Update on ANCA-Associated Vasculitis

Diagnosis, Management, and Other Strategies in Granulomatosis with Polyangiitis

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CME Disclosure Statements

Carol A. Langford, MD, MHS

Unlabeled use of commercial products

To date there is only one FDA approved agent for the treatment of granulomatosis with polyangiitis (GPA)

All other references to use of a commercial product for the treatment of GPA discussed in this presentation constitute an unlabeled use of the product

Speaker relationship to commercial products

Provide funding for clinical trials on which the speaker is an investigator
- Bristol-Myers Squibb
- Genentech
- GlaxoSmithKline
- ChemoCentryx

Non-paid consultant: Bristol-Myers Squibb, AbbVie, AstraZeneca

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Granulomatosis with Polyangiitis (GPA)
Topics for Today's Discussion

- Diagnostic approaches in GPA
- Treatment options in 2019
- Strategies for optimizing patient outcome
- GPA – what lies ahead

Let's think about these using questions / clinical scenarios

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Question 1:

Which of the following statements about diagnostic testing in granulomatosis with polyangiitis (GPA) is true ?

A. Nasal biopsy has > 30% positive yield to diagnose GPA

B. Transbronchial lung biopsy has > 30% positive yield to diagnose GPA

C. Surgical biopsy of radiographically abnormal lung has the highest positive yield to diagnose GPA

D. (+) PR3-cANCA has a positive predictive value equal to biopsy in a patient with sinus and lung disease

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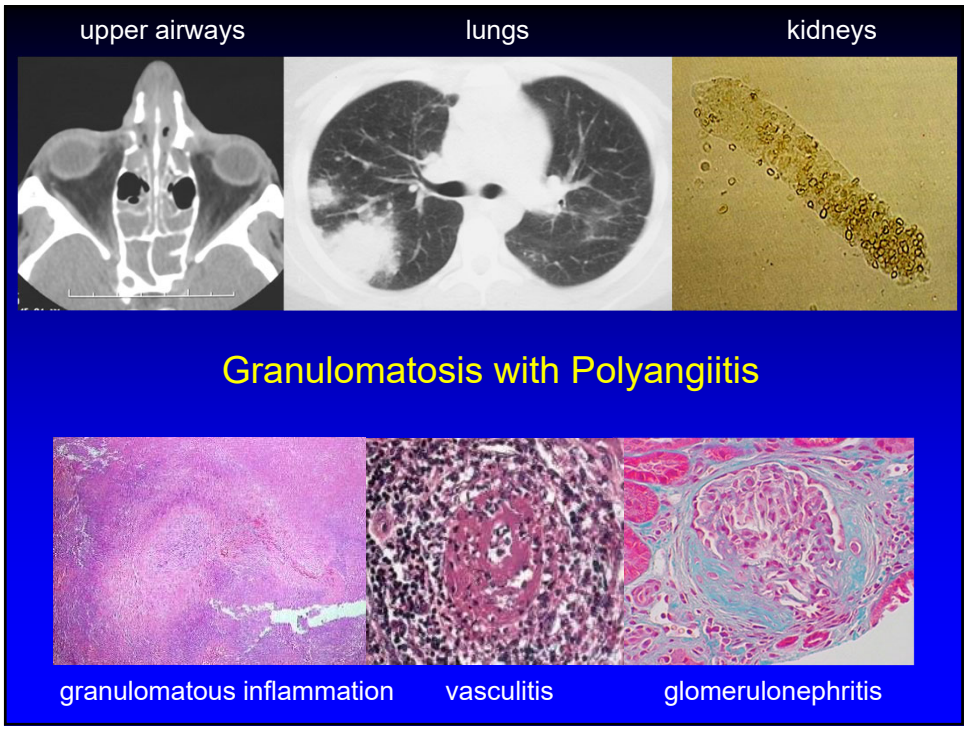
upper airways
lungs
kidneys
Granulomatosis with Polyangiitis
granulomatous inflammation
vasculitis
glomerulonephritis

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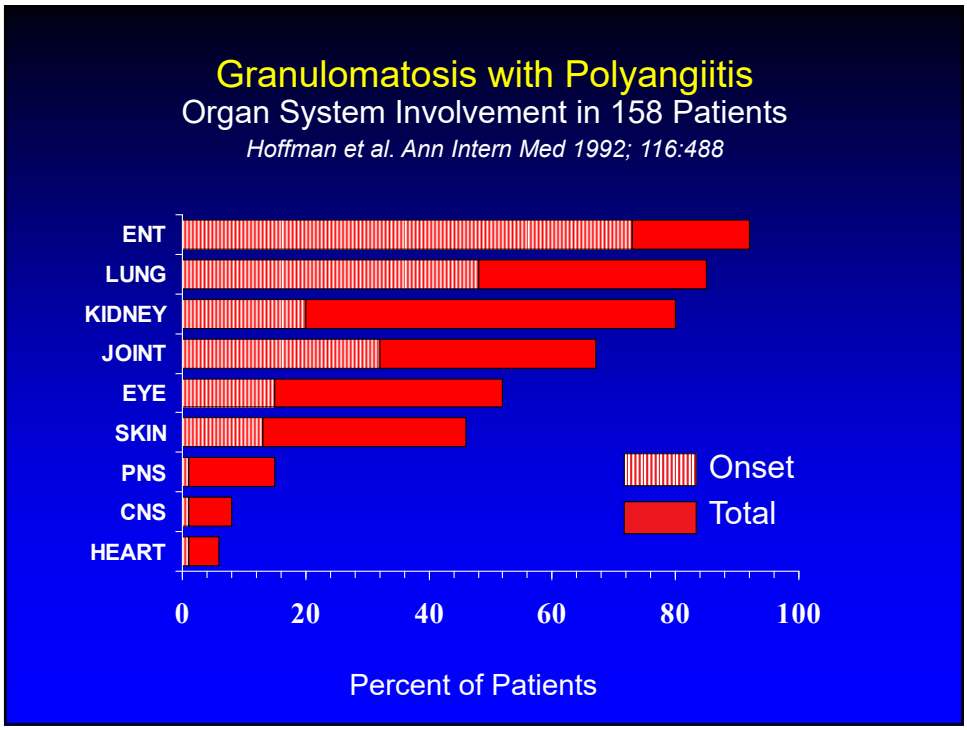
Granulomatosis with Polyangiitis
Organ System Involvement in 158 Patients
Hoffman et al. Ann Intern Med 1992; 116:488
ENT
LUNG
KIDNEY
JOINT
EYE
SKIN
PNS
CNS
HEART
Onset
Total
0
20
40
60
80
100
Percent of Patients

