How do You Treat ANCA-Associated Vasculitis

Anousheh Haghighi M.D.
Rheumatologist
Professor of IUMS
2024

A 66 years old male with a 40 pack-year smoking history admitted in our hospital with fever and cough from 2 months ago. He was febrile (38°C). Chest CT scan revealed 8.3 x 9.4 cm cavitating right upper lobe lesion, bilateral hilar and mediastinal adenopathy and innumerable, bilateral parenchymal and pleural-based nodules.

Patient was admitted with a diagnosis of pneumonia and a high suspicion for stage 4 lung cancer.

Metabolic profile demonstrated a creatinine of 2.72 mg/dl and a UA with 3+ blood and +1 protein and anti-PR3 was positive.

Renal biopsy revealed segmental necrotizing and crescentic glomerulonephritis.

What is the best treatment option for this patient?

GLUCOCORTICOID+ RITUXIMAB

OR

GLUCOCORTICOID+ CYCLOPHOSPHAMIDE?

HIGH DOSE **OR** LOW DOSE STEROID?

Induction Therapy

Rituximab VS Cyclophosphamide

RAVE: Rituximab VS Cyclophophamide in ANCA-Associated Vasculitis
2010

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

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

All studies approved non-inferiority of Rituximab

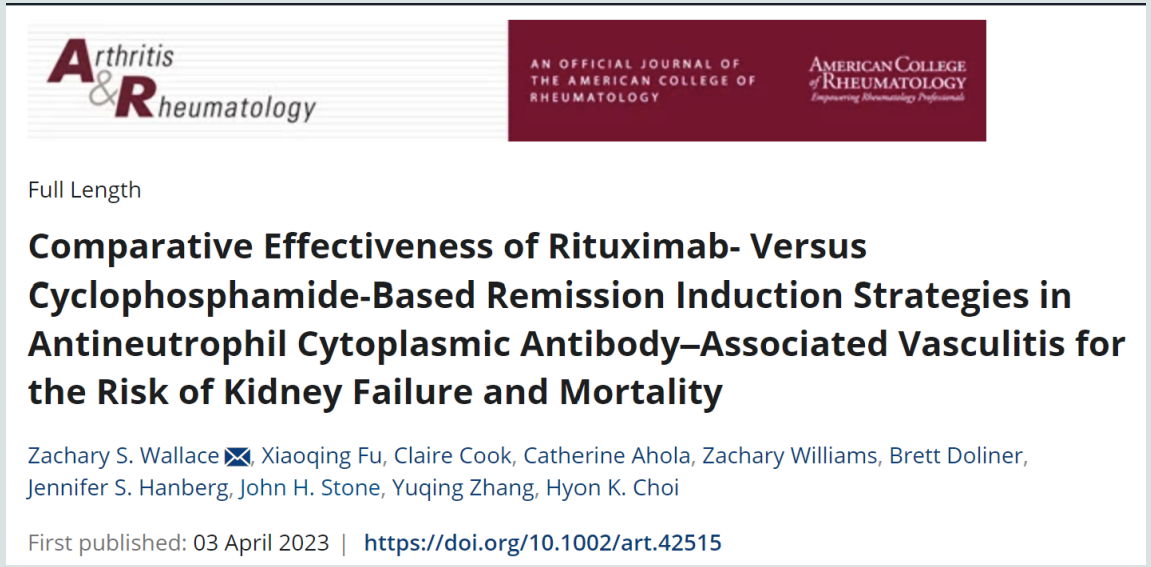
Rituximab is preferred for relapsing disease based on data from RAVE & RITAZAREM trials.

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



Arthritis & Rheumatology

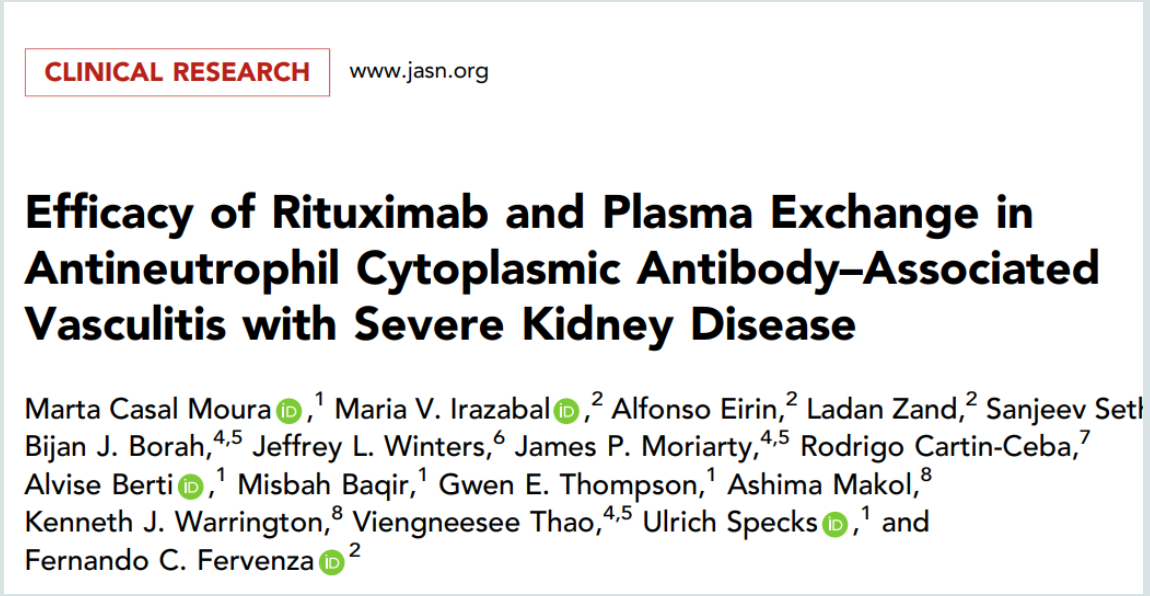
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

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 Seth, 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.

Vol. 68, No. 6, June 2016, pp 1467–1476
DOI 10.1002/art.39562

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 Specks[1]

- 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.

- Treatment responses were assessed among patients enrolled in the RAVE trial.
- **PR3-AAV patients respond better to RTX than to CYC/AZA**. An ANCA type based classification may guide immunosuppression in AAV.

Published in final edited form as:

Ann Rheum Dis. 2016 June ; 75(6): 1166–1169. doi:10.1136/annrheumdis-2015-208073.

Clinical Outcomes of Treatment of Anti-Neutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis Based on ANCA Type

JAMA Network 2022;5(11):e2243799

194 patients included in the analysis

80.8% had PR 3-ANCA positivity

JAMA Network | Open™

Original Investigation | Rheumatology

Rituximab vs Cyclophosphamide Induction Therapy for Patients With Granulomatosis With Polyangiitis

Xavier Puéchal, MD, PhD; Michele Iudici, MD, PhD; Elodie Perrodeau, PhD; Bernard Bonnotte, MD, PhD; François Lifermann, MD; Thomas Le Gallou, MD; Alexandre Karras, MD, PhD; Claire Blanchard-Delaunay, MD; Thomas Quéméneur, MD; Achille Aouba, MD, PhD; Olivier Aumaître, MD, PhD; Vincent Cottin, MD, PhD; Mohamed Hamidou, MD, PhD; Marc Ruivard, MD, PhD; Pascal Cohen, MD; Luc Mouthon, MD, PhD; Loïc Guillevin, MD; Philippe Ravaud, MD, PhD; Raphaël Porcher, MD, PhD; Benjamin Terrier, MD, PhD; for the French Vasculitis Study Group

- In this comparativeness effectiveness study using clinical data, rituximab induction therapy for GPA was more frequently associated with remission than cyclophosphamide.

