Vasculitis

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Eastern Health Clinical School
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....
Rapidly Progressive Glomerulonephritis (RPGN)

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

- Immune complex small-vessel vasculitis
  - Cryoglobulinemic vasculitis
  - IgA vasculitis (Henoch–Schönlein)
  - Hypocomplementemic urticarial vasculitis (Anti-C1q vasculitis)

- Medium-vessel vasculitis
  - Polyarteritis nodosa
  - Kawasaki disease

- Anti-GBM disease

- ANCA-associated small-vessel vasculitis
  - Microscopic polyangiitis
  - Granulomatosis with polyangiitis (Wegener)
  - Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)

- Large-vessel vasculitis
  - Takayasu arteritis
  - Giant cell arteritis
Kidneys are targets for a variety of systemic vasculitis, especially those that affect small vessels.
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

<table>
<thead>
<tr>
<th></th>
<th>Treatment resistance</th>
<th>Relapse</th>
<th>ESRD</th>
<th>Death</th>
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<tbody>
<tr>
<td>Chapel Hill</td>
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<tr>
<td>GPA %</td>
<td>17</td>
<td>60</td>
<td>21</td>
<td>17</td>
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<tr>
<td>MPA %</td>
<td>22</td>
<td>37</td>
<td>30</td>
<td>30</td>
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<tr>
<td>Renal ltd %</td>
<td>30</td>
<td>19</td>
<td>47</td>
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<tr>
<td>European %</td>
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<tr>
<td>GPA %</td>
<td>22</td>
<td>44</td>
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<td>26</td>
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<tr>
<td>MPA %</td>
<td>25</td>
<td>30</td>
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<td>ANCA spec</td>
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<tr>
<td>MPO</td>
<td>27</td>
<td>29</td>
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<td>31</td>
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<tr>
<td>PR3</td>
<td>17</td>
<td>51</td>
<td>26</td>
<td>23</td>
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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
Neutrophil type of white blood cell

ANCA (Anti-Neutrophil Cytoplasmic Autoantibody)

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

PR3-ANCA
- Genetics
  - HLA-DP1
  - PRTN3
  - SERPINA1
- Geographical pattern of incidence

MPO-ANCA
- Genetics
  - HLA-DQ
  - CTLA-4
- 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 x150.)

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 x150.)
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
True Believers
ALTERNATIVE CANCER CURES • WAS JESUS MARRIED? • PHYSICS & FREE WILL

SKEPTIC

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

ALTERNATIVE CANCER CURES
STEVE JOBS’S REALITY DISTORTION FIELD
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

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

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]

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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

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)

REMSSION

Cumulative Incidence of Remission (%)

- Rituximab group
- Control group

Months after Randomization

NEJM 2010
IV CYC vs rituximab (RITUXIVAS)

First Severe Adverse Event

Cumulative Proportion with Severe Adverse Event (%)

Months after Randomization

Rituximab group
Control group

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 18 months 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]

Oral CYC vs rituximab (RAVE)

NEJM 2010
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
  • 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

<table>
<thead>
<tr>
<th>Study</th>
<th>LR⁺</th>
<th>LR⁻</th>
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</thead>
<tbody>
<tr>
<td>Cohen-Tervaert et al. [8]</td>
<td>15.38</td>
<td>0.04</td>
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<tr>
<td>Petterson et al. [50]</td>
<td>3.67</td>
<td>0.73</td>
</tr>
<tr>
<td>Kerr et al. [10]</td>
<td>0.93</td>
<td>1.01</td>
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<td>Jayne et al. [51]</td>
<td>2.32</td>
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<td>Boomsma et al. [52]</td>
<td>4.64</td>
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<td>Han et al. [53]</td>
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<tr>
<td>Finkielman et al. [11]</td>
<td>0.84</td>
<td>1.09</td>
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<tr>
<td>Damoiseaux et al. [54]</td>
<td>3.33</td>
<td>0.65</td>
</tr>
<tr>
<td>Terrier et al. [55]</td>
<td>12.60</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td>2.84 (1.65, 4.90)</td>
<td>0.49 (0.27, 0.87)</td>
</tr>
</tbody>
</table>
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]

