Current clinical research in ANCA glomerulonephritis
With regards to the study and treatment of lupus nephritis, who is my #1 hero?

A. Ellen Ginzler, M.D.
B. Brad H. Rovin, M.D.
C. Michelle Petri, M.D.
D. Mary Anne Dooley, M.D.
MAIN OBJECTIVES

1. Identify best practices for diagnosing ANCA vasculitis

2. Adopt methods to detect ANCA vasculitis early and prevent renal deterioration
OUR PLAN…

1. Stress the importance of professional families

2a. Present several practical cases of import with ?s

2b. Sprinkle evidence on components of each case

2c. Highlight super hot clinical topics within each case

3. Provide several practical RITUXITIPS
ANTI-NEUTROPHIL CYTOPLASMIC AUTOANTIBODIES WITH SPECIFICITY FOR MYELOPEROXIDASE IN PATIENTS WITH SYSTEMIC VASCULITIS AND IDIOPATHIC NECROTIZING AND CRESCENTIC GLOMERULONEPHRITIS

Ronald J. Falk, M.D., and J. Charles Jennette, M.D.
Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis

Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease

Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis
(Anti-C1q Vasculitis)

Anti-GBM Disease

ANCA-Associated Small Vessel Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis (GPA)
(formerly Wegener’s)
Eosinophilic Granulomatosis with Polyangiitis (eGPA)
(formerly Churg-Strauss syndrome)

ANCA VASCULITIS

3 keys to therapeutic success:

1. START TREATMENT EARLY!
2. START TREATMENT EARLY!
3. START TREATMENT EARLY!

Quote from John L. Niles, M.D.
Entry serum creatinine predicts ESKD in ANCA vasculitis

Hogan JASN 1996
Cumulative Survival

With Pulmonary Hemorrhage

Survival Time (years)

Pulmonary Hemorrhage

- Yes
- No

Bottinger et al
ANCA VASCULITIS

EARLY TREATMENT DEPENDS ON EARLY DIAGNOSIS

1. Recognize clinical features
2. Check for ANCA positivity
3. Obtain tissue diagnosis if possible

Quote from John L. Niles, M.D.
Age distribution of patients with ANCA vasculitis

Proportion of the Group (%)

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>1.2</td>
</tr>
<tr>
<td>10-19</td>
<td>4.3</td>
</tr>
<tr>
<td>20-29</td>
<td>7.2</td>
</tr>
<tr>
<td>30-39</td>
<td>10.9</td>
</tr>
<tr>
<td>40-49</td>
<td>12.3</td>
</tr>
<tr>
<td>50-59</td>
<td>18.7</td>
</tr>
<tr>
<td>60-69</td>
<td>28.5</td>
</tr>
<tr>
<td>70-79</td>
<td>23.9</td>
</tr>
<tr>
<td>80+</td>
<td>3.9</td>
</tr>
</tbody>
</table>

UNC Kidney Biopsy Service 1980-2009, n=1175

Courtesy of SL Hogan and Y Hu, UNC Kidney Center
Early clinical features of ANCA vasculitis

- Non-specific
  - malaise, myalgia, arthralgia
  - anorexia
  - cough, rhinitis

- Unresponsive to multiple rounds of airway antibiosis

- Hemoptysis and shortness of breath may be first specific clinical feature

- Microscopic hematuria (often with RBC casts) may be the first available clue!
THE CASE OF THE SWEDISH DUCK

HISTORY OF PRESENT ILLNESS:

66 year old gentleman…

December 26\textsuperscript{th}: unable to complete sentences and hoarse

December 28\textsuperscript{th}: went to PCP reporting dyspnea and cough
- CTA chest revealed bilateral patchy opacities
- antibiotics started for atypical pneumonia

January 7\textsuperscript{th}: symptoms persist → admitted to local hospital
- bronchoscopy unrevealing, discharged with antibiotics

January 18\textsuperscript{th}: urgent vasculitis clinic appointment
- persistent fatigue
- intermittent febrility (100.6-101.2° C)
- constant non-productive coughing spasms
- right maxillary sinus pressure
- daily tissue-like bloody discharge from nose
- daily diarrhea, no appetite, 20 pound weight loss
PAST MEDICAL HISTORY:

