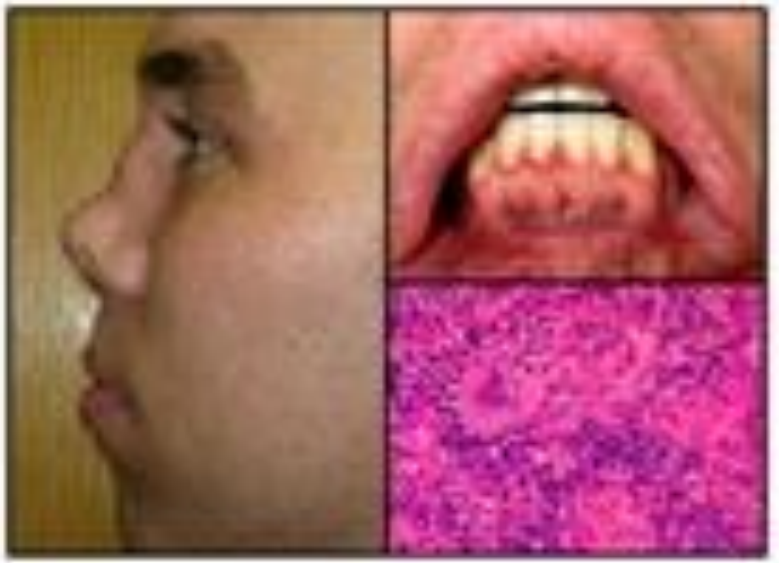
Treatment of ANCA Associated Vasculitis: Is There Still a Role for Cyclophosphamide?

Learning Objectives

- Discuss therapeutic conditions and principles for diagnosis of ANCA Associated Vasculitis (AAV)
- Describe the role cyclosporine plays in the treatment of AAV
- Review new therapies available and in development for the treatment of AAV

ANCA Associated Vasculitis (AAV)

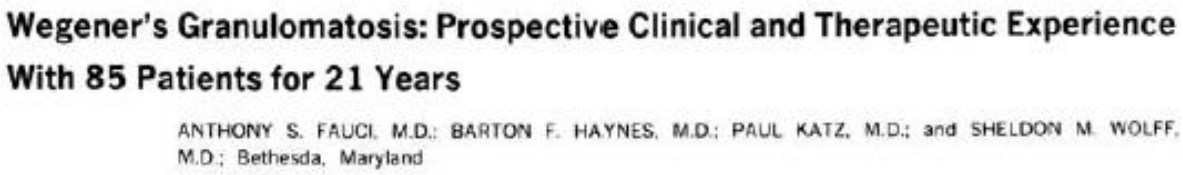
- Systemic small vessel vasculidites
  - Granulomatosis with polyangiitis (Wegener's)
  - Microscopic polyangitis
  - Eosinophilic GPA (Churg-Strauss)
- Term can be misleading as not all patients with clinical/histological disease have ANCA



History of Treatment

- 1930s – no treatment available
- 1950s – corticosteroids
- 1970s – cyclophosphamide
- 1990s – methotrexate
- 2000s – biologics?

Induction Therapy – Cytoxan



Wegener's Granulomatosis: Prospective Clinical and Therapeutic Experience With 85 Patients for 21 Years

ANTHONY S. FAUCI, M.D.; BARTON F. HAYNES, M.D.; PAUL KATZ, M.D.; and SHELDON M. WOLFF, M.D.; Bethesda, Maryland

- Prior to 1970s, mean survival of untreated GPA was 5mo, with 82% patients dying within 1 year and >90% dying within 2 years
- Oral Cytoxan + prednisone was able to induce remission in WG (93%)

Fauci et al. *Annals Int Med*. 1983.

Cyclophosphamide

Good News	***Bad News***
• 91% marked improvement • 75% complete remission (CR) • Only 13% died	• 50% of CRs relapsed. Only 37% remitted on first course • Remission less than half of all F/U time • Prolonged exposure to toxic drugs

GPA: Permanent Disease-related Morbidity: 86%

- Renal 42% (mean CR=2.6)
- Dialysis – 11%
- Sinus – 47%
- Hearing – 35%
- Trachea – 16%
- Lung – 17%
- Visual loss – 8%

Hoffman et al. Wegener Granulomatosis: An Analysis of 158 Patients. *Ann Int Med.* 1992.

GPA: Permanent Treatment-related Morbidity: 42%

- Hemorrhage cystitis – 43%
- 16% bladder cancer (33-fold risk)
- 11-fold increase in lymphoma /leukemia
- Infertility – 57% of women of childbearing potential
- Infections (46%) 11% risk of serious infection each year

Hoffman et al. Wegener Granulomatosis: An Analysis of 158 Patients. *Ann Int Med*. 1992.

AAV Induction: The Bad News

- 9-fold increased mortality risk in the first year of AAV compared with healthy controls
- >50% early mortality from treatment related adverse events vs <30% from active vasculitis
- 2.7-fold increase mortality overall
- 15-38% of patients develop ESRD within 5 years
- Higher cumulative steroid doses associated with increased infection risk and increased damage

Lugmani, R el al. *Rheumatology*. 2010; Little, MA et al. *Ann Rheum Dis*. 2010.

AAV: General Therapeutic Considerations

- “SEVERE” vs “LIMITED” disease
- Remission “induction” vs “maintenance”
- Distinguish “activity” from “damage”
- Attention to co-morbidities
- Attention to patient specific issues in choosing therapies
- **GOAL*: Maximize disease control and minimize adverse impact and damage from disease and therapy***

AAV: Treatment Principles

- Tailor treatments to disease severity
  - Severe vs Non-severe (limited)
- Induction of Remission
- Maintenance of Remission
- Avoid accrual of damage
- Treat active disease NOT damage
- Minimize toxicity of therapies

BVAS for Wegeners' Granulomatosis Evaluation Form

Draft

Tick box (□ or O) only if abnormality is ascribable to the prescence of active Wegener's Granulomatosis (chronic damage should be scored separately in the Vasculitis Damage Index, VDI.)

□ Tick box only if the abnormality is **persistent disease activity** since the last assessment and not worse within the **previous 28 days**.
O Tick box only if the abnormality is **newly present or worse** within the **previous 28 days**
( ) If no items are present in any section, tick "none".
Major items are in bold and marked with *
All WG-related clinical features need to be documented on the this form if they are related to active diseases. Use "OTHER" category as needed.