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Granulomatosis with Polyangiitis
Differential Diagnosis

- infection
- neoplasm / lymphoproliferative disease
- connective tissue disease
- granulomatous disease
- other causes of glomerulonephritis (when present)

Differentiation from GPA is essential
as the treatment is different in many instances

Diagnosis is made in a clinically compatible setting
often supported by specific histologic features

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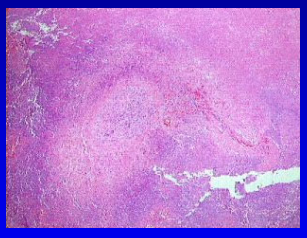
Granulomatosis with Polyangiitis
Diagnosis - Biopsy

Not all biopsies are diagnostic

- Presence of granulomas and/or vasculitis can be patchy
- Positive yield associated with the amount of tissue obtained

ENT	21%	sinus>nasal
Lung	91%	open lung biopsy
	7%	transbronchial biopsy
Kidney	focal, segmental, necrotizing glomerulonephritis with few to no immune deposits (pauci-immune)	
Skin	usually insufficient evidence for diagnosis cutaneous vasculitis can be seen in many settings	



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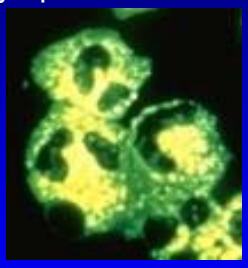
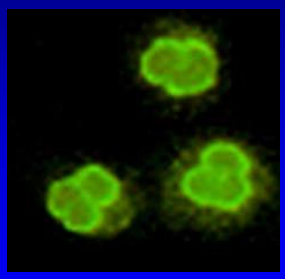
Antineutrophil Cytoplasmic Antibodies (ANCA)

cANCA
cytoplasmic staining



pANCA
perinuclear staining



Proteinase 3
(PR 3)

Target
Antigens
In Vasculitis

Myeloperoxidase
(MPO)

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	PR3-cANCA	MPO-pANCA	(-) ANCA
GPA	75-90%	5-20%	up to 20%

Question: Can (+) ANCA be used to diagnose GPA in place of a tissue biopsy?

It depends upon the likelihood of disease based upon the clinical scenario

Influenced by GPA being uncommon and treatment toxicity

- sinus, lung, renal disease – predictive value 90%
- sinus and lung disease – predictive value of ANCA ~30-60%
  remains a high potential of infection/neoplasm

(+) PR3-cANCA has poor positive predictive value in low prevalence settings

Diagnosis by biopsy often remains necessary to consider

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Question 1:

Which of the following statements about diagnostic testing in granulomatosis with polyangiitis (GPA) is true ?

A. Nasal biopsy has > 30% positive yield to diagnose GPA

No – nasal biopsy yield is < 10%

B. Transbronchial lung biopsy has > 30% positive yield to diagnose GPA

No – transbronchial biopsy yield is < 10%

C. Surgical biopsy of radiographically abnormal lung has the highest positive yield to diagnose GPA

Yes – surgical biopsy has the highest positive yield

D. (+) PR3-cANCA has a positive predictive value equal to biopsy in a patient with sinus and lung disease

No – PR3-ANCA has a predictive value of 30-60% in sinus+lung disease, which is lower than the potential yield from a lung biopsy

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Question 2:

A 34 year old female is newly diagnosed with GPA. Her features include involvement of the nose/sinus, joint, and lung (two 2 cm nodular lesions without respiratory compromise).

