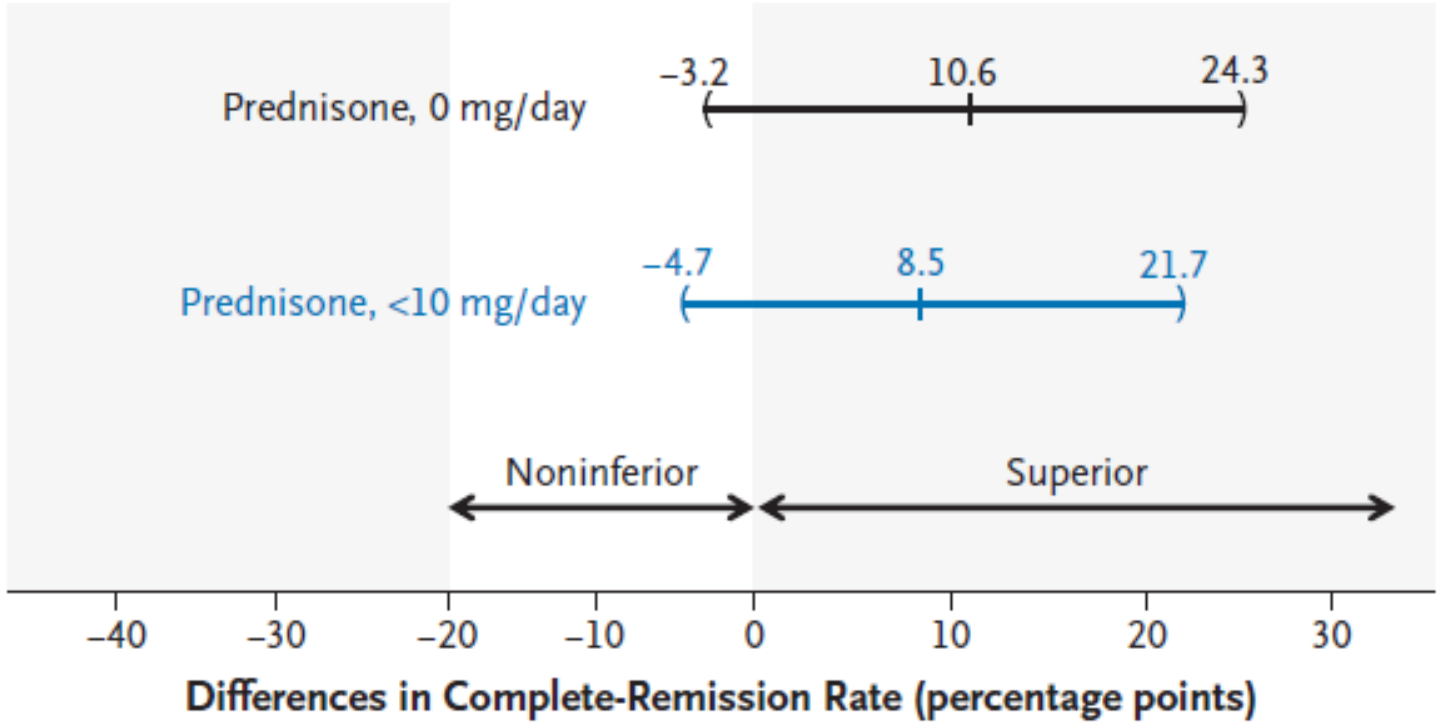
Treatments

Rituximab

- RAVE trial
  - Rituximab for ANCA-Associated Vasculitis
  - Single rituximab course in combination with glucocorticoids was non-inferior for remission induction compared with 18months conventional therapy with oral cyclophosphamide in combination with glucocorticoids followed by azathioprine [1,2]
  - Remission could be re-induced in majority of patients who had a severe relapse [3]
  - Superior to cyclophosphamide in patients with relapsing disease [1,4]

[1] Stone JH, Merkel PA, Spiera R et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010; 363: 221–232
[2] Specks U, Merkel PA, Seo P et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013; 369: 417–427
[3] Miloslavsky EM, Specks U, Merkel PA et al. Rituximab for the treatment of relapses in antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol 2014; 66: 3151–3159
[4] Miloslavsky EM, Specks U, Merkel PA et al. Clinical outcomes of remission induction therapy for severe antineutrophil cytoplasmic antibody- associated vasculitis. Arthritis Rheum 2013; 65: 2441–2449

Oral CYC vs rituximab (RAVE)



NEJM 2010


DON'T
DRINK
AND FLY

Summary

- Elderly with Co- morbidity!
- Lung and Rena Disease with Crescents
- Vote time
- Induction
  - PE
  - Pred (Methyl Pred in Particular)
  - Cyclo
  - Ritux
  - IVIg
  - Other

MAINTENANCE TREATMENT

Case 2 – My Nice 81 YO

- **PROBLEM LIST:**
- 1. PR-3 ANCA positive vasculitis (2010) with concurrent membranous changes and significant chronic parenchymal injury – biopsy proven – Induction Cyclo/Pred followed by 2-3 years of Azathioprine at reducing doses
- 2. Hypertension
- 3. Significant restrictive airways disease. Slow decline.
- 4. Dyslipidaemia; previous intolerance to Lipitor (generally unwell)
- 5. Osteopenia. DEXA scan June 2013
- 6. Vitamin B 12 deficiency – having monthly injections
- 7. Deafness
- **MEDICATIONS:**
- Aspirin 100mg M/W/F, Irbesartan 300mg od, Cal-sup 1 bd, Cholecalciferol 1,000 units od, Perindopril/Amlodipine 10/5 mg od, Simvastatin 10mg
- Pramin prn (for nausea) Salbutamol inhaler prn Fish oil 1 daily Endep 25mg Ranitidine 150mg prn

Case 2 continued

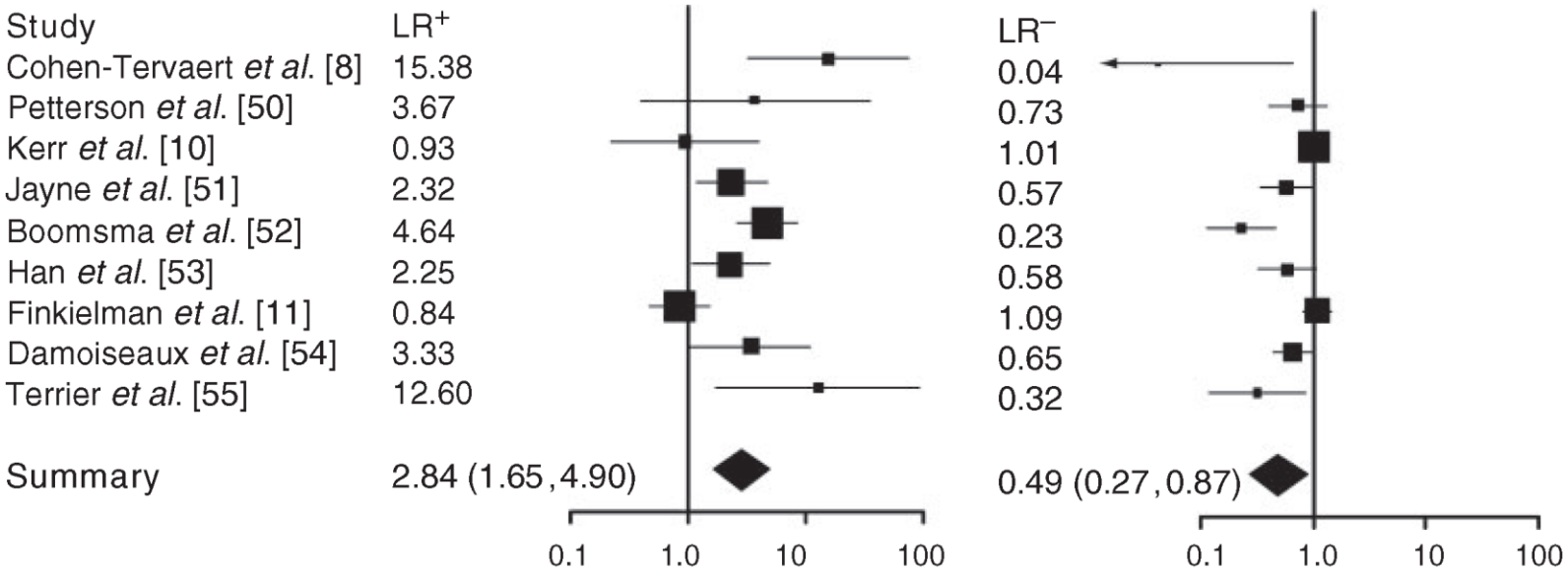
INVESTIGATIONS:

- Recent CR 166umol/l and stable (140-170 for 2 years) but
- ANCA pos, PR3 83 (slow rise over 6 months 30 – 40 -80 – never negative)
- negative Urine – no protein or blood
- She had Haemoptysis with her previous ANCA disease and some UTRI symptoms
- What to do????

