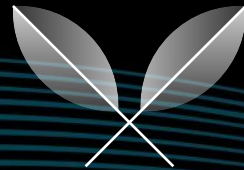


ANCA-Associated Vasculitis



Anousheh Haghighi M.D.

Rheumatologist

Professor of IUMS

Gorgan 2025

A 20-year-old male with no past medical history presents to the emergency department with low grade fever, left ear pain and dyspnea for 4 weeks. Review of systems was positive for chronic sinusitis.



On presentation, patient was febrile (38.2 degrees Celsius), heart rate of 110, blood pressure of 110/60 and oxygen saturation 94%.

CT. scan of the chest showed numerous bilateral pulmonary nodules/masses, ranging from 20-60 mm in diameter.



Metabolic profile:

Cr: 2.72 mg/dl

UA: 3+ blood and +1 protein

Anti-PR3 was positive

What is the
best treatment
option for this
patient?

Glucocorticoid+ Rituximab?

Glucocorticoid+Cyclophosphamide?

Glucocorticoid+Cyclophosphamide+
Rituximab?

High dose or low dose steroid?

Induction Therapy

Rituximab VS Cyclophosphamide

RAVE: Rituximab VS
Cyclophosphamide in
ANCA-Associated
Vasculitis
2010



RITUXVAS: Rituximab
VS Cyclophosphamide in
ANCA-Associated Renal
Vasculitis
2010



RITAZAREM: Rituximab
VS Azathioprine in
relapsing ANCA-
Associated Vasculitis
2017

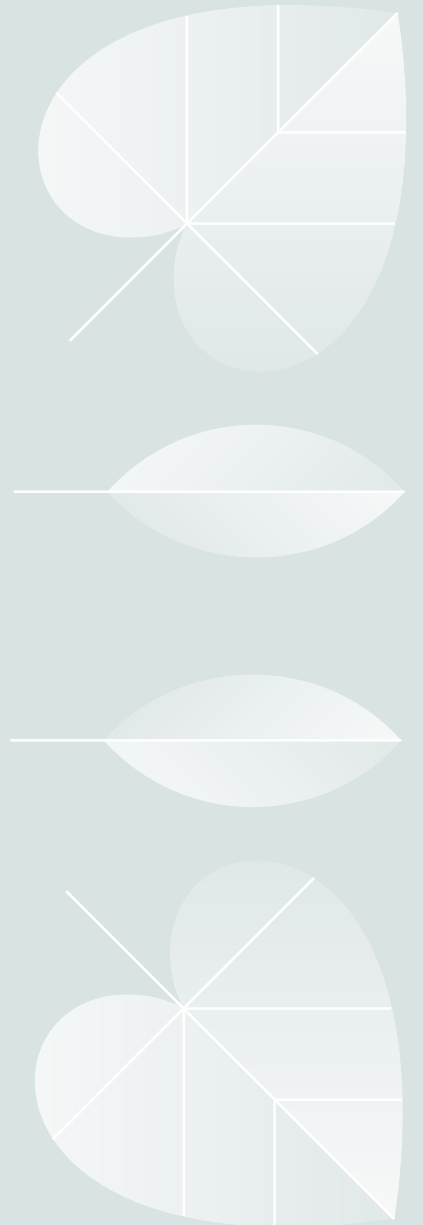


**All studies
approved non-
inferiority of
Rituximab**

**Rituximab is preferred for relapsing disease based on data from
RAVE & RITAZAREM trials.**

But ...

- An important consideration when reviewing these trials is that patients with **alveolar hemorrhage requiring mechanical ventilation** or with serum **creatinine levels >4 mg/dL** were excluded from enrollment in the RAVE and RITAZAREM trials.
- It remains uncertain whether the **ANCA serotype** affects the response to the specific induction regimen.



Arthritis & Rheumatology 2023

JASN
2020



AN OFFICIAL JOURNAL OF
THE AMERICAN COLLEGE OF
RHEUMATOLOGY

AMERICAN COLLEGE
of RHEUMATOLOGY
Empowering Rheumatology Professionals

Full Length

Comparative Effectiveness of Rituximab- Versus Cyclophosphamide-Based Remission Induction Strategies in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis for the Risk of Kidney Failure and Mortality

Zachary S. Wallace , Xiaoqing Fu, Claire Cook, Catherine Ahola, Zachary Williams, Brett Doliner, Jennifer S. Hanberg, John H. Stone, Yuqing Zhang, Hyon K. Choi

First published: 03 April 2023 | <https://doi.org/10.1002/art.42515>

CLINICAL RESEARCH

www.jasn.org

Efficacy of Rituximab and Plasma Exchange in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis with Severe Kidney Disease

Marta Casal Moura ¹, Maria V. Irazabal ², Alfonso Eirin,² Ladan Zand,² Sanjeev Setl
Bijan J. Borah,^{4,5} Jeffrey L. Winters,⁶ James P. Moriarty,^{4,5} Rodrigo Cartin-Ceba,⁷
Alvise Berti ¹, Misbah Baqir,¹ Gwen E. Thompson,¹ Ashima Makol,⁸
Kenneth J. Warrington,⁸ Viengneesee Thao,^{4,5} Ulrich Specks ¹ and
Fernando C. Fervenza ²

median estimated glomerular filtration rate 37.3 ml/minute/1.73 m²
Rituximab- and cyclophosphamide-based remission induction strategies for AAV are associated with similar risks of kidney failure and death.

eGFR <30 ml/min per 1.73 m²

The apparent benefits and risks of using CYC or RTX for the treatment of patients with AAV and severe kidney disease are balanced.

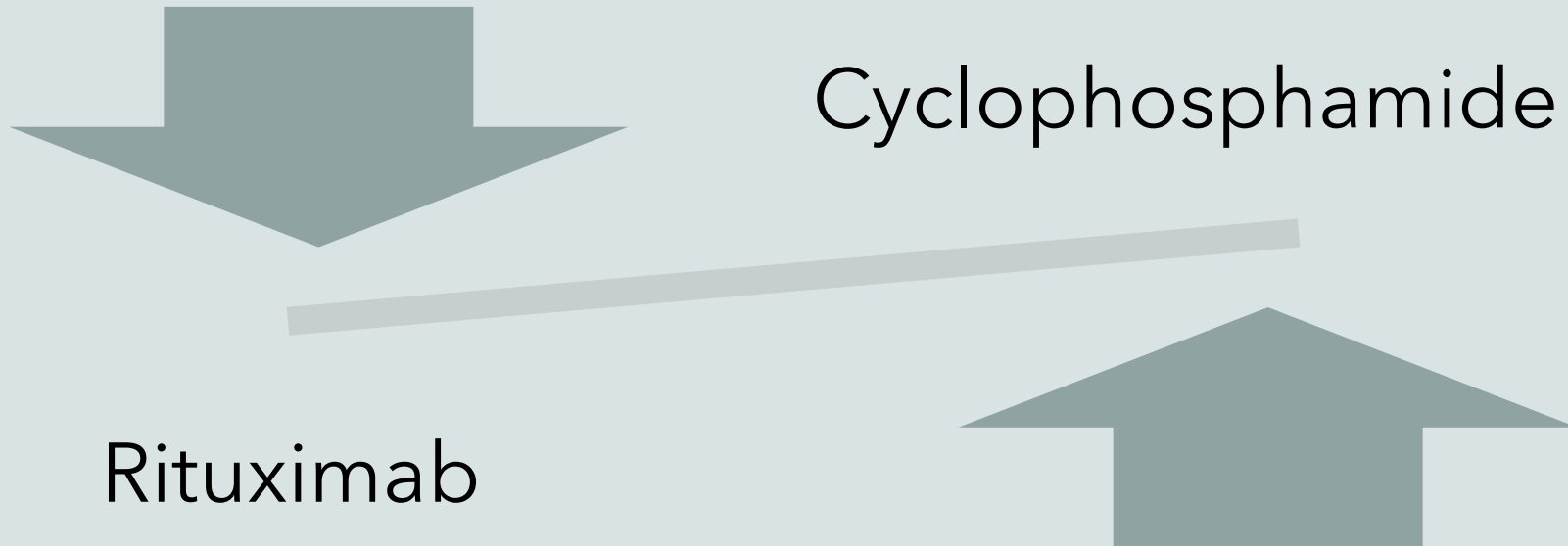
Diffuse Alveolar Hemorrhage Secondary to Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Predictors of Respiratory Failure and Clinical Outcomes

