A. A. Vasculitis Update

Sohrab Fallahi, M.D., F.A.C.P., F.A.C.R

Clinical Assistant Professor of Medicine
University of Alabama at Birmingham
Montgomery program
**Vasculitis: Definition**

**Pathologist**

- Inflammation of vessel wall with inflammatory destruction of blood vessels
- Inflammatory cells;
  - Leukocytoclasis
  - Elastic membrane disruption
- Fibrinoid Necrosis of the vessel wall
- Ischemia, occlusion, thrombosis
- Aneurysm formation
- Rupture, hemorrhage

**Rheumatologist**

- A clinicopathologic process characterized by;

  Inflammatory destruction of blood vessel that results in occlusion or destruction of the vessel and ischemia of tissue supplied by that vessel.

  “Systemic Vasculitis”
Consider where we are now:

Vasculitis classification schemes/patterns

Based on distinctions in…

**Vessel size**
- Small, medium, large

**Histopathology** – what we see as a reaction pattern
- Granulomatous, non-granulomatous, eosinophilic

**Sub-classify: organ distribution and unique features**
- ENT, lungs, kidneys (Wegener’s granulomatosis)
- Mucosal ulcers (Behcet’s syndrome)
Vasculitis is classified by vessel size

- **Large vessel vasculitis**
  - Takayasu’s arteritis, giant cell arteritis

- **Medium vessel vasculitis**
  - polyarteritis nodosa
  - Thromboangiitis obliterans (Buerger’s)

- **Small vessel vasculitis**
  - Pauci-immune (ANCA – asso.): WG, MPA, CSS

- **Immune – complex mediated**: cryoglobulinemia, HSP, hypersensitivity, isolated cutaneous, etc.
How big is big?

- Large vessel
  - Aorta and its immediate branches

- Medium vessel
  - "named vessel"

- Small vessel
  - Everything else
  - predominantly: Lungs, Kidneys, Skin
Vasculitis Classification

• Classification refers to the size of the most characteristic vessels involved.
  -This is not set in stone!

• Classification allows you to predict outcomes.

• Classify the form of vasculitis by working backward from the patient’s complaints.
Approach to Therapy

Standard therapy of vasculitis:

Glucocorticoid +/- Steroid sparing agent

Q: How do you decide what steroid sparing agent?

A: Let the punishment fit the crime.
Misdemeanor

• Not life threatening
• Chronic, associated with significant morbidity
• Consider antimetabolite:
  - Methotrexate 20-25 mg po q week
  - Azathioprine 2.0 mg / kg / day
  - Mycophenolate mofetil 1.5 mg po bid

( 3 gram/ day )
Felony

- **Life threatening** vasculitis, or vasculitis that threatens function of a vital organ (lungs, kidneys, CNS)
- This should be treated with our most aggressive therapy.
- A **cytotoxic agent** and **high dose** steroid would be standard of care.
1992

NIH longitudinal series for Wegener’s Granulomatosis

( began 1968 )

“The Fauci-Wolff protocol”

• Cyclophosphamide (CYC) 2mg / kg / day

• Glucocorticoids:
  - Pulse methylprednisolone (1g/d x 3)
  - Prednisone 1 mg / kg / day
  - Tapered to qod after 3 months

• Typical duration of therapy:
  - Glucocorticoids: 12 months (at best)
  - Cyclophosphamide: 24 months
Large vessel vasculitis: Treatment

- Solumedrol 1g IV 3 d
  - Visual Sxm irreversible within hours
- Prednisone 1mg/kg 2-4 weeks
- Taper by:
  - 10 mg q 2-4 wks until 40 mg / day
  - 5 mg q 2-4 wks until 20 mg / day
  - 2.5 mg q 2-4 wks until 10 mg / day
  - 1 mg increments

Glucocorticoid side effects
- Osteoporosis
- Coronary artery disease
- Steroid myopathy
- Cognitive effects
- Cataracts
- Weight gain
- Bruising
- Avascular necrosis
- Diabetes mellitus
- PUD
- Risk of infections
CYC : The Good / The Bad

- 91% marked improvement
- 75% complete remission

- 42% permanent morbidity
- 46% serious infections
- 43% hemorrhagic cystitis
- 33 fold↑ risk of bladder cancer
- 11 fold↑ risk of lymphoma
- 57% infertility
- Steroid-induced damage:
  Cushingoid features, weight gain, D.M., hypertension, cataract, fractures
# Small Vessel Vasculitis