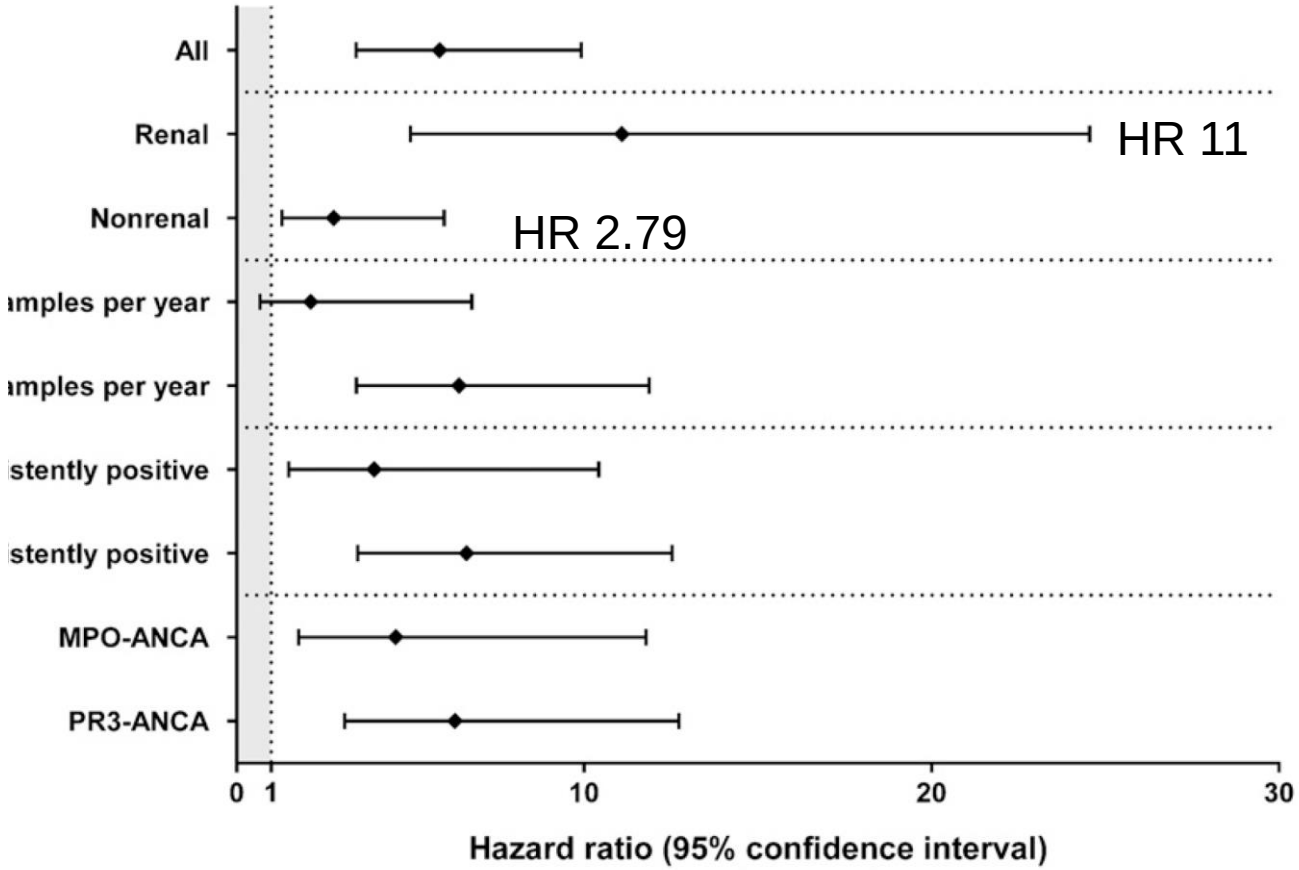
ANCA to monitor disease activity

- The use of serial ANCA monitoring alone is insufficient to predict relapse or monitor disease activity
- Serial ANCA testing may be useful:
  1. disappearance of ANCA is associated with disease remission and a lower risk of relapse
  2. reappearance or rising ANCA titre is of greater relevance in the setting of worsening clinical features
  3. persistence of anti-PR3 antibodies is associated with a higher risk of relapse.

ANCA persistence as predictor of relapse



ANCA rise predicts relapse if renal involvement



Kenna JASN 2015

Relapse

- relapse rate at 2 years: 8% MPA, 18–60% GPA
- 50% relapse rate at 5 years
- associated with:
  - URT and LRT disease
  - anti-PR3 ANCA
  - persistently positive ANCA (80% vs 20% at 5 years)
  - nasal staph aureus carriage
  - serum CCL18 (macrophage derived chemokine)

Treatments

- The concept of ‘maintenance therapy’ emerged in the 1990s
- Apparent that many patients relapsed after withdrawal of drugs
- Immunosuppressants that could
  - Prevent relapses after remission induction
  - Limit the cumulative exposure to cyclophosphamide and glucocorticoids

Maintenance immunosuppression

- **prednisolone** + **antiproliferative agent**
  - cyclophosphamide
  - azathioprine
  - newer alternatives: mycophenolate, methotrexate, leflunomide, rituximab
- maintained for at least 18 months
- relapse 18 -40%: treated as per induction

Treatments

- Azathioprine
  - CYCAZAREM trial [1]
  - First large prospective randomized study
  - Showed switching cyclophosphamide to azathioprine early after remission was as effective as longer exposure to cyclophosphamide in maintaining remission
- Methotrexate
  - As effective as azathioprine [2]
- Rituximab
  - More effective than azathioprine [3]
- MMF
  - Less effective [4]

[1] Jayne et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003; 349: 36–44
[2] Pagnoux et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med 2008; 359: 2790–2803
[3] Guillevin et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014; 371: 1771–1780
[4] Hiemstra et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody- associated vasculitis: a randomized controlled trial. JAMA 2010; 304: 2381–2388

How long to continue maintenance?