- Post hoc analysis of trial data from 131 patients with PR3-AAV showed that **patients with PR3-AAV were more than twice as likely to achieve complete remission at 6 months when treated with rituximab rather than with cyclophosphamide.**

JAMA Network | Open™

Original Investigation | Rheumatology

Rituximab vs Cyclophosphamide Induction Therapy for Patients With Granulomatosis With Polyangiitis

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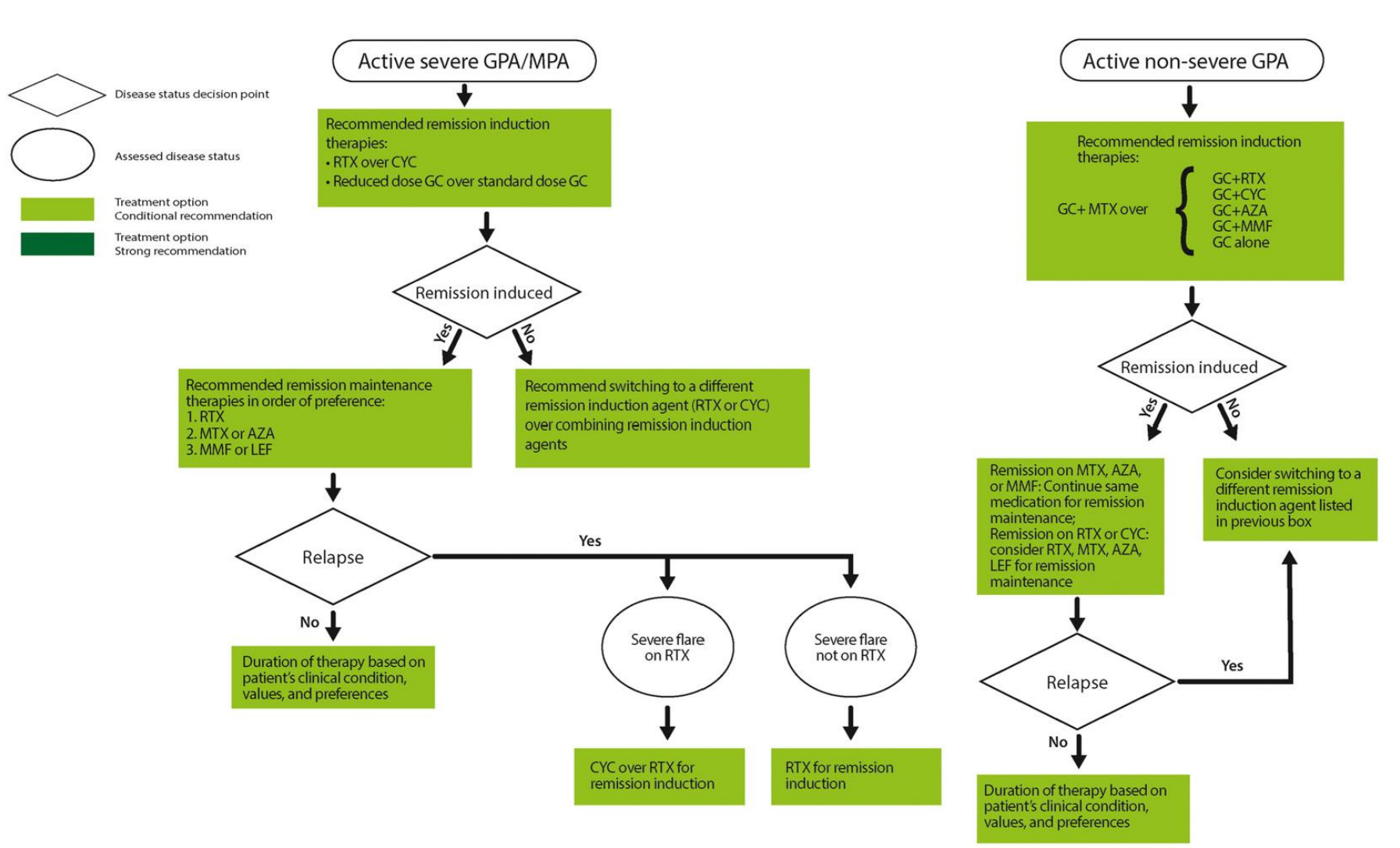
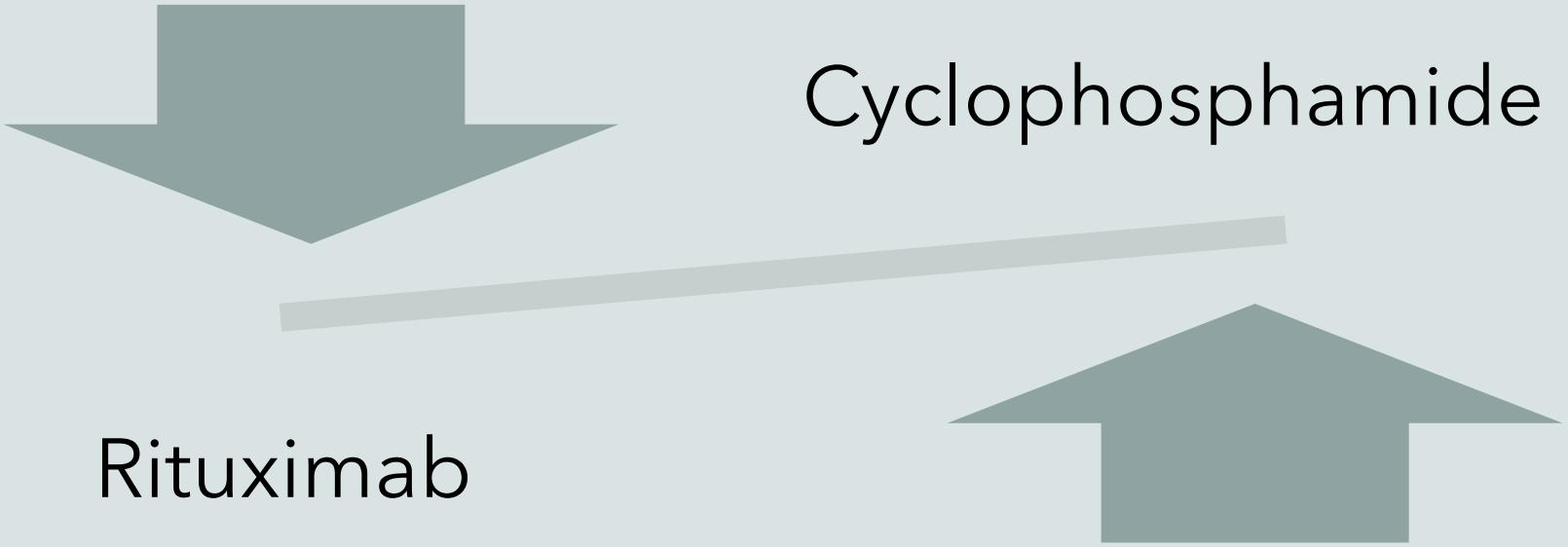
ACR 2021 Guideline



Which One Is Better?!



Low Dose vs High Dose Glucocorticoid

WHICH ONE IS BETTER?!

February 13, 2020

PEXIVAS Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

M. Walsh, P.A. Merkel, C.-A. Peh, W.M. Szpirt, X. Puéchal, S. Fujimoto, C.M. Hawley, N. Khalidi, O. Floßmann, R. Wald, L.P. Girard, A. Levin, G. Gregorini, L. Harper, W.F. Clark, C. Pagnoux, U. Specks, L. Smyth, V. Tesar, T. Ito-Ihara, J.R. de Zoysa, W. Szczeklik, L.F. Flores-Suárez, S. Carette, L. Guillevin, C.D. Pusey, A.L. Casian, B. Brezina, A. Mazzetti, C.A. McAlear, E. Broadhurst, D. Reidlinger, S. Mehta, N. Ives, and D.R.W. Jayne.