## Differential Diagnosis

### Immune-Complex Mediated
- Idiopathic cutaneous angiitis
- Sjogren’s syndrome
- Systemic lupus erythematosus
- Urticarial vasculitis
- Henoch-Schonlein purpura (IgA)
- Cryoglobulinemic vasculitis

### Pauci-Immune
- Wegener’s granulomatosis
- Microscopic polyangiitis
- Churg-Strauss Syndrome
- Renal-limited vasculitis
- Drug-induced ANCA-associated vasculitis (PTU, minocycline)
Chapel Hill Consensus Conference

- **Wegener’s granulomatosis**: granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels.

- **Microscopic polyangiitis**: Necrotizing vasculitis affecting the small vessels.

- **Churg-Strauss syndrome**: Eosinophil-rich and granulomatous inflammatory involving the medium-sized vessel, and associated with asthma and eosinophilia.
Treatment of Severe AAV: Standard Approach

- **Remission induction:**
  - CYC 2 mg/kg po qd x 3 – 6 month
    ( or 15 mg/kg IV q 2 Wks.x 3, then, q 3 Wks. X 6 – 12 months )
  - Prednisone 1 mg/kg po qd x 1 month, then taper
  - ( Bactrim, Calcium, Vitamin D )

- **Remission maintenance:** ( minimum 1 year )
  - Methotrexate 20 -25 mg po q wk. + folate
  - Azathioprine 2 mg/kg po qd
  - MMF 1.5 gram po BID
  - Leflunomide 20 – 30 mg po BID
Systemic vasculitis: 1980s and now

- Rx - considerably different c/w 1980s.
- New strategies/new drugs. Observational => RCT
- Disease control with less toxicity is available for most pts
- *But*, causes and cures still *not known* & long-term risks of newer therapies have not been fully defined.
- With partial understanding of efficacy and risks, we still need to use available data to answer questions: *is it time to change SOC?* For which diseases, and with what caveats?

*Most relevant to AAV*
AAV – what are they?

- Wegener’s granulomatosis – now known as granulomatosiis with polyangiitis (GPA)
- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA)

All life-threatening, each targets vessels and…..
FIGURE. Proteinase-3 (PR3)-ANCA and myeloperoxidase (MPO)-ANCA are key findings. On ethanol-fixed neutrophils, PR3-ANCA cause a characteristic cytoplasmic granular centrally accentuated immunofluorescence pattern, referred to as cANCA (middle), while MPO-ANCA causes a perinuclear immunofluorescence pattern, referred to as pANCA (right).

• MPA - Necrotizing arteritis … necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. *Inflammation centered on vessels, not granulomatous inflammation.*

• GPA – necrotizing *granulomatous* inflammation usually involving *upper* & lower respiratory tract, and necrotizing vasculitis … *granulomatous and non-granulomatous extravascular inflammation common.*
AAV - Distinctions

EGPA (CSS) – vascular and extravascular

– Why am I not going to include EGPA (CSS)?

– ANCA present in only 40%. What is better and more unique surrogate marker of this form of granulomatous vasculitis?
EGPA (CSS) – AAV? Only 40% ANCA+, 100% ...?
Unique approach to treatments for EGPA (CSS)

- **IL-5 high in CSS.** IL-5 amplifies eos production in BM, activates eos and prolongs survival

- Mepolizumab binds free IL-5 w/ high affinity & specificity; prevents association IL-5R on eos

- Preliminary data => studies planned for start in 2013
“Pilot studies”: Mepolizumab (GSK, anti-IL-5) in CSS


7 patients – monthly x 4 - 750 mg IV doses mepolizumab


10 patients - Stopped previous medication (3 Cyc, 4 MTX, 2 AZA, 1 MTX+LEF). 750mg mepolizumab i.v. Q4wks.
Churg Strauss treatment with anti-IL-5

Disease activity (BVAS)

No relapses on Mepolizumab
Stopped Mep, 7/8 relapses w/in 10 months

Secondary endpoint: eosinophil counts

EGPA (CSS) is very different c/w GPA and MPA

IL-5 blockade is not relevant to GPA and MPA
How similar are the other forms of AAV?