- induction with oral CYC and CS
- maintenance with azathioprine for 12 months or 48 months then tapered
- no difference in relapse-free survival

Sanders NDT 2016

- REMAIN trial (low dose long-term IS vs withdrawal) - results awaited

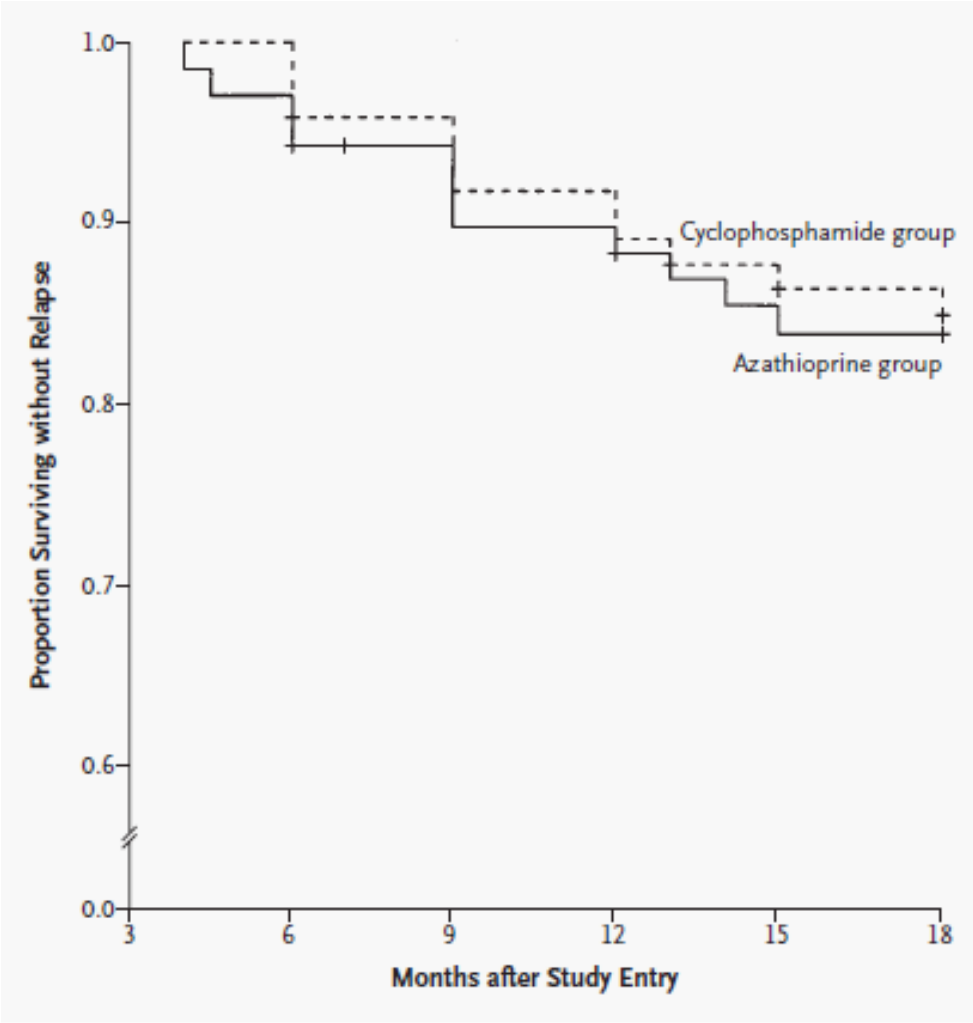
Table 1. Ongoing clinical trials to induce remission in microscopic polyangeitis and granulomatosis with polyangeitis

Name of the study and drug tested	Type, number of patients and geographic localization	Inclusion (I) and exclusion (E) criteria	Study arms (SA), primary (I) and secondary (II) endpoint(s)	Start date and estimated year of completion	Clinicaltrials.gov identifying number
LoVAS Low-dose versus high-dose glucocorticoids plus RTX	Phase IV, randomized, open label, multicentric, 140, Japan	I: >20 years MPA or GPA with C- or P-ANCA + E: eGFR <15	SA: low dose (starting at 0.5 mg/kg/day) versus high dose corticosteroid (starting at 1 mg/kg), plus RTX infusion in both arms I: remission at 6 months: BVAS = 0 and prednisone <10 II: time to remission	2015–17	NCT02198248
SCOUT Short-course corticosteroids and RTX	Phase IV, single group, open label, monocentric, 20, USA	I: 18–85 years MPA or GPA with C- or P-ANCA + BVAS ≥3 E: eGFR <30 or severe DAH	SA: RTX and 8 weeks of corticosteroids (starting at 60 mg/day with rapid tapering) I: remission at 6 months: BVAS = 0 and prednisone<10 II: disease response and partial remission	2014–16	NCT02169219
PEXIVAS Plasma exchange and corticosteroids	Phase III, randomized, 700, international	I: >15 years MPA or GPA with C- or P-ANCA + with either severe renal involvement (eGFR <50) or DAH	SA: without PEX: normal versus reduced corticosteroids With PEX: normal versus reduced corticosteroids I: all-cause mortality and ESRD at 2 years II: remission, infectious diseases	2010–18	NCT00987389

Can glucocorticoid exposure be decreased safely?

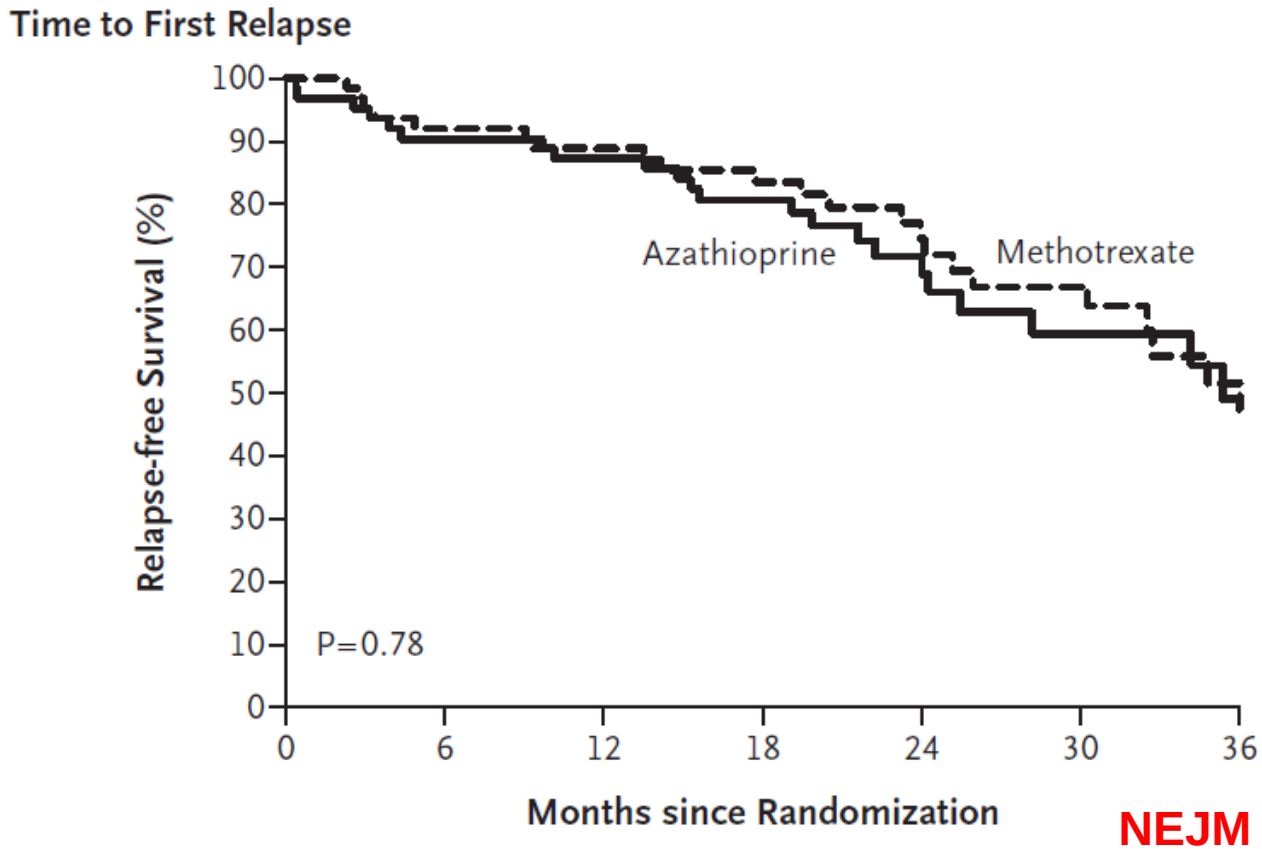
- PEXIVAS study
  - Aiming 700 patients with severe disease
- LoVAS study
  - Comparing pred 0.5 vs 1mg/kg/day
- SCOUT study
  - Rituximab with short course prednisolone