PEXIVAS Trial

- We conducted a randomized trial with a 2-by-2 factorial design to evaluate the use of **plasma exchange and two regimens of oral glucocorticoids** in patients with **severe ANCA-associated vasculitis** (defined by an estimated glomerular filtration rate of <50 ml per minute per 1.73 m2 of body-surface area or diffuse pulmonary hemorrhage).
- Patients were **followed for up to 7 years** for the primary composite outcome of death from any cause or end-stage kidney disease (ESKD).

PEXIVAS Trial

Among patients with severe ANCA-associated vasculitis, the use of plasma exchange did not reduce the incidence of death or ESKD. A reduced-dose regimen of glucocorticoids was noninferior to a standard-dose regimen with respect to death or ESKD.

JAMA. 2021 Jun 1; 325(21): 1–10.
Published online 2021 Jun 1. doi: 10.1001/jama.2021.6615

Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis

Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis

140 patients with newly diagnosed ANCA-associated vasculitis without severe glomerulonephritis or alveolar hemorrhage

Patients were randomized to receive reduced-dose prednisolone (0.5 mg/kg/d) plus rituximab (375 mg/m^2/wk, 4 doses) (n = 70) or high-dose prednisolone (1 mg/kg/d) plus rituximab (n = 70).

Reduced-dose glucocorticoid plus rituximab regimen was noninferior to high-dose glucocorticoid plus rituximab regimen with regard to induction of disease remission at 6 months.

In a study titled **Real-Life Use of the PEXIVAS Reduced-dose Glucocorticoid Regimen in Granulomatosis with Polyangiitis and Microscopic Polyangiitis,** Nagle et al. evaluated the efficacy and safety of the reduced-dose glucocorticoid regimen in a real-world setting.

Reduced-Dose Glucocorticoids for GPA & Microscopic Polyangiitis

Arthritis & Rheumatology | December 1, 2023

- Nagle et al. conducted a retrospective, multicenter study comparing the PEXIVAS reduced-dose GC regimen with a standard regimen in patients with severe GPA or MPA flare between January 2018 and April 2022. The primary composite endpoint included the occurrence of **death, ESKD, progression before remission requiring treatment modification or relapse**, whichever occurred first.
- In multivariate analysis, a **reduced GC regimen was significantly associated with the occurrence of the endpoint compared to a standard regimen but was not associated with an increased risk of death or ESKD**. There was no significant difference in serious infections at 1 year.

Reduced-Dose Glucocorticoids for GPA & Microscopic Polyangiitis

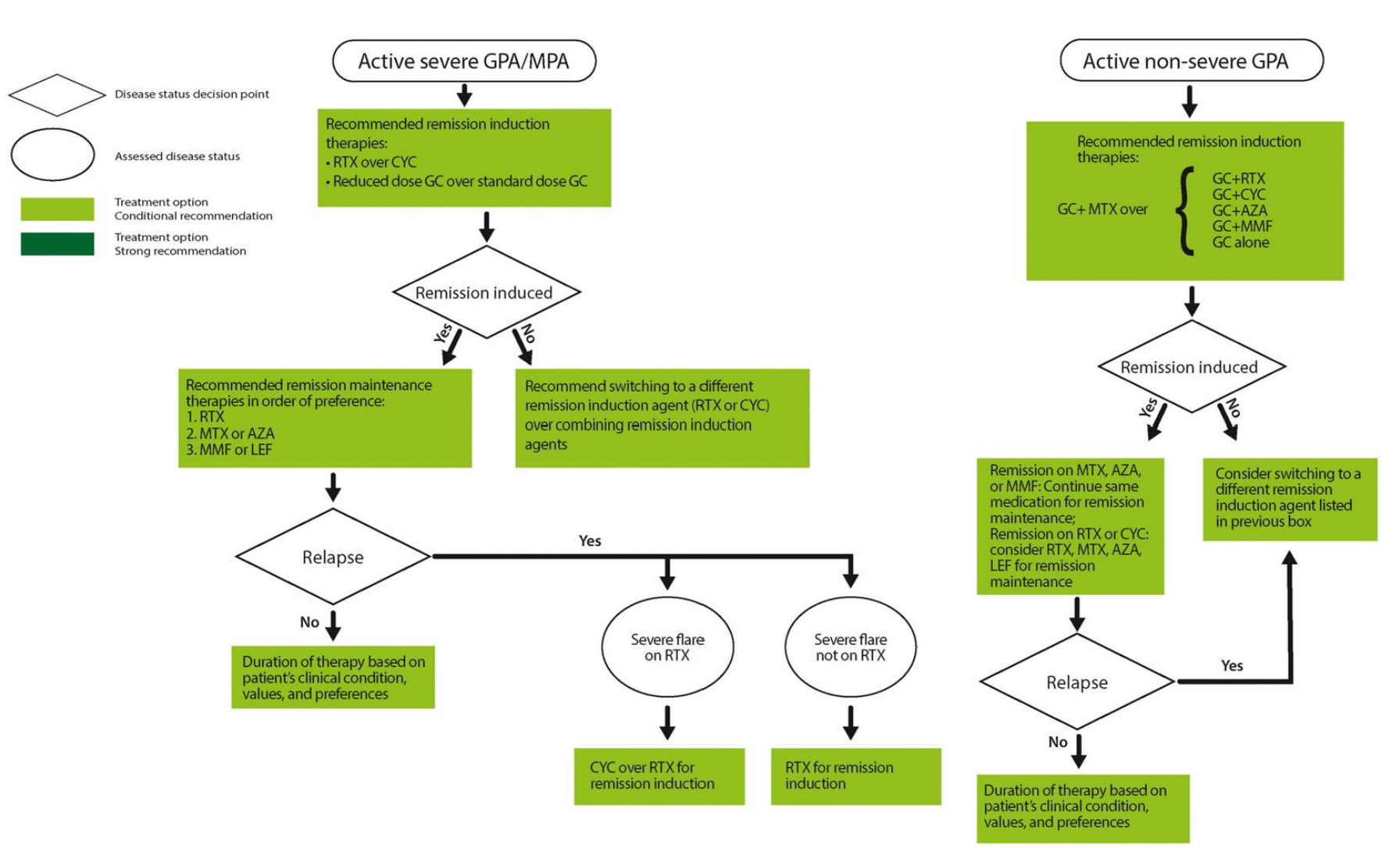
Arthritis & Rheumatology | December 1, 2023

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.