HTN: diagnosed 2004
HYPERLIPIDEMIA
ARTHRITIS: long-standing, etiology unclear
s/p 1973 surgery for annular pancreas
s/p November 2011 tick bite x 2 treated with doxycycline
- serologies unrevealing about which he perseverates

MEDICATIONS:

Amlodipine 5 mg PO daily
B12 2000 mcg PO daily
Lisinopril/HCTZ 20/12.5 PO daily
ASA 81 mg PO daily
Omeprazole 40 mg PO daily
Simvastatin 60 mg PO daily
Testosterone injection SC Q2weeks
Celebrex 200 mg PO daily
THE CASE OF THE SWEDISH DUCK

ALLERGIES: none known

FAMILY HISTORY:
Mom: thyroid removed at age of 50, HTN
Dad: died at 64 from complications related to long-standing arthritis

SOCIAL HISTORY: married, two kids, works as international IT director for pharmaceutical GIANT
- tobacco: quit in 1979
- EtOH: denies
- illicits: denies (even with wife absent when asked “WHEN” not “IF”)
- tattoos: denies
- transfusions: denies
- birth weight: “over 8 pounds” at “38 weeks or so”
PHYSICAL EXAM:

**VITALS:** 162 lbs (down from baseline of 185 per patient) 96.3 68 110/72 20 100% RA

**GENERAL:** ill-appearing, NAD, medium frame, pleasant, professional

**HEENT:** anicteric, moist membranes, good dentition, no lymphadenopathy

**CV:** warm and well-perfused, no JVD, PMI non-displaced, normal S1/S2, rrr, no audible mrg, no appreciable edema

**PULM:** scattered rhonchi and basilar rales

**ABDOMEN:** scaphoid, old midline surgical scar c/d/i, +bs, soft, nt, nd

**NEURO/MSK:** strength and sensation grossly intact, no asterixis

**GU:** no CVA tenderness

**SKIN:** male pattern baldness, no visible rash
THE CASE OF THE SWEDISH DUCK

RELEVANT LABS FROM OUTSIDE HOSPITAL:

Cr 1.5 (up from 0.75 three weeks prior)
Rheumatoid Factor 8
ESR 74
PPD and infectious work-up negative to date
LABORATORY VALUES

AG = 18, albumin = 3.5  (baseline Cr 0.9)

URINALYSIS: 1.009/5.0, 3+ blood, 1+ protein
spot UPC ratio = 0.35

ANA, dsDNA, lupus anticoagulant: negative    C3 145 (86-184), C4 18 (16-38)
HBV sAg/sAb negative, HCV negative, HIV negative, ARMPIT cryos negative

RENAL ULTRASOUND: unremarkable, no hydronephrosis

ANCA test: C-ANCA positive by IF  →  PR3-ANCA titer 4045
IMMUNOFLUORESCENCE MICROSCOPY OF ETHANOL-FIXED HUMAN NEUTROPHILS
ONE ANCA VASCULITIS INDUCTION OF REMISSION REGIMEN

1. CYCLOPHOSPHAMIDE
   - 4 mg/kg PO daily x 1 week*
   - 2 mg/kg PO daily x 7 weeks
     
     **CrCl 40-60 cc/min (reduce dose by 25%)**
     **CrCl 20-39 cc/min (reduce dose by 33%)**
     **CrCl <20 cc/min (reduce dose by 50%)**

     NOTE: PO:IV equivalency (IV if non-compliant)

     * use 2 mg/kg PO daily x 8 weeks if
     1) on rituxan and 2) non-organ-threatening disease as defined in #4 below.