Azathioprine equivalent to cyclophosphamide for maintenance therapy (CYCAZAREM)



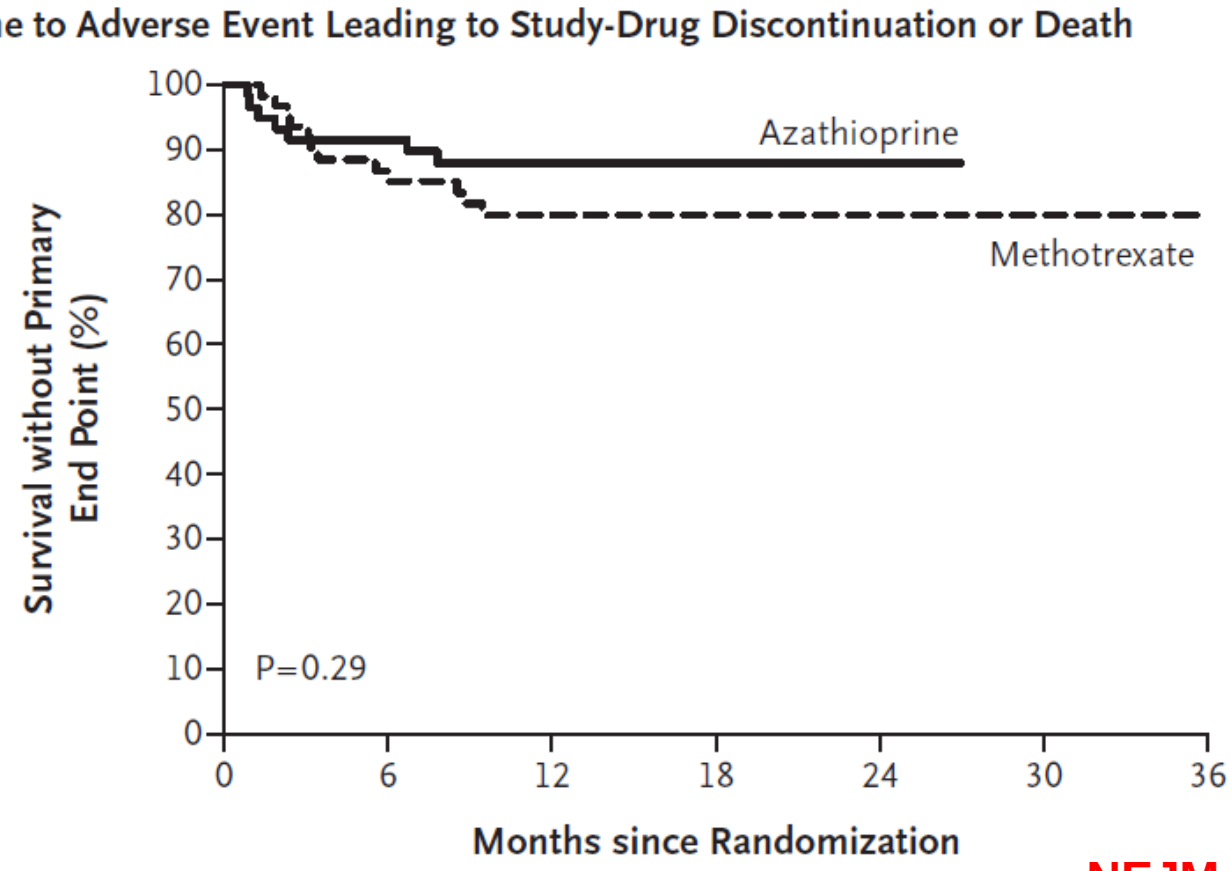
NEJM 2003

AZA and MTX equivalent efficacy for maintenance therapy



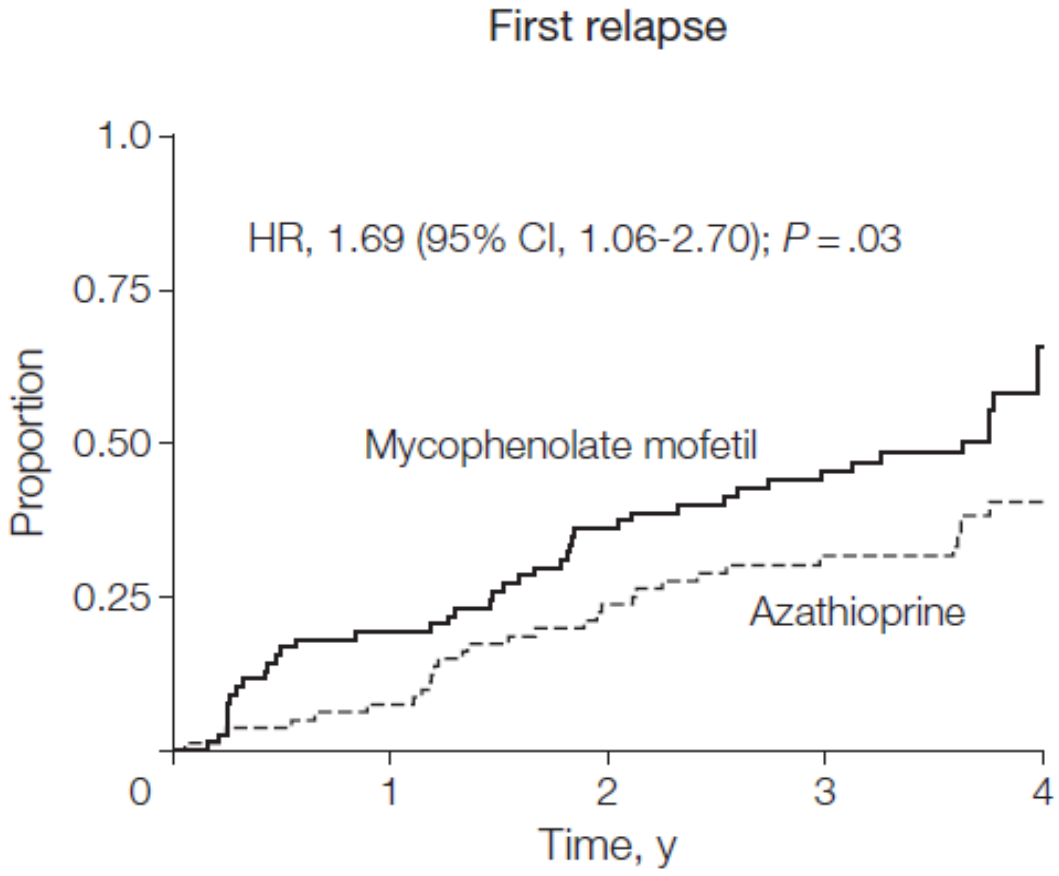
NEJM 2008

AZA and MTX equivalent in maintenance therapy but no difference in toxicity (WEGENT)



