Update on Small(ish)-Vessel Vasculitis
(What's new and interesting)

February 1, 2024

Peter A. Merkel, M.D., M.P.H.
Chief, Division of Rheumatology
PI, Vasculitis Clinical Research Consortium
Director, Penn Vasculitis Center
Professor of Medicine and Epidemiology
University of Pennsylvania
Philadelphia, PA, USA
pmerkel@upenn.edu; 215-614-4401

Penn
University of Pennsylvania

PENN VASCULITIS CENTER

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Financial Disclosures for Peter A. Merkel, M.D., M.P.H.

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- Q32
- Takeda

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- EULAR
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- US Food and Drug Administration
- The Patient-Centered Outcomes Research Institute
- The Vasculitis Foundation

Off-label use of various medications will be discussed in this presentation

2

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3

Unpublished data will be presented

Slides of the unpublishes data are not included in this syllabus
(however, this material will be published in 2024)

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Lecture Outline

- **Review the standard of care for the treatment of ANCA-associated vasculitis in the context of the results of the latest major clinical trial**
  - **Emphasis on prolonged use of rituximab for maintenance of remission in AAV**
- **Ponder the role of therapy with CAR T cells for ANCA-associated vasculitis**
- **Report the findings of a recent clinical trial of benralizumab for eosinophilic granulomatosis with polyangiitis**
  - **Discuss the implications for use of anti-IL-5 treatments in EGPA**
- **Present new data from a large cohort of patients with polyarteritis nodosa**
  - **Discuss the implications for management of PAN**
- **Questions/Answers/Discussion**

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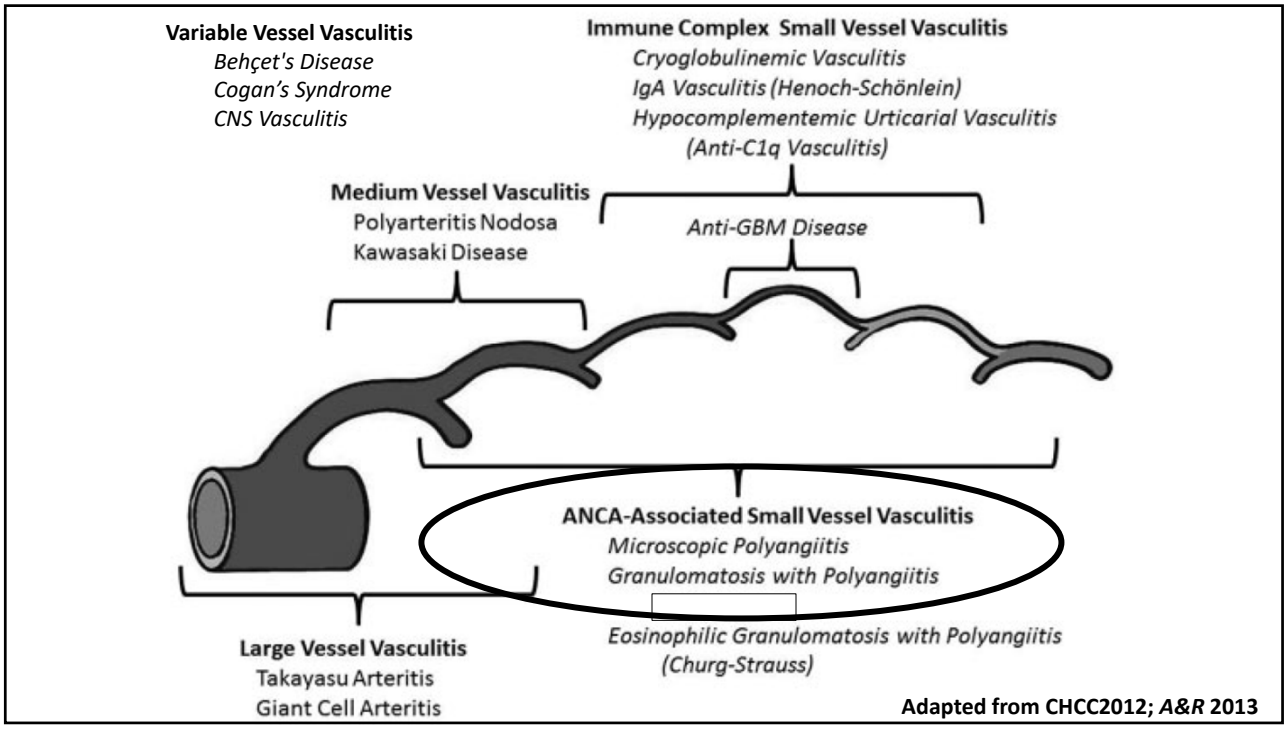

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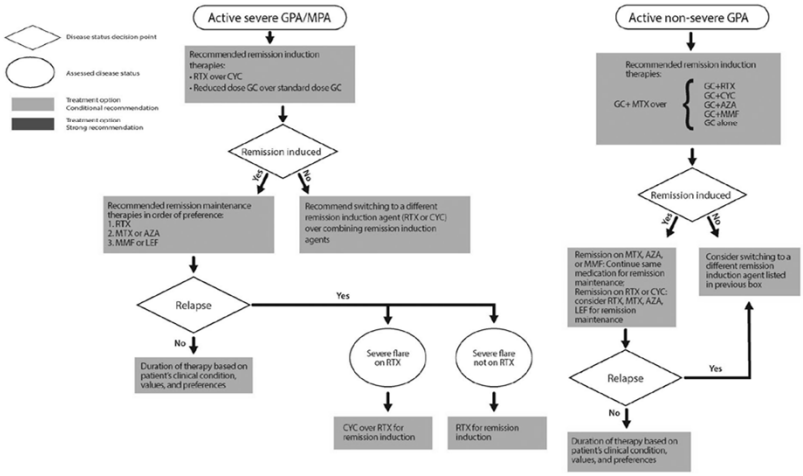
Arthritis & Rheumatology
Vol. 73, No. 8, August 2021, pp 1366–1383
DOI 10.1002/art.41773

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

Sharon A. Chung,[1] Carol A. Langford,[2] Mehrdad Maz,[3] Andy Abril,[4] Mark Gorelik,[5] Gordon Guyatt,[6] Amy M. Archer,[7] Doyt L. Conn,[8] Kathy A. Full,[9] Peter C. Grayson,[10] Maria F. Ibarra,[11] Lisa F. Imundo,[5] Susan Kim,[1] Peter A. Merkel,[12] Rennie L. Rhee,[12] Philip Seo,[13] John H. Stone,[14] Sangeeta Sule,[15] Robert P. Sundel,[16] Omar I. Vitobaldi,[17] Ann Warner,[18] Kevin Byram,[19] Anisha B. Dua,[7] Nedaa Husainat,[20] Karen E. James,[21] Mohamad A. Kalot,[22] Yih Chang Lin,[23] Jason M. Springer,[3] Marat Turgunbaev,[24] Alexandra Villa-Forte,[2] Amy S. Turner,[24] and Reem A. Mustafa[25]