2. PREDNISONE
   - 1000 mg IV daily x 3 days
   - 60 mg PO Q12h x 4 days
   - 60 mg PO daily x 1 week
   - 40 mg PO daily x 1 week
   - 30 mg PO daily x 1 week
   - 20 mg PO daily x 1 week
   - 15 mg PO daily x 1 month
   - 12.5 mg PO daily x 1 month
   - 10 mg PO daily x 1 month
   - 7.5 mg PO daily x 1 month
   - 5.0 mg PO daily x 1 month
   - 2.5 mg PO daily x 1 month
   - 2.5 mg PO every other day x 1 month

3. RITUXIMAB: DOSE 1: 1 gram IV x 1 during week 1, DOSE 2: 1 gram IV x 1 within three weeks after DOSE 1
   - 1 gram IV x 1 Q4 months after DOSE 2 x 2 years thereafter followed by Q6 months (hold if IgG < ½ lower limit of normal)

4. PLASMA EXCHANGE: performed if severe renal and/or pulmonary involvement (7 exchanges over 10-12 days)
   - severe involvement defined as Cr > 5 and/or dialysis-dependence for no more than 2 weeks and/or alveolar hemorrhage
   - NOTE: will also be performed for 2.5-fold increase in ANCA titer and/or doubling of serum creatinine within one week of presentation
Should we offer plasma exchange?

A. Yes because his life expectancy over 10 years will be improved with this treatment modality
B. Yes because his life expectancy over the first 12 months after plasma exchange will be improved with this treatment modality
C. Yes because his likelihood of reaching ESRD will be significantly less over the first year if we do
D. No because corticosteroids are equally effective as an alternative.
WHY DO WE USE PLASMA EXCHANGE?

THE MEPEX TRIAL 137 patients with ANCA vasculitis and Cr > 5.8 mg/dL

treatment arms: plasma exchange x 7 sessions OR IV methylprednisolone

Jayne and colleagues. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. JASN 18(7): 2180-8, 2007.
WHY DO WE USE PLASMA EXCHANGE?

THE MEPEX TRIAL: LONG-TERM OUTCOMES

Graph showing survival analysis with time in years and proportion free of ESRD or death. The number at risk for each group is provided:

- IV MeP: 68, 25, 23, 15, 7, 1
- PLEX: 69, 32, 26, 13, 6, 0

The PEXIVAS trial (ongoing)

Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasmic autoantibody-associated vasculitis (n=500)

Figure 1 General schema of treatment allocation.
How do we administer cyclophosphamide?

A. IV
B. PO
C. IM
D. A or B
EFFEY OF CYCLOPHOSPHAMIDE UPON THE IMMUNE RESPONSE IN WEGENER'S GRANULOMATOSIS

Anthony S. Fauci, M.D., Sheldon M. Wolff, M.D., and John S. Johnson, M.D.