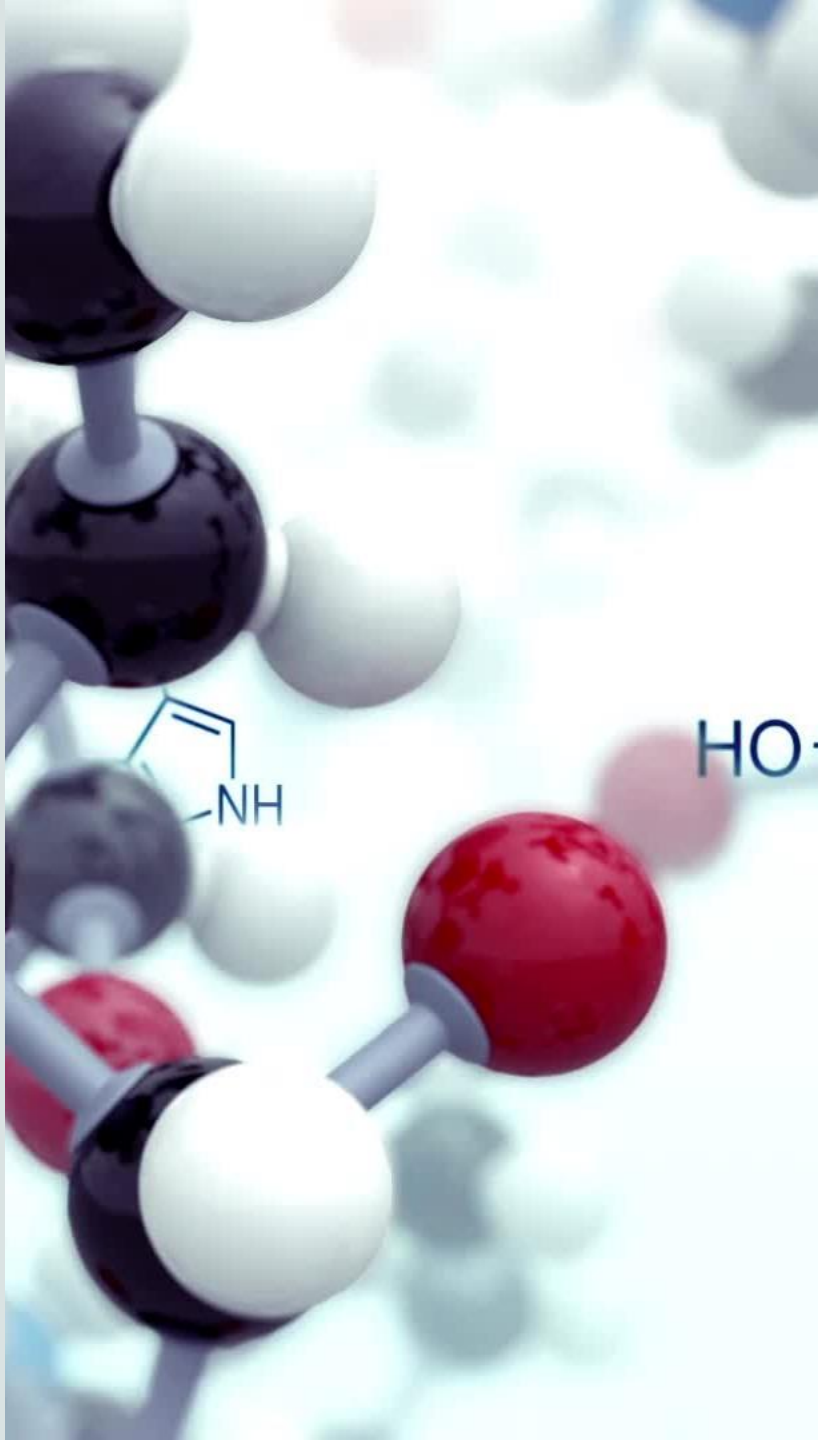
For now, lower GC starting doses of 0.5 mg/kg/day may be considered on an individual basis in selected patients **without life-threatening or organ-threatening disease.**

ACR 2021 Guideline



Avacopan

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



RITUXIMAB + CYCLOPHOSPHAMIDE

Kidney International Reports (2018) 3, 394–402

KI REPORTS
KIReports.org

CLINICAL RESEARCH

Combination Therapy With Rituximab and Cyclophosphamide for Remission Induction in ANCA Vasculitis

Frank B. Cortazar[1,2], Saif A. Muhsin[1,3], William F. Pendergraft III[4], Zachary S. Wallace[5], Colleen Dunbar[2], Karen Laliberte[2] and John L. Niles[1,2]

[1]Division of Nephrology, Massachusetts General Hospital, Boston, Massachusetts, USA; [2]Vasculitis and Glomerulonephritis Center, Massachusetts General Hospital, Boston, Massachusetts, USA; [3]Center for Systems Biology, Program in Membrane Biology, Massachusetts General Hospital, Boston, Massachusetts, USA; [4]University of North Carolina Kidney Center, Division of Nephrology and Hypertension, Department of Medicine, Chapel Hill, North Carolina, USA; and [5]Division of Rheumatology, Massachusetts General Hospital, Boston, Massachusetts, USA

Nephrol Dial Transplant (2019) 34: 63–73
doi: 10.1093/ndt/gfx378
Advance Access publication 14 February 2018

ndt
Nephrology Dialysis Transplantation

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-Thomas[2], Seerapani Gopaluni[3], Anisha Tanna[1,2], Nicholas Mansfield[2], Jack Galliford[1,2], Megan Griffith[1,2], Jeremy Levy[1,2], Thomas D. Cairns[2], David Jayne[3], Alan D. Salama[4] and Charles D. Pusey[1,2]

Rheumatology 2019; 58:260268

RHEUMATOLOGY

Rheumatology 2019;58:260–268
doi:10.1093/rheumatology/key288
Advance Access publication 18 September 2018

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. Moran[4], Dearbhla Kelly[4], Jennifer Scott[4], Sally Hamour[1], Aine Burns[1], Megan Griffith[2,3], Jack Galliford[3], Jeremy B. Levy[2,3], Thomas D. Cairns[3], Seerapani Gopaluni[5], Rachel B. Jones[5], David Jayne[5], Mark A. Little [4,6], Charles D. Pusey[2,3,†] and Alan D. Salama[1,†]

Kidney International (2021) 100, 1316–1324

clinical investigation

www.kidney-international.org

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

Check for updates

OPEN

Kavita Gulati[1,2,3], Helena Edwards[1,3], Maria Prendecki[1,2], Thomas D. Cairns[1], Marie Condon[1], Jack Galliford[1], Megan Griffith[1,2], Jeremy B. Levy[1,2], Frederick W.K. Tam[1,2], Anisha Tanna[1], Charles D. Pusey[1,2] and Stephen P. McAdoo[1,2]

Journal of Translational Autoimmunity 6 (2023) 100178

Contents lists available at ScienceDirect

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,*]

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 ritixumab and cyclophosphamide

UpToDate 2024

- This approach remains **controversial,** and 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.

Role of Plasma Exchange

Role of Plasma Exchange UpToDate 2024

- **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** –Plasma exchange for all patients who present with pulmonary hemorrhage or patients with pulmonary hemorrhage not readily responding to other therapies.

Randomized Controlled Trial > J Am Soc Nephrol. 2007 Jul;18(7):2180-8.

doi: 10.1681/ASN.2007010090. Epub 2007 Jun 20.

Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis

David R W Jayne [1], Gill Gaskin, Niels Rasmussen, Daniel Abramowicz, Franco Ferrario, Loic Guillevin, Eduardo Mirapeix, Caroline O S Savage, Renato A Sinico, Coen A Stegeman, Kerstin W Westman, Fokko J van der Woude, Robert A F de Lind van Wijngaarden, Charles D Pusey; European Vasculitis Study Group

Plasma exchange increased the rate of renal recovery in ANCA-associated systemic vasculitis that presented with renal failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis

M. Walsh, P.A. Merkel, C.-A. Peh, W.M. Szpirt, X. Puéchal, S. Fujimoto, C.M. Hawley, N. Khalidi, O. Floßmann, R. Wald, L.P. Girard, A. Levin, G. Gregorini, L. Harper, W.F. Clark, C. Pagnoux, U. Specks, L. Smyth, V. Tesar, T. Ito-Ihara, J.R. de Zoysa, W. Szczeklik, L.F. Flores-Suárez, S. Carette, L. Guillevin, C.D. Pusey, A.L. Casian, B. Brezina, A. Mazzetti, C.A. McAlear, E. Broadhurst, D. Reidlinger, S. Mehta, N. Ives, and D.R.W. Jayne, for the PEXIVAS Investigators*

Among patients with severe ANCA-associated vasculitis, the use of plasma exchange did not reduce the incidence of death or ESKD.