7

EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update

Bernhard Hellmich,[1] Beatriz Sanchez-Alamo,[2] Jan H Schirmer,[3] Alvise Berti,[4,5] Daniel Blockmans,[6] Maria C Cid,[7] Julia U Holle,[8] Nicole Hollinger,[1] Omer Karadag,[9] Andreas Kronbichler,[10,11] Mark A Little,[12] Raashid A Luqmani,[13] Alfred Mahr,[14] Peter A Merkel,[15] Aladdin J Mohammad,[11,16] Sara Monti,[17,18] Chetan B Mukhtyar,[19] Jacek Musial,[20] Fiona Price-Kuehne,[11] Mårten Segelmark,[21] Y K Onno Teng,[22] Benjamin Terrier,[23] Gunnar Tomasson,[24,25] Augusto Vaglio,[26] Dimitrios Vassilopoulos,[27] Peter Verhoeven,[28] David Jayne[11]

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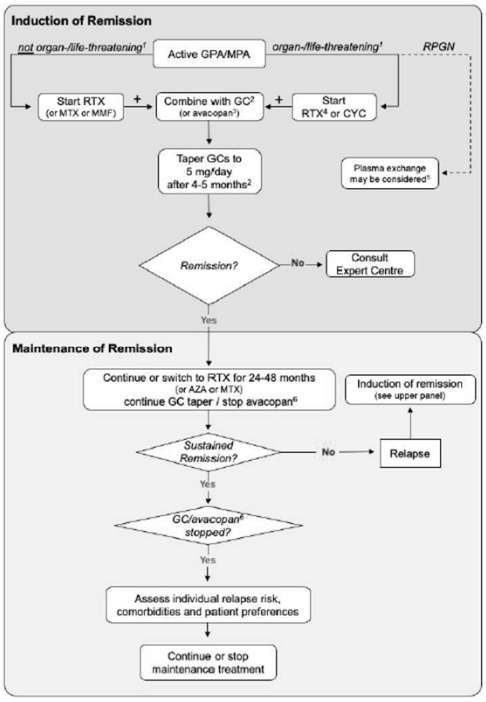

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Standard of Care Treatment for AAV

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Treatment of Non-Severe AAV

Non-severe = not organ- or life-threatening

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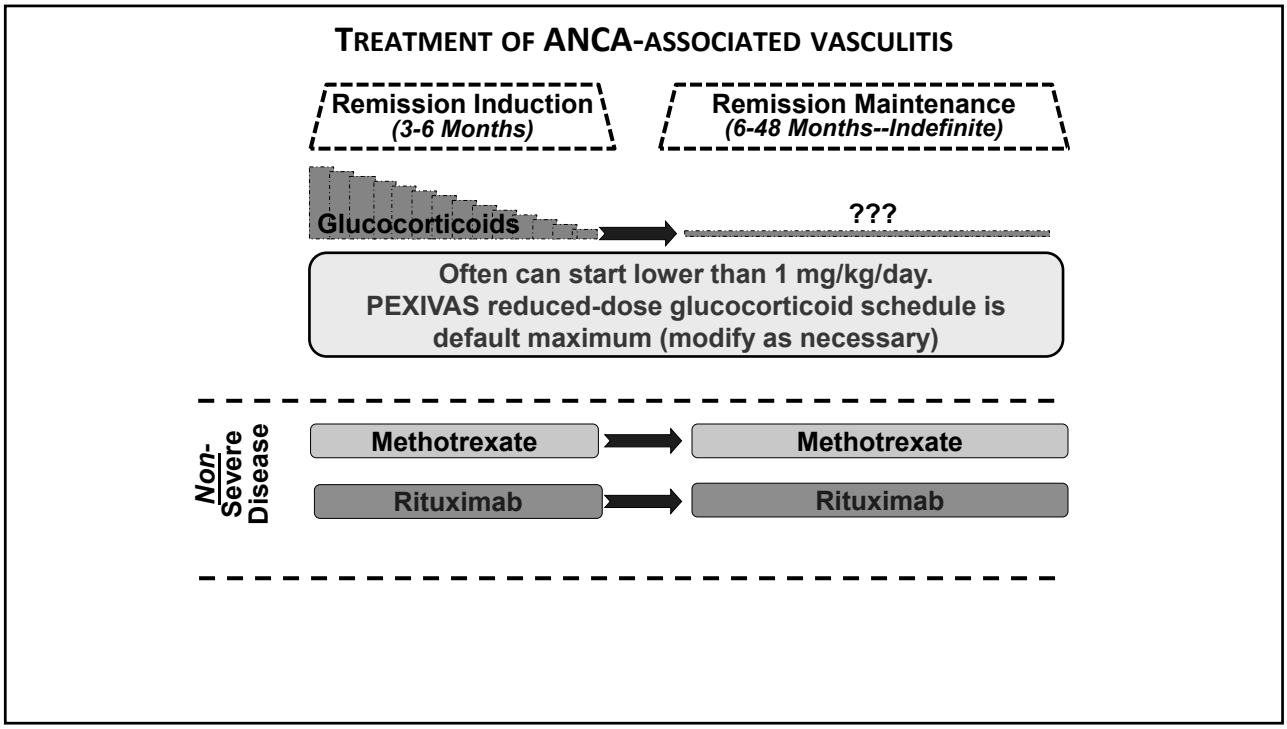

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Treatment of Severe AAV

Severe = organ- or life-threatening

- **The majority of *new* presentations of AAV involve severe disease**
- **Many *relapses* of AAV involve non-severe disease**

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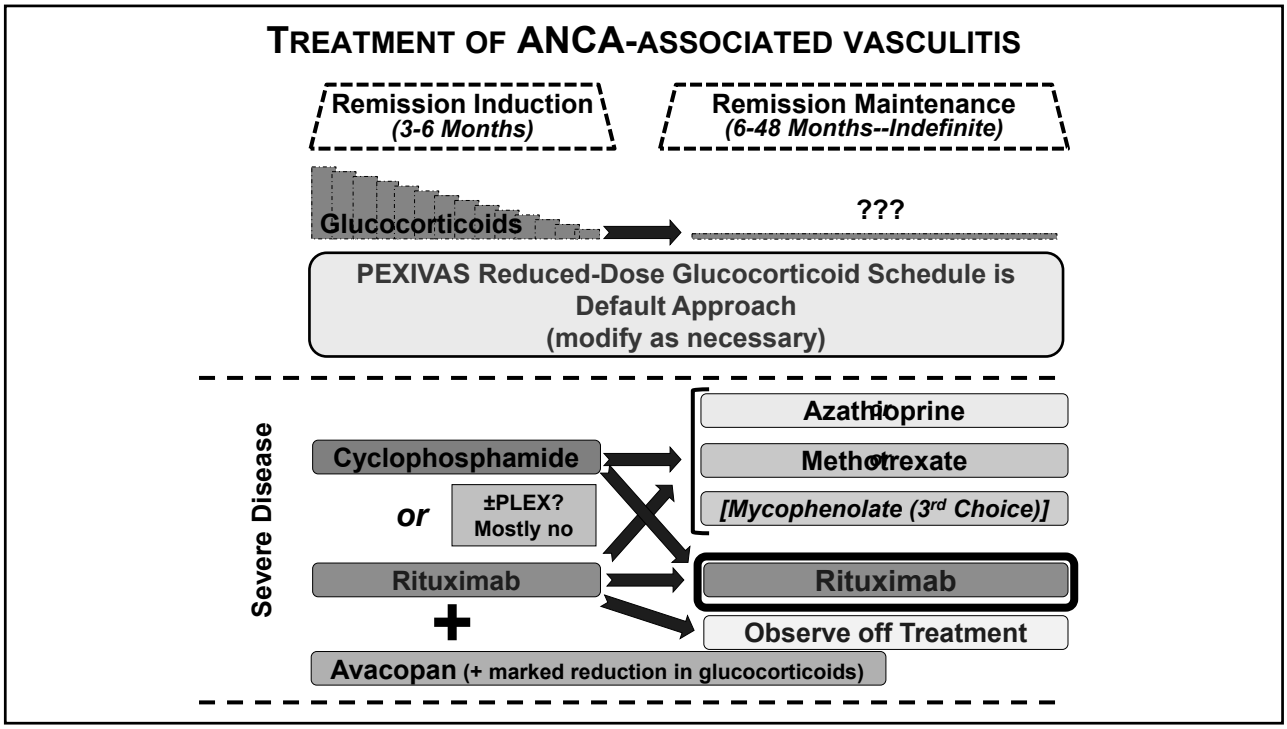