Abstract Nine patients with Wegener's granulomatosis were studied before and after treatment with cyclophosphamide alone. The study was undertaken to determine any immunologic abnormalities associated with the disease, to observe the effect of cyclophosphamide on the clinical course, as well as on the immune response in man, and to observe any correlation between clinical response and immunosuppression. Untreated patients had elevated mean serum IgA levels of 470 as compared with 200 mg per 100 ml in normal controls and elevated mean parotid-fluid secretory IgA levels of 4.7 as compared with 1.8 mg per 100 ml in normal controls. Seven of nine patients receiving cyclophosphamide had undetectable humoral and delayed hypersensitivity responses to a new antigenic stimulus, and five of the seven retained previously established delayed hypersensitivity. A favorable clinical response to cyclophosphamide and immunosuppression appeared to be correlated.
Table 1. Clinical Data on Nine Patients with Wegener's Granulomatosis Treated with Cyclophosphamide Alone.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (Yr)</th>
<th>Sex</th>
<th>Extent of Disease before Treatment*</th>
<th>Interval from Onset of Disease to Study (Mo)</th>
<th>Dose of Cyclophosphamide (Mg/DAY)†</th>
<th>Duration of Treatment (Mo)</th>
<th>Clinical Status at Time of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td>59</td>
<td>F</td>
<td>Renal, pulmonary, sinus, nasal septum</td>
<td>20</td>
<td>125</td>
<td>1</td>
<td>Partial remission</td>
</tr>
<tr>
<td>PD</td>
<td>25</td>
<td>M</td>
<td>Renal, pulmonary, sinus</td>
<td>12</td>
<td>100</td>
<td>9</td>
<td>Complete remission</td>
</tr>
<tr>
<td>MG</td>
<td>44</td>
<td>M</td>
<td>Renal, pulmonary</td>
<td>25</td>
<td>125</td>
<td>25</td>
<td>Complete remission</td>
</tr>
<tr>
<td>GW</td>
<td>63</td>
<td>F</td>
<td>Renal, pulmonary, nasopharynx</td>
<td>44</td>
<td>50</td>
<td>39</td>
<td>Complete remission</td>
</tr>
<tr>
<td>JT</td>
<td>28</td>
<td>F</td>
<td>Pulmonary, nasopharynx</td>
<td>50</td>
<td>75</td>
<td>15</td>
<td>Focal glomerulitis developed during therapy</td>
</tr>
<tr>
<td>LD</td>
<td>63</td>
<td>F</td>
<td>Renal, pulmonary, sinus</td>
<td>33</td>
<td>50</td>
<td>20</td>
<td>Complete remission</td>
</tr>
<tr>
<td>ET</td>
<td>43</td>
<td>M</td>
<td>Renal, pulmonary, sinus, parotid gland, skin, tympanic membrane</td>
<td>40</td>
<td>50</td>
<td>29</td>
<td>No active disease; end-stage renal disease; patient maintained on hemodialysis.</td>
</tr>
<tr>
<td>AS</td>
<td>37</td>
<td>M</td>
<td>Pulmonary</td>
<td>22</td>
<td>50</td>
<td>15</td>
<td>Complete remission</td>
</tr>
<tr>
<td>HS</td>
<td>34</td>
<td>M</td>
<td>Pulmonary, sinus</td>
<td>18</td>
<td>125</td>
<td>1</td>
<td>Partial remission</td>
</tr>
</tbody>
</table>

*All patients had renal biopsies; 5 of 9 had lung biopsies, all of which showed granulomatous arteritis; all patients had pulmonary infiltrates on chest x-ray study.
†All patients were treated with 100-125 mg of cyclophosphamide/day early in the course of their disease; doses given are those at time of study.
The CYCLOPS trial

**Article**

*Annals of Internal Medicine*

**Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Randomized Trial**

Kirsten de Groot, MD; Lorraine Harper, MD, PhD; David R.W. Jayne, MD, PhD; Luis Felipe Flores Suarez, MD, PhD; Gina Gregorini, MD; Wolfgang L. Gross, MD; Rashid Laqmani, MD; Charles D. Pusey, MD, PhD; Niels Rasmussen, MD; Renato A. Sinico, MD; Vladimir Tesar, MD, PhD; Philippe Vanhille, MD; Kerstin Westman, MD, PhD; and Caroline O.S. Savage, MD, PhD, for the EUVAS (European Vasculitis Study Group)

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**Entry**
(diagnosis of generalised, previously untreated AASV, creatinine > 150 < 500)

↓

**Randomisation**
(80 patients per limb)

↓

**daily oral CYC**
(2mg/kg/day)

↓

**pulse CYC**
(15mg/kg every 2-3 weeks)

↓

**Induction phase**
(continue CYC until remission + 3 months, minimum 6 months, maximum 12 months)

↓

**Remission maintenance phase**
(start azathioprine, 2mg/kg, at remission + 3 months)
( evaluations every 3 months)

↓

**Study end**
(18 months)
Pulse vs Daily Cyclophosphamide (long-term)

Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA vasculitis

- 140 patients across 25 centers
  - key exclusion criteria: requiring dialysis or eGFR < 15 ml/min, rapidly declining renal function and/or immediately life-threatening disease
- **Primary Outcome**: remission within 6 months (sustained BVAS=0 and GC taper adherence)

<table>
<thead>
<tr>
<th></th>
<th>MMF n=70</th>
<th>IV CYC n=70</th>
<th>Difference (90% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>46 (66%)</td>
<td>48 (69%)</td>
<td>-3% (-16 to 10)</td>
<td>0.06</td>
</tr>
<tr>
<td>Secondary</td>
<td>61 (87%)</td>
<td>54 (77%)</td>
<td>10% (-1 to 21)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

PRESENTLY…

FEELING “GREAT”

JUST FINISHED CROSS COUNTRY ROAD TRIP

Cr 1.6

PR3-ANCA titer: 4045 → 1127 → 666 → 102 → 90
The risk of relapse is not uniform among all patients with ANCA-vasculitis.