For remission induction:	Which of these is an option ?	Which of these will you use ?
A. Prednisone + cyclophosphamide		
B. Prednisone + azathioprine		
C. Prednisone + methotrexate		
D. Prednisone + mycophenolate		
E. Prednisone + rituximab		

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Granulomatosis with Polyangiitis – Goals of Treatment

- Patient survival
- Induce remission of active disease

  Remission - absence of disease activity
- Avoid disease relapse

  Relapse - return of disease activity after remission
- Minimize therapeutic toxicity

Current management must take into consideration:

- GPA can be associated with long-term survival
- Relapses occur in 50-70% of patients
- All therapies have potential short- and long-term toxicity

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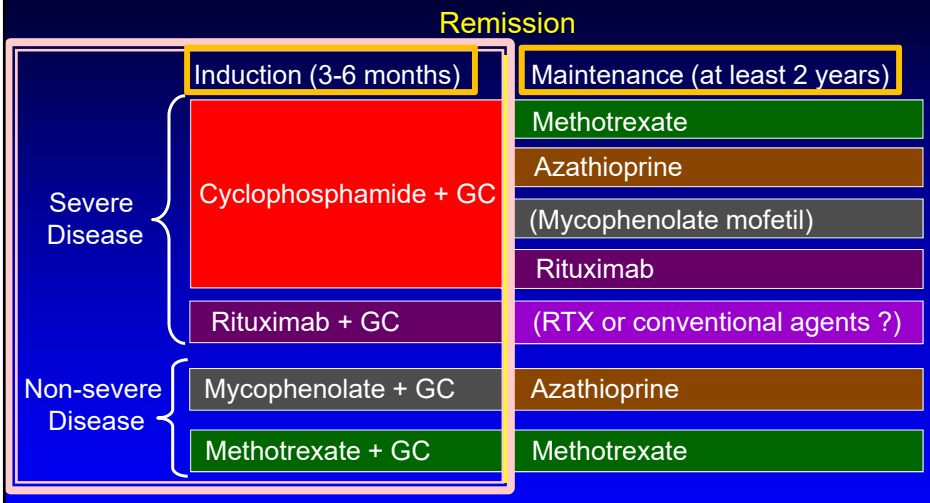
Granulomatosis with Polyangiitis – Treatment Options In 2019



How do we choose ?

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Treatment of Granulomatosis with Polyangiitis
Historical Experience

Untreated disease

Walton. BMJ 1958;2(5091):265

- median survival time 5 months

Glucocorticoids alone

Hollander & Manning. Ann Int Med 1967;67:393

- median survival time 12.5 months

Daily cyclophosphamide and prednisone

Fauci & Wolff. Medicine 1973:52:535

- remission in 12 / 14 patients

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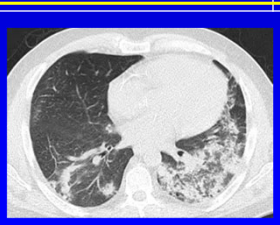
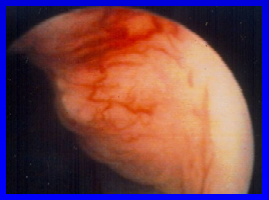
Cyclophosphamide – Effective But Not the Final Answer

Fauci et al. Ann Int Med 1983;98:76, Hoffman et al. Ann Int Med 1992;116:488

	Fauci 1983	Hoffman 1992
Mean follow-up	51 months (+ 4.3)	96 months
Rate of remission induction	93%	75%
Relapse rate	32%	50%
Cystitis	34%	43%
Serious infection	2%	46%
Bladder cancer	0%	2.8%

Pneumocystis jirovecii





Transitional Cell Carcinoma

Approaches beyond cyclophosphamide were needed

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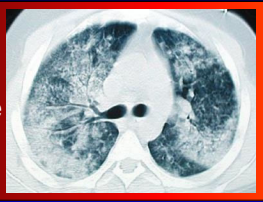
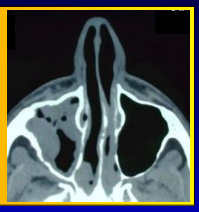
Disease Spectrum of Granulomatosis with Polyangiitis

Severe



Non-Severe



- Alveolar hemorrhage
- Glomerulonephritis
- CNS
- Mononeuritis multiplex
- Pericarditis
- Vision threatening scleritis

- Sinonasal disease
- Oral mucosa
- Skin
- Joint
- Conductive hearing
- Lung – no respiratory compromise

Influences patient outcome and treatment decisions

Cyclophosphamide or rituximab → Methotrexate or mycophenolate

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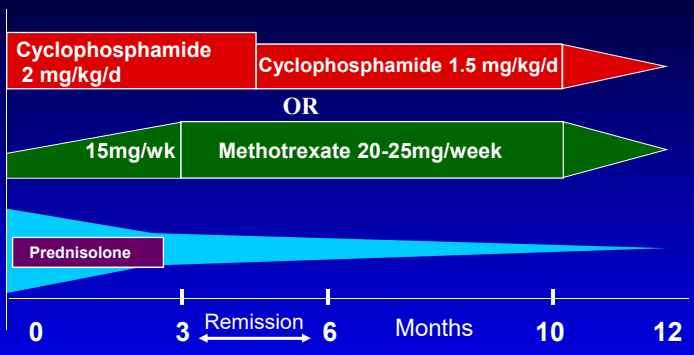
Non-Severe Disease – Cyclophosphamide vs Methotrexate

deGroot et al. Arthritis Rheum 2005;52:2461



100 patients

Induction of remission within 6 months

Methotrexate	90%
Cyclophosphamide	93%

Methotrexate is not inferior to cyclophosphamide for remission induction of non-severe disease