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PEXIVA glucocorticoid dose schedules

Table 1 Glucocorticoid dosing in the standard and reduced-dose groups of PEXIVAS

Week	Standard			Reduced-dose		
	<50 kg	50-75 kg	>75 kg	<50 kg	50-75 kg	>75 kg
	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse
1	50	60	75	50	60	75
2	50	60	75	25	30	40
3-4	40	50	60	20	25	30
5-6	30	40	50	15	20	25
7-8	25	30	40	12.5	15	20
9-10	20	25	30	10	12.5	15
11-12	15	20	25	7.5	10	12.5
13-14	12.5	15	20	6	7.5	10
15-16	10	10	15	5	5	7.5
17-18	10	10	15	5	5	7.5
19-20	7.5	7.5	10	5	5	5
21-22	7.5	7.5	7.5	5	5	5
23-52	5	5	5	5	5	5
>52	Investigators' Local Practice			Investigators' Local Practice		

PEXIVAS

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Use of avacopan to treat severe AAV (new or relapsing)

- Use of avacopan is almost fully based on results of the ADVOCATE trial
- Avacopan indicated as <u>adjunctive</u> therapy for patients with severe AAV (new or relapsing) with a goal of reduced total dose of glucocorticoids
  - Given <u>with</u> rituximab or cyclophosphamide
- Per trial, once avacopan started, prednisone reduced to ≤ 20 mg/day
  - Adjust per individual situation
  - Reasonable goal is to get to prednisone 0 mg/day by 4-6 weeks (4 per trial)
- How long to treat with avacopan?
  - ADVOCATE: 12 months of data; no long-term data on safety (yet)
  - Extended use is being explored in practice and likely in trials
- What to do at 6 months regarding rituximab?
  - Re-treat ± continue avacopan?

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What about *repeat* dosing of rituximab for maintenance of remission?

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Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

The NEW ENGLAND JOURNAL *of* MEDICINE **2014**

- **AKA "MAINRITSAN"**
- **Open-labeled RCT by French Vasculitis Study Group**
- **115 patients with AAV with remission induced with <u>cyclophosphamide</u> and glucocorticoids**
  - **Mostly *new-onset* disease**
  - **Mostly GPA**
- **Randomized after remission: rituximab vs. azathioprine**
- **Azathioprine dose tapered at 1 year**
- **Rituximab doses were <u>500 mg IV</u>**

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Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

L. Guillevin, C. Pagnoux, A. Karras, C. Khouatra, O. Aumaître, P. Cohen, F. Maurier, O. Decaux, J. Ninet, P. Gobert, T. Quémeneur, C. Blanchard-Delaunay, P. Godmer, X. Puéchal, P.-L. Carron, P.-Y. Hatron, N. Limal, M. Hamidou, M. Ducret, E. Daugas, T. Papo, B. Bonnotte, A. Mahr, P. Ravaud, and L. Mouthon, for the French Vasculitis Study Group*

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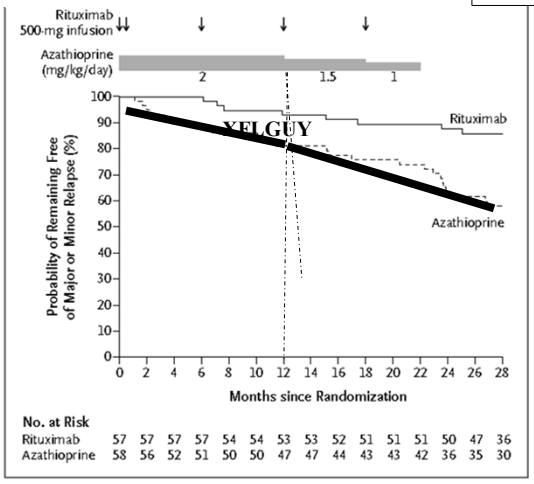

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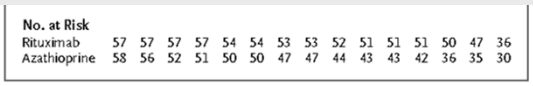
Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis

Remaining Questions:

- **What about patients who did *not* receive cyclophosphamide for induction?**
- **What about patients with relapsing disease?**
- **What about full-dose azathioprine?**
- **What about higher-dose rituximab?**
- **Will lower-dose glucocorticoids work as well?**
- **What happens after 2 years? (when/who to stop?)**
- **What predicts relapse or sustained remission?**



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An International, Open Label, Randomised Controlled Trial Comparing Rituximab with Azathioprine as Maintenance Therapy in Relapsing ANCA-Associated Vasculitis (RITAZAREM)

David Jayne[1] and Peter A. Merkel[2]
[1]Addenbrooke's Hospital; [2]University of Pennsylvania

Annals of the Rheumatic Diseases, 2023

European Vasculitis Society EUVAS

VASCULITIS CLINICAL RESEARCH CONSORTIUM

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Rituximab versus azathioprine for maintenance of remission for patients with ANCA-associated vasculitis and relapsing disease: an international randomised controlled trial

Rona M Smith [1], Rachel B Jones,[2] Ulrich Specks,[3] Simon Bond,[4] Marianna Nodale [4], Reem Al-jayyousi,[5] Jacqueline Andrews,[6] Annette Bruchfeld,[7] Brian Camilleri,[8] Simon Carette,[9] Chee Kay Cheung,[10] Vimal Derebail,[11] Tim Doulton,[12] Alastair Ferraro,[13] Lindsy Forbess,[14] Shouichi Fujimoto [15], Shunsuke Furuta [16], Ora Gewurz-Singer,[17] Lorraine Harper [18], Toshiko Ito-Ihara,[19] Nader Khalidi [20], Rainer Klocke,[21] Curry Koening,[22] Yoshinori Komagata,[23] Carol Langford,[24] Peter Lanyon,[25] Raashid Luqmani,[26] Carol McAlear,[27] Larry W Moreland,[28] Kim Mynard,[29] Patrick Nachman,[30] Christian Pagnoux,[31] Chen Au Peh,[32] Charles Pusey,[33] Dwarakanathan Ranganathan,[34] Rennie L Rhee [35], Robert Spiera [36], Antoine G Sreih,[27] Vladamir Tesar,[37] Giles Walters [38], Caroline Wroe,[39] David Jayne [40], Peter A Merkel,[41] RITAZAREM co-investigators

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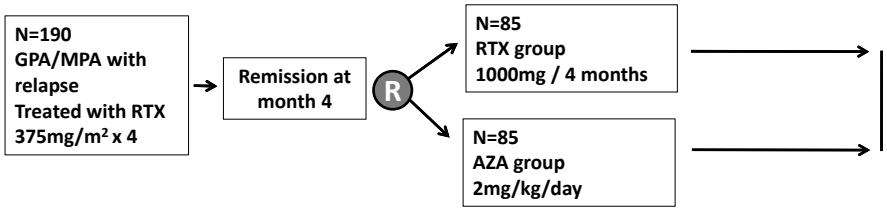
RITAZAREM