1. Subject ID: ☐☐☐☐☐

2. Clinic ID: ☐☐☐☐☐

3. Date form completed: ☐☐ / ☐☐ / ☐☐ (day / month / year)

4. Investigator: ☐

	Persistent	New/Worse	None
6. GENERAL			( )
a. arthralgia/arthritis	□	O	
b. fever (>= 38 degrees C)	□	O	
7. CUTANEOUS			( )
a. purpura	□	O	
b. skin ulcer	□	O	
c. *** gangrene**	□	O	
8. MUCOUS MEMBRANES/EYES			( )
a. mouth ulcers	□	O	
b. conjunctivitis/episcleritis	□	O	
c. retro-orbital mass/proptosis	□	O	
d. uveitis	□	O	
e. ***scleritis**	□	O	
f. *** retinal exudates/haemorrhage**	□	O	
9. EAR, NOSE & THROAT			( )
a. bloody nasal discharge / nasal crusting / ulcer	□	O	
b. sinus involvement	□	O	
c. swollen salivary gland	□	O	
d. subglottic inflammation	□	O	
e. conductive deafness	□	O	
f. *** sensorineural deafness**	□	O	
10. CARDIOVASCULAR			( )
a. pericaritis	□	O	
11. GASTROINTESTINAL			( )
a. *** mesenteric ischemia**	□	O	
12. PULMONARY			( )
a. pleurisy	□	O	
b. nodules or cavities	□	O	
c. other infiltrate secondary to WG	□	O	
d. endobronchial involvement	□	O	
e. *** alveolar hemorrhage**	□	O	
f. *** respiratory failure**	□	O	

	Persistent	New/Worse	None
13. RENAL			( )
a. hematuia (no RBC casts) (>= 1 + or >= 10 RBC/hpf)	□	O	
b. *** RBC casts**	□	O	
c. *** rise in creatinine > 30% or fall in creatinine clearance > 25%**	□	O	
14. NERVOUS SYSTEM			( )
a. *** meningitis**	□	O	
b. *** cord lesion**	□	O	
c. *** stroke**	□	O	
d. *** cranial nerve palsy**	□	O	
e. *** sensory peripheral neuropathy**	□	O	
f. *** motor mononeuritis multiplex**	□	O	
15. OTHER (describe all items and * items deemed major)			( )
☐	□	O	
☐	□	O	
☐	□	O	
☐	□	O	

Note: *If both hematuria and RBC casts are present, score only the RBC casts (the major item).*

16. TOTAL NUMBER OF ITEMS: ( )

a.	b.	c.	d.
☐☐	☐☐	☐☐	☐☐
Major New / Worse	Minor New / Worse	Major Persistent	Minor Persistent

DETERMINING DISEASE STATUS:
Severe Disease / Flare: >= 1 new/worse Major item.
Limited Disease / Flare: >= new/worse Minor item.
Persistent Disease: Continued (but not new/worse) activity.
Remission: No active disease, including either new /worse or persistent items.

17. CURRENT DISEASE STATUS *(check only one)*

Severe Disease/Flare ( )
Limited Disease/Flare ( )
Persistent Disease ( )
Remission ( )

18. PHYSICIAN'S GLOBAL ASSESSMENT (PGA)
Mark line to indicate the amount of WG disease activity (not including longstanding damage) within the previous 28 days:

Remission 0 ——————————— 10 **Maximum activity**

19. Value in item #18: ☐☐☐.☐ *(distance from 0 to tick mark in millimeters)*

20. DATE FORM REVIEWED: (day / month / year) ☐☐ / ☐☐ / ☐☐

23. CLINIC COORDIINATOR ID: ☐☐☐

21. STUDY PHYSICIAN ID: ☐☐☐

24. CLINIC COORDINATOR SIGNATURE:

22. STUDY PHYSICIAN SIGNATURE:

Figure 1. Evaluation form for the Birmigham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG). RBC = red blood cell; hpf = high-power field

Trial Name	Design	Primary End Point	Results
Induction			
CYCLOPS[45]	PO vs IV-CYC in newly diagnosed AAV with renal involvement	Time to remission	IV-CYC noninferior to PO CYC, lower cumulative dose and less leukopenia with IV, long-term follow up suggested higher relapse rate with IV
NORAM[39]	MTX vs PO CYC in patients with limited disease	Remission at 6 months	No difference in remission rates at 6 months between groups, in long-term follow-up lower rate of relapse-free survival in MTX group
RAVE[3]	RTX vs PO CYC, new or relapsing AAV	Steroid-free remission at 6 months	RTX noninferior to CYC for induction of remission and may be more effective in relapsing disease
RITUXIVAS[4]	IV-CYC + RTX vs IV-CYC + placebo in newly diagnosed AAV with renal involvement	Remission at 12 months	RTX + IV-CYC noninferior to IV-CYC alone with similar rates of adverse events
Maintenance			
CYCAZAREM[52]	AZA vs PO CYC in new or relapsing AAV after induction with PO CYC	Relapse rate	No difference in rates of relapse between the treatment groups
WEGENT[53]	AZA vs MTX after induction with IV-CYC	Adverse events requiring discontinuation of treatment or death	No difference in adverse events and similar relapse rate in both treatment arms, majority of relapses occurred after study medication tapered off
IMPROVE[55]	MMF vs AZA in newly diagnosed AAV patients following induction in CYCLOPS trial	Relapse-free survival	Relapse more common in MMF group with similar rates of adverse events
German Network of Rheumatic Diseases Study[54]	LEF vs MTX in GPA after induction with PO CYC	Relapse rate	Study terminated early because of high incidence of major relapses in MTX-arm, though increased frequency of adverse events in LEF-arm (LEF dose 30mg/day)
Dutch Co-trimoxazole Study[57]	TMP-SMX vs placebo, in GPA patients during/after remission induction with PO-CYC	Disease-free interval	Fewer relapses in patients receiving TMP-SMX, though 20% patients discontinued TMP-SMX due to side effects
WGET[40]	Etanercept vs placebo in addition to CYC (severe) or MTX (limited) for active GPA	Sustained remission for ≥6 months	Etanercept not effective for remission maintenance, 6 malignancies in Etanercept group (all in patients on prior CYC)

Lally, L et al. *Rheumatic Dis Clin North Am*. 2014.