Rodrigo Cartin-Ceba,¹ Luis Diaz-Caballero,² Mazen O. Al-Qadi,³ Stavros Tryfon,⁴
Fernando C. Fervenza,¹ Steven R. Ytterberg,¹ and Ulrich Specks¹

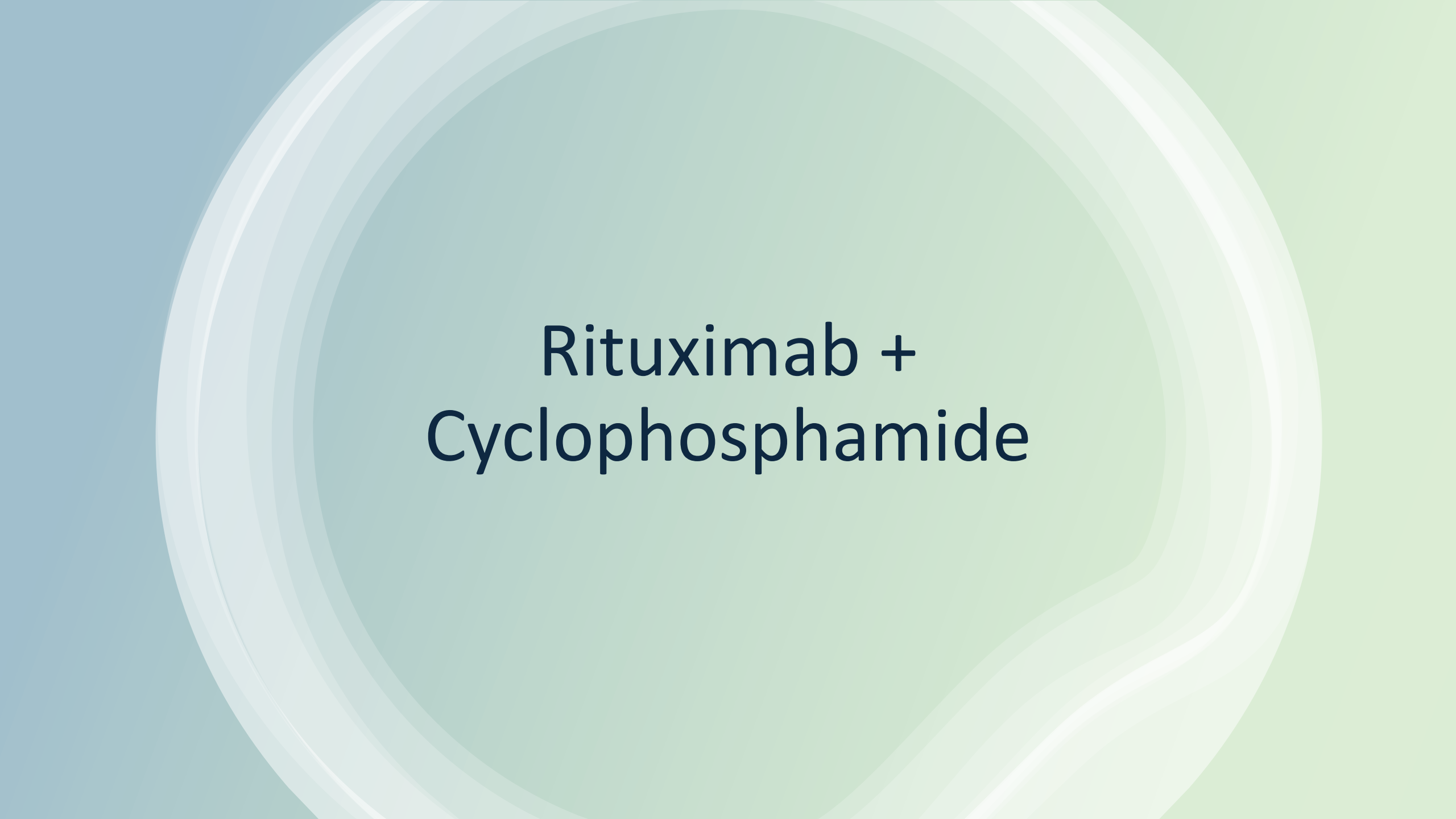
- Complete remission at six months was achieved at a higher rate with rituximab than with cyclophosphamide in patients with DAH secondary to AAV including those needing mechanical ventilation.

Which One Is Better?!



KDIGO 2024

Rituximab preferred	Cyclophosphamide preferred
• Children and adolescents • Premenopausal women and men concerned about their fertility • Frail older adults • Glucocorticoid-sparing especially important • Relapsing disease • PR3–ANCA disease	• Rituximab difficult to access • Severe GN (SCr >4 mg/dl [354 µmol/l]), combination of 2 intravenous pulses of cyclophosphamide with rituximab can be considered



Rituximab + Cyclophosphamide

Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis

Stephen P. McAdoo^{1,2}, Nicholas Medjeral-Thomas², Seerapani Gopaluni³, Anisha Tanna^{1,2}, Nicholas Mansfield², Jack Galliford^{1,2}, Megan Griffith^{1,2}, Jeremy Levy^{1,2}, Thomas D. Cairns², David Jayne³, Alan D. Salama⁴ and Charles D. Pusey^{1,2}

¹Renal and Vascular Inflammation Section, Department of Medicine, Imperial College London, London, UK, ²Vasculitis Clinic, Imperial College Healthcare NHS Trust, London, UK, ³Department of Medicine, University of Cambridge, Cambridge, UK and ⁴Centre for Nephrology, University College London, London, UK

This regimen is potentially superior to current standards of care (disease remission, rates of major relapse, risk of death, serious infection rate).