• GPA (WG)
• MPA
Granulomatosis with polyangiitis (WG)

Distinctions from MPA

Granulomatous vs. non-granulomatous path

Mass lesions due to WG
- Brain
- Renal
- Orbit
- Lung

Breast
- Prostate
- Ovary
- Parotid

CNS
- Otitis
  - Vestibular/auditory nerve injury
- Subglottic stenosis
- Endobronchial stenosis
- Myocarditis
- Pericarditis
- Endocarditis

Rhinitis/sinusitis
- Septal perforation
  - “Saddle nose”
- Oral and nasal ulcers

Pulmonary infiltrates
- Nodules
- Pleurisy

Glomerulonephritis
- Myalgias
- Arthritis/arthralgias
- Peripheral neuropathy

Skin
- Leucocytoclastic vasculitis
- Subcutaneous nodules
- Ulcers
- Gangrene

ANCA
- Usually cytoplasmic pattern
- Anti-PR3 >>> MPO

CCF © 1999
Nasal turbinates – active disease

GPA (WG), not MPA
GPA (WG), not MPA
Medial lid destruction and ethmoid-cutaneous fistula

GPA (WG), not MPA
GPA (WG), not MPA

either
FIGURE. Computed tomography demonstrating two radiographic presentations of granulomatosis with polyangiitis (Wegener's granulomatosis): (A) cavitary lung disease; (B) bilateral ground glass infiltrates in a patient with alveolar hemorrhage.
GPA (WG), not MPA
GPA (WG), not MPA

Subglottic stenosis
Lung biopsies – vasculitis
- Granulomatous + extravascular (GPA)
- Only vasculitis
  (MPA, but could also be GPA)
How similar are the other forms of AAV?

- GPA (WG)
- MPA
GPA and MPA genetically distinct autoimmune syndromes. Strongest assoc w/ Ag specific target of ANCA, not clinical syndrome. Anti–PR 3 ANCA assoc w/ HLA-DP (rs3117242 (G) (P = 6.2×10^{-89}) & gene encoding α1-antitrypsin (P = 2.6×10^{-7}). Anti–MPO w/ HLA-DQ (rs5000634) (P = 2.1×10^{-8})
“…fact that PR3–ANCA and MPO-ANCA polyangiitis have distinct genetic causes suggests that clinical trials that have considered AAV as a single entity must be interpreted carefully, since subsets defined by ANCA specificity may respond differently to therapeutic intervention.”

(Dr. Gary Hoffman emphasis)

Also see “ANCA vasculitis: to lump or split? Why we should study MPA and GPA separately”. RA Watts and DGI Scott. Rheumatology. 2012. 51: 2115-17.
Treatment

The legacy – started with WG

The present

The future
## Wegener’s granulomatosis: outcomes

### Milestones

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mean survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>50% at 5 months (&lt;1960)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>50% at 1 year (1960–)</td>
</tr>
<tr>
<td>Glucocorticoids + cyclophosphamide</td>
<td>80% at 8 years (&gt;1970)</td>
</tr>
<tr>
<td></td>
<td>F/U</td>
</tr>
</tbody>
</table>
### TABLE 1
Cyclophosphamide-related treatment outcomes¹

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent morbidity</td>
<td>100%</td>
</tr>
<tr>
<td>Disease-related morbidity</td>
<td>86%</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>42%</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>35%</td>
</tr>
<tr>
<td>Nasal deformities</td>
<td>28%</td>
</tr>
<tr>
<td>Tracheal stenosis</td>
<td>13%</td>
</tr>
<tr>
<td>Visual loss</td>
<td>8%</td>
</tr>
<tr>
<td>Disease and/or treatment-related morbidity</td>
<td></td>
</tr>
<tr>
<td>Chronic sinus dysfunction</td>
<td>47%</td>
</tr>
<tr>
<td>Pulmonary insufficiency</td>
<td>17%</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>42%</td>
</tr>
<tr>
<td>Infertility</td>
<td>57%</td>
</tr>
<tr>
<td>Cystitis</td>
<td>43%</td>
</tr>
<tr>
<td>Hair loss</td>
<td>17%</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>3%</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>2%</td>
</tr>
<tr>
<td>Risk of bladder cancer</td>
<td>33-fold increase</td>
</tr>
<tr>
<td>Risk of lymphoma</td>
<td>11-fold increase</td>
</tr>
<tr>
<td>Relapse</td>
<td>50%</td>
</tr>
</tbody>
</table>
Nasal collapse
Anosmia
Aguesia
Deafness
Cataracts
Diabetes
Myopathy
Cystitis
Sterility
OIs
(Cancer)
# Microscopic polyangiitis (MPA): outcomes