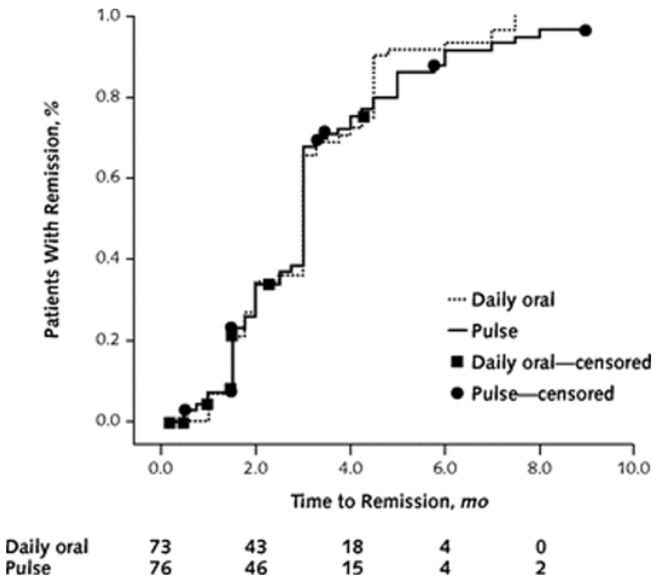
AAV: Is There Still a Role for CYC?

- MPA and GPA
  - Remission induction
  - Remission maintenance
- EGPA (Churg Strauss)

GPA/MPA: Remission Induction-Trial Based Evidence

- Cyclophosphamide: Oral vs IV administration (Cyclops trial)
- Cyclophosphamide vs MTX (NORAM)
- Cyclophosphamide vs MMF (MYCYC)
- Cyclophosphamide vs RTX
  - RAVE
  - RITUXVAS

“CYCLOPS” Trial: Oral vs IV CYC for Remission Induction



- Randomized, non-blinded
- 149 newly diagnosed AAV with renal disease

CYC-IV 15mg/kg q 2-3 wk vs CYC-PO 2mg/kg daily

- Primary Outcome = time to remission
  - No difference
  - Lower cumulative dose and less leucopenia in IV-CYC
- Long-term f/u higher relapse in IV-CYC but no difference in mortality, ESRD

De Groot et al. *Ann Intern Med*. 2009.

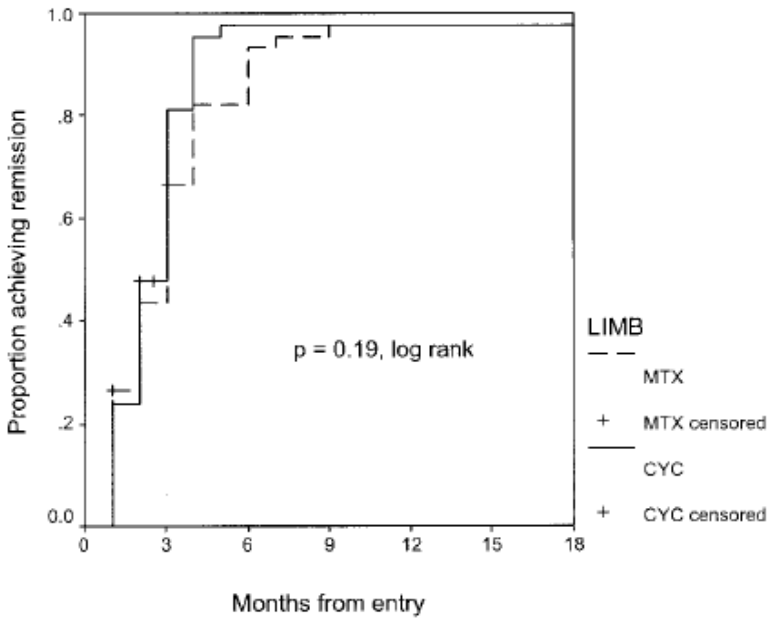
CYCLOPS: Considerations in Practice

- Patients on po CYC received higher cumulative CYC doses
- Oral regimen was associated with higher rates of leucopenia, but NOT other adverse events (infection, malignancy, hemorrhagic cystitis)
- Lower rates of relapse with oral regimen but NOT differences in survival or renal function
- ***Be attentive to dosing regimen: 15mg/kg q 2-3 weeks, NOT our typical monthly IV CYC derived from NIH lupus protocols!!!!***

GPA/MPA: Remission Induction: “NORAM”

- Population: Early systemic disease without organ damage but DID allow low grade renal disease (microhematuria)
- Design: Randomized controlled trial
- Primary Outcome: Remission at six months
- Result: MTX was non-inferior to CYC at 6 months for achievement of remission
- Caveats:
  - Time to remission was later with MTX
  - Relapse rates were higher with MTX (69.5% vs 46.5%)

MTX vs CYC for Induction of Remission in Limited GPA: NORAM



- Open-label, prospective, randomized
- 100 pts with newly diagnosed AAV (94% GPA) with limited disease
- CYC 2mg/kg PO daily vs MTX 20-25mg qwk
- Primary endpoint = CR at 6mths
  - MTX (89.8%) vs CYC (93.5%) non-inferior
- Long-term f/u showed no difference in adverse events
  - MTX group received steroids/immunosuppressives for longer period of time and had lower rate of cumulative relapse-free survival

De Groot K et al. *Arthritis Rheum*. 2005; Fauraschou M et al. *Arthritis Rheum.* 2012.

GPA/MPA: Remission Induction – MMF

Vasculitis

CLINICAL SCIENCE

Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial

Rachel B Jones,[1] Thomas F Hiemstra,[2,3] Jose Ballarin,[4] Daniel Engelbert Blockmans,[5] Paul Brogan,[6,7] Annette Bruchfeld,[8] Maria C Cid,[9] Karen Dahlsveen,[1] Janak de Zoysa,[10,11] Georgína Espigol-Frigolé,[9] Peter Lanyon,[12] Chen Au Peh,[13] Vladimir Tesar,[14] Augusto Vaglio,[15,16] Michael Walsh,[17] Dorothy Walsh,[1] Giles Walters,[18] Lorraine Harper,[19] David Jayne,[1,2] for the European Vasculitis Study Group (EUVAS)

“MYCYC”: MMF vs CYC in AAV

- RCT, open label, multi-center NON-INFERORITY trial, 18 months
- AAV= MPA and GPA (not EGPA)
- New disease (vs other AAV trials: new and relapsing disease)
- MMF vs CYC (IV) with standard GC taper
- AZA for remission maintenance in both groups
- Primary endpoint: remission at 6 months with adherence to GC taper
- Secondary
  - Time to remission
  - Relapse
  - VDI
  - ANCA positivity at 6 months