Original article

A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody–associated vasculitis

Ruth J. Pepper^{1,†}, Stephen P. McAdoo^{2,3,†}, Sarah M. Moran⁴, Dearbhla Kelly⁴, Jennifer Scott⁴, Sally Hamour¹, Aine Burns¹, Megan Griffith^{2,3}, Jack Galliford³, Jeremy B. Levy^{2,3}, Thomas D. Cairns³, Seerapani Gopaluni⁵, Rachel B. Jones⁵, David Jayne⁵, Mark A. Little ^{4,6}, Charles D. Pusey^{2,3,†} and Alan D. Salama^{1,†}

Combination treatment with rituximab, low-dose cyclophosphamide and plasma exchange for severe antineutrophil cytoplasmic antibody-associated vasculitis



OPEN

2021

Kavita Gulati^{1,2,3}, Helena Edwards^{1,3}, Maria Prendecki^{1,2}, Thomas D. Cairns¹, Marie Condon¹, Jack Galliford¹, Megan Griffith^{1,2}, Jeremy B. Levy^{1,2}, Frederick W.K. Tam^{1,2}, Anisha Tanna¹, Charles D. Pusey^{1,2} and Stephen P. McAdoo^{1,2}

¹Vasculitis Clinic, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; and ²Centre for Inflammatory Disease, Immunology & Inflammation, Imperial College London, London, UK

Permit glucocorticoid avoidance and provide rapid and prolonged disease control



Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity



Adding low dose cyclophosphamide to rituximab for remission-induction may prolong relapse-free survival in patients with ANCA vasculitis: A retrospective study

Renée Ysermans^a, Matthias H. Busch^a, Joop P. Aendekerk^a, Jan G.M.C. Damoiseaux^b,
Pieter van Paassen^{a,*}

^a Department of Internal Medicine, Division of Nephrology and Clinical Immunology, Maastricht University Medical Center, P. Debyelaan 25, 6202AZ, Maastricht, the Netherlands

^b Central Diagnostic Laboratory, Maastricht University Medical Center, P. Debyelaan 25, 6202AZ, Maastricht, the Netherlands

The rate of infections, hypogammaglobulinemia, end-stage renal disease, malignancies, and mortality did not differ after two and five years

Combination Cyclophosphamide and Rituximab to Minimize Glucocorticoid Use in Antineutrophil Cytoplasm Antibody–Associated Vasculitis

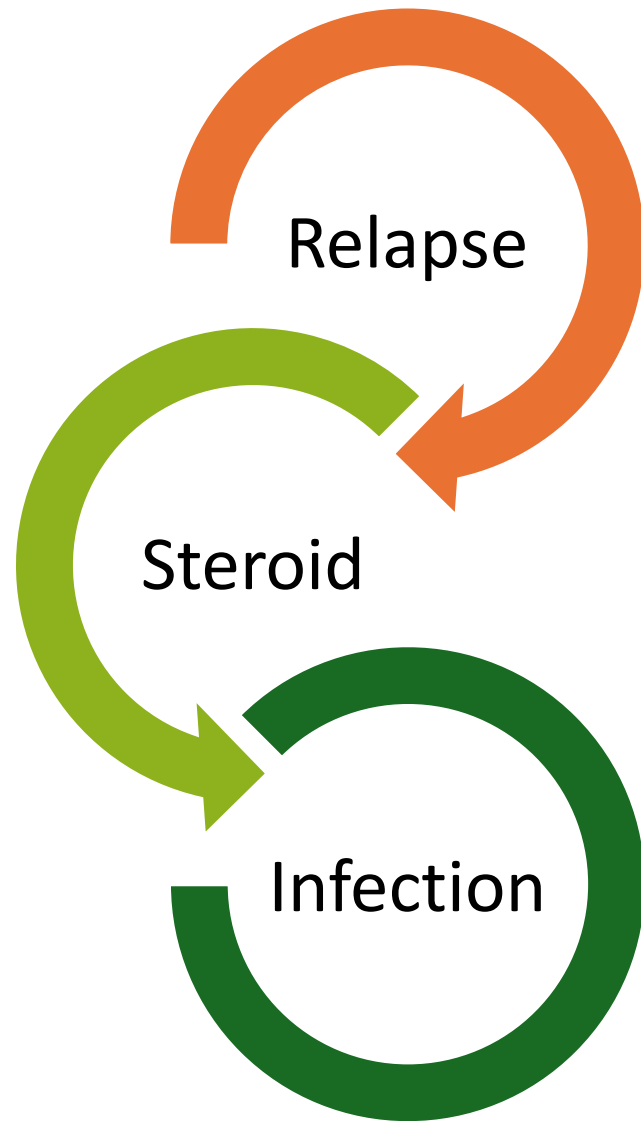


2025

Tania Salehi^{1,2}, Gavin B. Chapman^{1,3}, Tariq E. Farrah^{1,3}, Fiona A. Chapman^{1,3}, Dan Pugh^{1,3}, Robert W. Hunter^{1,3} and Neeraj Dhaun^{1,3}

¹Department of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK; ²Central and Northern Adelaide Renal and Transplantation Service, Adelaide, South Australia, Australia; and ³Edinburgh Kidney Research Group, University/BHF Centre for Cardiovascular Science, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

Initial treatment with i.v. methylprednisolone may be unnecessary



Combination
Therapy ?

RTX/CYC combination in Guidelines

ACR 2021: Data regarding the efficacy of combined cyclophosphamide and rituximab therapy for remission induction remain limited, and potential toxicity of this combination remains a concern..



EULAR 2022: The RTX/CYC combination has been shown to be CYC reducing in RITUXVAS, and retrospective studies have indicated the possibility of GC minimization and improved responses that **require investigation** in an RCT .



KDIGO 2024: Severe GN (**Cr >4 mg/dl**), combination of 2 intravenous pulses of cyclophosphamide with rituximab **can be considered**.

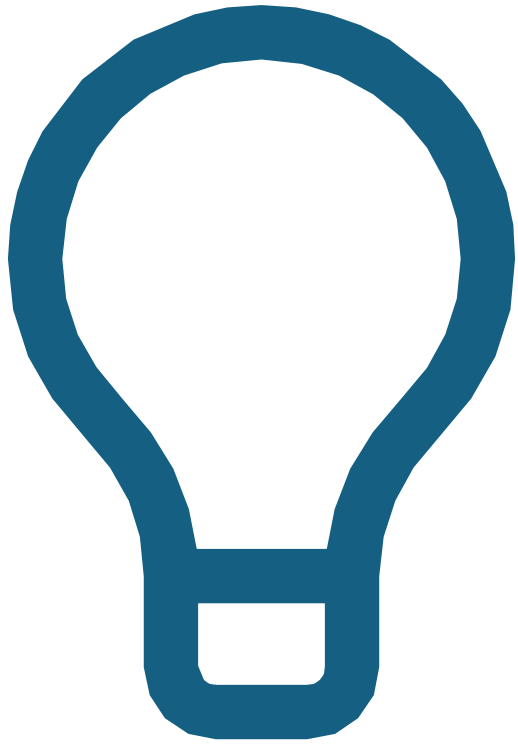


Combination with rituximab and cyclophosphamide

UpToDate 2025



- there is **no expert consensus** as to which patients should receive the combination of rituximab and cyclophosphamide for induction of remission for GPA or MPA. This approach is based on several observational studies and limited trial data suggesting there may be a benefit in terms of **lower exposure to glucocorticoids and lower infectious complications**, while maintaining similar remission rates



So, consider combination
therapy for severe cases!