RITAZAREM Trial

Rituximab (RTX) or azathioprine (AZA) for maintenance of remission after induction of remission with RTX



Induction	Maintenance	Follow-up
0-4 months	4-24 months	24-48 months

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Time to first relapse

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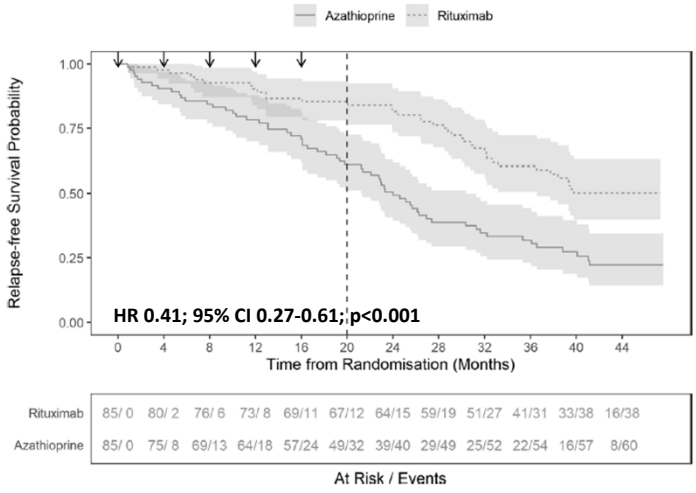

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Relapses are common regardless of which maintenance agent was used

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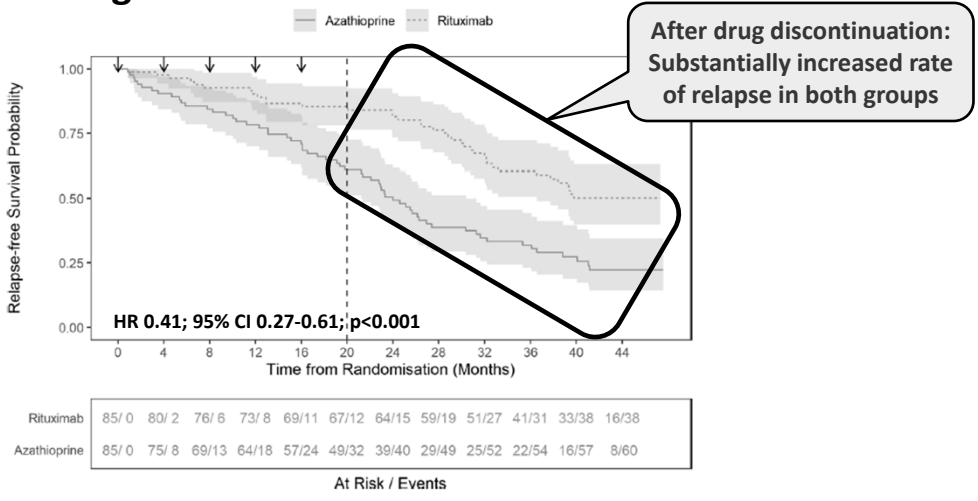

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Predictors of relapse

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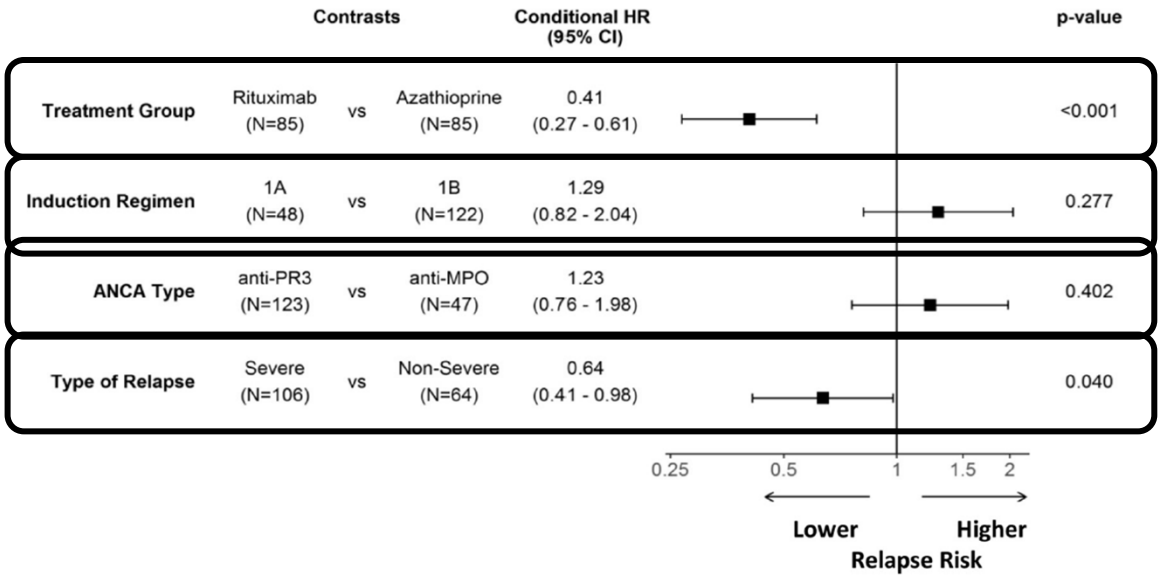

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Adverse Events

RITAZAREM

Table 2 Adverse events according to treatment regimen in the RITAZAREM trial

	Total (N=188)	Rituximab (N=85)	Azathioprine (N=85)	Not randomised (N=18)
Number (%) of patients with a serious adverse event	92 (49%)	37 (44%)	48 (56%)	7 (39%)
Number (%) of patients with a serious infection	39 (21%)	15 (18%)	19 (22%)	5 (28%)
Number (%) of patients with a non-serious infection	119 (63%)	54 (64%)	62 (73%)	3 (17%)
Number (%) of patients with plasma IgG<5 g/L	66 (35%)	36 (42%)	26 (31%)	4 (22%)
Number (%) of patients with plasma IgG<3 g/L	17 (9%)	8 (9%)	6 (7%)	3 (17%)

- **AEs/SAEs were common in both groups, especially infections**
- **No difference in rate or types of AEs/SAEs between treatments**

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RITAZAREM

Conclusions

- Following induction of remission with rituximab, rituximab is superior to azathioprine for preventing disease relapse in patients with AAV with a prior history of relapse
- No new major safety signals were identified for use of these medications in this population
- Relapses remain quite common regardless of which therapy for maintenance of remission is used, especially upon cessation of treatment with immunosuppressive medications
- The effect of higher-dose rituximab is not sustained beyond the treatment period
- Additional analyses of the 24-48 month data will provide insights into predictors of relapse, and the roles & impact of B cells, ANCA, and IgG levels, and more

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Options for remission-maintenance in AAV following induction of remission with rituximab (2024)

- **Watch & wait after one course of rituximab or 18 months of azathioprine/cyclophosphamide**
  - Reasonable if low-risk of relapse (new-onset anti-MPO+; drug-induced AAV)
- **Treat with azathioprine or methotrexate**
  - Results MAINRITSAN & RITAZAREM lead to caution for this approach but appropriate in some cases
- **Treat with rituximab**
  - Frequency: every 4-6 months
  - Dose?
    - 2000 mg? • 500 mg? • 1000 mg? • Other? • Base on B cells?