Remission= BVAS 0 on 2 observations (at least one month apart) and adherence to GC taper

MYCYC: Patients

- Inclusion
  - Newly diagnosed MPA, GPA
  - Positive ANCA or histologic confirmation
- Exclusion
  - Imminently life threatening
  - Rapidly declining renal function
  - GFR< 15
  - Prior rx
    - > 2 weeks oral CYC or MMF
    - > 1 dose IV CYC

MYCYC: Therapy

- MMF: 2 gms/day; increase to 3 gm/d if not controlled at 4 weeks
  - (76% pts 2000mg, 6%> 2 gm, 18%, 2 gm)
- CYC: 15mg/kg q 2-3 weeks
  - (83% pts >6 doses, 33% pts 7-10 doses)
- GC: 1 mg/kg/d with taper to 5 mg by 6 month
- Remission maintenance: at 3 -6 months
  - AZA 2mg/kg/d
    - (at 18 months, 26 patients in each group not on Aza, ~1/2 “intolerance”)

MYCYC: Outcomes

- Primary – remission at 6 mos: 67% MMF vs 61% CYC (ITT)
  - “Per-protocol” 74% MMF (n=58), 62% CYC (n=53)
  - No interaction by ANCA specificity, age, renal function, other therapies
- Secondary
  - No difference in time to primary remission (median, days) MMF:91, CYC:87
  - Relapses after remission : More common with MMF (p=.049)
    - MMF: 23/63 (36%), 4 major, 19 minor
    - CYC: 13/64 (20%), 3 major, 10 minor
  - No difference in progressive disease requiring “rescue” rx (MMF 7%, CYC 11%)
  - No difference in cumulative GC dose (MMF 6194 mg, CYC 5800mg)
  - No difference in ESRD (2 in each group), VDI at study end

MYCYC: Conclusions

- MMF non-inferior to CYC for remission induction in newly diagnosed MPA, GPA
- MMF is an option for remission in GPA, MPA
  - NOT for patients with imminently life threatening disease (similar to RAVE)
  - Alternative to RTX (access), MTX (renal insufficiency)
- MMF induction resulted in earlier and more frequent relapses than induction with CYC (similar to NORAM and CYCLOPS experience: More CYC means less late flares)

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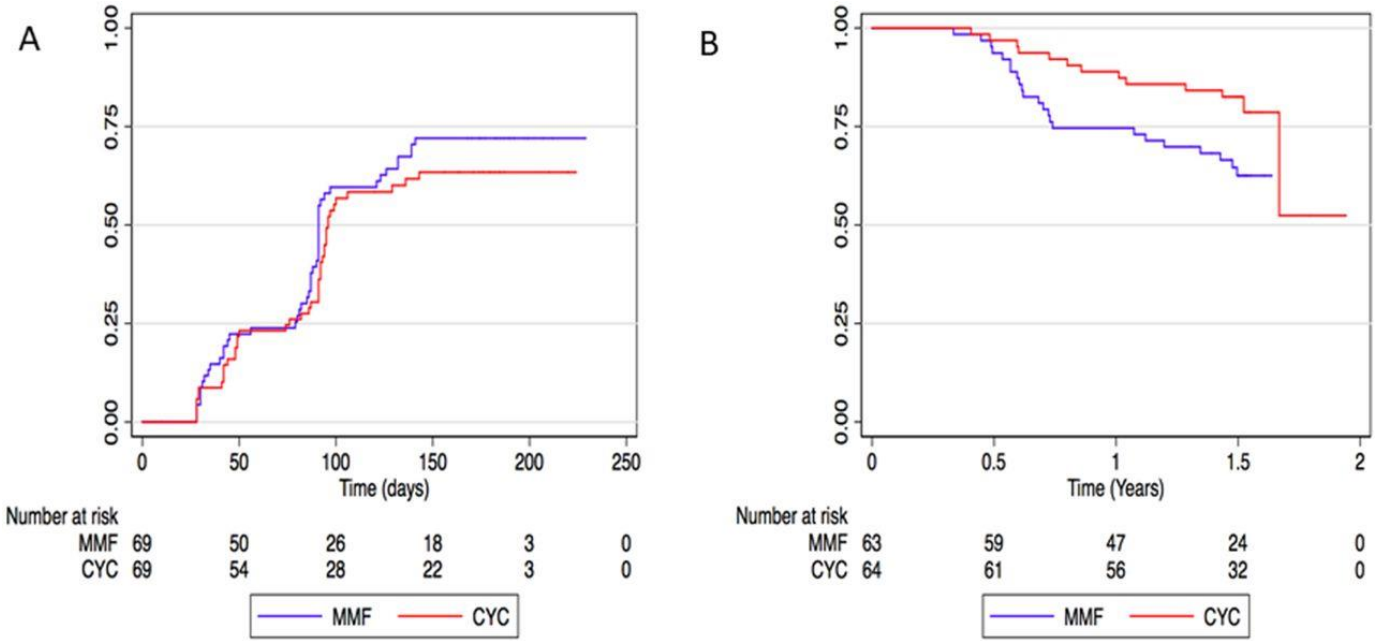
Remission and Relapse



Rachel B Jones et al. *Ann Rheum Dis*. 2019;78:399-405.

ARD

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MYCYC

- Strengths
  - Largest RCT to assess MMF efficacy in AAV
  - Included pediatric patients (but only 8)
- Weaknesses
  - Not blinded
  - Relatively short follow-up (18 months)
    - Probably to short to capture late CYC related AEs: bladder, malignancy
    - Limits ability to capture differences in relapse rates (CYC already superior though)
  - Did not compare MMF to RTX for either remission induction
  - Aza utilized for remission maintenance (and RTX known to be superior to RTX for maintenance)