RTX/CYC combination

Rituximab 500 mg/week $\times$ 4 weeks

Cyclophosphamide 15 mg/kg at weeks 0 and 2

OR

Rituximab 1 g at 0 and 2 weeks with
Cyclophosphamide 500 mg/2 weeks $\times$ 6

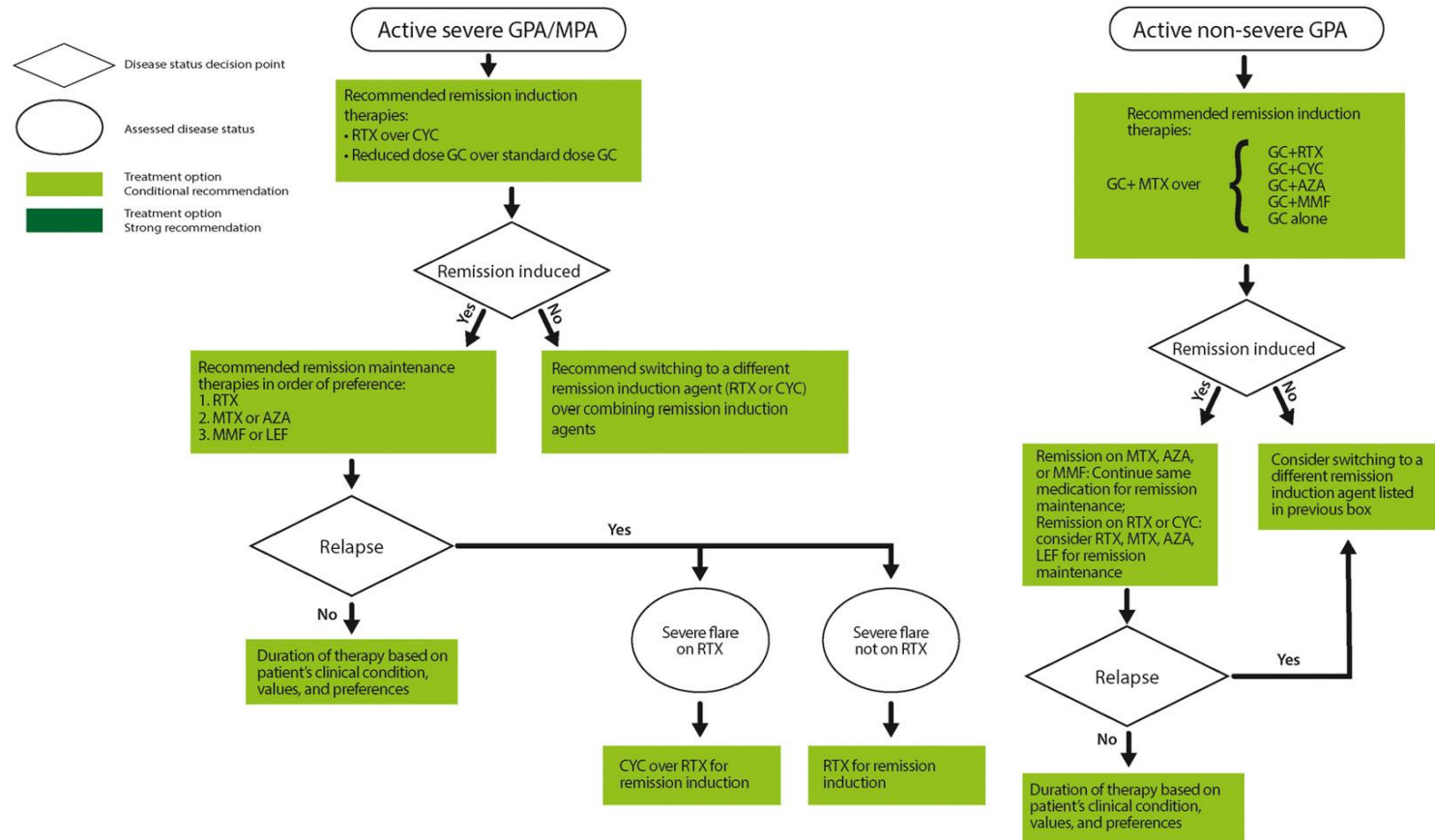
A collection of various colorful pills and capsules scattered on a light surface. The pills include blue, pink, white, yellow, green, and red ones, some with markings like 'X' or 'L'.

Low Dose vs High Dose Glucocorticoid



WHICH ONE IS BETTER?!

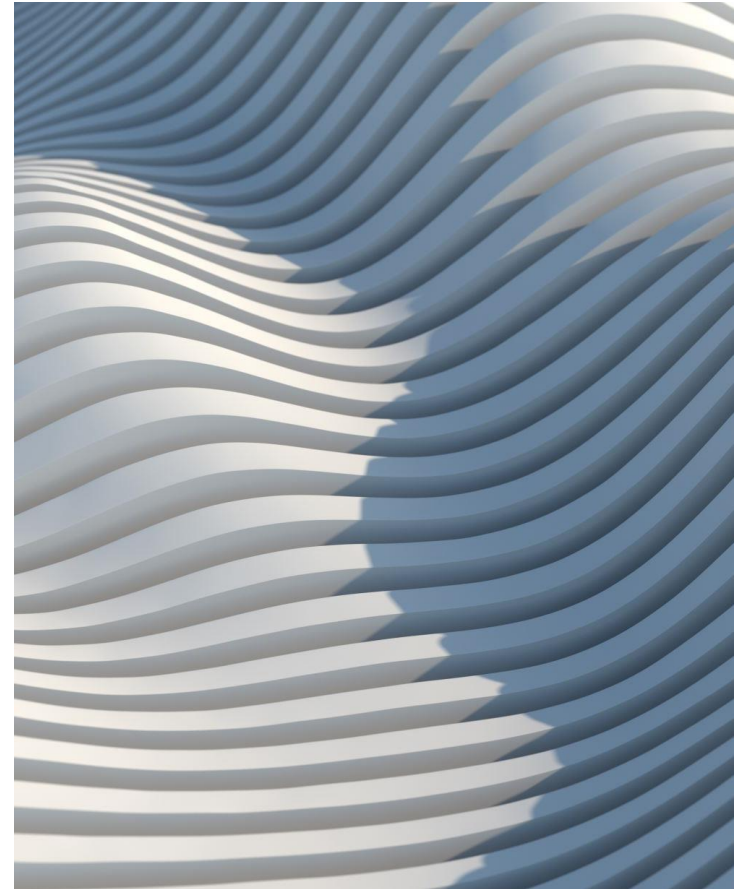
ACR 2021



EULAR 2022

It is **premature** to give a general recommendation to use lower GC starting doses of 0.5mg/kg for remission induction in all patients with active AAV.

For now, lower GC starting doses of 0.5 mg/kg/day may be considered on an individual basis in selected patients **without life-threatening or organ-threatening disease.**



KDIGO 2024

Oral glucocorticoids with rapid tapering are preferred over slower tapering.