## Intervention

<table>
<thead>
<tr>
<th>None (&lt;1960)</th>
<th>No clean data, pulm-renal syndrome usually fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pulm hemorrhage RR death = 8.64</td>
</tr>
</tbody>
</table>

## Treatment

<table>
<thead>
<tr>
<th>85% remission w/ CYC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of death decreased 5.56 fold (RR 0.18) if Rx included CYC vs. GCS only; REL hi w/ GCS only</td>
</tr>
</tbody>
</table>
Agreed – CYC is an effective agent, but extended use should be avoided.

Alternative Rx to chronic CYC…..
Biologic agents

Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis

Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis

RITUXVAS

RAVE
basis for FDA approval for severe AAV in 2011
197 Eligible patients underwent randomization

99 Were assigned to receive rituximab plus placebo
- 17 Did not complete treatment
  - 7 Had early treatment failure
  - 6 Crossed over
  - 8 Switched to nonstudy regimen
  - 6 Were dropped from the study
  - 82 Remained on assigned treatment at 6-mo follow-up
  - 8 Did not complete treatment
    - 4 Switched to nonstudy regimen
    - 4 Switched to open-label therapy
  - 74 Remained on assigned treatment at 12-mo follow-up
    - 13 Did not complete treatment
      - 3 Switched to nonstudy regimen
      - 10 Switched to open-label therapy
      - 3 Were dropped from the study
      - 61 Remained on assigned treatment at 18-mo follow-up

98 Were assigned to receive cyclophosphamide–azathioprine plus placebo
- 20 Did not complete treatment
  - 2 Had early treatment failure
  - 8 Crossed over
  - 7 Switched to nonstudy regimen
  - 8 Were dropped from the study
  - 78 Remained on assigned treatment at 6-mo follow-up
  - 11 Did not complete treatment
    - 4 Switched to nonstudy regimen
    - 4 Switched to open-label therapy
    - 1 Was dropped from the study
  - 67 Remained on assigned treatment at 12-mo follow-up
    - 4 Did not complete treatment
      - 1 Switched to nonstudy regimen
      - 3 Switched to open-label therapy
      - 1 Was dropped from the study
    - 63 Remained on assigned treatment at 18-mo follow-up
<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>Rituximab (N=99)</th>
<th>Cyclophosphamide–Azathioprine (N=98)</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td>percentage points (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>63 (64)</td>
<td>52 (53)</td>
<td>11 (-3 to 24)</td>
<td>0.13</td>
</tr>
<tr>
<td>12 mo</td>
<td>47 (47)</td>
<td>38 (39)</td>
<td>9 (-5 to 22)</td>
<td>0.22</td>
</tr>
<tr>
<td>18 mo</td>
<td>39 (39)</td>
<td>32 (33)</td>
<td>7 (-7 to 20)</td>
<td>0.32</td>
</tr>
<tr>
<td>Remission and &lt;10 mg/day of prednisone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>70 (71)</td>
<td>60 (61)</td>
<td>10 (-4 to 23)</td>
<td>0.16</td>
</tr>
<tr>
<td>12 mo</td>
<td>59 (60)</td>
<td>60 (61)</td>
<td>-2 (-15 to 12)</td>
<td>0.82</td>
</tr>
<tr>
<td>18 mo</td>
<td>54 (55)</td>
<td>52 (53)</td>
<td>2 (-12 to 15)</td>
<td>0.84</td>
</tr>
<tr>
<td>Complete remission at any time†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>76 (77)</td>
<td>70 (71)</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Remission and &lt;10 mg/day of prednisone at any time‡</td>
<td></td>
<td></td>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td>Remission at any time‡</td>
<td></td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>Complete remission in patients with relapsing disease at baseline†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo</td>
<td>34/51 (67)</td>
<td>21/50 (42)</td>
<td>25 (6 to 44)</td>
<td>0.01</td>
</tr>
<tr>
<td>12 mo</td>
<td>25/51 (49)</td>
<td>12/50 (24)</td>
<td>25 (7 to 43)</td>
<td>0.009</td>
</tr>
<tr>
<td>18 mo</td>
<td>19/51 (37)</td>
<td>10/50 (20)</td>
<td>17 (0 to 34)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Estimated creatinine clearance**