MYCYC: Considerations

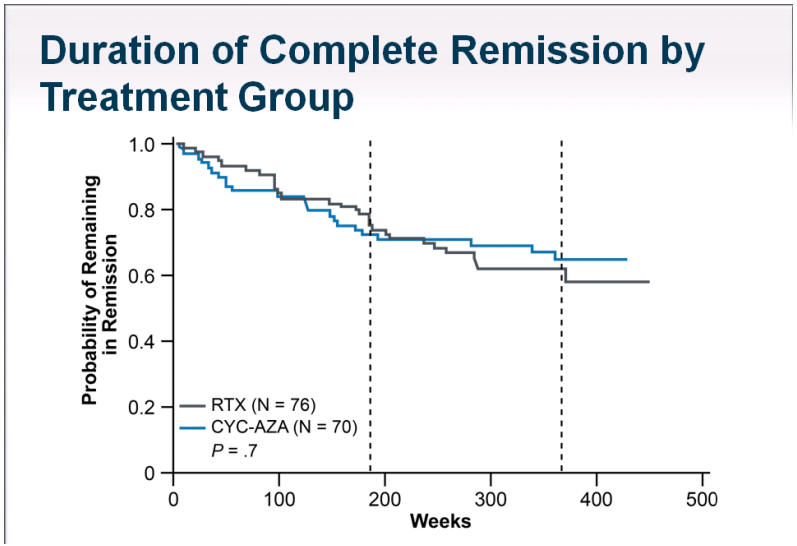
- Non-inferiority trial
- Dose of MMF relatively low – may have impact on efficacy
  - Primary outcome: might it have been superior?
  - Secondary outcomes: might it have been as effective for *durability* of remission?
  - Safety: might it have been *less safe* than IV CYC if used at our usual doses?
- Enrolled patients with NEW disease, not relapsing disease
  - In patients with relapsing AAV, RTX is SUPERIOR to CYC
  - Patients with relapsing disease more likely to relapse again

MMF is a remission induction option

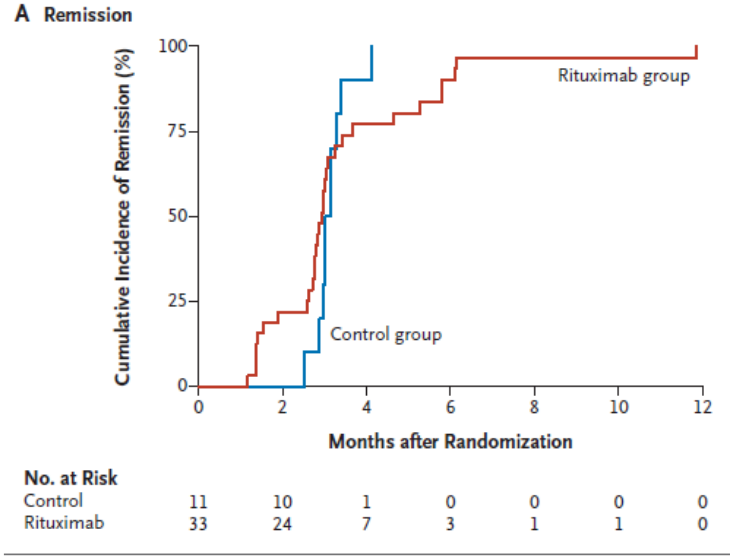
GPA Remission Induction: Rituximab

First FDA Approved Remission Induction Agent for AAV

RAVE



RITUXVAS



RTX = 375 mg/m2 IV weekly x 4 weeks; CYC = 2 mg/kg/day; AZA = 2 mg/kg/day.

Specks U, et al. For the RAVE study group. ANCA-Vasculitis Workshop. 2011; Stone JH, et al. *NEJM.* 2010; Jones RB, et al. *NEJM.* 2010.

Original Article

Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis

John H. Stone, M.D., M.P.H., Peter A. Merkel, M.D., M.P.H., Robert Spiera, M.D., Philip Seo, M.D., M.H.S., Carol A. Langford, M.D., M.H.S., Gary S. Hoffman, M.D., Cees G.M. Kallenberg, M.D., Ph.D., E. William St. Clair, M.D., Anthony Turkiewicz, M.D., Nadia K. Tchao, M.D., Lisa Webber, R.N., Linna Ding, M.D., Ph.D., Lourdes P. Sejismundo, R.N., B.S.N., Kathleen Mieras, C.C.R.P., David Weitzenkamp, Ph.D., David Ikle, Ph.D., Vicki Seyfert-Margolis, Ph.D., Mark Mueller, B.S., C.C.R.P., Paul Brunetta, M.D., Nancy B. Allen, M.D., Fernando C. Fervenza, M.D., Ph.D., Duvuru Geetha, M.D., Karina A. Keogh, M.D., Eugene Y. Kissin, M.D., Paul A. Monach, M.D., Ph.D., Tobias Peikert, M.D., Coen Stegeman, M.D., Ph.D., Steven R. Ytterberg, M.D., Ulrich Specks, M.D., for the RAVE−ITN Research Group

N Engl J Med. Volume 363(3):221-232. July 15, 2010.

The NEW ENGLAND JOURNAL of MEDICINE

RAVE: Rituximab for ANCA-Associated Vasculitis

Primary Objectives:

- Determine efficacy of rituximab on remission induction in pts with AAV compared with conventional therapy
- Compare safety profile of rituximab with that of conventional therapy

Primary Endpoint:

Non-inferiority study

- Percentage of patients who have achieved clinical remission and completed the steroid taper by 6 months (“complete remission”)

Important Inclusion Criteria

- Active severe AAV (WG or MPA)
  - According to Chapel Hill definitions
  - BVAS/WG ≥ 3
  - At least one “major” item on BVAS/WG or deemed severe enough to require CYC
  - *Allows enrollment of both “new” disease, as well as patients having SEVERE relapses of longer-standing disease*
- PR3-ANCA or MPO-ANCA positive at screening

RAVE: Important Exclusion Criteria

- Disease severity:
  - Limited disease, not requiring CYC
  - “Too severe” disease:
    - Mechanical ventilation because of alveolar hemorrhage
    - Serum creatinine > 4.0 mg/dl
    - ***Excluded the most severely ill patients***
- CYC use within 4 months prior to enrollment
- History of CYC toxicity or unresponsiveness
- Any previous RTX use