Following cyclophosphamide induction, oral prednisolone should be reduced to a dose of 5 mg/d by 6 months.

Following rituximab induction, prednisolone can be withdrawn by 6 months.



2025 BSR Management recommendations for AAV



Striving to improve care for people living with AAV



(1) Management of GPA and MPA

- All people with active (newly diagnosed or relapsed) GPA/MPA should be considered as having potentially life or organ-threatening disease
- Treatment should follow 2 paradigms: Remission induction and remission maintenance
- CYC or RTX are recommended for induction remission. RTX is preferred in those with active relapsing disease
- Reduced dose GC tapering regimens are recommended.
- Avacopan should be considered in active disease to reduce GC-related morbidity
- Adjunctive plasmapheresis should be considered in cases of severe kidney involvement but NOT pulmonary haemorrhage alone



(2) Management of SGS and ENT disease associated with GPA

- Both subglottic stenosis and sino-nasal disease are challenging disease manifestations that require expert management by an ENT ± specialist with expertise in vasculitis
- The term 'limited GPA' may underestimate disease burden; terms such as 'ENT-localised GPA' or 'sino-nasal GPA' are preferred
- Systemic therapy with CYC or RTX can provide early disease control, delay need for recurrent dilatations in SGS, and limit morbidity in ENT disease
- Care is required to identify potential sino-nasal disease mimics, including recognition of cocaine-associated vasculitis conditions

(3) Management of EGPA



- EGPA should be considered in anyone with asthma, rhinosinusitis and an eosinophil count $\geq 1 \times 10^9/L$
- Treatment should follow 2 paradigms: Remission induction and remission maintenance
- Anti-IL-5/5R biologics are recommended (if available) in non-life and non-organ-threatening disease to reduce glucocorticoid-related morbidity
- Life-threatening disease should be treated with CYC or RTX, if there is intolerance or contraindication to CYC

(4) AAV Service specification



- Specialist vasculitis review within 7 days for people with new suspected AAV is associated with fewer serious infections, hospital admissions and reduced mortality
- Nurse-led components of care, specialist vasculitis MDT meetings and cohorted clinics are associated with improved health outcomes

(5) Patient education and support

- All adults, children and young people with AAV (and their families and carers) should receive ongoing, tailored information and education about AAV
- People with AAV should be empowered to collaborate in shared decision making with their healthcare team to reach a joint decision about their care

- AAV = ANCA-associated vasculitis
- Anti-IL-5/5R = anti-interleukin 5/5 receptor
- CYC = cyclophosphamide
- EGPA = eosinophilic granulomatosis with polyangiitis
- ENT = ear, nose and throat
- GC = glucocorticoid

- GPA = granulomatosis with polyangiitis
- MDT = multidisciplinary team
- MPA = microscopic polyangiitis
- RTX = rituximab
- SGS = subglottic stenosis

Scan the QR code for the full guideline
or visit rheumatology.org.uk/guidelines



Week	'Reduced-corticosteroid dose' in PEXIVAS trial		
	<50 kg	50–75 kg	>75 kg
1	50	60	75
2	25	30	40
3–4	20	25	30
5–6	15	20	25
7–8	12.5	15	20
9–10	10	12.5	15
11–12	7.5	10	12.5
13–14	6	7.5	10
15–16	5	5	7.5
17–18	5	5	7.5
19–20	5	5	5
21–22	5	5	5
23–52	5	5	5
>52	Investigators' local practice		



Avacopan

Some clinicians use the complement C5a receptor inhibitor avacopan as an adjunctive agent with standard induction therapy to limit the use of glucocorticoids.

The background features decorative leaf patterns in the corners. The top-left and top-right corners contain clusters of several elongated, pointed leaves. The bottom-left and bottom-right corners contain a single large, rounded leaf with internal vein lines, and a small cluster of two leaves below it.

Role of Plasma Exchange



EULAR 2022

- *PLEX may be considered as part of therapy to induce remission in GPA or MPA for those with a serum **creatinine** >3.4 due to active glomerulonephritis.*
 - *Routine use of PLEX to treat alveolar hemorrhage in GPA and MPA is not recommended.*
-

KDIGO 2024 PLEX

Add plasma exchange for patients with an overlap syndrome of ANCA-associated vasculitis and **Anti-GBM**

Consider plasma exchange for patients with **Cr >3.4 mg/dl**, patients requiring **dialysis** or with **rapidly increasing Cr**, and patients with diffuse **alveolar hemorrhage who have hypoxemia**.

Role of Plasma Exchange UpToDate 2025

- **Double-positive anti-GBM and ANCA-associated disease**
- **Severe kidney disease** -controversial, serum creatinine ≥4.0 mg/dL? Presence of active inflammation without significant glomerulosclerosis in kidney biopsy?
- **Pulmonary hemorrhage** -There is more uncertainty regarding the efficacy of plasma exchange in patients with GPA or MPA and severe diffuse alveolar hemorrhage.





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- MPA = microscopic polyangiitis
- RTX = rituximab
- SGS = subglottic stenosis

Scan the QR code for the full guideline
or visit rheumatology.org.uk/guidelines



- Adjunctive plasmapheresis should be considered in cases of severe kidney involvement but NOT pulmonary haemorrhage alone

Maintenance Therapy

When to Start Maintenance Therapy?

For patients treated with rituximab, maintenance therapy typically begins between **months four and six** after the last induction dose.

For patients treated with cyclophosphamide, maintenance therapy is started **two to four weeks** after the last dose of cyclophosphamide if WBC is >3500, and the ANC is >1500.

Choice of Maintenance Therapy



Choice of maintenance therapy



Dosing of Maintenance Therapy





ACR Guideline 2021

- For patients with GPA/MPA who are receiving rituximab for remission maintenance, we conditionally recommend **scheduled re-dosing** over using ANCA titers or CD19 + B cell counts to guide re-dosing.
-

EULAR Guideline 2022

*We recommend **structured clinical assessment**, rather than ANCA and/or CD19+ B cell testing alone.*

*We recommend **measurement of serum immunoglobulin concentrations** prior to each course of RTX.*



KDIGO Guideline 2024

- Scheduled dosing protocol:

500 mg at mo 6, 12, and 18 thereafter (MAINRITSAN scheme)

OR

1000 mg at mo 4, 8, 12, and 16 after the first infusion (RITAZAREM scheme, in relapsing cases)



UpToDate 2025

It is not clear whether there is any best option!