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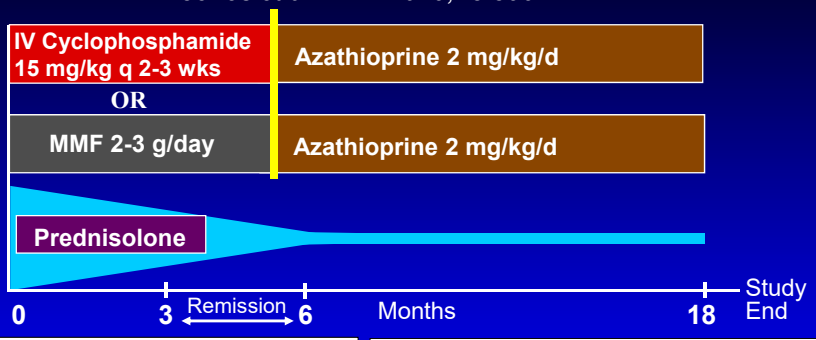
Non-Severe Disease – Cyclophosphamide vs Mycophenolate

Jones et al. ARD 2019;78:399



140 patients

Induction of remission by 6 months

Mycophenolate mofetil	67%
Cyclophosphamide	61%

Relapse: MMF 33%, CYC 19% (p=0.049)
Serious adverse events: MMF = CYC
Serious infections: MMF = CYC

CYC affects fertility but MMF teratogenic (FDA advisories for both women and men)

MMF is not inferior to cyclophosphamide for remission induction of non-life-threatening disease but has a higher relapse rate

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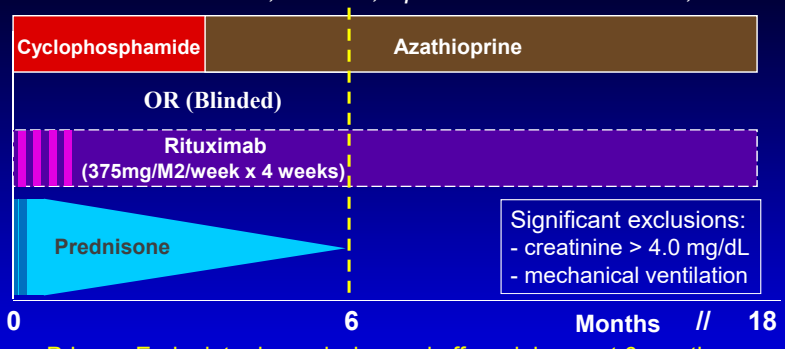
Cyclophosphamide vs Rituximab for Remission Induction (RAVE)

Stone et al. NEJM 2010;363:221, Specks et al. NEJM 2013;369:417



Primary Endpoint = in remission and off prednisone at 6 months

197 ANCA (+) GPA or MPA

Meeting primary endpoint
All patients: RTX 64%, CYC 53% (p<0.001)
Relapsing patients: RTX 67%, CYC 42%

Rate of adverse events: RTX = CYC
Infections: RTX = CYC
Mortality rate: 2% (1 RTX, 2 CYC)

For remission induction, rituximab is as effective as cyclophosphamide
This was the basis for FDA approval of RTX for GPA/MPA in April 2011

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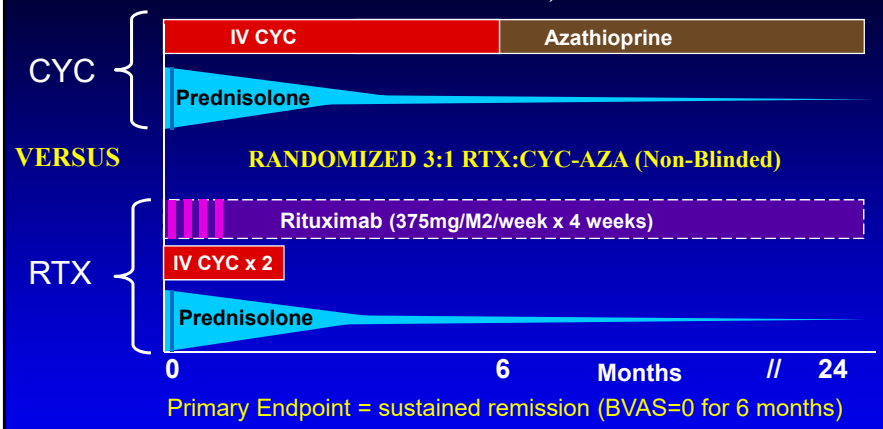
Cyclophosphamide vs Rituximab for Remission Induction (RITUXVAS)

Jones et al. NEJM 2010;363:211



Primary Endpoint = sustained remission (BVAS=0 for 6 months)

44 ANCA (+) GPA or MPA, new dx

Hypothesis: RTX better than CYC
Primary endpoint: RTX 76%, CYC 82%

Rate of adverse events: RTX = CYC
Mortality rate: 18% (6 RTX, 2 CYC)
- Median age 68, 20% dialysis
- GFR: RTX 20, CYC 12 ml/min

Rituximab was effective but was not superior to cyclophosphamide

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Cyclophosphamide vs Rituximab for Remission Induction

Question
Rituximab is as effective as cyclophosphamide for remission induction of severe disease – does that mean it should be used in place of cyclophosphamide to induce remission in all patients with GPA ?