<table>
<thead>
<tr>
<th></th>
<th>Total cohort</th>
<th>Patients with major renal disease¶</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 mo</td>
</tr>
<tr>
<td></td>
<td>76.83±3.77</td>
<td>78.59±3.75</td>
</tr>
<tr>
<td>6 mo</td>
<td></td>
<td>91.56±3.75</td>
</tr>
<tr>
<td>12 mo</td>
<td></td>
<td>93.14±3.73</td>
</tr>
<tr>
<td>18 mo‖</td>
<td></td>
<td>96.30±4.12</td>
</tr>
</tbody>
</table>

*Data are from patients with complete baseline data, unless otherwise stated.
†Data are based on an intent-to-treat analysis.
‡Data are based on an on-treatment analysis.
§Data are based on an on-treatment analysis for patients with relapsing disease at baseline.
¶Data are based on an intent-to-treat analysis for patients with major renal disease.

**Units:** milliliters per minute
### Table 2. Adverse Events through 18 Months.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rituximab (N = 99)</th>
<th>Cyclophosphamide–Azathioprine (N = 98)</th>
<th>Total (N = 197)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of participant-months</td>
<td>1371.5</td>
<td>1331.9</td>
<td>2703.4</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of events</td>
<td>1399</td>
<td>1420</td>
<td>2819</td>
<td></td>
</tr>
<tr>
<td>Participants with ≥1 event — no. (%)</td>
<td>98 (99)</td>
<td>98 (100)</td>
<td>196 (99)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Events/participant-mo</td>
<td>1.02</td>
<td>1.07</td>
<td>1.04</td>
<td>0.24</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of events</td>
<td>59</td>
<td>63</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Participants with ≥1 event — no. (%)</td>
<td>42 (42)</td>
<td>37 (38)</td>
<td>79 (40)</td>
<td>0.50</td>
</tr>
<tr>
<td>Events/participant-mo</td>
<td>0.04</td>
<td>0.05</td>
<td>0.05</td>
<td>0.63</td>
</tr>
<tr>
<td>Deaths — no. (%)†</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>4 (2)</td>
<td></td>
</tr>
<tr>
<td>Participants with ≥1 episode of leukopenia of grade 2 or higher — no. (%)</td>
<td>5 (5)</td>
<td>23 (23)</td>
<td>28 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Participants with ≥1 episode of infection of grade 3 or higher — no. (%)</td>
<td>12 (12)</td>
<td>11 (11)</td>
<td>23 (12)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Pneumonia-related adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of events</td>
<td>4</td>
<td>11</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Participants with ≥1 episode of pneumonia — no. (%)</td>
<td>3 (3)</td>
<td>11 (11)</td>
<td>14 (7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pneumonia-related adverse events / participant-mo</td>
<td>0.0029</td>
<td>0.0083</td>
<td>0.0055</td>
<td>0.08</td>
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</tbody>
</table>
RAVE – Clinical Outcomes for Severe ANCA-Associated Vasculitis

Miloslavsky EM et al. RAVE/ITN Research Group (submitted; ACR 2012)

- 197 pts: GPA & MPA - 1st end-point – remission and  GCS-free at 6mos
- RTX vs. CYC/AZA for remission induction: (64% vs. 53%, NS)

  In 1st 6 mos – 82/197 (42%) failed 1st outcome (GPA>MPA), but
  - 86% pts achieved remission, regardless of pred dose
  - 3 deaths (1.5%)
  - 5% uncontrolled disease (10 pts, all PR3+, all GPA)
  - 19% relapses (PR3+ > MPO+)
  - ANCA & B-cell detection - poor predictors of relapses & remission
Mean BVAS/WG by Treatment Group

Month 0 1 2 4 6

RTX: 99 CYC/AZA: 98
RTX: 95 CYC/AZA: 94
RTX: 91 CYC/AZA: 90
RTX: 88 CYC/AZA: 89
RTX: 85 CYC/AZA: 81
**Comparison of Rituximab vs. Cyclophosphamide**

- **New disease**
  - Rituximab: 60.4%
  - Cyclophosphamide: 64.6%
  - $P = 0.67$

- **Severe flare**
  - Rituximab: 66.7%
  - Cyclophosphamide: 42.0%
  - $P = 0.013$

Sample sizes:
- New disease: $n = 96$
- Severe flare: $n = 101$
What if you give Rituximab repeatedly?