The effects of plasma exchange in patients with ANCA-associat vasculitis: an updated systematic review and meta-analysis

Michael Walsh,[1,2,3] David Collister,[3,4] Linan Zeng,[2,5] Peter A Merkel,[6] Charles D Pusey,[7] Gordon Guyatt,[1,2] Chen Au Peh,[8,9] Wladimir Szpirt,[10] Toshiko Ito-Hara,[11,12] David R W Jayne,[13] on behalf of the Plasma exchange and glucocorticoid dosing for patients with ANCA-associat vasculitis BMJ Rapid Recommendations Group*

BMJ 2022;376:e064604

- The current review reliably concludes that PLEX reduces the risk of **ESKD** within 12 months but is responsible for a concomitant increase in the risk of serious **infections** not previously appreciated. This is an important finding as it may explain the lack of effect of PLEX on **mortality** despite the large effect on ESKD.

- So, **plasma exchange has no important effect on mortality, reduces the 12-month risk of ESKD, but increases the risk of serious infections.**

Multicenter Study > J Am Soc Nephrol. 2022 Mar;33(3):628-637. doi: 10.1681/ASN.2021060771.
Epub 2022 Jan 24.

Kidney Histopathology Can Predict Kidney Function in ANCA–Associated Vasculitides with Acute Kidney Injury Treated with Plasma Exchanges

Dorian Nezam [1], Raphaël Porcher [2], François Grolleau [2], Pauline Morel [3], Dimitri Titeca-Beauport [4], Stanislas Faguer [5], Alexandre Karras [6], Justine Solignac [7], Noémie Jourde-Chiche [7], François Maurier [8], Hamza Sakhi [9] [10], Khalil El Karoui [9] [10], Rafik Mesbah [11], Pierre Louis Carron [12], Vincent Audard [9] [10], Didier Ducloux [13], Romain Paule [14], Jean-François Augusto [15], Julien Aniort [16], Aurélien Tiple [17], Cédric Rafat [18], Séverine Beaudreuil [19], Xavier Puéchal [20], Pierre Gobert [21], Ziad Massy [22], Catherine Hanrotel [23], Stéphane Bally [24], Nihal Martis [25], Cécile-Audrey Durel [26], Geoffroy Desbuissons [27], Pascal Godmer [28], Aurélie Hummel [29], François Perrin [30], Antoine Néel [31], Claire De Moreuil [32], Tiphaine Goulenok [33], Dominique Guerrot [1], Steven Grange [34], Aurélie Foucher [35], Alban Deroux [36], Carole Cordonnier [37], Céline Guilbeau-Frugier [38], Anne Modesto-Segonds [38], Dominique Nochy [39], Laurent Daniel [40], Anissa Moktefi [41], Marion Rabant [42], Loïc Guillevin [20], Alexis Régent [20], Benjamin Terrier [20];
on behalf of the French Vasculitis Study Group

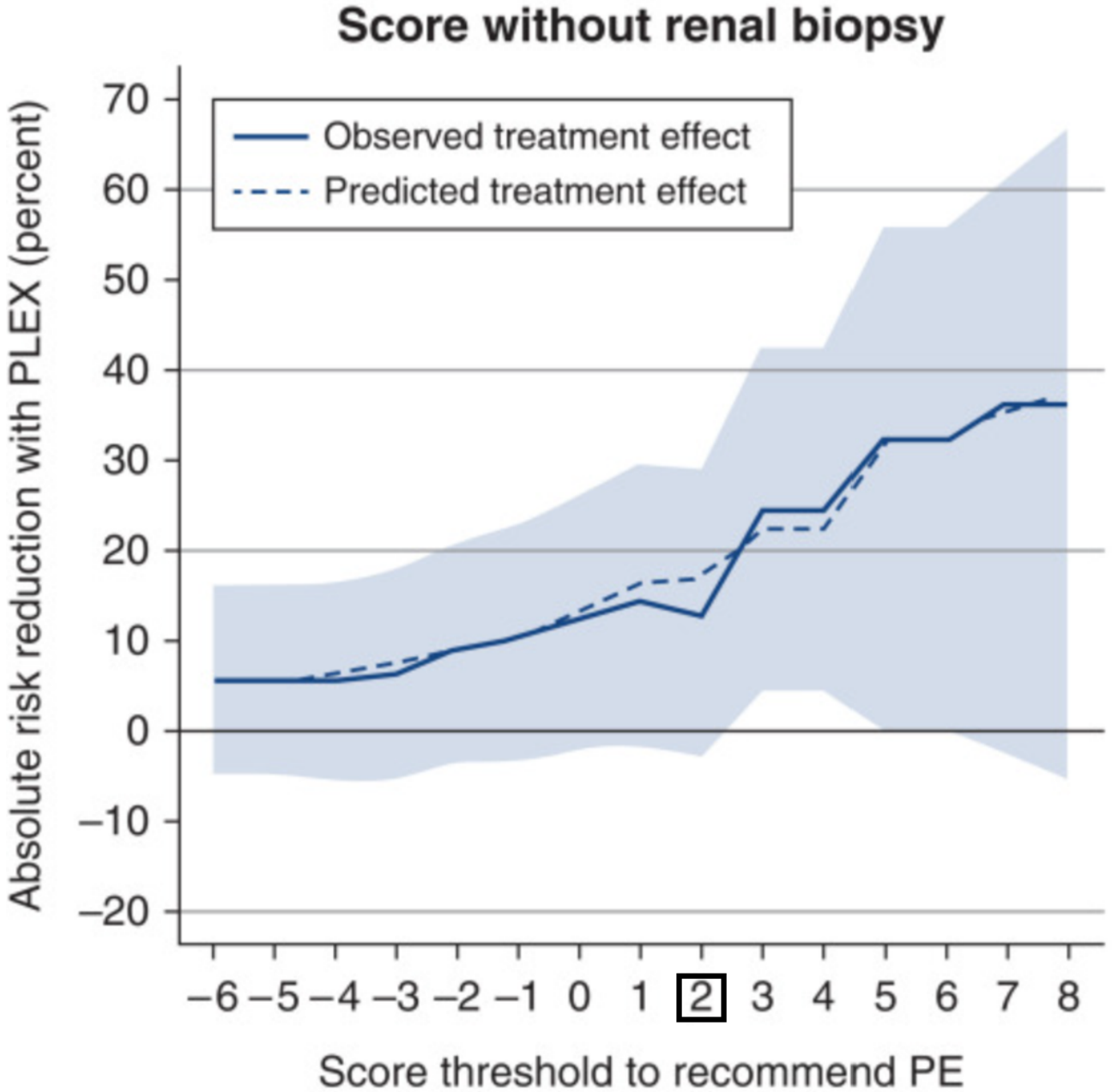
Multicenter Study > J Am Soc Nephrol. 2022 Mar;33(3):628-637. doi: 10.1681/ASN.2021060771. Epub 2022 Jan 24.