- **500 to 1000 mg every six months**
 - **500 every four months**
 - **"on-demand" dosing strategy** (in patients whose CD19-positive cell count increased above 20 cells/microL and whose PR3-ANCA titers were positive). Some studies found that about one third of relapsing patients had depleted CD19-positive cell counts.
 - Some experts also routinely monitor **serum immunoglobulin** levels and reduce the dose of rituximab in patients who develop hypogammaglobulinemia. Others only monitor serum immunoglobulin levels if the patient develops frequent infections.
-

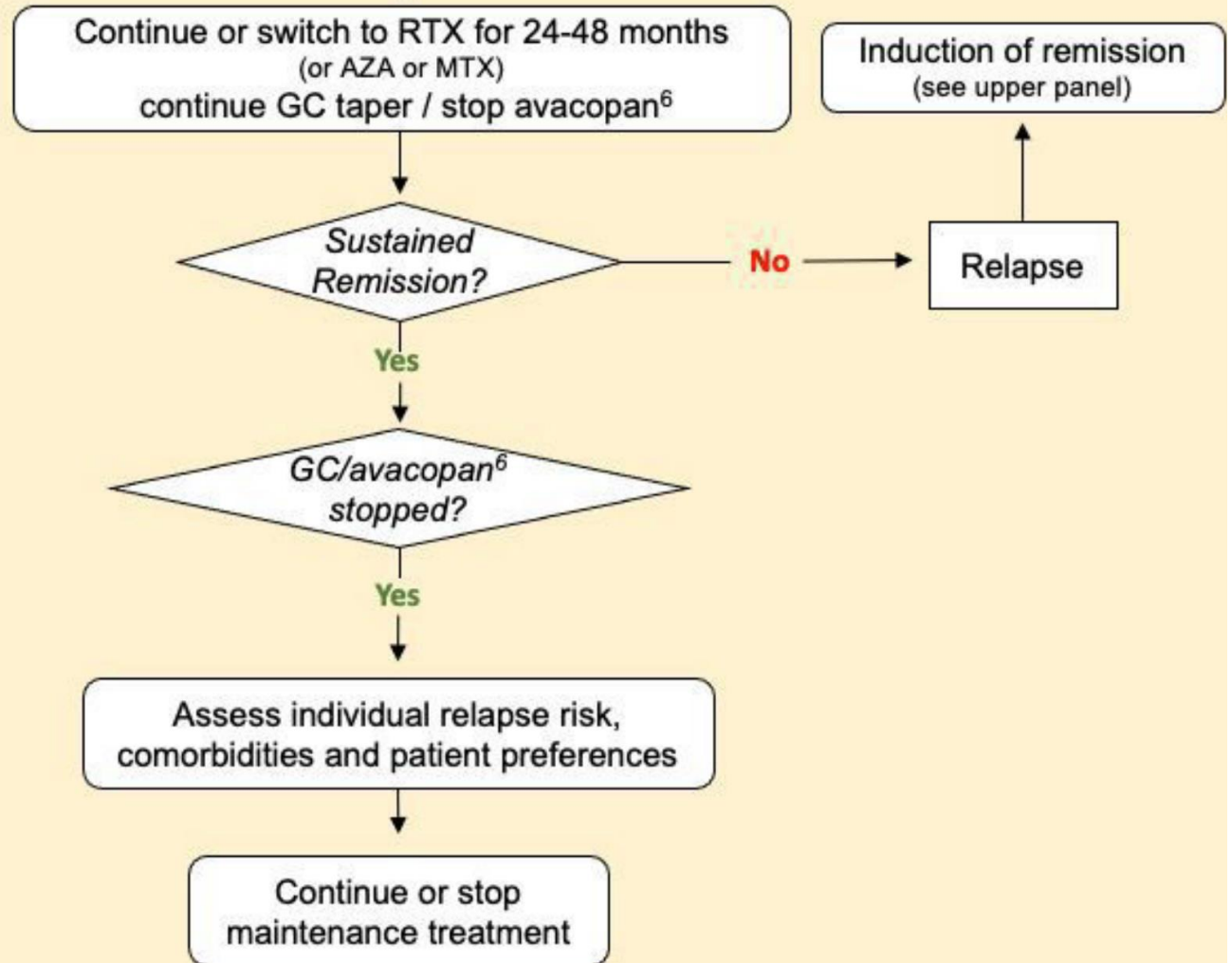
Duration of Maintenance Therapy



Duration of Maintenance Therapy

EULAR 2022

Maintenance of Remission



Duration of Maintenance Therapy

KDIGO
2024

The optimal duration of remission therapy is between 18 months and 4 years after induction of remission.

Duration of Maintenance Therapy

UpToDate
2025

6-36 months

In what situation maintenance therapy should be continued indefinitely?

in patients who have had one or more prior relapses, particularly in those who sustained significant organ damage (e.g., those with limited residual kidney function) and therefore would not tolerate further injury due to relapse.

So ...

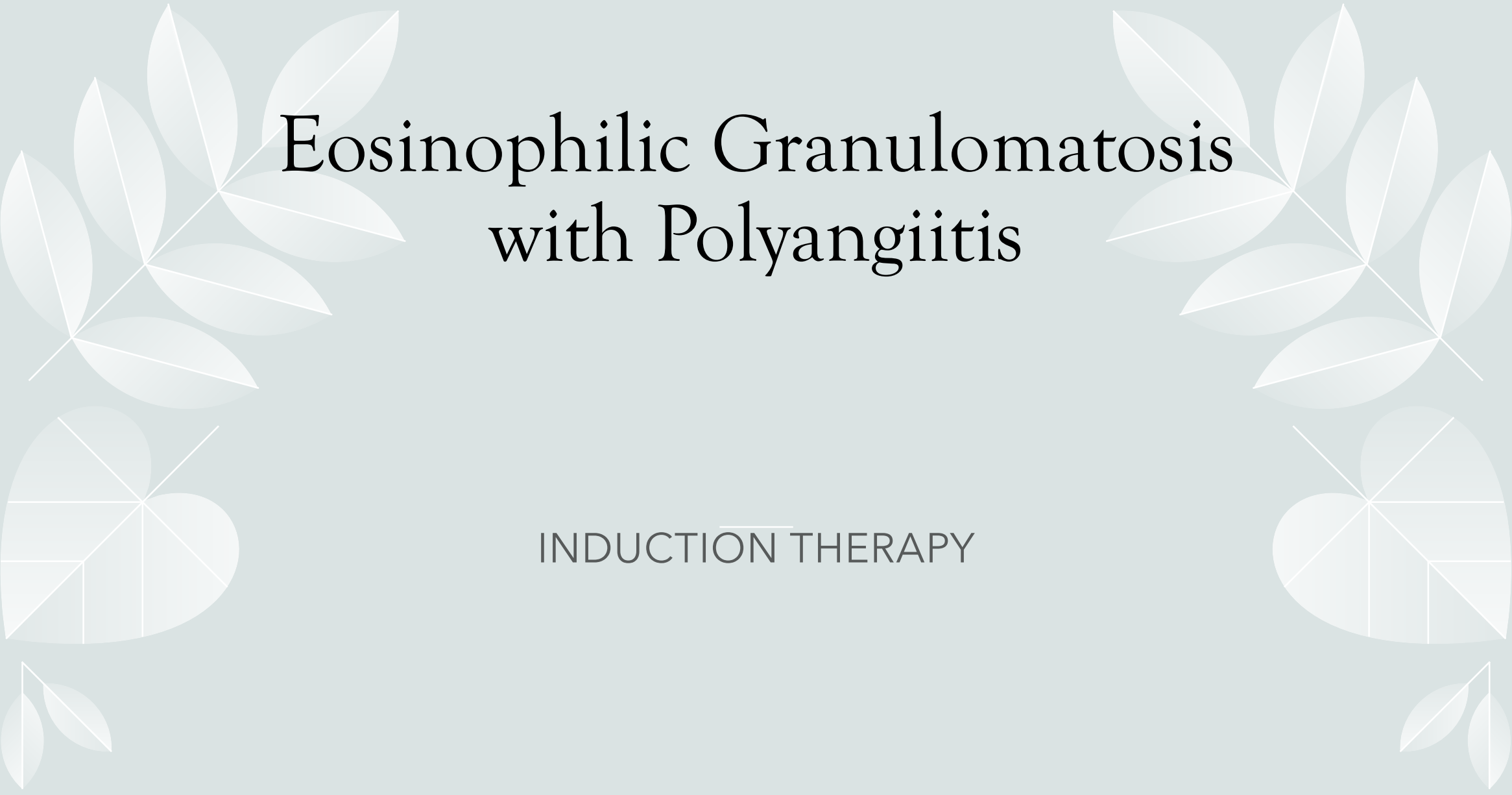
- Currently: **at least 18 months**
- May be more in severe cases