No – there is varying strength of evidence for different settings

Strength of evidence for use

Relapsing severe disease
Newly diagnosed severe disease
Non-severe relapse, occurring on methotrexate
Non-severe relapse, never received methotrexate
Newly diagnosed non-severe disease
Fulminant disease (creatinine > 4.0, mechanical ventilation)

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Cyclophosphamide vs Rituximab for Remission Induction

Settings in which I consider cyclophosphamide:

- Fulminant disease (RPGN creatinine > 4.0 mg/dL, mechanical ventilation)
- Severe disease with intolerance to rituximab
- Worsening severe disease despite rituximab
- Still a option in newly diagnosed patients

Settings in which I consider rituximab:

- Relapsing severe disease
- Newly diagnosed patients who are: younger or older
- Patients with leucopenia, thrombocytopenia
- Patients with urinary retention
- Patients with malignancy history
- Patients with infections (glucocorticoids remain a problem)

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Question 2:

A 34 year old female is newly diagnosed with GPA. Her features include involvement of the nose/sinus, joint, lung (two 2 cm nodular lesions without respiratory compromise).

For remission induction:	Which of these is an option ?	Which of these will you use ?
A. Prednisone + cyclophosphamide	No (other better choices)	
B. Prednisone + azathioprine	No (induces poorly)	
C. Prednisone + methotrexate	Yes	Young female - Decision will depend on desire for future children, compliance, individual factors
D. Prednisone + mycophenolate	Yes	
E. Prednisone + rituximab	Yes	

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Question 3:

54 year old male with GPA presented with alveolar hemorrhage, RPGN, sinus, skin, and scleral disease. He was treated with daily cyclophosphamide and glucocorticoids. He is now in remission and has a creatinine of 2.6 mg/dL.

For remission maintenance:

Which of these is an option ?

Which of these will you use ?

A. Rituximab

B. Azathioprine

C. Mycophenolate

D. Methotrexate

E. Belimumab

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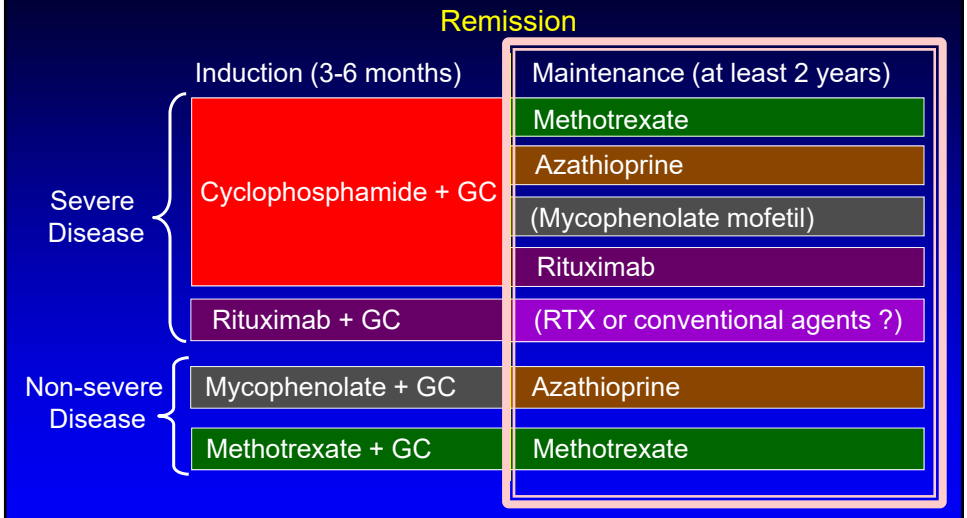
Granulomatosis with Polyangiitis – Treatment Options In 2019



What has been the experience with these approaches for remission maintenance ?

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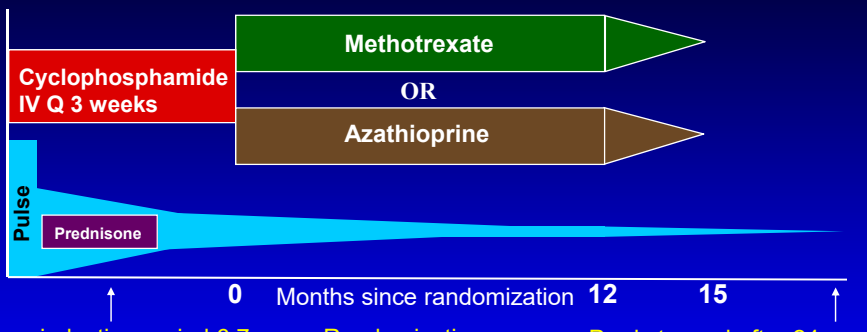
Methotrexate vs Azathioprine for Remission Maintenance (WEGENT)

Pagnoux et al. NEJM 2008;359:2790, Puéchal et al. A&R 2016;68:690



159 patients – 126 (79%) Remission

	Toxicity		Relapse	
Methotrexate	46%	p=0.29	36%	p=0.71
Azathioprine	56%		33%	

10 Year Follow-up

	Relapse-free:	
Methotrexate	34%	p=0.29
Azathioprine	26%	

Azathioprine and methotrexate are equivalent maintenance options

Relapses occur at a high rate once treatment is stopped

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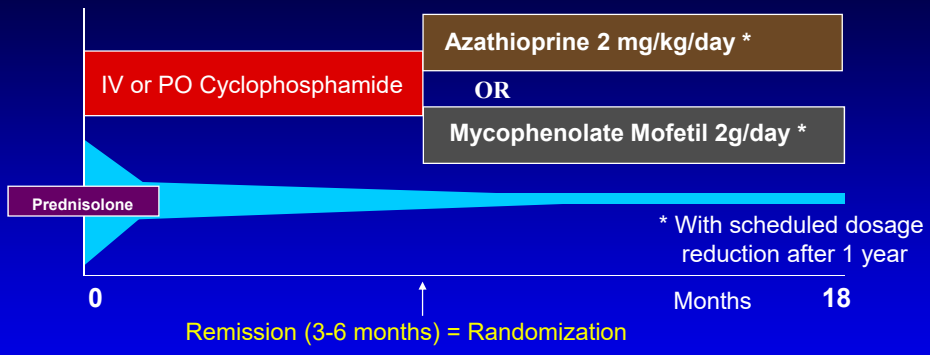
Mycophenolate Mofetil vs Azathioprine for Remission Maintenance