US FDA-approved dose for maintenance

- **Concerns:**
  - Rituximab
    - Costs
    - Vaccine responsiveness and efficacy
    - Infectious risk of long-term treatment
  - When/how to use of low-dose glucocorticoids

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How long to treat with rituximab for maintenance of remission in AAV?

- This is a more complicated issue than it may at first appear
- For patients with a history of relapse, regular administration of rituximab helps, but does not eliminate, the risk of relapse
- There are negative consequences to prolonged B cell depletion
  - Increased risk of infections
  - Reduced vaccine responsiveness
  - Potential hematologic and other adverse events
  - Substantial cost
- When rituximab is discontinued, relapse rates are high, even after several years of treatment
- No good evidence that prolonged B cell depletion with current treatments "re-sets" the immune system
  - Are we simply "kicking the can down the road"?

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What does all this mean?

- Should we reconsider recommendations for extended treatment with rituximab for most patients with GPA/MPA?
- Factors to consider:
  - Risk of relapse in terms of *likelihood of relapse*
    - New-onset disease: PR3-ANCA vs. MPO-ANCA; upper airway disease
    - Relapsing disease: Non-severe disease/upper airway disease
    - Mixed evidence and unclear meaning: rise or persistently positive ANCA titers
  - Risk of relapse in terms of *risk to patient's health of a relapse*
    - Low eGFR means less "room" to absorb renal decline before need for dialysis
    - Comorbidities and risk of treatment-related damage (e.g. diabetes mellitus)
- Needed:
  - Good predictive biomarkers, likely in combination with clinical factors, for i) relapse; ii) prolonged remission; iii) ability to stop treatment.

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Consideration of therapy for CAR T 19 for ANCA-associated vasculitis

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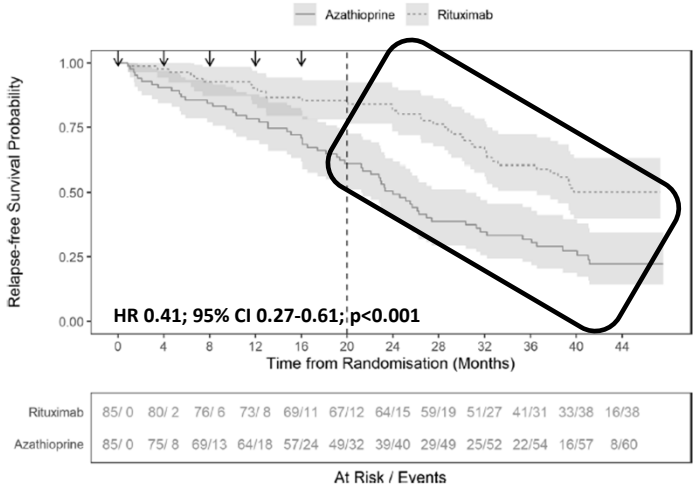
Relapses are common regardless of maintenance agent used

RITAZAREM



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Role of B-Cells in Autoimmune Diseases: The Promise and Pathway to Better Treatments

What about CAR T19 for ANCA-Associated Vasculitis?

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Impact of Dr. Schett's groundbreaking work…

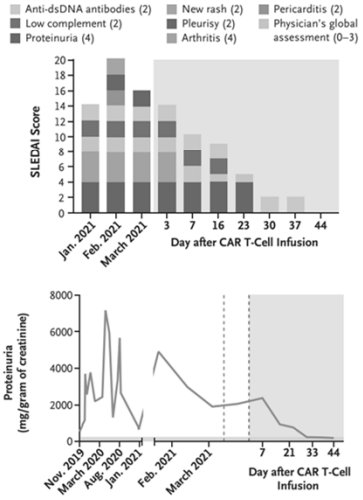
The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus

N ENGL J MED AUGUST 5, 2021

Simon Völkl, Ph.D.
Sascha Kretschmann, Ph.D.
Michael Aigner, Ph.D.
Soraya Kharboutli, M.D.
Sebastian Böltz, M.D.
Bernhard Manger, M.D.
Andreas Mackensen, M.D.
Georg Schett, M.D.



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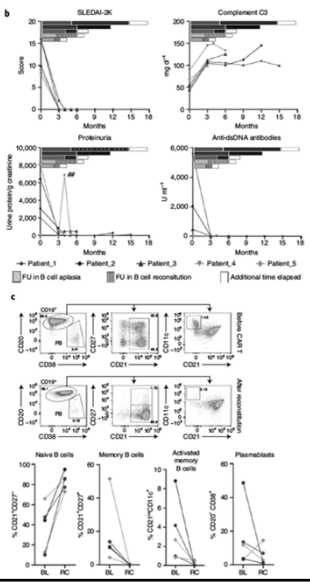
Impact of Dr. Schett's groundbreaking work…

ARTICLES
https://doi.org/10.1038/s41591-022-02017-5
nature medicine
Check for updates

Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen[1,2,8], Fabian Müller[1,2,8], Dimitrios Mougiakakos[1,2,3,8], Sebastian Böltz[2,4], Artur Wilhelm[2,4], Michael Aigner[1,2], Simon Völkl[1,2], David Simon[2,4], Arnd Kleyer[2,4], Luis Munoz[2,4], Sascha Kretschmann[1,2], Soraya Kharboutli[1,2], Regina Gary[1,2], Hannah Reimann[1,2], Wolf Rösler[1,2], Stefan Uderhardt[2,4], Holger Bang[5], Martin Herrmann[2,4], Arif Bülent Ekici[6], Christian Buettner[6], Katharina Marie Habenicht[7], Thomas H. Winkler[7], Gerhard Krönke[2,4,8] and Georg Schett[2,4,8]

NATURE MEDICINE | VOL 28 | OCTOBER 2022 |



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A CD19 CAR T Therapeutic Approach Has the Potential to be Transformative for Patients with B-Cell-Driven Autoimmune Diseases

Unmet Medical Need	Reasons to Believe	Targeted Patient Outcomes
Tissue-resident pathogenic B cells are central to the pathogenesis of multiple autoimmune diseases <u>and</u> are resistant to depletion	Cell therapy approach → *Unencumbered access to inflamed tissues*	**Transformative Efficacy** *Lasting immune re-set may be possible*
	More Complete & Tissue-Based Depletion of B-Cells and other CD19+ Cells→ *Support higher efficacy*	**Withdrawal of Background Immunosuppressants** *Avoids consequences of lifelong immunosuppression*
	Sufficient Cell Aplasia → *Effect a durable clinical response*	