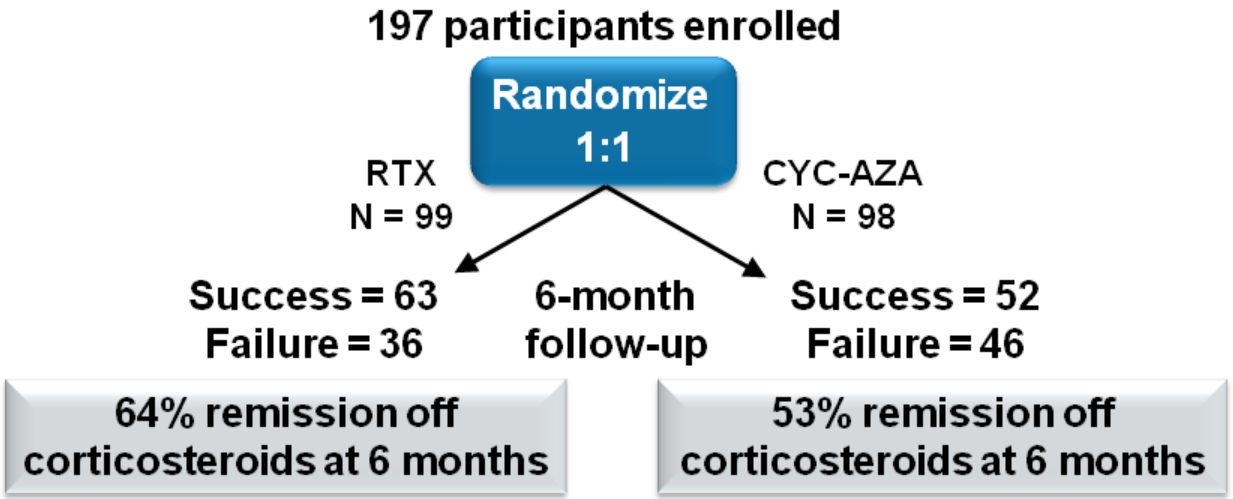
Important Exclusion Criteria

- Disease severity
  - **Limited disease, not requiring CYC**
  - **“Too severe” disease**:
    - Mechanical ventilation because of alveolar hemorrhage
    - Serum creatinine > 4.0 mg/dl
    - *Excluded the most severely ill patients*
- CYC use within 4 months prior to enrollment
- History of CYC toxicity or unresponsiveness
- Any previous RTX use

RAVE Design

Success/complete remission:

- BVAS/WG = 0
- Prednisone = 0
- No failure reason



Specks U, et al. For the RAVE study group. ANCA-Vasculitis Workshop. 2011; Clinical & Experimental Immunology Special Issue: 15th International Vasculitis and ANCA Workshop. May 2011; Volume 164, Issue Supplement s1:1-154.

Primary Efficacy Endpoint Analysis

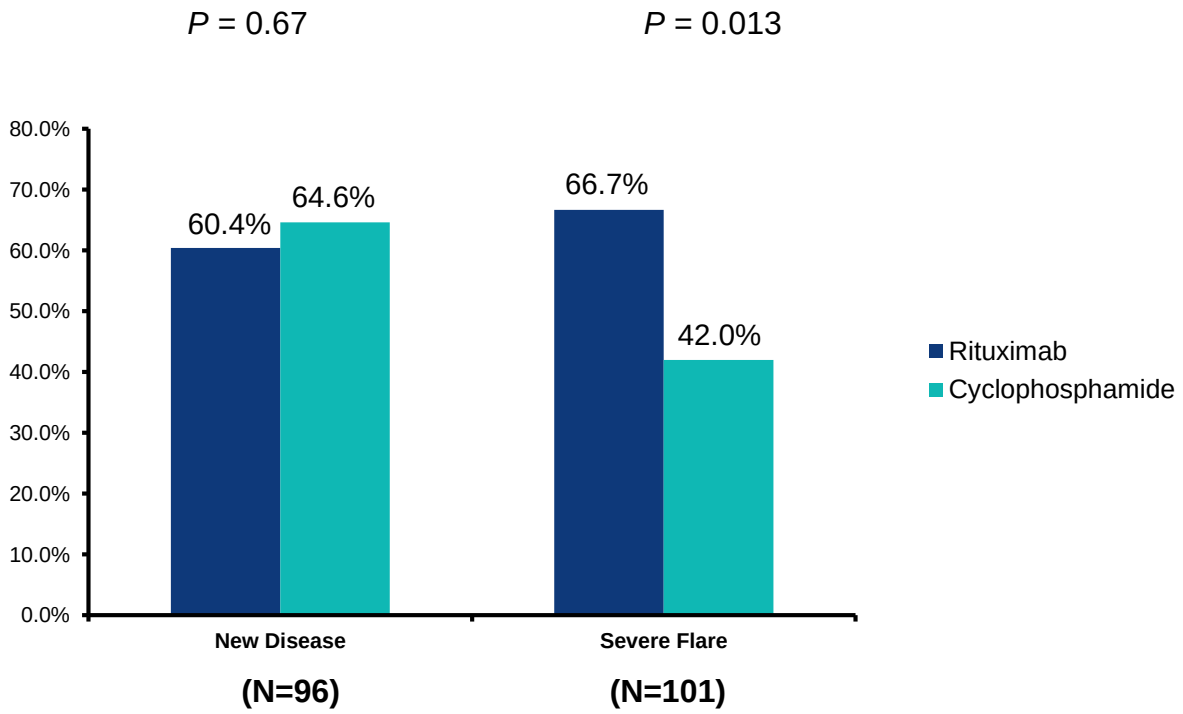
Complete Remission at 6 Months

BVAS/WG = 0 *and* Prednisone = **0 mg**

	Rituximab (N=99)	Cyclophosphamide (N=98)	Difference (%)	*P*
Yes 95% CI (%)	**63** (63.6%) 54.1, 73.2	**52** (53.1%) 43.1, 63.0	10.6	*0.089*

ITT analysis, worst case imputation

Treatment Response by Disease Status at Baseline



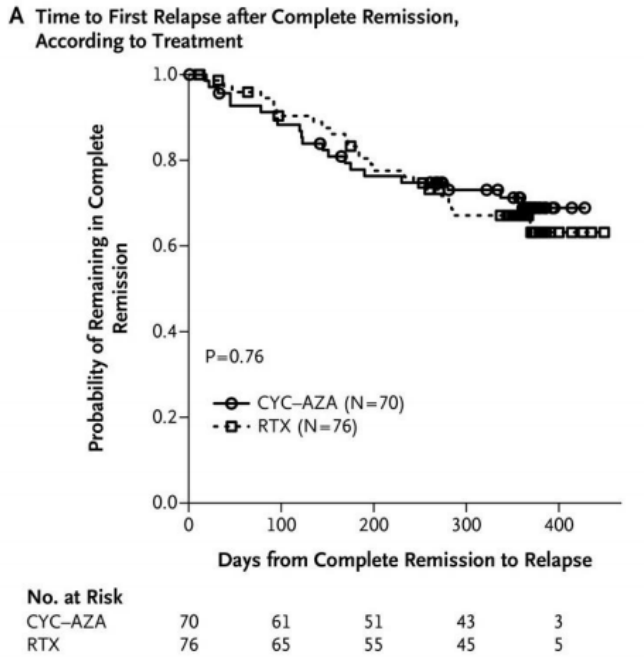
RAVE: Summary

- Demographic characteristics, disease phenotype and disease activity of patients were distributed equally across both treatment arms.
- Rituximab is not inferior to cyclophosphamide for remission induction in patients with severe AAV.
- There was no difference in treatment response to rituximab or cyclophosphamide in patients with major renal disease or alveolar hemorrhage.
- The treatment response to rituximab was superior to cyclophosphamide in patients who entered the trial with a severe disease flare.
- There was no difference in severe or limited disease flares by 6 months.
- There was no difference in severe adverse events rate by 6 months.
- Fewer patients in the rituximab arm had one or more of the protocol-selected AEs by 6 months.