Kidney Histopathology Can Predict Kidney Function in ANCA–Associated Vasculitides with Acute Kidney Injury Treated with Plasma Exchanges

We performed a multicenter, retrospective study on **188 patients with AAV and AKI treated with PLEX and 237 not treated with PLEX.** The primary outcome was mortality or KRT at 12 months

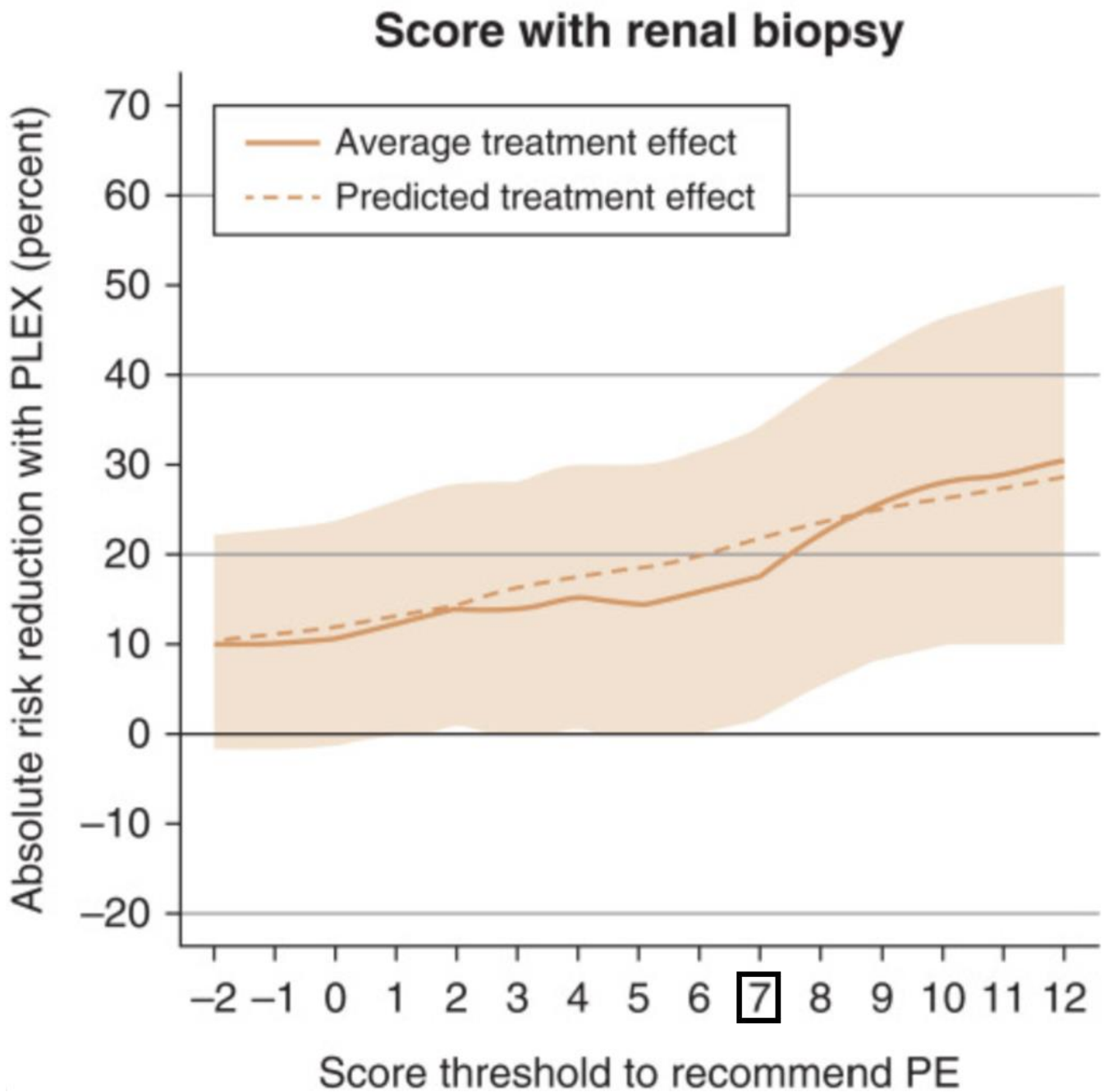
PLEX was not associated with a better primary outcome in the whole study population, but we identified **a subset of patients** who could benefit from PLEX.

A



Variable	Score points
Age >45 y	−2
MPA vasculitis	2
PR3 positive	−5
MPO positive	−2
Serum creatinine	
251...400 μmol/L	4
401...600 μmol/L	6
>600 μmol/L	11

B



Variable	Score points
Male sex	1
MPA	5
RLV	3
PR3 positive	−10
MPO positive	−3
Serum creatinine	
251...400 μmol/L	5
401...600 μmol/L	8
>600 μmol/L	16
Brix score ≥ 7	1
Berden score	
Crescentic	6
Mixed	−8

American Journal of Respiratory and Critical Care Medicine Volume 209 Number 9 | May 1 2024

ORIGINAL ARTICLE

Alveolar Hemorrhage in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Results of an International Randomized Controlled Trial (PEXIVAS)

Lynn A. Fussner[1], Luis Felipe Flores-Suárez[2], Rodrigo Cartin-Ceba[3], Ulrich Specks[4], P. Gerard Cox[5], David R. W. Jayne[9], Peter A. Merkel[10,11], and Michael Walsh[6,7,8]; for the PEXIVAS Investigators

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, The Ohio State University, Columbus, Ohio; [2]La Clínica de Vasculitis Sistémicas Primarias, Instituto Nacional de Enfermedades Respiratorias, Tlalpan, Ciudad de México, Mexico; [3]Division of Pulmonary Medicine, Department of Internal Medicine, Mayo Clinic, Scottsdale, Arizona; [4]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; [5]Division of Respirology and [6]Division of Nephrology, Department of Medicine, [7]Department of Health Research Methods, Evidence, and Impact, and [8]Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada; [9]Department of Medicine, University of Cambridge, Cambridge, United Kingdom; [10]Division of Rheumatology, Department of Medicine, and [11]Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania

PEXIVAS randomized 704 participants to PLEX or no-PLEX and reduced or standard-dose glucocorticoids (GC).

ORIGINAL ARTICLE

Alveolar Hemorrhage in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Results of an International Randomized Controlled Trial (PEXIVAS)

Lynn A. Fussner[1], Luis Felipe Flores-Suárez[2], Rodrigo Cartin-Ceba[3], Ulrich Specks[4], P. Gerard Cox[5], David R. W. Jayne[9], Peter A. Merkel[10,11], and Michael Walsh[6,7,8]; for the PEXIVAS Investigators

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Internal Medicine, The Ohio State University, Columbus, Ohio; [2]La Clínica de Vasculitis Sistémicas Primarias, Instituto Nacional de Enfermedades Respiratorias, Tlalpan, Ciudad de México, Mexico; [3]Division of Pulmonary Medicine, Department of Internal Medicine, Mayo Clinic, Scottsdale, Arizona; [4]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; [5]Division of Respirology and [6]Division of Nephrology, Department of Medicine, [7]Department of Health Research Methods, Evidence, and Impact, and [8]Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada; [9]Department of Medicine, University of Cambridge, Cambridge, United Kingdom; [10]Division of Rheumatology, Department of Medicine, and [11]Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania

- **Ventilator-free days may be a more sensitive measure of treatment effects in the most severe DAH.**
- There was no change in ventilator-free days with PLEX compared with no-PLEX, but there was a difference between GC dosing regimens, with **fewer ventilator-free days among participants receiving the reduced-dose regimen**
- **AAV patients with lung hemorrhage and hypoxia at presentation, showed a trend to reduced mortality with plasma exchange.** An increased risk of infection with plasma exchange was observed in the meta-analysis and this risk needs to be balanced against potential benefits.