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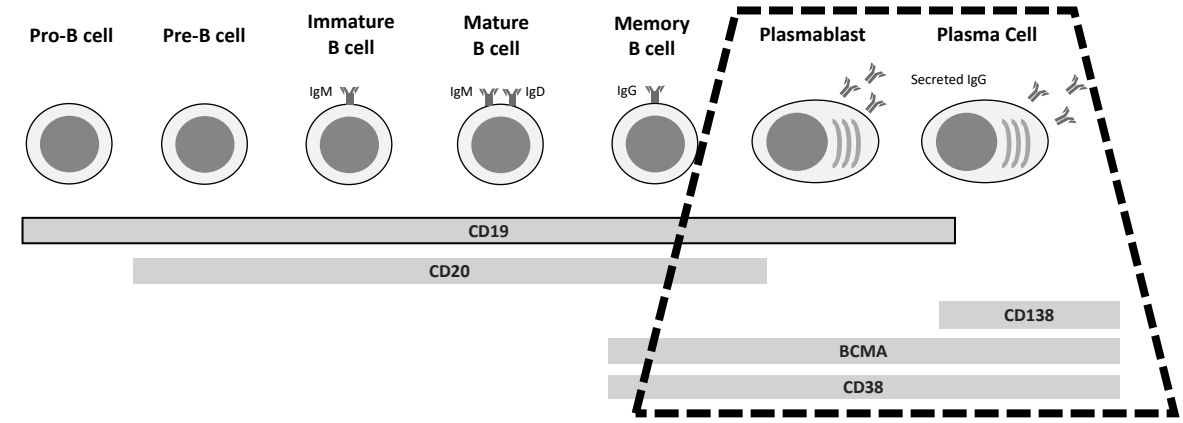
CD19 Expressed on Broader Range of B Cell Subsets Compared With CD20



CD19-targeted depletion of B cells eliminates the broadest range of B cell subsets while sparing long-lived plasma cells, the reservoir of established humoral immunity

Adapted from Jejeune et al, Front Immunol 2020;11:762

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Indication Selection: Studies of B Cell-Targeting mAbs Provide a Roadmap, Scientific Rationale, Unmet Need, and Established Biomarkers/Clinical Endpoints

	Lupus Nephritis	ANCA-Associated Vasculitis	Rheumatoid Arthritis	Systemic Sclerosis	Dermatomyositis	Polymyositis
Rationale for role for B cells	Clinical validation (belimumab, obinutuzumab)	Clinical validation Rituximab: FDA-Approved	Clinical validation Rituximab: FDA-Approved	Clinical validation (rituximab) Supportive data	Clinical validation IVIg: FDA-Approved Supportive data	Supportive data
Unmet medical need	> 60% do not achieve CR	Few options beyond CYC, rituximab	10%-20% fail conventional & biologic DMARDS	Treatment options remain limited		
Biomarkers & clinical end points	Proteinuria, GFR, dsDNA, C3, C4, kidney biopsy	PR3 Ab, MPO Ab, BVAS	CRP, ACR 20/50/70, DAS28	Skin biopsy, CRISS, MRSS, PFTs, PROs, possibly Auto-Abs	MRC, CDASI, muscle/skin biopsy, possibly Auto-Abs	MRC, muscle/skin biopsy, possibly Auto-Abs
Regulatory precedents & endpoints	Defined path & established end points			Defined path & established end points		

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CAR T 19 for Treatment of ANCA-Associated Vasculitis

- **Makes biologic sense to consider**
- **There is an unmet need to new treatments, especially long-term**
- **Trials are appropriate but we need to be careful**
  - **Safety is top priority**
  - **Be highly selective with eligibility**
  - **Multidisciplinary team**

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What's Next for Treatment of AAV (GPA/MPA)?

(informed speculation but still speculative!)

- **More and more about "glucocorticoid-sparing"**
- **More about complement inhibition: C5a and much more**
- **Novel methods for B cell depletion**
  - **Anti-CD20 beyond rituximab: obinutuzumab, etc.**
  - **Anti-CD19, BCMA, other**
  - **CAR T (Anti-CD 19)**
- **Addressing T cells**
  - **Abatacept**
  - **Other approaches**
- **New ways to clear ANCA…?**
- **New and cool stuff I can't talk about**
- **More personalized medicine**
  - **Need for reliable predictors of relapse/remission**

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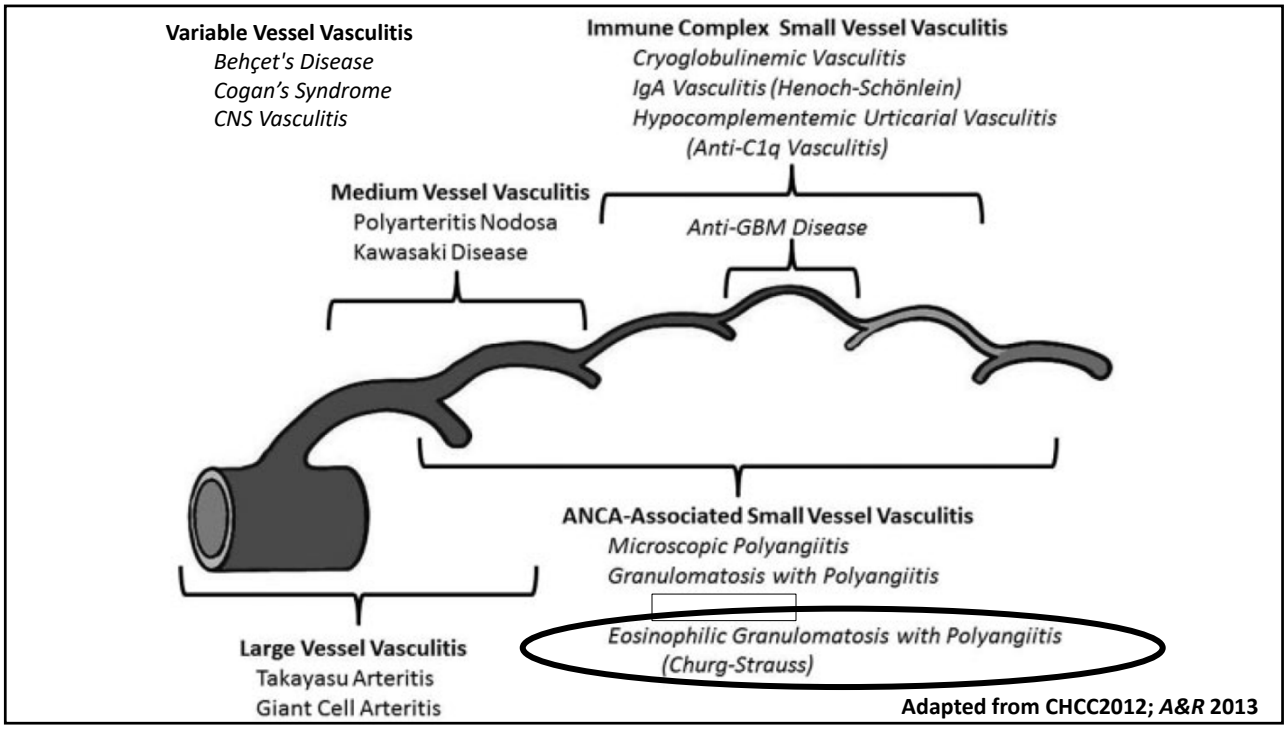
Variable Vessel Vasculitis
Behçet's Disease
Cogan's Syndrome
CNS Vasculitis
Immune Complex Small Vessel Vasculitis
Cryoglobulinemic Vasculitis
IgA Vasculitis (Henoch-Schönlein)
Hypocomplementemic Urticarial Vasculitis
(Anti-C1q Vasculitis)
Medium Vessel Vasculitis
Polyarteritis Nodosa
Kawasaki Disease
Anti-GBM Disease
ANCA-Associated Small Vessel Vasculitis
Microscopic Polyangiitis
Granulomatosis with Polyangiitis
Eosinophilic Granulomatosis with Polyangiitis
(Churg-Strauss)
Large Vessel Vasculitis
Takayasu Arteritis
Giant Cell Arteritis
Adapted from CHCC2012; A&R 2013