Hiemstra et al. JAMA 2010;304:2381



156 patients

	Relapse	
Mycophenolate	55%	P=0.03
Azathioprine	38%	

Toxicity (severe adverse events)

Mycophenolate	7.5%	P=0.12
Azathioprine	16%	

MMF was less effective than azathioprine for maintaining remission

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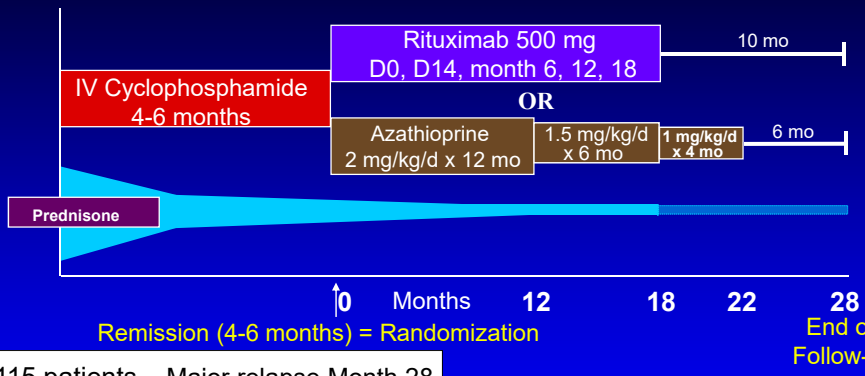
Maintenance Rituximab vs Azathioprine (MAINRITSAN)

Guillevin et al. NEJM 2014;371:1771, Terrier et al. ARD 2018;77:1150



Remission (4-6 months) = Randomization

115 patients – Major relapse Month 28

3 (5%) RTX
17 (29%) AZA P=0.002

(Could AZA dosing have impacted this ?)

Month 60 Follow-up

- RTX still superior – but 42% relapsed

How long to continue RTX ?

Rituximab was more effective than azathioprine to maintain remission but questions remains about rituximab treatment duration

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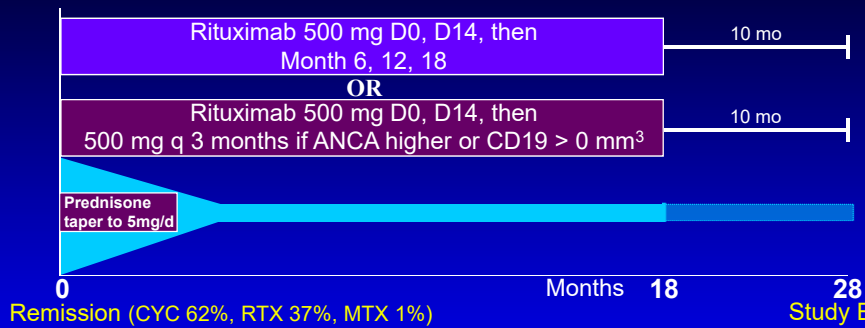
Maintenance Rituximab Fixed-Schedule vs Tailored (MAINRITSAN 2)

Charles et al. ARD 2018;77:1143



Remission (CYC 62%, RTX 37%, MTX 1%)

Goal: Compare scheduled RTX q 6months to RTX based on ANCA/CD19

162 patients – Relapses Month 28

14 (17%) Scheduled RTX
8 (10%) Lab-driven RTX P=0.20

Number of RTX infusions:

Scheduled = 5
Lab-driven = 3 (range 2-4)

No difference in relapse when rituximab was based on ANCA/CD19
Lab-driven received a fewer number of infusions

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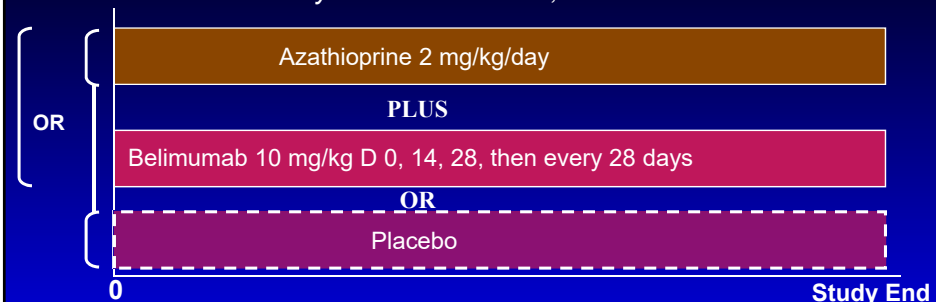
Belimumab vs Azathioprine for Remission Maintenance

Jayne et al. A&R 2019;71:952



In remission after CYC (74%) or RTX (26%) on ≤ prednisone 10mg/day

105 patients - Relapse
(BVAS≥6, BVAS major item, need other Rx)

8 (15%) Belimumab+AZA
6 (11%) Placebo+AZA
P=0.82

RTX followed by belimumab+AZA
- Higher rate of infection
- No relapses (0 in 14)