JASN Journal of the American Society of Nephrology

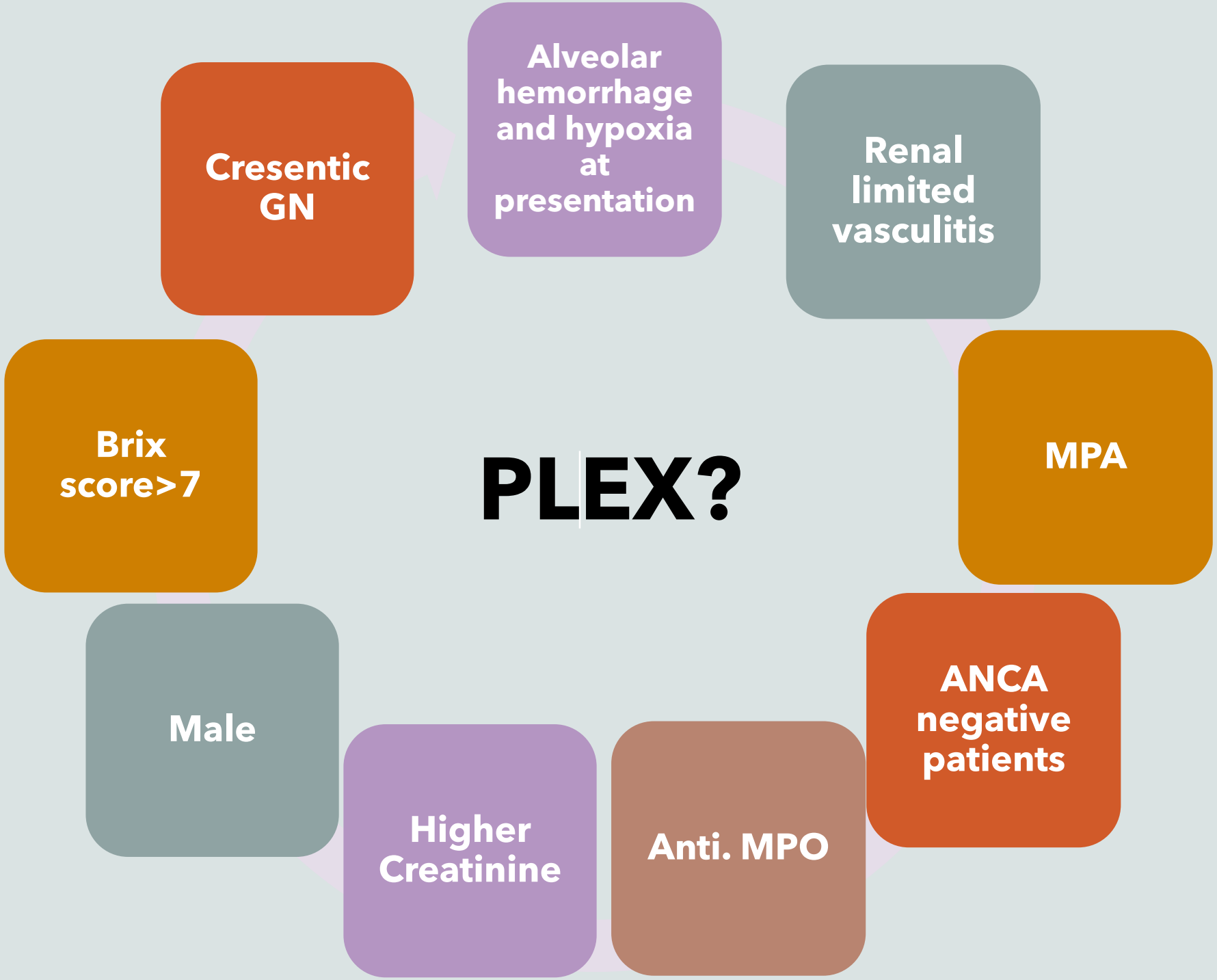
Plasma Exchange in ANCA-Associated Vasculitis: For Whom (If Any)?

Walsh, Michael

Author Information

JASN 33(3):p 465-466, March 2022. | ***DOI:*** 10.1681/ASN.2021121550

The degree to which an individual patient might expect benefits (and harms) depends on their baseline risks.


Cresentic GN
Alveolar hemorrhage and hypoxia at presentation
Renal limited vasculitis
Brix score>7
PLEX?
MPA
Male
ANCA negative patients
Higher Creatinine
Anti. MPO

MAINTENANCE THERAPY

When to Start Maintenance Therapy?

For patients treated with rituximab for induction of remission, maintenance therapy typically begins between **months four and six** after the last induction dose, regardless of the maintenance agent that is used.

For patients treated with cyclophosphamide for induction of remission, maintenance therapy is started **two to four weeks** after the last dose of cyclophosphamide if the following white blood cell criteria are met: The white blood cell count is >3500 cells/microL, and the absolute neutrophil count is >1500 cells/microL.

Choice of Maintenance Therapy

Choice of maintenance therapy

The best **data supporting the use of rituximab** as maintenance therapy after induction of remission with rituximab come from the **RITAZAREM trial**.

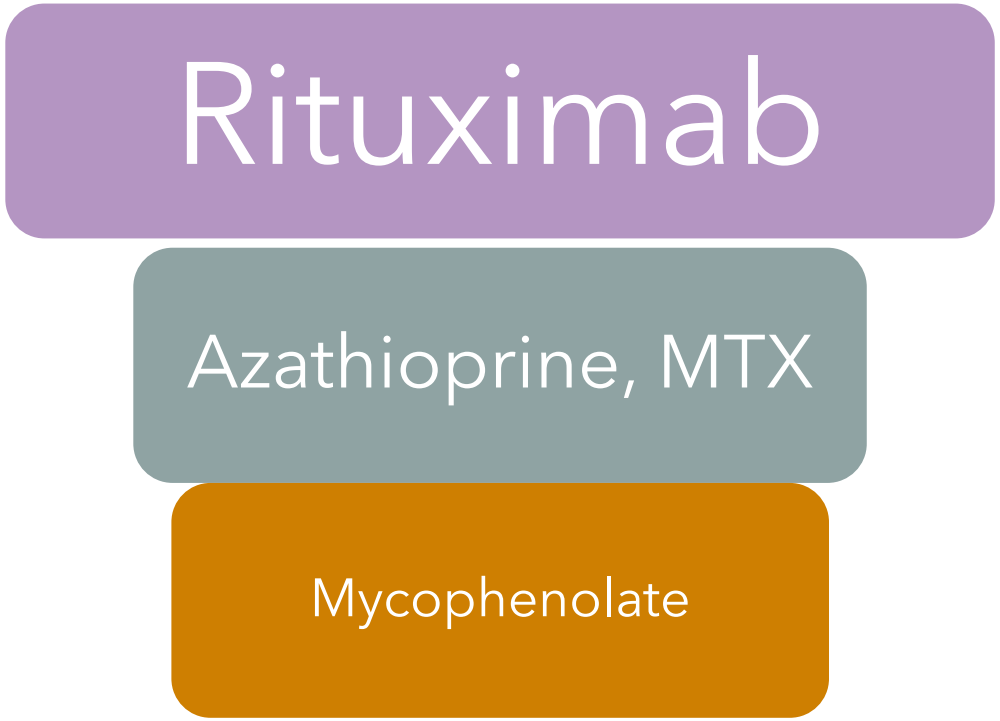
Patients receiving rituximab had a lower risk of relapse, and **fewer patients in the rituximab group had at least one serious adverse event**.

Choice of maintenance therapy

International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (**IMPROVE**) trial

They found that **azathioprine was more effective than mycophenolate for maintenance therapy.**

Choice of maintenance therapy



Dosing of Maintenance Therapy

Best Strategy of Rituximab Maintenance Dosage

UpToDate 2024

- it is not clear whether there is any one best option.

- 500 to 1000 mg every six months
- 500 every four months
- "on-demand" dosing strategy

- 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.

EULAR Guidline 2022 recommends:

In the management of patients with AAV, we recommend that structured clinical assessment, rather than ANCA and/or CD19+ B cell testing alone, should inform decisions on changes in treatment.

In patients with AAV receiving RTX, we recommend measurement of serum immunoglobulin concentrations prior to each course of RTX to detect secondary immunodeficiency.