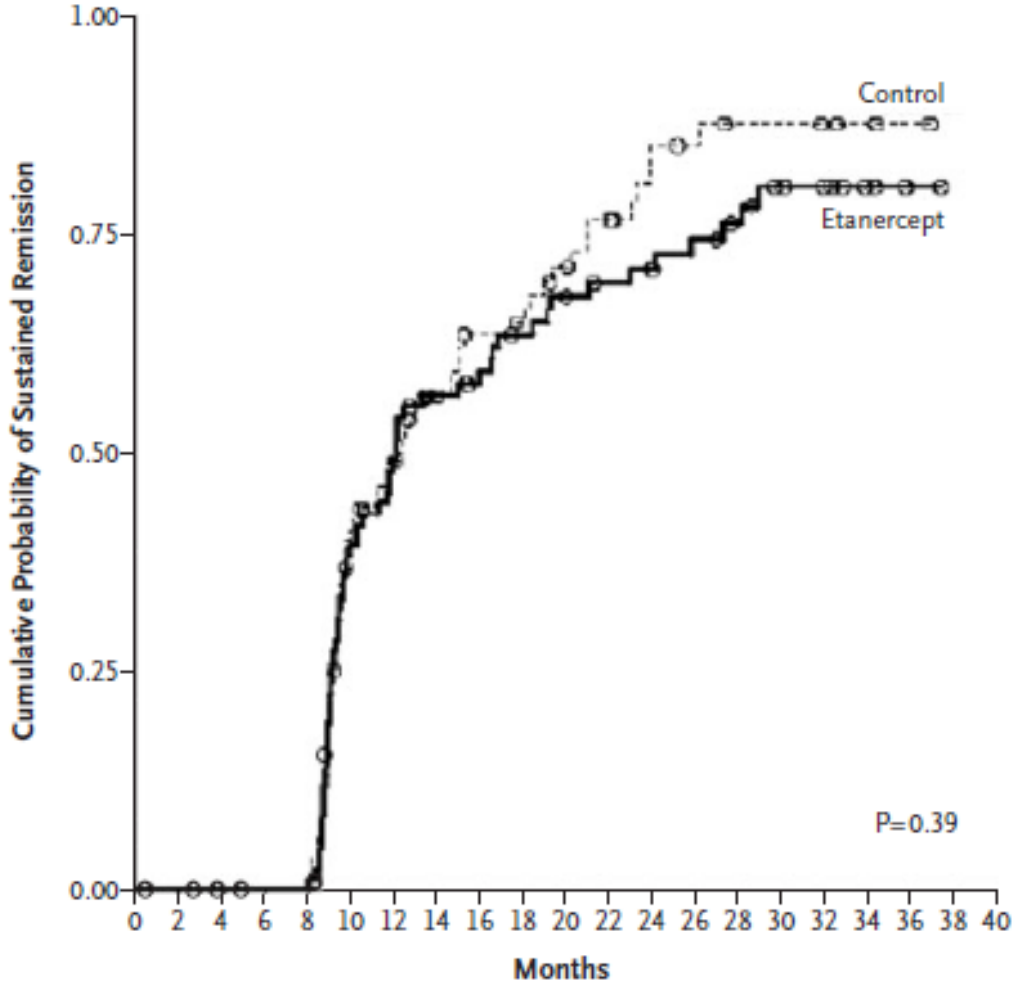
NEJM 2008

MMF inferior to AZA for maintenance therapy (IMPROVE)



JAMA 2010

Etanercept no benefit in maintaining remission (WGET)

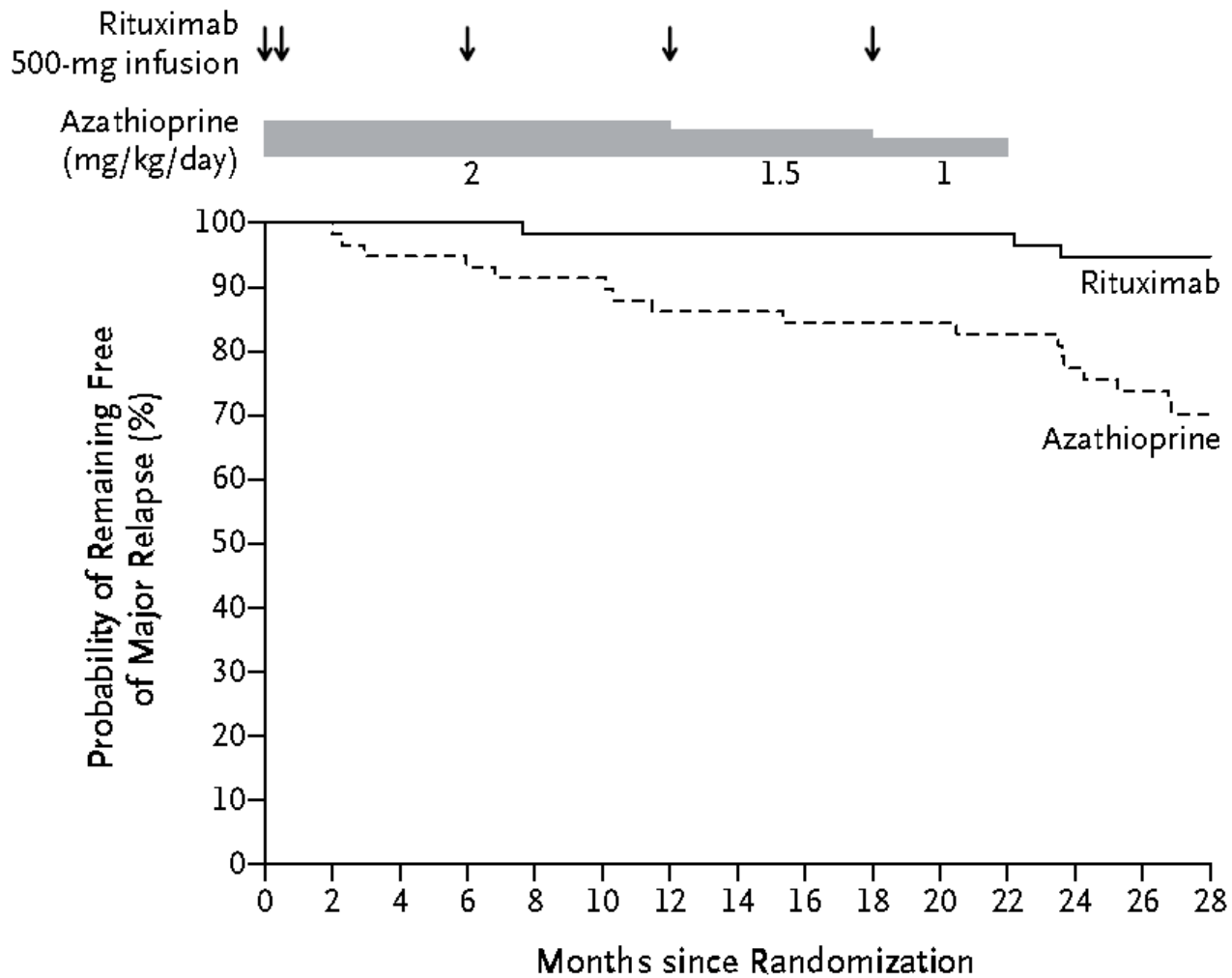


NEJM 2005

MAINRITSAN (NEJM 2014)

- GPA or MPA new diagnosis or relapse
- induction with CS and IVI cyclophosphamide
- maintenance 22 months with azathioprine 2mg/kg or rituximab 500mg x 5
- at 28 months major relapse 29% with aza vs 5% with RTX (HR 6.61)
- comparable toxicity