Single center study – Cambridge – 73 pts
- Premise – most pts who respond to RTX will ultimately relapse
- Providing regularly scheduled re-treatment may be superior than treating relapses when they occur
- **Different eras** - patients with GPA (75%) and MPA.

28pts – Rx w/ ritux if relapsed
Concurrent GCS + other ISRx
2002-2006

45pts – Q6 mo ritux
Concurrent GCS + other ISRx
2006-2010

90% both gps achieved initial RTX-induced complete or “partial” remission
Rituximab regimens

Non-protocolized re-treatment 2002-2006
375mg/m² x 4 or 1g x 2
Re-treatment based on clinical relapse

Protocolized re-treatment 2006-2010

Immunosuppressive agents other than GCS withdrawn at time 0 and steroids tapered
RTX per schedule vs. per indication

- No significant difference in rate of **serious infections** (18% RTX per indication vs. 14% per RTX 6 mos schedule)
- No difference in **deaths** (3%@gp) or
- Malignancies – 0% RTX by indication vs. Q6 mos - 4%.

Caution: numbers are small

Sets stage for large international multicenter RCT (2013).
FVSG – 1st RCT of repeated RTX c/w conventional treatment - “Maintenance of remission using rituximab in systemic ANCA-associated vasculitis.” = MAINRITSAN. Guillevin L et al. ACR 2012. For FVSG.

- Enrolled after REM w/ traditional agents.
- 114 pts: GPA (#86), MPA (#23), RLV (#5).
- RTX gp - retreatment Q6 mos (500mg, 5x over 18 mos) vs. maintenance AZA (2mg/kg/d x 22 mos)
- 1st endpoint = major relapses @ 28 mos. (Interim analysis: 74% pts completed 28 mos)
Maintenance treatment

R = 500 mg of rituximab

Azathioprine 2 mg/kg/d then tapered 22 mo

Endpoint 28 mo

2 wk 5 mo + 6 mo 6 mo
**MAINRITSAN.** Guillevin L et al.

Major relapses: 5% RTX vs. 25% AZA

SAEs: AZA 51% vs. 50% RTX

Deaths 5% AZA, 0 RTX
RTX – suggested use based on current knowledge

- **Consider as Rx of choice for induction of remission in:**
  - Reproductive age, severe dis, **fertility** is important concern.
  - In pts for whom CYC utilized in past, with severe relapse

- **Maintenance therapy** consider for pts w/ prior RTX-mediated complete remission of ≥ 6 mos.
  - And who have had severe critical organ damage & in whom further damage is likely to cause profound disability or death (CRF, CLD, sight-threatening eye disease or CNS involvement).
RTX – unknowns in GPA and MPA

- Most effective dose and intervals.

Q6 mo has been very effective (500-1000mg)

- Long-term risks of many years of RTX in AAV.
FIGURE 5. Brain magnetic resonance image of a patient with progressive multifocal leukoencephalopathy.
Provisos

- **GPA, MPA, CSS and RLV** should be studied separately.
  - Not clear if need for re-Rx is same in all.
  - RTX + GCS *not adequately evaluated in immediately life-threatening-diseases.*
  - In this setting CYC + GCS has been organ and life-saving.
  - For pts in whom relapses are likely to cause profound disability or death, *extreme caution is advised when successful maintenance therapy of any kind is discontinued.*
Long-term safety of RTX -
Is data from RA relevant to GPA and MPA?
Long-term safety of RTX in RA


3194 pts Rx w/ up to 17 rituximab courses w/ F/U up to 9.5 yrs

- Ig: 22.4% RTX pts - low IgM, 3.5% low IgG & 1.1% low IgA for ≥4 months after ≥1 course.

- No increases in infections during/after time of low IgM or IgG
In 20 years we have learned to achieve remissions more safely and have dramatically reduced SAEs in GPA and MPA.

- **Chronic long-term CYC therapy is no longer justified.**
- Limited CYC use continues to be life-saving, albeit not without significant risks.
- RTX is preferred treatment in several settings.
- GPA & MPA are **clinically, pathologically, serologically & genetically** different and should be studied separately.
Thank You...