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.**

Duration of Maintenance Therapy

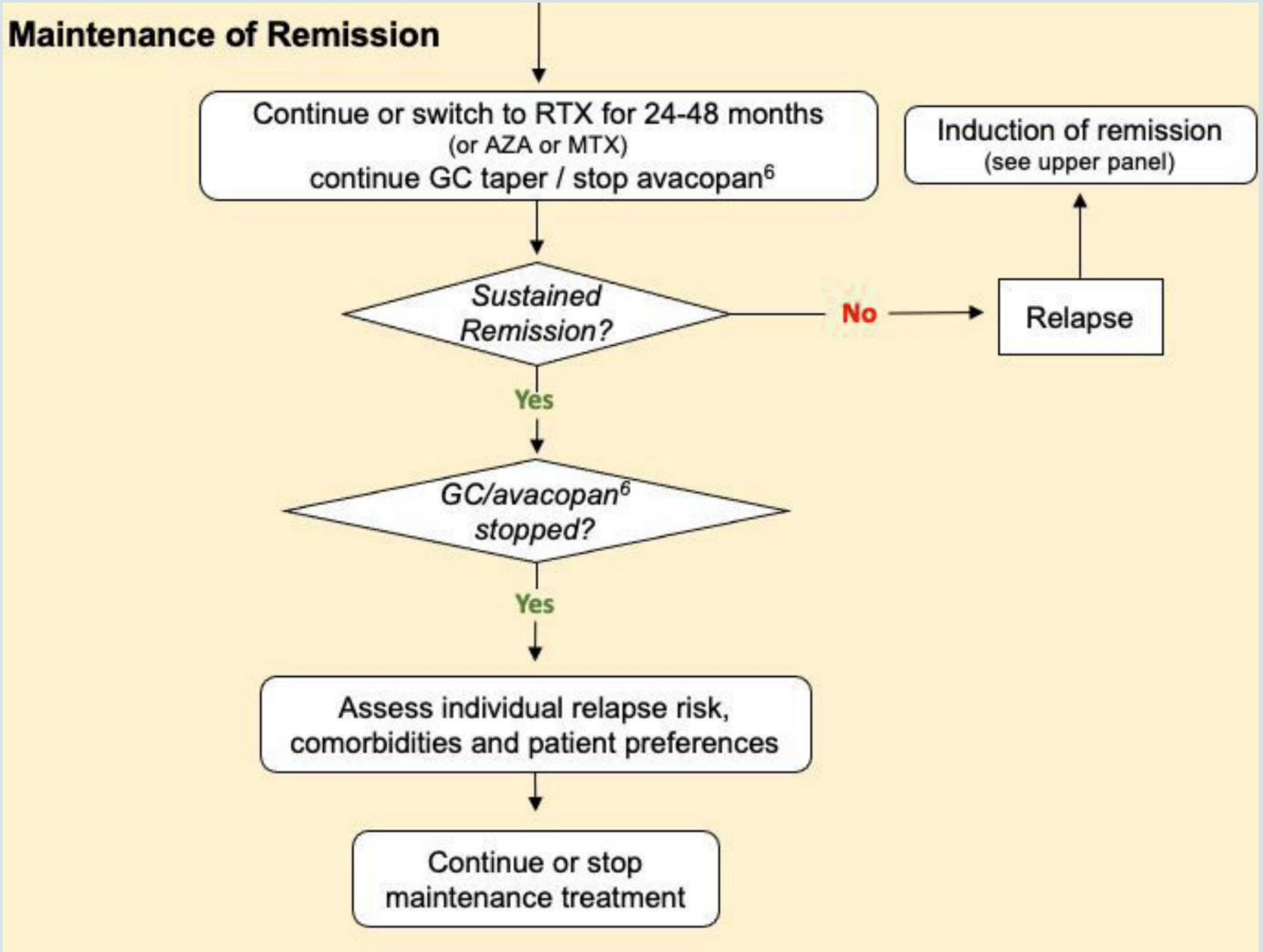
Duration of Maintenance Therapy UpToDate 2024

- **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.

Duration of Maintenance Therapy , EULAR 2022



LANDMARK TRIALS IN

RITUXIMAB FOR ANCA

2010

RITUXVAS

4x Ritux + 2x IV CYC
vs
3-6 months of IV CYC

INDUCTION
Ritux not superior to CYC

2010

4x Ritux + PO placebo
vs
IV Placebo + PO CYC

INDUCTION
Ritux non inferior to CYC

RAVE

2014

MAINRITSAN

Ritux 500mg regimen
vs
AZA

MAINTENANCE
Ritux had fewer relapses

2018

Ritux fixed regimen
vs
Ritux tailored regimen

MAINTENANCE
No difference

MAINRITSAN 2

2019

RITAZAREM

5x Ritux 1g
vs
AZA

MAINTENANCE
RTX had fewer relapses

2020

Ritux 500 mg q6months
vs
Placebo

MAINTENANCE
RTX had fewer relapses

MAINRITSAN 3

LANDMARK NEPHROL

CLINICAL SCIENCE

Rituximab as maintenance therapy for ANCA-associated vasculitides: pooled analysis and long-term outcome of 277 patients included in the MAINRITSAN trials

Florence Delestre ,[1,2] Pierre Charles,[2,3] Alexandre Karras,[2,4] Christian Pagnoux,[5,6] Antoine Néel,[7] Pascal Cohen,[1] Olivier Aumaître,[8] Stanislas Faguer ,[9] Pierre Gobert,[10] François Maurier,[11] Maxime Samson ,[12] Pascal Godmer,[13] Bernard Bonnotte ,[12] Vincent Cottin ,[14] Catherine Hanrotel-Saliou,[15] Thomas Le Gallou,[16] Pierre-Louis Carron,[17] Hélène Desmurs-Clavel,[18] Guillaume Direz,[19] Noémie Jourde-Chiche ,[20] Francois Lifermann,[21] Nicolas Martin-Silva,[22] Grégory Pugnet,[23] Thomas Quéméneur,[24] Marie Matignon,[25] Ygal Benhamou,[26] Eric Daugas ,[27] Estibaliz Lazaro,[28] Nicolas Limal,[29] Maïzé Ducret,[30] Antoine Huart,[31] Jean-François Viallard,[28] Eric Hachulla ,[32] Elodie Perrodeau,[33] Xavier Puechal ,[1,2] Loïc Guillevin,[1,2] Raphaël Porcher,[2,33] Benjamin Terrier ,[1,2] for the French Vasculitis Study Group (FVSG)

BMJ Journals
2024
Annals of the
Rheumatic Diseases

Patients from MAINRITSAN trial were followed prospectively through month 84. The primary endpoint was relapse-free survival at month 84.

It appears that the 84-month remission rate is higher with an 18-month fixed RTX regimen compared with AZA and 18-month tailored RTX. Also, extending RTX to 36 months does not appear to reduce the long-term relapse rate compared with the 18-month fixed RTX regimen

So ...

- Currently, it seems that fixed RTX regimen of at least 18 months should be considered the gold standard.

Investigational Agents

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

Kidney transplantation

Patients who develop ESKD due to GPA or MPA are potential candidates for kidney transplantation.

Transplantation should be delayed for **at least six months** from the time of initial presentation or most recent relapse.

Persistence of an isolated positive ANCA titer is not a contraindication to kidney transplantation.

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

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.

Take Home Massages

- **Induction therapy of GPA & MPA**: Rituximab is better than cyclophosphamide for PR3 positive patients and for relapses.
- PLEX for severe GPA & MPA: may be effective in some situations. (ANCA negative, RLV, 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 18 months is the best for maintenance therapy.

Take Home Massages

- **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.

Thank you