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
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)
AZA and MTX equivalent efficacy for maintenance therapy

**Graph:**
- **Time to First Relapse**
- **Relapse-free Survival (%)**
- **Months since Randomization**

- Azathioprine
- Methotrexate

**Statistical Note:**
- P = 0.78

**Source:** NEJM 2008
AZA and MTX equivalent in maintenance therapy but no difference in toxicity (WEGENT)

Time to Adverse Event Leading to Study-Drug Discontinuation or Death

Survival without Primary End Point (%)

0 10 20 30 40 50 60 70 80 90 100

P = 0.29

Azathioprine

Methotrexate

Months since Randomization

NEJM 2008
MMF inferior to AZA for maintenance therapy (IMPROVE)

First relapse

HR, 1.69 (95% CI, 1.06-2.70); P = .03

Mycophenolate mofetil

Azathioprine

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
Cotrimoxazole reduces relapse rate

**Diagram:**

- **Patients in Remission (%)**
  - Co-trimoxazole
  - Placebo

**No. of Patients in Remission**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0 Months</th>
<th>6 Months</th>
<th>12 Months</th>
<th>18 Months</th>
<th>24 Months</th>
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<tr>
<td>Co-trimoxazole</td>
<td>41</td>
<td>38</td>
<td>31</td>
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<tr>
<td>Placebo</td>
<td>40</td>
<td>32</td>
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*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

log-rank: $P = 0.249$  
Relapse-free survival
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 lxs
  • 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. ANCA 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 to 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
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
<table>
<thead>
<tr>
<th>Study Name</th>
<th>Design</th>
<th>Criteria</th>
<th>Intervention</th>
<th>Duration</th>
<th>Study ID</th>
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<tbody>
<tr>
<td>CLEAR C5 inhibitor CCX168</td>
<td>Phase II, randomized versus placebo, 67, Europe</td>
<td>I: &gt;18 years MPA or GPA with C- or P-ANCA—at least 1 major/3 other/2 renal BVAS items E: eGFR &lt;20 or severe DAH</td>
<td>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</td>
<td>2011–16</td>
<td>NCT01363388</td>
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<tr>
<td>CLASSIC C5 inhibitor CCX168</td>
<td>Phase II, randomized versus placebo, 42, USA and Canada</td>
<td>Same criteria</td>
<td>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</td>
<td>2014–16</td>
<td>NCT02222155</td>
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</table>

- **CCX168**
  - C5a receptor inhibitor
  - Possible glucocorticoid sparing agent or alternative for remission induction
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 18 months
• 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 6 months for 2 years is superior to azathioprine in preventing relapses

• **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
<table>
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<th>Trial</th>
<th>Design</th>
<th>Key Details</th>
<th>Duration</th>
<th>Reference</th>
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<tbody>
<tr>
<td>REMAIN trial</td>
<td>Phase 4, randomized,</td>
<td>( \text{I: } &gt;18 \text{ years, AAV diagnosis, remission after CYC, AZA started for less than 18 months} )</td>
<td>1998-2013</td>
<td><a href="http://www.vasculitis.org/">http://www.vasculitis.org/</a></td>
</tr>
<tr>
<td></td>
<td>110, Europe</td>
<td>( \text{E: previous life-threatening relapse} )</td>
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<tr>
<td>MAINRITSAN 3</td>
<td>Phase 3, multicenter,</td>
<td>( \text{I: participation in the MAINRITSAN 2 study and complete remission (BVAS 0) at 28 months of MAINRITSAN 2 study} )</td>
<td>2015-19</td>
<td>NCT02433522</td>
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<td></td>
<td>placebo-controlled,</td>
<td>( \text{II: kidney function, damage, adverse events} )</td>
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<tr>
<td></td>
<td>118, France</td>
<td>( \text{SA: 500 mg RTX infusion every 6 months for 18 months versus placebo} )</td>
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<td></td>
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<td>( \text{II: number of relapses at 28 months} )</td>
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<td>( \text{II: steroid use, adverse events} )</td>
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<td>( \text{SA: prednisone withdrawal} )</td>
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- **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
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!