<table>
<thead>
<tr>
<th>Consistent Predictors of Relapse</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR3-ANCA</td>
<td>1.87 (1.1, 3.1)</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>1.71 (1.04, 2.8)</td>
</tr>
<tr>
<td>Upper respiratory involvement</td>
<td>1.73 (1.04, 2.9)</td>
</tr>
<tr>
<td>With all of the above</td>
<td>3.7 (1.4, 9.7)</td>
</tr>
</tbody>
</table>

A 56 year old woman with HTN treated with carvedilol and hydralazine presents with 3 months of arthralgias and night sweats and is found to have Cr = 2.1 mg/dL (baseline 0.9 mg/dL) and glomerular hematuria.

Additional testing: MPO-ANCA titer = 11,000 units (anti-GBM immunoblot is negative)

This patient most likely has:

A. granulomatosis with polyangiitis (GPA, formerly Wegener’s)
B. pulmonary-renal syndrome NOS
C. microscopic polyarteritis nodosum articulum
D. drug-associated ANCA vasculitis
Table 1. Clinical characteristics of ANCA vasculitis associated with hydralazine, minocycline, propylthiouracil (PTU) and levamisole-adulterated cocaine

<table>
<thead>
<tr>
<th></th>
<th>Hydralazine</th>
<th>Minocycline</th>
<th>PTU</th>
<th>Levamisole-adulterated cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for use</td>
<td>Hypertension</td>
<td>Acne vulgaris</td>
<td>Hyperthyroidism</td>
<td>Illicit euphoric agent</td>
</tr>
<tr>
<td></td>
<td>Heart failure</td>
<td>Tick-borne disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanism(s) of action</td>
<td>SM relaxation</td>
<td>Inhibits bacterial protein synthesis</td>
<td>Prevents TG iodination and T4 → T3 conversion</td>
<td>Serotonin-norepinephrine-dopamine reuptake inhibitor&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sex most affected</td>
<td>M &gt; F</td>
<td>M &gt; F</td>
<td>F &gt; M</td>
<td>M &gt; F</td>
</tr>
<tr>
<td>Age most affected</td>
<td>Middle-aged to elderly</td>
<td>Adolescents, young adults</td>
<td>Young to middle-aged adults</td>
<td>Middle-aged</td>
</tr>
<tr>
<td>Drug duration at time of disease onset</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td>Arthralgias, rash, dyspnea</td>
<td>PAN</td>
<td>Fever, arthralgias, rash, agranulocytosis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Fever, arthralgias, myalgias, painful and purpuric rash</td>
</tr>
<tr>
<td>Organs involved</td>
<td>S, L, K</td>
<td>S, A</td>
<td>S, J, L, K, H&lt;sub&gt;PMN&lt;/sub&gt;</td>
<td>S, J, UA, L, H&lt;sub&gt;PMN&lt;/sub&gt;, K</td>
</tr>
<tr>
<td>ANCA serotype</td>
<td>MPO-ANCA</td>
<td>MPO-ANCA</td>
<td>MPO-ANCA</td>
<td>MPO-ANCA and PR3-ANCA</td>
</tr>
<tr>
<td>ANCA IF pattern</td>
<td>Perinuclear</td>
<td>Perinuclear</td>
<td>Perinuclear</td>
<td>Perinuclear</td>
</tr>
<tr>
<td>MPO-ANCA and PR3-ANCA double positivity</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Very common</td>
</tr>
<tr>
<td>Antinuclear Abs (ANA)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-dsDNA Abs</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Antihistone Abs</td>
<td>+</td>
<td>-</td>
<td>+/−</td>
<td>Unknown</td>
</tr>
<tr>
<td>Antiphospholipid Abs</td>
<td>+/−</td>
<td>-</td>
<td>+/−</td>
<td>Unknown</td>
</tr>
<tr>
<td>Other ANCA autoantigens</td>
<td>HNE, lactoferrin</td>
<td>HNE, cathepsin G, BPI</td>
<td>HNE, lactoferrin, BPI, azurocidin, cathepsin G</td>
<td>HNE, cathepsin G, lactoferrin</td>
</tr>
<tr>
<td>Treatment</td>
<td>Withdrawal</td>
<td>Withdrawal</td>
<td>Withdrawal</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Extensive</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Continue drug?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Use drug in future?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Alternative agents</td>
<td>Any other class</td>
<td>Doxycycline</td>
<td>Methimazole</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Urine cocaine and levamisole</td>
</tr>
</tbody>
</table>