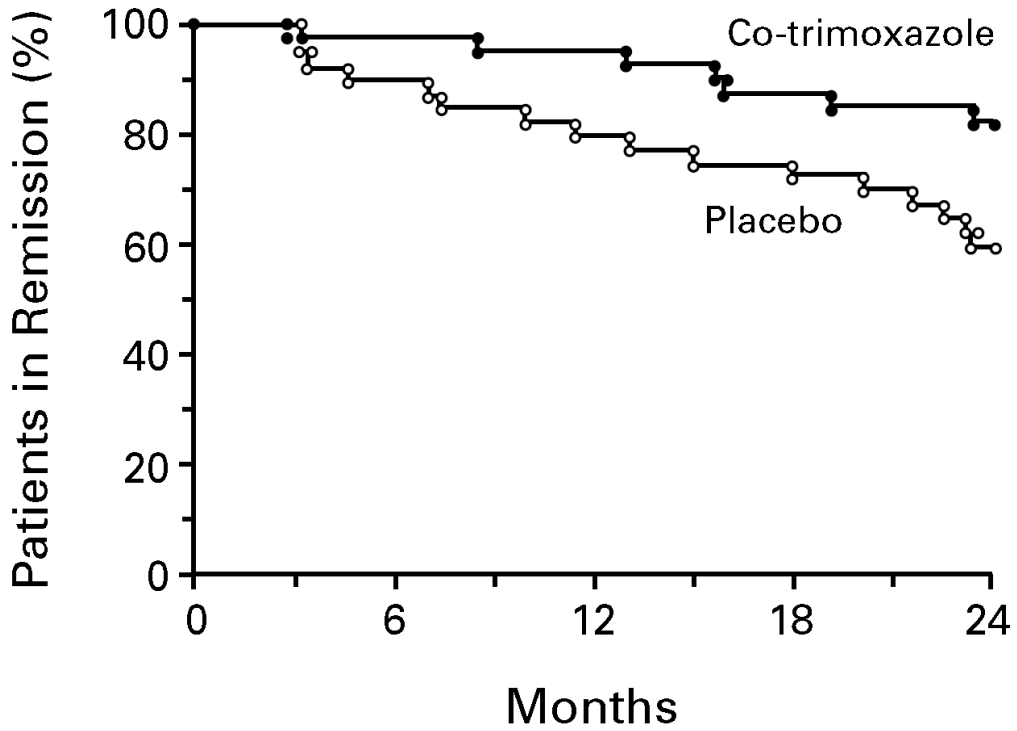
- RITAZAREM: induction with RTX then aza or RTX



No. at Risk

Rituximab	57	57	57	57	56	56	56	56	56	56	56	56	54	52	39
Azathioprine	58	58	55	54	53	53	50	50	48	48	48	47	44	41	33

Cotrimoxazole reduces relapse rate



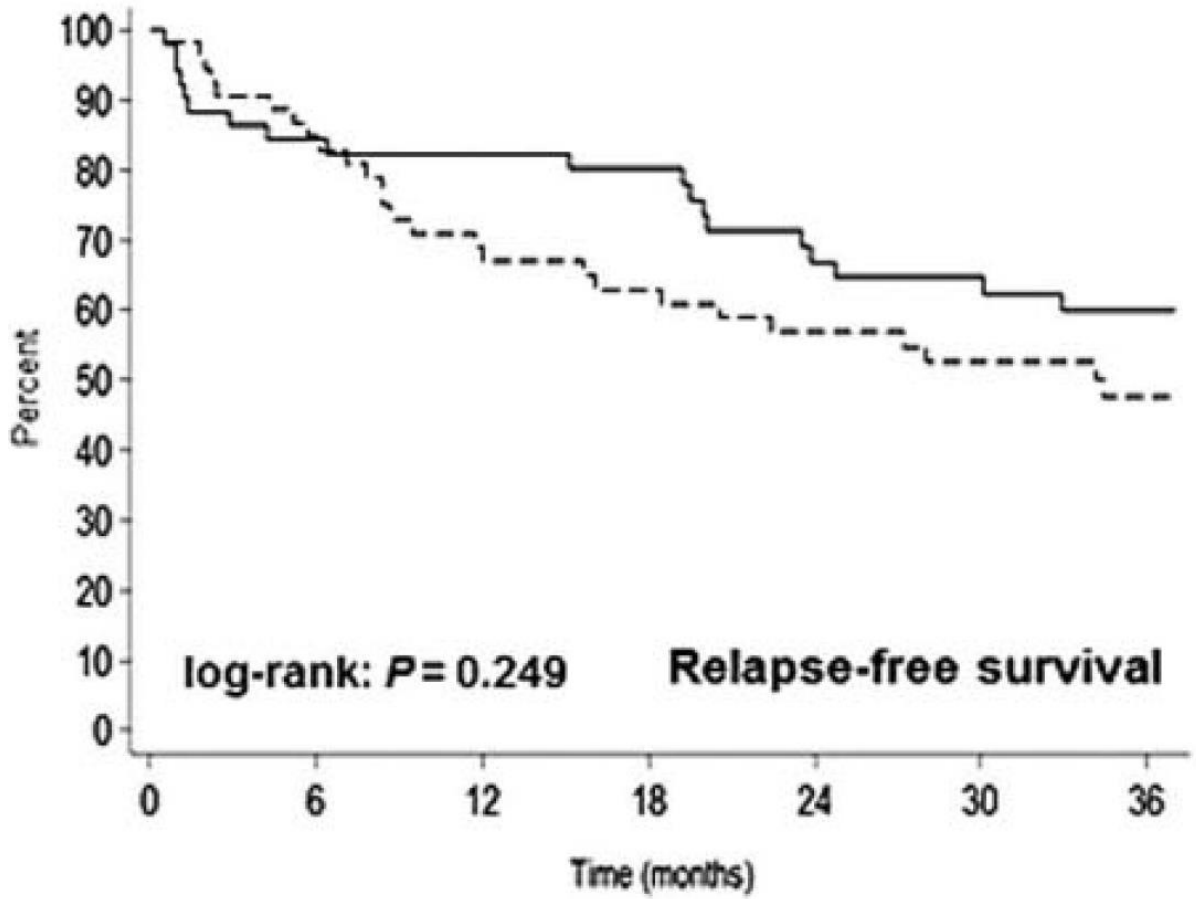
No. of Patients in Remission			
Co-trimoxazole	41	38	31
Placebo	40	32	23