Conclusions

- Rituximab represents the first proven alternative to cyclophosphamide for remission induction in severe ANCA-associated vasculitis.
- This is of particular importance for patients:
  - Who present with a severe disease flare
  - Who want to preserve their fertility

RAVE: Longer Term Follow-up at 18 Months



- 76 CR in the rituximab group
- 24 (32%) relapsed before month 18
- 70 CR in the CYC/AZA group
- 20 (29%) relapsed before month18 (P = 0.16)

Specks, et. *NEJM*. 2013.

Efficacy of Remission-Induction Regimens for AAV

1. A single course of RTX is as effective as 18 months of CYC-AZA.
    a. 39% CR in RTX vs 33% CR CYC/AZA at 18mths
    b. RTX superior in relapsing pts at 6 and 12mths but not 18mths
    c. 88% of RTX-treated pts who relapsed had detectable B cells at time of relapse
2. Relapses were more common in patients with:
    a. PR3-ANCA than MPO-ANCA
    b. GPA than MPA
    c. Severe relapse than new diagnosis at baseline
    d. No renal disease than renal disease at baseline
3. B cell depletion occurred in both treatment arms.
4. ANCA or B cell counts in isolation were poor predictors of relapse.
5. However, for as long as B cells remain depleted AND ANCA remains negative the risk of a severe flare is low.

NEJM. 2013.

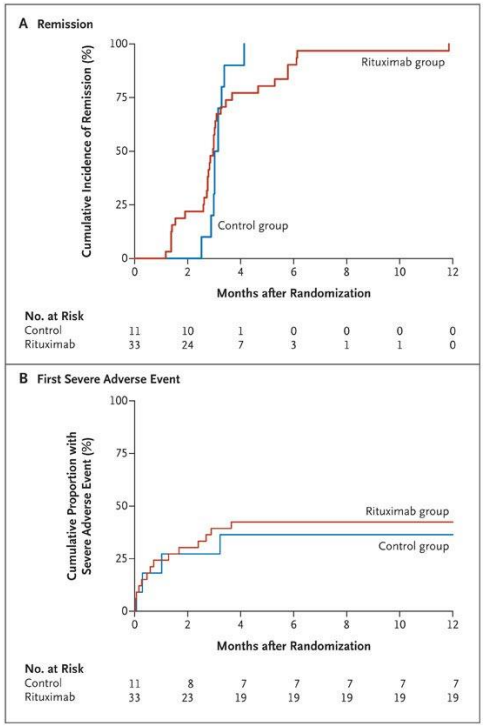
RAVE: *Caution*

- Did NOT include most severely ill AAV patients
- Did NOT include Churg Strauss (EGPA) patients
- Did NOT address remission induction in *limited* AAV
- Did NOT demonstrate *superior* safety profile to CYC with exception of expected hematologic complications
- Did NOT demonstrate *superior* efficacy to CYC, except in relapsing severe disease (PR3)
- Did NOT address remission maintenance
- Dose: “lymphoma” regimen (**375mg/m2 qwk x 4 wks)**

RITUXVAS

- AAV patients with newly diagnosed severe disease with renal involvement
- 3:1 randomized to
  - RTX (375mg/m2 x 4 doses) +IV-CYC x 2 doses vs
  - CYC IV followed by Aza
- Primary Endpoint: sustained remission at 12mths
  - 76% in RTX vs 82% CYC achieved primary endpoint
  - No difference in adverse events
- At 2 years, no difference in relapse, ESRD or death

Induction Therapy – RITUXIVAS



- Rituximab (plus Cyclophosphamide) was not inferior to Cyclophosphamide/azathioprine in inducing remission at 12mo
- No difference in severe adverse events
- High mortality rate of 18%

Jones RB et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *N Engl J Med*. 2010;363:211-220.

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RITUXVAS vs RAVE Considerations

- RITUXVAS enrolled sicker patient population than did RAVE
  - Relatively high mortality rate ~ 18% seen
- RITUXVAS was not blinded
- **RTX in RITUXVAS was NOT just rituximab, but RTX plus IV CYC x 2**
- Remission definition did not require to be off corticosteroids entirely (therefore higher remission rate than reported in RAVE)

AAV: Remission Induction in Severe Disease

- CYC and RTX both effective
- RTX more effective than CYC in patients with severe relapses of pre-existing disease (especially GPA)
- Non-inferiority of RTX has NOT been demonstrated in patients with the most severe disease: excluded from RAVE
  - Patients requiring mechanical ventilation
  - Patients with Creatinine >4 (attributable to AAV)
  - RITUXVAS did include those patients but gave them 2 doses IV CYC
- Fertility considerations
- Long term better safety of RTX vs CYC has been assumed/implied, but *never demonstrated* in the context of a clinical trial…cautionary tale – early CYC experience

Remission Induction of GPA/MPA: NOT Aalways CYC

- SEVERE dz: CYC (po>iv), RTX, ? MMF
  - RTX superior in patients with relapsing disease
  - In the most severe disease, favor CYC, or “RITUXVAS” regimen (CYC IVx2 plus RTX)
- LIMITED dz: MTX, MMF, RTX (probably AZA, ?TMP/SMX)