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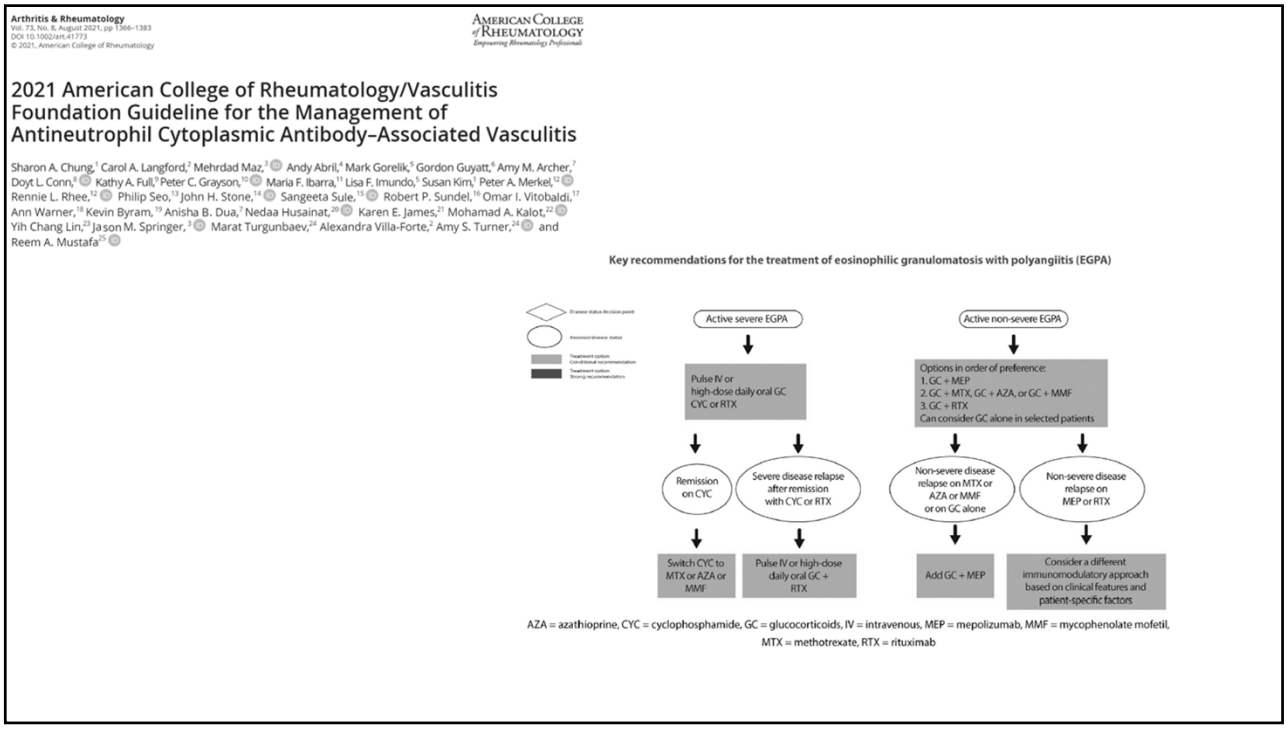
Arthritis & Rheumatology
Vol. 73, No. 8, August 2021, pp 1366–1383
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American College of Rheumatology
Empowering Rheumatology Professionals
2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis
Sharon A. Chung, Carol A. Langford, Mehrdad Maz, Andy Abril, Mark Gorelik, Gordon Guyatt, Amy M. Archer, Doyt L. Conn, Kathy A. Full, Peter C. Grayson, Maria F. Ibarra, Lisa F. Imundo, Susan Kim, Peter A. Merkel, Rennie L. Rhee, Philip Seo, John H. Stone, Sangeeta Sule, Robert P. Sundel, Omar I. Vitobaldi, Ann Warner, Kevin Byram, Anisha B. Dua, Nedaa Husainat, Karen E. James, Mohamad A. Kalot, Yih Chang Lin, Jason M. Springer, Marat Turgunbaev, Alexandra Villa-Forte, Amy S. Turner, and Reem A. Mustafa
Key recommendations for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA)
Active severe EGPA
Pulse IV or high-dose daily oral GC CYC or RTX
Remission on CYC
Severe disease relapse after remission with CYC or RTX
Switch CYC to MTX or AZA or MMF
Pulse IV or high-dose daily oral GC + RTX
Active non-severe EGPA
Options in order of preference:
1. GC + MEP
2. GC + MTX, GC + AZA, or GC + MMF
3. GC + RTX
Can consider GC alone in selected patients
Non-severe disease relapse on MTX or AZA or MMF or on GC alone
Non-severe disease relapse on MEP or RTX
Add GC + MEP
Consider a different immunomodulatory approach based on clinical features and patient-specific factors
AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, IV = intravenous, MEP = mepolizumab, MMF = mycophenolate mofetil, MTX = methotrexate, RTX = rituximab

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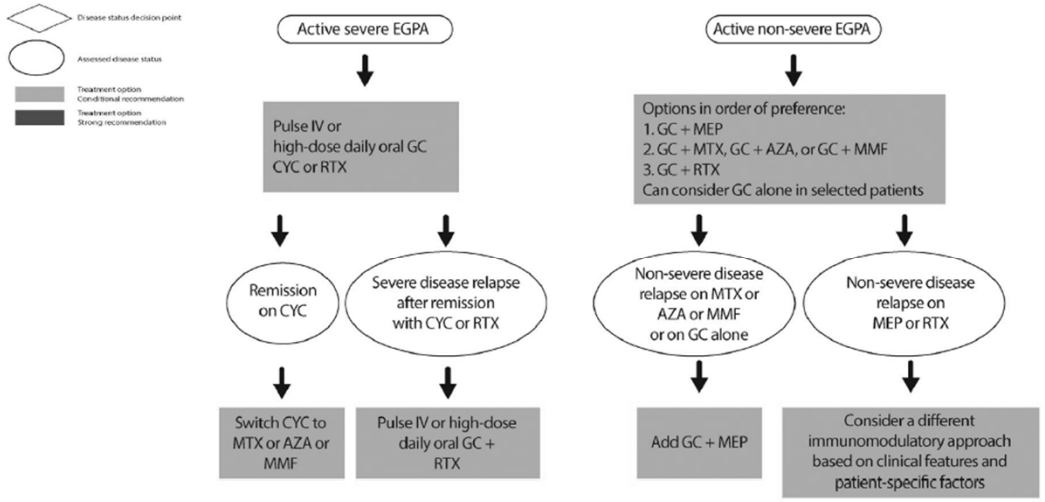
Key recommendations for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA)



AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, IV = intravenous, MEP = mepolizumab, MMF = mycophenolate mofetil, MTX = methotrexate, RTX = rituximab

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Empowering Rheumatology Professionals

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ORIGINAL ARTICLE

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

M.E. Wechsler, P. Akuthota, D. Jayne, P. Khoury, A. Klion, C.A. Langford, P.A. Merkel, F. Moosig, U. Specks, M.C. Cid, R. Luqmani, J. Brown, S. Mallett, R. Philipson, S.W. Yancey, J. Steinfeld, P.F. Weller, and G.J. Gleich, for the EGPA Mepolizumab Study Team*

The NEW ENGLAND JOURNAL of MEDICINE 2017

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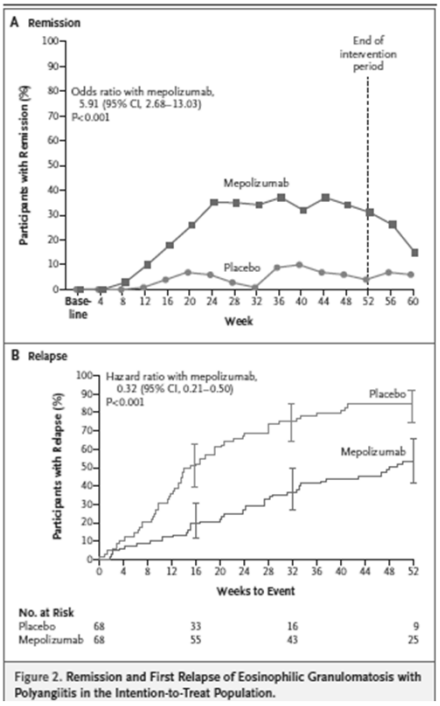

Figure 2. Remission and First Relapse of Eosinophilic Granulomatosis with Polyangiitis in the Intention-to-Treat Population.