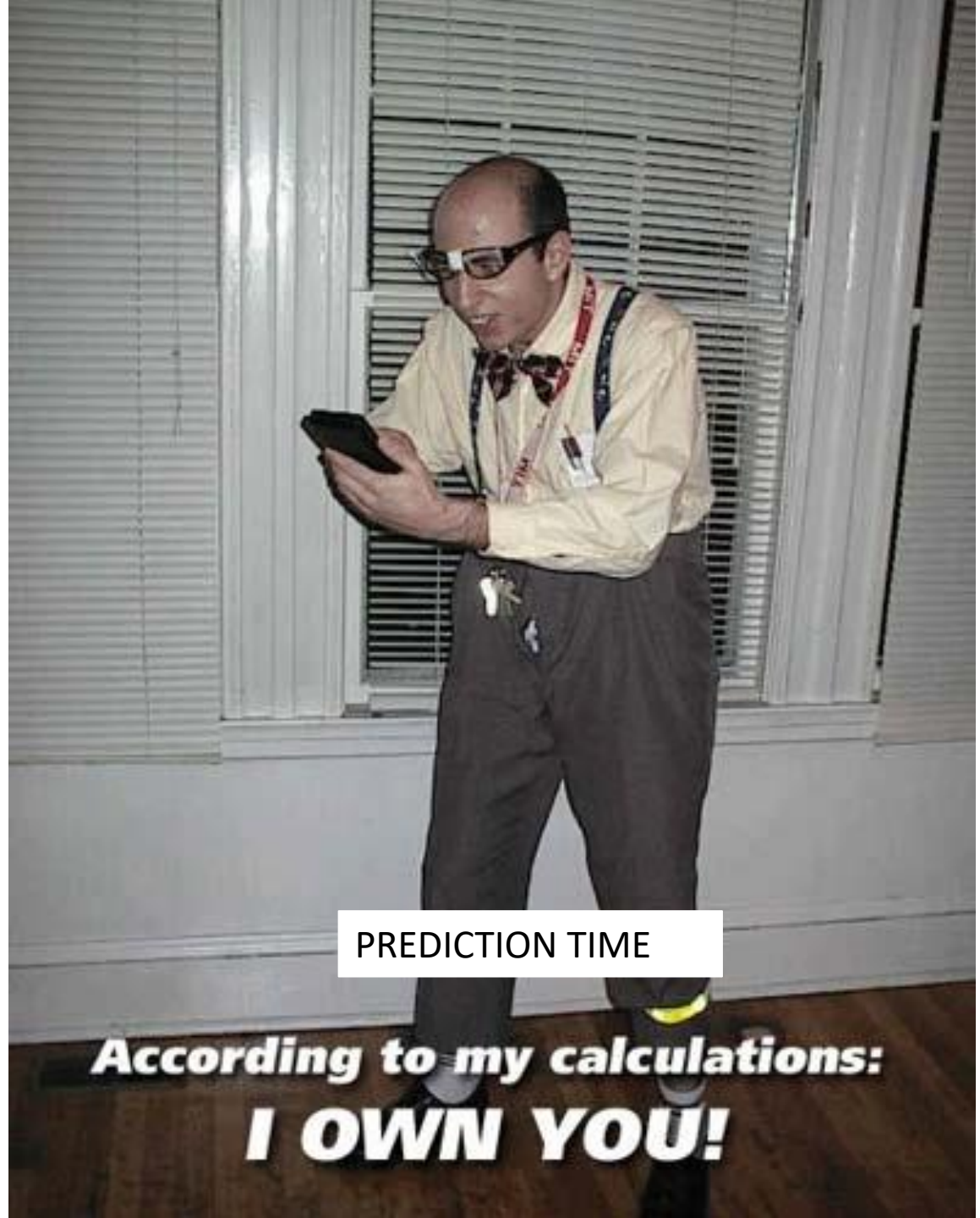
NEJM 1996

Older patients?

- CORTAGE –systemic vasculitis age >65 (Arth Rheum 2015)
- CS 9 months with IV CYC 500mg X 6 **OR**
- CS 26 months with IV CYC 500mg/m2 till remission
- 108 patients with average age 75
- significantly fewer SAEs (60% vs 78%)
- similar remission and relapse rate

CORTAGE


100
90
80
70
60
50
40
30
20
10
0
Percent
log-rank: P = 0.249
Relapse-free survival
0
6
12
18
24
30
36
Time (months)


PREDICTION TIME
According to my calculations:
I OWN YOU!

Summary of Case 2

- Elderly with lots of Comorbidities
- Lost of Immunosupression
- What to do
  - Watch
  - Push Resp Ixs
  - Biopsy
  - Treat


NEXT
BIG THING
AHEAD

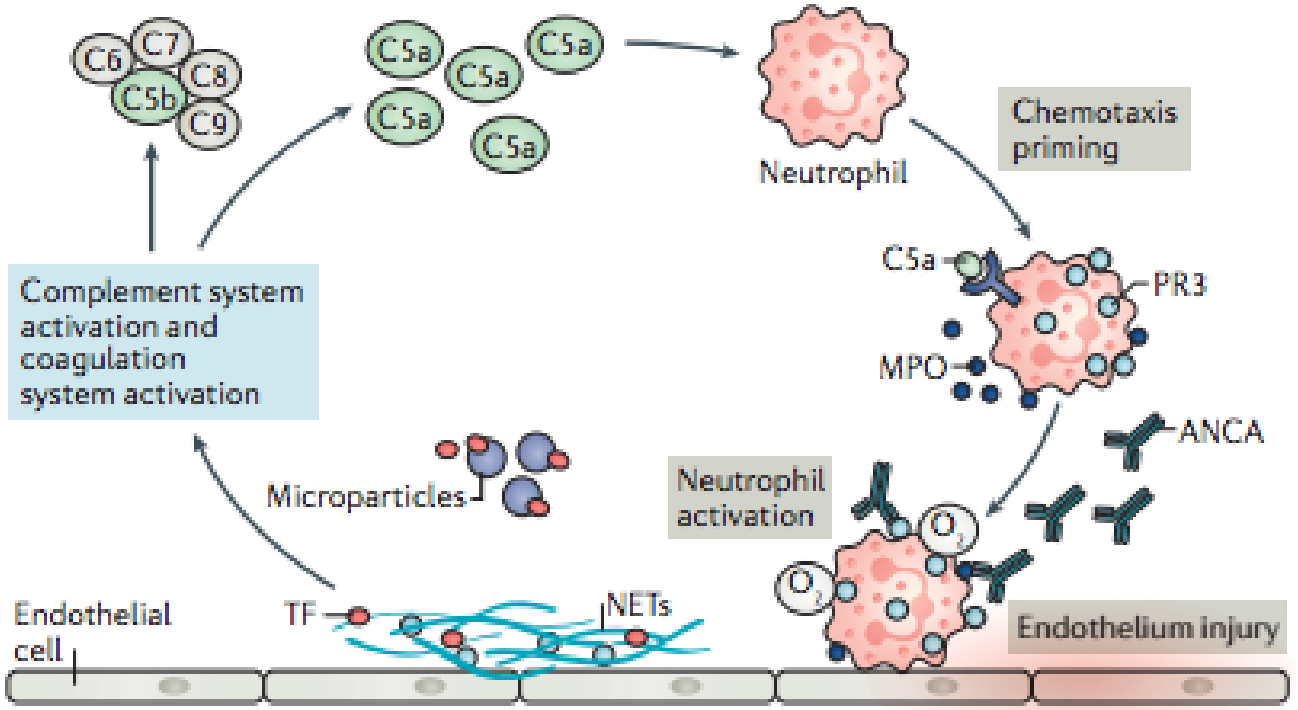


Figure 3 | **Proposed model for the interaction of anti-neutrophil cytoplasmic antibody (ANCA), neutrophils and complement activation in the pathogenesis of ANCA-associated vasculitis.** Priming of neutrophils by cytokines, such as C5a or tumour necrosis factor, leads to the translocation of ANCA antigens such as myeloperoxidase (MPO) or proteinase-3 (PR3) from the cytoplasm to the cell surface. ANCAs can further activate primed neutrophils to undergo respiratory burst and degranulation, and to release tissue factor (TF)-bearing microparticles and neutrophil extracellular traps (NETs). Neutrophil activation can lead endothelial cell injury, activation of the coagulation system, and activation of the alternative complement pathway via their cell membranes, microparticles and NETs. Activation of the alternative complement pathway and NETs in turn leads to the generation of C5a, which amplifies the inflammatory response through enhanced neutrophil recruitment and priming of neutrophils for ANCA-mediated activation.

Future therapies?