AAV Maintenance: No Role for CYC

Maintenance			
CYCAZAREM	AZA vs PO CYC in new or relapsing AAV after induction with PO CYC	Relapse rate	No difference in rates of relapse between treatment groups
WEGENT	AZA vs MTX after induction with IV CYC	Adverse events requiring discontinuation of treatment or death	No difference in adverse events and similar rates of relapse in both arms, majority of relapses occurred after study medication tapered off
IMPROVE	MMF vs AZA in newly diagnosed AAV after induction in CYCLOPS	Relapse-free survival	Relapse more common in MMF group with similar rates of adverse events
German Network of Rheumatic Disease Study	LEF vs MTX in GPA after induction with PO CYC	Relapse rate	Study terminated early because of high incidence of major relapse in MTX arm, though increased frequency of adverse events in LEF arm (dose 30mg/day)
Dutch Co-trimazole Study	TMP-SMX vs placebo in GPA during/after induction with PO CYC	Disease-free interval	Fewer relapses in patients on active treatment, though 20% discontinued TMP-SMX due to side effects
WGET	Etanercept vs placebo in addition to CYC (severe) or MTX (limited) for active GPA	Sustained remission for ≥6 months	Etanercept not effective for remission maintenance, 6 malignancies in etanercept group (all patients had prior CYC)
MAINRITSAN	AZA vs RTX (500mg q 6mth) in new or relapsing AAV after induction with IV CYC	% of patients with major relapse at month 28	Greater than 6-fold reduction in major relapse in RTX arm, NNT with RTX to prevent 1 major relapse = 4

CYCAZAREM

AZA vs CYC

- 155pts in remission randomized to PO CYC vs AZA
- All on AZA after 12mths
- Primary Outcome = relapse (major or minor)
- No difference between groups for relapse or adverse events
- Relapse rate lower in MPA pts

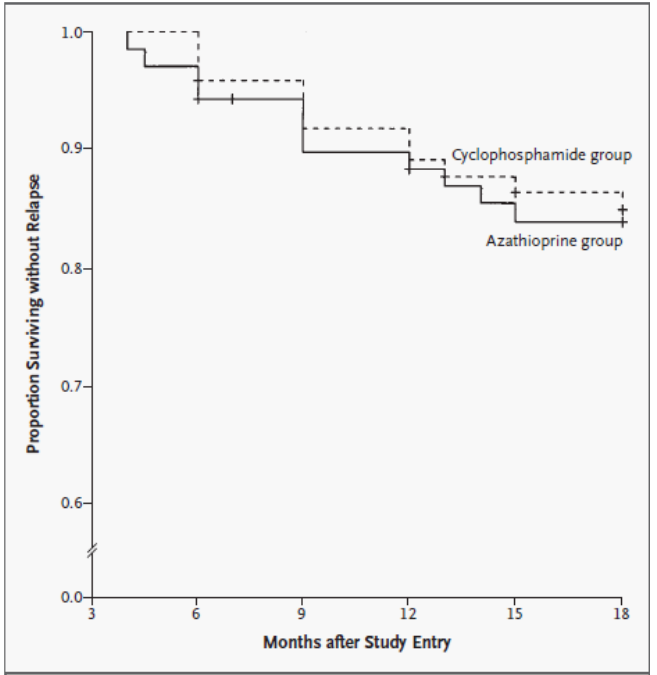

Figure 1. Kaplan–Meier Analysis of the Time to First Relapse in the Azathioprine and Cyclophosphamide Groups.

Jayne D et al. *NEJM.* 2003.

AAV: Remission Maintenance

- AZA as effective as CYC
- MTX and AZA comparable in efficacy
- AZA possibly superior to MMF
- Rituximab superior to AZA (MAINRITSAN trial)
- NET
  - RTX> AZA, MTX, ?> MMF

NO ROLE FOR CYC IN REMISSION MAINTENANCE

EGPA (Churg-Strauss)

- Small vessel vasculitis
- ANCA present in ~40% patients (usually MPO)
- Asthma
- ENT involvement
- Peripheral hyper-eosinophilia
- Necrotizing vasculitis with tissue infiltration of eosinophils and granulomatous inflammation
  - Skin
  - Renal
  - Nervous system (peripheral and central)
  - GI
  - Cardiac

EGPA vs GPA/MPA: Therapeutic Considerations

- Can treat some patients with CS alone (without concurrent immunosuppressives) (consider “Five Factor Score”)
- Frequent diagnostic uncertainty regarding disease “activity”
  - **Pulmonary disease: asthma or “disease”?**
  - **Sinonasal disease: allergic rhinitis or “disease”?**
- Absence of prospective trials to guide management
- Open label descriptive experiences with retrospective analysis of factors influencing prognosis
- Often difficult to fully wean CS due to sinonasal and pulmonary issues – ***generally not “vasculitic” manifestations***

EGPA: General Therapeutic Approach

- Asthma, sino-nasal allergic component: optimize supportive management
  - Collaboration with pulmonary, ENT, allergist
- Vasculitis
  - Corticosteroids
  - Immunosuppressives
    - Role in “remission induction” (if FFS≥2 or cardiac, CNS, renal disease)
    - Role in “remission maintenance”
    - Role as “steroid sparing” intervention

EGPA: Immunosuppressive Rx

No Prospective RDBCT to Inform Decisions (Except Mepolizumab, NOT for Induction)

- Remission Induction
  - Cyclophosphamide (FFS>2, or FFS 1 with cardiac or CNS disease, ?? *or* if +ANCA)
  - MTX, AZA (FFS 1, but less severe organ involvement)
  - RTX (one retrospective study, 41 patients)
    - Better efficacy in patients with +ANCA
    - Not clear that has steroid sparing benefit in lower dose (<10mg/d) range
- Remission Maintenance
  - Azathioprine
  - MTX
  - MMF, LEF
  - Mepolizumab (anti-IL5)
  - Misc??: Hydroxyurea, IFNa, omalizumab (anti-IgE)

EGPA: Role for CYC

- Probably YES for
  - Severe disease, in particular cardiac or CNS involvement especially if ANCA negative

Summary: Is There Still a Role for Cyclophosphamide in AAV?

- Consider concepts of remission induction vs maintenance, severe vs limited disease, and treating disease activity, not damage
- Probably no role for CYC in disease that is not severe or in remission maintenance
- Route of CYC: IV probably as effective as po, may be safer, but less durable in terms of later relapses
- CYC is probably safer than what we glean from older literature
  - Shorter courses, better awareness/management of complications
- Rituximab preferable to CYC in most GPA/MPA
  - Fertility concerns with CYC
  - Exception: Most severe disease; consider RITUXVAS regimen: RTX plus IV CYC x 2
- CYC probably preferable in severe EGPA, especially ANCA negative with CNS or cardiac involvement