Mid-trial change in design and endpoint which reduced sample size

Addition of belimumab to azathioprine did not reduce relapse

RTX followed by belimumab+AZA - low relapse rate but higher infection

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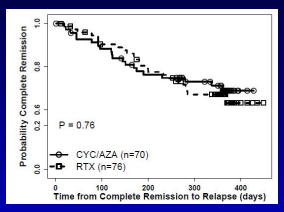
Relapse After Rituximab Induction in ANCA-Associated Vasculitis

Specks et al. N Engl J Med 2013;369:417

- No difference in RTX vs CYC/AZA
- 30% relapse within 1 year



Factors associated with an increased risk of relapse:

- Previous relapse
- (+) PR3-ANCA
- GPA phenotype

Also risk factors in non-rituximab based series:

Nachman JASN 1996;7:33, Jayne NEJM 2003;349:36
Lionaki A&R 2012;64:3452, Walsh A&R 2012;64:542

Relapses occur after rituximab so a plan for remission maintenance also needs to be considered for rituximab-treated patients

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How Should Remission Maintenance be Approached ?

What can we say from the data ?

- Rituximab given for 18 months has a lower relapse rate than azathioprine
- Relapses occur if rituximab is stopped (also true for conventional agents)
- Risk vs benefit of long-term use of rituximab in GPA is unclear
- Best approach to manage long-term maintenance is unclear

What are the possible approaches to maintenance ?

To use rituximab maintenance for 18-24 months and then:

- Stop rituximab maintenance and retreat if relapse occurs
- Continue rituximab every 6 months
- Continue rituximab but lengthen out infusions (9 months, 12 months)
- Base re-treatment on ANCA, CD19
- Azathioprine (or other agent) after 2 years of rituximab maintenance

To not use rituximab maintenance and instead:

- Use azathioprine (or other agent) immediately following induction
- To not give any maintenance after rituximab and retreat if relapse occurs
  - Factors some consider: ANCA type, GPA/MPA, prior relapse, damage

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Question 3:

54 year old male with GPA presented with alveolar hemorrhage, RPGN, sinus, skin, and scleral disease. He was treated with daily cyclophosphamide and glucocorticoids. He is now in remission and has a creatinine of 2.6 mg/dL.

For remission maintenance:	Which of these is an option ?	Which of these will you use ?
A. Rituximab	Yes	Lower relapse rate but how long to continue ?
B. Azathioprine	Yes	Higher relapse rate but experience with long-term use
C. Mycophenolate	Yes	Higher relapse rate than AZA
D. Methotrexate	No (renal function)	
E. Belimumab	No (no benefit)	

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Question 4:

A 64 year old male had active GPA involving the sinus, lung, kidney, and nerve for which he was treated with rituximab and glucocorticoids. 4 months later he continues to have fatigue, nasal crusting, trace protein in his urine (2+ diagnosis), and paresthesias in his R foot which were present at diagnosis.

Which of the following would you recommend ?

A. Start cyclophosphamide

B. Increase prednisone

C. Make sure he is doing nasal rinses

D. Add azathioprine

E. Retreat with rituximab

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A Critical Question – Damage vs Active Disease ?

New clinical features:

Characteristic features are NOT always indicative of activity

- Pulmonary infiltrates (infection, methotrexate)
- Hematuria (cyclophosphamide bladder injury, UTI, stones)

Always consider: infection or medication side effect (or other)

Persistent clinical features:

Differentiate active disease from chronic damage

- Renal: creatinine may not go down and proteinuria may persist
- Nerve: persist motor / sensory deficits and pain are common
- Persistent radiographic changes: lung, orbit, sinus
- Endobronchial or subglottic stenosis
- Sinonasal symptoms

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Question 4:

A 64 year old male had active GPA involving the sinus, lung, kidney, and nerve for which he was treated with rituximab and glucocorticoids. 4 months later he continues to have fatigue, nasal crusting, trace protein in his urine (2+ diagnosis), and paresthesias in his R foot which were present at diagnosis.

Which of the following would you recommend ?

A. Start cyclophosphamide
B. Increase prednisone

} Active disease

C. Make sure he is doing nasal rinses — Can be used to address damage

D. Add azathioprine
E. Retreat with rituximab

} Active disease

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Question 5:

A 65 year old female with GPA recently had a renal relapse. Her creatinine is 1.2 mg/dL, UA shows 2+ protein. She is ambulating normally. At her one month visit you note painless B/L symmetric lower extremity swelling with 1-2+ pitting. She is taking prednisone 60 mg daily and rituximab and she has been on amlodipine for hypertension.

Which of the following should you do first:

A. Stop amlodipine

B. Prescribe B/L compression hose

C. Add an ACE to reduce her proteinuria

D. Have her get a same-day venous duplex

E. Reduce the prednisone dose

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Lower Extremity Swelling in GPA

Patients with GPA can have many reasons for leg swelling*

- Glucocorticoids
- Antihypertensives
- Proteinuria
- Heart failure
- DVT

* Can be unilateral or bilateral

Merkel P et al. Ann Intern Med 2005;142:620

- 180 patients in the Wegener's granulomatosis etanercept trial (WGET)
- Higher rate of DVT/PE compared to other groups
- Most thrombotic events were during/within 2 months of active disease

Study	DVT / PE rate
WGET	7.0
General Population	0.3
JHU Lupus	1.0
RA Etanercept	0.3

Remember risk of DVT/PE in active GPA
If a patient with GPA has a DVT/PE – look for active disease

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Question 5:

A 65-year-old female with GPA recently had a renal relapse. Her creatinine is 1.2 mg/dL, UA shows 2+ protein. She is ambulating normally. At her one month visit you note painless B/L symmetric lower extremity swelling with 1-2+ pitting. She is taking prednisone 60 mg daily and rituximab and she has been on amlodipine for hypertension.