Investigational Agents

- Abatacept, Belimumab, Vilobelimab,
and B cell-targeted immunotherapy
- Additional studies are required



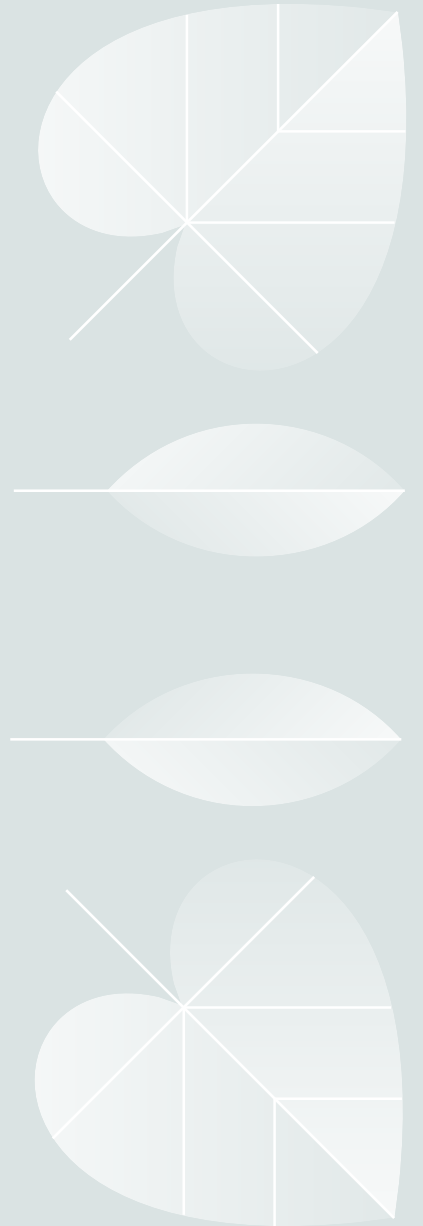
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Eosinophilic Granulomatosis with Polyangiitis

INDUCTION THERAPY

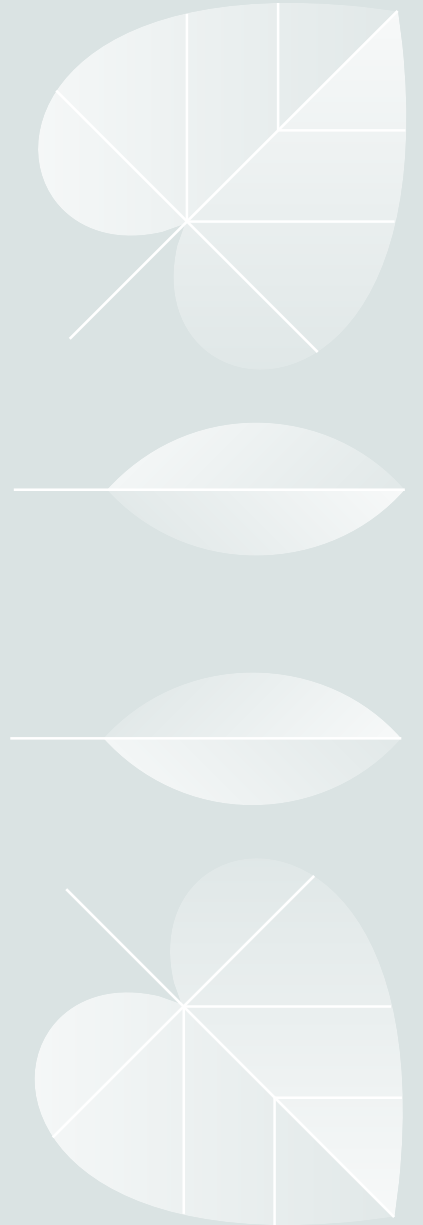
Severe EGPA

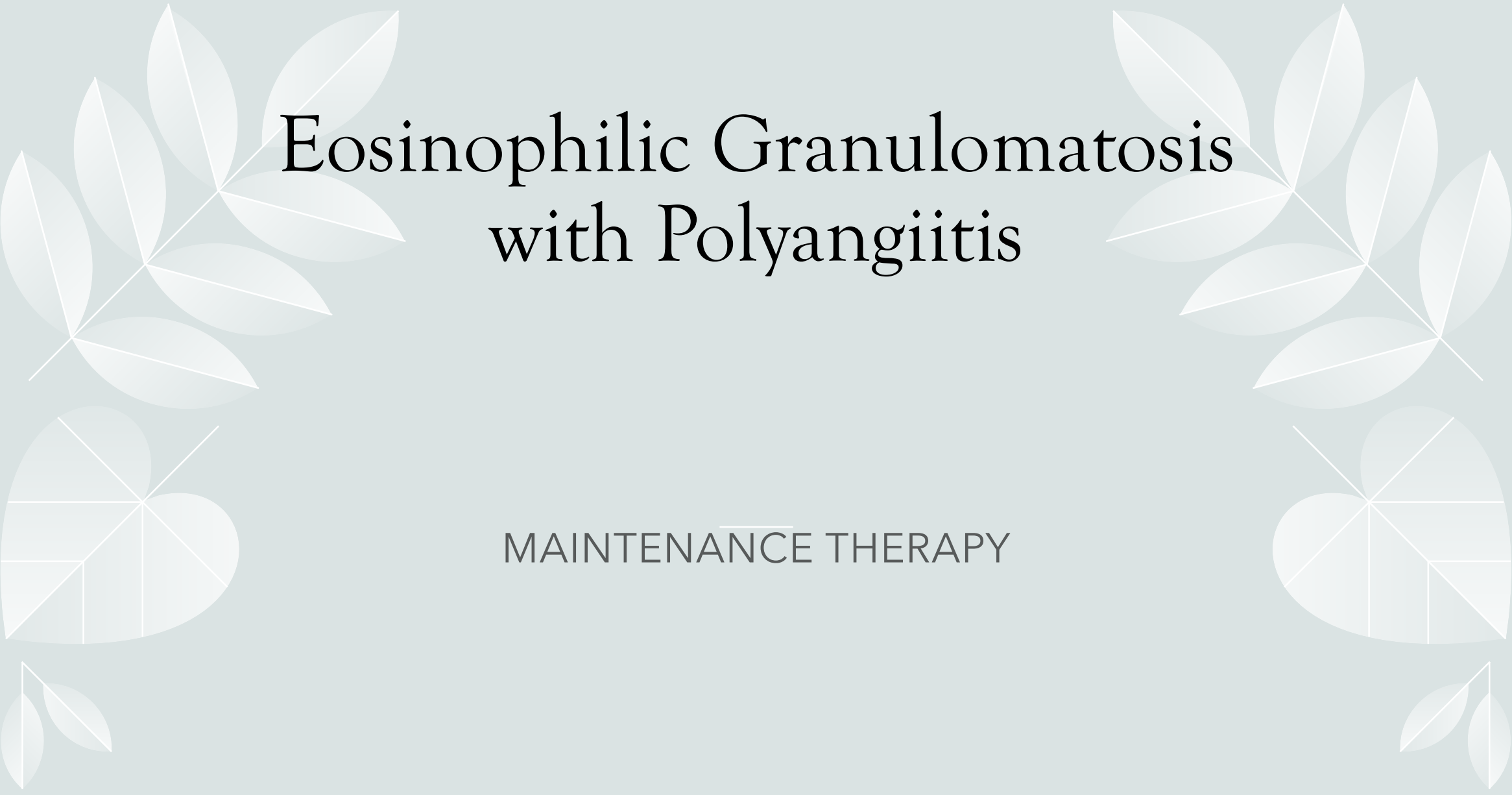
- **Preference for cyclophosphamide** – Cyclophosphamide may be preferred in patients with active cardiac involvement because cardiomyopathy is an independent predictor of mortality in EGPA and experience with cyclophosphamide is more robust in these patients. In addition, cyclophosphamide may be preferred over rituximab in patients who are antineutrophil cytoplasmic antibody (ANCA)-negative and have severe neurologic or gastrointestinal manifestations.
- **Preference for rituximab** – Rituximab may be preferred in patients with a positive ANCA, active glomerulonephritis, prior cyclophosphamide therapy, and those at risk for gonadal toxicity.