A, arteries; Abs, antibodies; BPI, bactericidal permeability increasing protein; F, female; H, hematologic compartment; HNE, human neutrophil elastase; IF, immunofluorescence; J, joints; K, kidney; L, lung; M, male; MPO, myeloperoxidase; PMN, polymorphonuclear leukocyte or neutrophil; PR3, proteinase 3; S, skin; SM, smooth muscle; TG, thyroglobulin; UA, upper airway +, present; −, absent; +/− can be present or absent.

<sup>a</sup>Cocaine's mechanism of action, levamisole mechanism of action = nematoide nicotnergic acetylcholine receptor antagonist.

<sup>b</sup>Agranulocytosis can occur in the absence of ANCA.

<sup>c</sup>Immediate immunosuppression warranted for organ-threatening disease.
Rituximab is FDA-approved for induction of remission for GPA and MPA.

How should we use rituximab to maintain durable remission?

A. 300 mg IV Q3 months based on recent results from the RITUXILOW trial.
B. 500 mg IV Q6 months once remission is achieved based on recent results from the MAINRITSAN1 trial.
C. 1000 mg IV Q6 months once remission is achieved based on the large retrospective single-center Re-Rhee study.
D. TBD
The Benefits of Rituxan

Learn how Rituxan can treat WG and MPA and put your disease into remission, as well as the potential side effects.

Learn More

Patient Stories

Listen to people talk about their experiences with WG and MPA.

Learn More  Share Your Story

Financial Services & Support

Learn more about Rituxan Access Solutions®, a resource that can help connect you to the medicine you need.

Learn More
EXCLUDED PATIENTS WITH:

1. Cr > 4.0 mg/dL and/or
2. pulmonary hemorrhage requiring ventilator support

PRIMARY ENDPOINT:
BVAS/WG = 0 with no prednisone at 6 months

RTX (n=99) 64%
CYC (n=98) 53%
non-inferiority p < 0.001
Efficacy of Remission-Induction Regimens for ANCA-Associated Vasculitis

Table 1. Efficacy Outcomes.*

<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>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>
</tbody>
</table>

Specks and colleagues, NEJM 369(5): 417-27, August 2013
Survival of ANCA vasculitis patients at MGH undergoing continuous B cell depletion mirrors the general population

Cumulative Survival (%)

Time from start of remission maintenance therapy (years)

Number at risk 172 140 102 69 49 24 7

Pendergraft et al. CJASN, 2014
The RITAZAREM trial (ongoing)

An international, open label, randomized controlled trial comparing rituximab with azathioprine as maintenance therapy in relapsing ANCA-associated vasculitis

(RECRUITMENT GOAL n=160)

**Induction**
- MP pulses d1–3
- 0.5 or 1 mg/kg
- CS 10 mg/d
- 3 mo
- ± Plasmapheresis

**Maintenance**
- Rituximab 1,000 mg
- Azathioprine 2 mg/kg/d (MTX or MMF)

**Timeline**
- 4 mo
- 18 mo
- 24 mo
- End point: 36 → 48
- Closure: last patient reaches 36 mo

Abbreviations: CS = corticosteroids; d = day; MMF = mycophenolate mofetil; mo = months; MP = methylprednisolone; MTX = methotrexate
The MAINRITSAN 1 trial