Which of the following should you do first:

A. Stop amlodipine

B. Prescribe B/L compression hose

C. Add an ACE to reduce her proteinuria

D. Reduce the prednisone dose

All are reasonable But not what you would do first

E. Have her get a same-day venous duplex — Yes

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Question 6:

Which of the following is not an important preventive tool in patients with granulomatosis with polyangiitis ?

A. Pneumocystis prophylaxis with cyclophosphamide

B. Pneumocystis prophylaxis with rituximab

C. Sunscreen

D. Influenza vaccination

E. Avoidance of family gatherings

F. Education about hand washing

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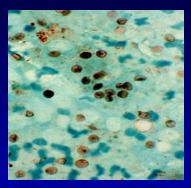
Pneumocystis jirovecii Pneumonia

Pneumocystis - risk in GPA



- Seen in ~10% of AAV patients receiving induction therapy
  (Ognibene et al. Crit Care Med 1995; 151:795)
- Mortality rate can reach 35%
- Main risk factor is lymphopenia
- Cases have been reported with:
  - Methotrexate
  - Cyclophosphamide
  - Rituximab

Prophylaxis

- Trimethoprim 160mg/sulfamethoxazole 800mg 1 tablet 3 times a week
- Trimethoprim 80mg/sulfamethoxazole 400mg 1 tablet daily
- Sulfa allergy options: inhaled pentamidine, dapsone, atovaquone

Prophylaxis should be given to all AAV patients receiving prednisone + another immunosuppressive (including rituximab)

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Use of Vaccinations in GPA

Vaccinations play an important role in preventive care for immunosuppressed patients

Live vaccines:

- Measles, Mumps, Rubella (MMR)
- Live Herpes zoster (Zostavax®)
- Varicella vaccine
- Nasal influenza
- Yellow fever
- BCG
- Oral polio (OPV)

Non-live vaccines

- IM influenza
- Pneumococcal vaccines
- Tetanus
- HPV
- Diphtheria
- *Meningococcus*
- Haemophilus influenzae
- Hepatitis A, B
- Non-live Herpes zoster (Shingrix®)
- Inactivated polio (IPV)

* Challenge – may not always form a protective response

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Question 6:

Which of the following is not an important preventive tool in patients with granulomatosis with polyangiitis ?

A. Pneumocystis prophylaxis with cyclophosphamide	Important
B. Pneumocystis prophylaxis with rituximab	Important
C. Education about hand washing	Important
D. Influenza vaccination	Important
E. Avoidance of family gatherings	It depends
F. Sunscreen	Important Increased skin cancer risk Sun sensitivity (T/S, MTX)

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Question 7:

Which of the following are important monitoring tools in patients with granulomatosis with polyangiitis ?

A. Physician visits

B. CBC with differential + chemistries

C. ESR and/or CRP

D. Urinalysis

E. Serum lipids

F. Colonoscopy

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Monitoring in Granulomatosis with Polyangiitis

What is the purpose of monitoring ?

- Detect disease relapse
- Identify treatment-related toxicity
- Watch for emergence of other disease entities

What constitutes monitoring ?

- Physician visits
- Laboratories
  - CBC, chemistries, ESR/CRP, urinalysis
  - (ANCA-personal decision)
  - Immunoglobulins
  - Urine cytology – in cyclophosphamide treated patients

Frequency depends on treatment

- Cardiovascular
- General health (colonoscopy, mammography, other screening)

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Question 7:

Which of the following are important monitoring tools in patients with granulomatosis with polyangiitis ?

A. Physician visits

B. CBC with differential + chemistries

C. ESR and/or CRP

D. Urinalysis

E. Serum lipids

F. Colonoscopy

They all are !

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What Are the Keys to Optimizing Patient Outcome ?

- Use of evidence-based treatment regimens to fit individual patient setting
- Recognition of relapse vs damage vs infection vs side effect vs other
- Aggressive use of preventive / prophylactic strategies
  - Infection (includes non-live vaccination)
  - Medication specific side effects (ie: bone health, folic acid with MTX)
  - Day-to-day activities (ie: hand washing, being sun-sensible)
- Monitoring - for disease relapse, treatment toxicity, other diseases
  - Physician visits and labs
  - Cardiovascular
  - General health (colonoscopy, mammography, other screening)
- Patient and family education

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Conclusion: Granulomatosis with Polyangiitis

In 2019, GPA is treatable and can be associated with long-term survival
Ongoing concerns - relapse, treatment toxicity, and organ damage

What lies ahead ?

- Biomarkers
  - Identifying relapse and those at risk of relapse
  - Guiding maintenance treatment – who needs what and when
- Greater understanding of pathogenesis – including genetics
- Tools for disease activity assessment
  - Patient reported outcomes
- Cost-effectiveness assessments
- New (and refined) treatment approaches
  - Can we use less glucocorticoids ?
  - Novel approaches – abatacept (CTLA4-Ig), avacopan (C5R inhibitor)
  - Personalized treatment