Non-severe EGPA

- ACR 2021: Mepolizumab or Benralizumab + systemic glucocorticoids
- EULAR 2022: Only glucocorticoid, Mepolizumab for refractory or relapsing cases
- Alternative agents: MTX, Azathioprine, Mycophenolate



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Eosinophilic Granulomatosis with Polyangiitis

MAINTENANCE THERAPY

Maintenance Therapy for Severe EGPA



If cyclophosphamide is used for induction therapy, change it with another agent.



If rituximab is used for induction therapy, continue it for maintenance therapy.

Maintenance Therapy for Non-Severe EGPA

Continue the agent which is used for induction therapy.





Cotrimoxazole for Prevention of Relapse?



Observational Study > Rheumatology (Oxford). 2020 Jan 1;59(1):77-83.

doi: 10.1093/rheumatology/kez236.

No evident association of nasal carriage of *Staphylococcus aureus* or its small-colony variants with cotrimoxazole use or ANCA-associated vasculitis relapses

Boun Kim Tan¹, Yoann Crabol¹, Jason Tasse², Frédéric Laurent², Narimane Nekkab³, Christine Vinter¹, Xavier Puéchal¹, Loïc Guillevin¹

Affiliations + expand

PMID: 31834404 DOI: 10.1093/rheumatology/kez236

Rheumatology International (2023) 43:467–475
https://doi.org/10.1007/s00296-022-05228-8

Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH



The effect of nasal *Staphylococcus aureus* colonization and antibiotic treatment on disease activity in ANCA-associated vasculitis: a retrospective cohort study in the Netherlands

Caroline M. Schaap¹ · Roline M. Krol^{1,2} · Hilde H. F. Remmelts² · Ruth Klaasen³ · E. Christiaan Hagen² · Julia Spierings¹ · Marloes W. Heijstek¹

Received: 9 July 2022 / Accepted: 5 October 2022 / Published online: 26 October 2022
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Cotrimoxazole for Prevention of Serious Infection



ABSTRACT NUMBER: 1584

Effect of Trimethoprim Sulfamethoxazole Prophylaxis on Infections During Treatment of Granulomatosis with Polyangiitis with Rituximab: A Population-Based Study

Arielle Mendel¹, Hassan Behloul², Evelyne Vinet¹, Jeffrey Curtis³ and Sasha Bernatsky²,
¹McGill University Health Centre, Montréal, QC, Canada, ²Research Institute of the McGill University Health Centre, Montreal, QC, Canada, ³University of Alabama at Birmingham, Birmingham, AL

Meeting: [ACR Convergence 2023](#)



Clinical and epidemiological research

Trimethoprim–sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis

Andreas Kronbichler^{1, 2}, Julia Kerschbaum², Seerapani Gopaluni¹, Joanna Tieu¹, Federico Alberici^{1, 3}, Rachel Bronwen Jones¹, Rona M Smith¹, David R W Jayne^{1, 4}

Arthritis & Rheumatology

Vol. 77, No. 10, October 2025, pp 1407–1415

DOI 10.1002/art.43185

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Time-Dependent Effect of Prophylactic Trimethoprim-Sulfamethoxazole on the Incidence of Serious Infections in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Target Trial Emulation Study

Yun Kyu Kim,¹ Jeffrey R. Curtis,² Se Rim Choi,³ Jina Yeo,⁴ Min Jung Kim,⁵ Yun Jong Lee,⁶ Eun Bong Lee,⁷ and Jun Won Park¹



UpToDate®

November 2025

- We typically administer prophylaxis to prevent *Pneumocystis jirovecii* pneumonia in all patients initiating immunosuppressive therapy with cyclophosphamide or rituximab in combination with **prednisone at a dose ≥ 20 mg/day** (or equivalent dose of a different glucocorticoid). We discontinue prophylaxis when the dose of **prednisone is tapered to less than 5 to 10 mg/day**.

Take Home Messages

- **Induction therapy of GPA & MPA:**
Rituximab is better than cyclophosphamide for PR3 positive patients and for relapses.
- the combination of rituximab and cyclophosphamide may be considered in severe cases.
- PLEX for severe GPA & MPA: may be effective in severe kidney involvement, Alveolar hemorrhage with hypoxia?
- **Maintenance Therapy of GPA & MPA:**
Rituximab is better than azathioprine; azathioprine is better than mycophenolate.
- Currently, it seems that fixed-dose rituximab for at least 18 months is the best for maintenance therapy.

Take Home Messages

- **Induction therapy for EGPA:**

- Severe EGPA:
- Cyclophosphamide for Cardiac involvement or ANCA negative Neurologic and GI involvement, Rituximab for ANCA positive patients or active GN or prior cyclophosphamide.
- Non-severe EGPA:
- GC± Mepolizumab or Benralizumab

- **Maintenance Therapy for EGPA:**

- Severe EGPA:
- Change cyclophosphamide, continue rituximab
- Non-severe EGPA:
- Continue the agent which is used for induction therapy.

And The last Point!

Low dose glucocorticoid could be considered in induction therapy.

In cases of combination therapy, glucocorticoid pulses may be omitted.

Thank you