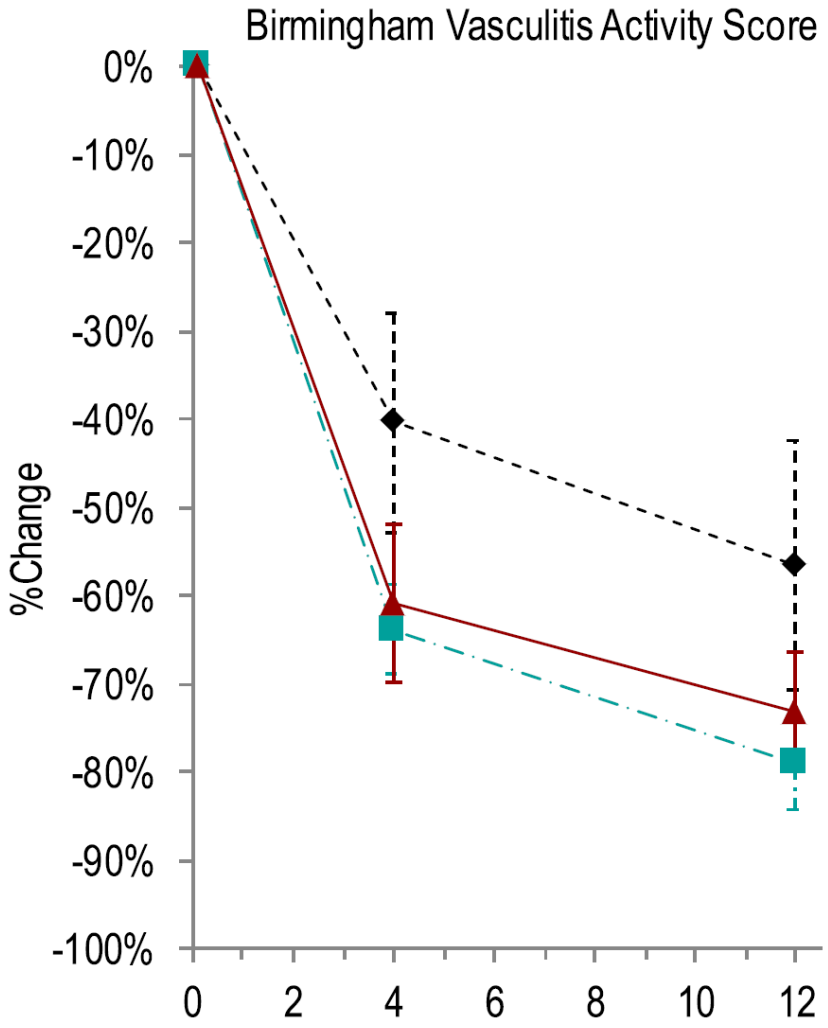
- abatacept - CTLA-4 ligand
- alemtuzumab – anti-CD52
- belimumab/blisibimab – BlyS/BAFF
- tocilizumab (IL6 inhibitor)
- C5a inhibitors (avacopan)
  - released by neutrophils primed by TNFα
  - neutrophil chemotaxis and reduced deformability
  - activation of vascular endothelial cells

CLEAR

- avacopan (CCX168): orally active C5a inhibitor
- steroid sparing trial:
  - prednisolone 60mg
  - prednisolone 20mg plus avacopan
  - avacopan alone
  - plus either cyclophosphamide or rituximab
- 50% reduction in BVAS score at 12 weeks
- similar efficacy in all groups
- reduction in albuminuria, urine MCP: creatinine
- improved eGFR

JASN 2017

CLEAR



JASN 2017

CLEAR C5 inhibitor CCX168	Phase II, randomized versus placebo, 67, Europe	I: >18 years MPA or GPA with C- or P-ANCA—at least 1 major/3 other/2 renal BVAS items E: eGFR <20 or severe DAH	SA: CCX168 low-dose versus high-dose versus placebo plus standard of care in each arm I: BVAS at 12 weeks II: eGFR, hematuria, albuminuria at 12 weeks	2011–16	NCT01363388
CLASSIC C5 inhibitor CCX168	Phase II, randomized versus placebo, 42, USA and Canada	Same criteria	SA: CCX168 low-dose versus high-dose versus placebo plus standard of care in each arm I: BVAS at 12 weeks II: systemic corticosteroid use based on total oral corticosteroid dose and duration at 24 weeks	2014–16	NCT02222155

- CCX168
  - C5a receptor inhibitor
  - Possible glucocorticoid sparing agent or alternative for remission induction

CLEAR C5 inhibitor CCX168	Phase II, randomized versus placebo, 67, Europe	I: >18 years MPA or GPA with C- or P-ANCA—at least 1 major/3 other/2 renal BVAS items E: eGFR <20 or severe DAH	SA: CCX168 low-dose versus high-dose versus placebo plus standard of care in each arm I: BVAS at 12 weeks II: eGFR, hematuria, albuminuria at 12 weeks	2011–16	NCT01363388
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CCX168

- C5a receptor inhibitor
- Possible glucocorticoid sparing agent or alternative for remission induction

- CLASSIC trial
  - Comparing safety and efficacy of 2 doses of CCX168 in addition to standard of care

How best to use rituximab?

- After a single rituximab course, relapses are frequent
- RAVE trial, only 39% were in sustained complete remission at 18months
- Suggestion that pre-emptive rituximab retreatment could decrease relapse risk
  - Fixed dosing using variable intervals and doses
  - Individually timed retreatment based of B-cell counts and ANCA levels
- MAINRITSAN trial [1]
  - Maintenance of Remission using Rituximab in Systemic ANCA-Associated Vasculitis
  - 500mg rituximab every 6months for 2years is superior to azathioprine in preventing relapses

[1] Guillevin L, Pagnoux C, Karras A et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014; 371: 1771–1780

Table 2. Ongoing clinical trials to maintain remission in microscopic polyangeitis and granulomatosis with polyangeitis

Name of the study and drug tested	Type, number of patients and geographic localization	Inclusion (I) and exclusion (E) criteria	Study arms (SA), primary (I) and secondary (II) endpoint(s)	Start date and estimated year of completion	Clinicaltrials.gov identifying number or website
MAINRITSAN 2 RTX, two administration protocols	Phase 3, multicenter, randomized, 166, France	I: >18 years, diagnosis of GPA/MPA, remission after standard of care induction therapy E: None related to AAV	SA: RTX fixed interval (500 mg/6 months for 2 years) versus based on ANCA and CD 19 lymphocytes I: number of relapses at 28 months II: steroid use, adverse events	2012–17	NCT01731561
RITAZAREM RTX versus AZA	Phase 3, randomized, 190, international	I: >15 years, relapsing AAV, positive ANCA, remission 4 months after induction therapy using RTX E: RTX in the last 6 months	SA: high-dose RTX (1 g/4 months, 2 years) versus AZA 2 mg/kg, standardized steroid taper I: time to relapse until 4 years II: remission at 24 and 48 months, steroid use	2013–18	NCT01697267
MAINTANCAVAS RTX, two administration protocols	Phase 4, randomized, 200, Massachusetts General Hospital	I: age 18–82 years, diagnosis of AAV, remission (BVAS-WG = 0 AND prednisone ≤7.5 mg) for at least 24 months using RTX, undetectable B cellsE: eGFR <30	SA: RTX re-dosing (two 1 g infusions) upon B cell return versus ANCA flare (rise >4 or 5), B cells and ANCA monitored every 6 months I: number of disease relapses (BVAS-WG ≥2) over 3 years II: total RTX dose, serious adverse events	2016–20	NCT02749292

- RITAZAREM
  - Rituximab Vasculitis Maintenance Study trial
  - 1g rituximab 4monthly to azathioprine
- MAINRITSAN 2
  - Randomized, controlled, prospective study
  - Fixed interval rituximab infusions to re-dosing of rituximab based on serial biomarker determination (CD19 lymphocytes and ANCA)
- MAINTANCAVAS
  - Compares intermittent rituximab dosing based on B-cell return or serologic ANCA flare

REMAIN Maintenance duration with AZA	Phase 4, randomized, 110, Europe	I: >18 years, AAV diagnosis, remission after CYC, AZA started for less than 18 months E: previous life-threatening relapse	SA: AZA standard duration (total 18–24 months of immunosuppression) versus prolonged AZA duration (total 48–54 months) I: relapse rate at study completion II: kidney function, damage, adverse events	1998–2013	http://www.vasculitis.org/
MAINRITSAN 3 Maintenance duration with RTX	Phase 3, multicenter, placebo-controlled, 118, France	I: participation in the MAINRITSAN 2 study and complete remission (BVAS 0) at 28 months of MAINRITSAN 2 study	SA: 500 mg RTX infusion every 6 months for 18 months versus placebo I: number of relapses at 28 months II: steroid use, adverse events	2015–19	NCT02433522

- REMAIN trial
  - Azathioprine with low-dose prednisolone randomized to 18-24months vs 48-54months
  - Preliminary results showed prolonged duration of maintenance therapy decreased relapse rate significantly
- MAINRITSAN 3 trial
  - Extension of MARTISAN 2 trial
  - Treatment with rituximab for 46months compared to 18months

www.EUVAS.org

Summary to End

- Hopefully I Convinced you that it’s a little tougher than the trial look!
- Choice is a big deal – nothing perfect
- Good Luck!