117 patients: 23 MPA, 89 GPA, 5 kidney-limited disease
- 93 newly diagnosed, 24 with relapsing disease
- 56% males

Induction treatment

- MPS 15 mg/kg
- CS 1 mg/kg/day
- 20 mg at 3 months
- 10 mg at 6 months

Maintenance treatment

- R = 500 mg of rituximab
- 2 weeks, 5 months, 6 months, 6 months
- Endpoint 28 months

Azathioprine 2 mg/kg/day then tapered 22 months

pCYC Day 0 0.6 g/m²
pCYC Day 14 0.6 g/m²
pCYC Day 28 0.6 g/m²
pCYC Day 3.49 0.7 g/m²
pCYC Day 70 0.7 g/m²
pCYC Day 91 0.7 g/m²

Figure 2. Event-free survival in azathioprine- and rituximab-treated groups

Azathioprine
Rituximab

CS = corticosteroids; MPS = methylprednisolone; R = rituximab; pCYC = pulse cyclophosphamide

The MAINRITSAN 1 trial

<table>
<thead>
<tr>
<th></th>
<th>Rituximab N=58</th>
<th>Azathioprine N=59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>3 (5.4%)</td>
<td>15 (24.5%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>15 (25.8%)</td>
<td>18 (30.5%)</td>
</tr>
<tr>
<td>Infections</td>
<td>11 (0 fatal)</td>
<td>12 (1 fatal)</td>
</tr>
</tbody>
</table>

Event free survival Rituximab >> Azathioprine, p=0.002
The MAINRITSAN 2 trial

ANCA status and CD19+ B cells monitored Q3 months and patients receive 500 mg RTX if the following occurs:
1. CD19>0/mm³ or 2. ANCA positive again or 3. ANCA titer rises significantly

ARM 1
- RTX
- d1
- d15

ARM 2
- RTX
- d1
- d15
- Month 6
- RTX
- Month 12
- RTX
- Month 18

http://clinicaltrials.gov/ct2/show/NCT01731561
RITUXITIPS!
Monday at 10:29 AM....

You return a page from the nurse in the transplant infusion clinic.

She tells you that a 24 year old woman with MPA is there for her second induction dose of rituximab.

The patient complains of an itchy throat and dry cough, and is currently in the bathroom (with IV pole and rituximab flowing) because she doesn’t feel very good.

What should we recommend to the nurse over the phone?

A. Stop RTX and re-attempt the following week
B. Stop the infusion and transition patient to azathioprine
C. Stop the infusion and transition patient to belimumab
D. Stop the infusion, wait for symptoms to subside and re-start RTX
Saturday at 10:29 AM....

A nice physician calls from a local ED.

He has a 23 year old woman with MPO-ANCA GPA in his ED who showed up with fatigue and a nagging sore throat.

The last vasculitis clinic note stated that she was in “durable rituximab-induced remission” (BVAS = 0, pBc < 0 cells/mm³, follow-up in 4 months).

Exam is unremarkable; however, ANC = 112 cells/mm³ (repeat identical)

What should we recommend to the physician on the phone?

A. ask patient to return in 2 days for repeat CBC with diff
B. give G-CSF (filgrastim) and re-check CBC with diff in 2 days
C. admit patient for monitoring
D. B and F
1. Educate patients and check CBC with differential:
   - every 2 months x 4 after any RTX infusion and
   - immediately at the onset of fever

2. If ANC < 1000 on repeat blood work and afebrile, then
   - Filgrastim (G-CSF, neupogen) 300 mcg SC x 1
   - repeat CBC with differential in 1-3 days

3. If ANC < 1000 and febrile, then NEUTROPENIC FEVER
   - admit, check cultures, administer antibiotics + filgrastim

4. If ANC < 1000 on multiple occasions, then STOP RTX
   - consider alternative remission maintenance agent(s)
THANKS!

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