***NEJM* 2017**

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Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis

J ALLERGY CLIN IMMUNOL
VOLUME 143, NUMBER 6

Jonathan Steinfeld, MD,[a] Eric S. Bradford, MD,[b] Judith Brown, PhD,[c] Stephen Mallett, MSc,[d] Steven W. Yancey, MSc,[b] Praveen Akuthota, MD,[e] Maria C. Cid, MD,[f] Gerald J. Gleich, MD,[g] David Jayne, FMedSci,[h] Paneez Khoury, MD, MHSc,[i] Carol A. Langford, MD, MHS,[j] Peter A. Merkel, MD, MPH,[k] Frank Moosig, MD,[l] Ulrich Specks, MD,[m] Peter F. Weller, MD,[n] and Michael E. Wechsler, MD[o] *Philadelphia, Pa, Research Triangle Park, NC, Uxbridge and Cambridge, United Kingdom, La Jolla, Calif, Barcelona, Spain, Salt Lake City, Utah, Bethesda, Md, Cleveland, Ohio, Neumünster, Germany, Boston, Mass, and Denver, Colo*

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Evaluation of clinical benefit from treatment with mepolizumab for eosinophilic granulomatosis with polyangiitis

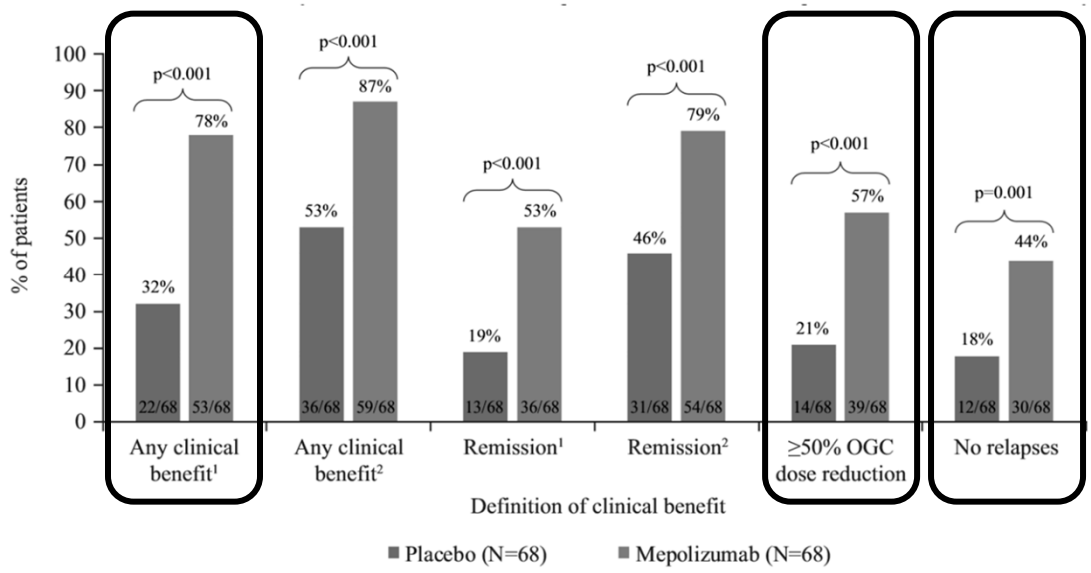

FIG 1. Summary of clinical benefit after treatment with placebo or mepolizumab (as-treated population).

J ALLERGY CLIN IMMUNOL
VOLUME 143, NUMBER 6

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Mepolizumab for EGPA

- **First drug proven in a randomized trial clearly effective for EGPA**
- **Not a cure but an important option**
- **Shows power and potential of "targeted therapies"**
- **Dosing**
  - **Dose approved for eosinophilic asthma is 100 mg SQ monthly**
  - **Dose approved for EGPA is 300 mg SQ monthly**
- **What about other anti-IL 5 agents for EGPA?**
  - **Benralizumab, reslizumab**

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Il-5 Inhibition

- **Mepolizumab: monoclonal antibody to IL-5**
- **Benralizumab: monoclonal antibody to IL-5Rα**

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Benralizumab versus mepolizumab for eosinophilic granulomatosis with polyangiitis

Michael E. Wechsler, M.D., M.M.Sc.[1], Parameswaran Nair, M.D., Ph.D.[2], Benjamin Terrier, M.D., Ph.D.[3], Bastian Walz, M.D.[4], Arnaud Bourdin, M.D., Ph.D.[5], David R. W. Jayne, M.D.[6], David J. Jackson, F.R.C.P., Ph.D.[7], Florence Roufosse, M.D., Ph.D.[8], Lena Börjesson Sjö, Ph.D.[9], Ying Fan, Ph.D.[10], Maria Jison, M.D.[10], Christopher McCrae, Ph.D.[11], Sofia Necander, M.D.[9], Anat Shavit, D.V.M.[12], Claire Walton, M.Sc.[13], Peter A. Merkel, M.D., M.P.H.[14] on behalf of the MANDARA Study Group

(Submitted for Publication)

The MANDARA Trial

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ABSTRACT NUMBER: L14

Efficacy and Safety of Benralizumab Compared with Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis in Patients Receiving Standard of Care Therapy: Phase 3 MANDARA Study

Michael Wechsler[1], Parameswaran Nair[2], Benjamin Terrier[3], Bastian Walz[4], Arnaud Bourdin[5], David Jayne[6], David Jackson[7], Florence Roufosse[8], Lena Börjesson Sjö[9], Ying Fan[10], Maria Jison[10], Christopher McCrae[11], Sofia Necander[9], Anat Shavit[12], Claire Walton[12] and **Peter Merkel**[13], [1]National Jewish Health, Denver, CO, [2]McMaster University, Hamilton, ON, Canada, [3]Cochin Hospital, Paris, France, [4]University of Tübingen, Kirchheim-Teck, Germany, [5]University of Montpellier, CHU Montpellier, INSERM, Montpellier, Montpellier, France, [6]Addenbrooke's Hospital, Cambridge, United Kingdom, [7]Guy's Severe Asthma Centre, School of Immunology & Microbial Sciences, King's College London,, London, United Kingdom, [8]Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium, [9]Late-stage Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden, [10]Late-stage Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca,, Gaithersburg, MD, [11]Translational Science & Experimental Medicine, Early Respiratory & Immunology, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, [12]BioPharmaceutials Medical, AstraZeneca, Cambridge, United Kingdom, [13]University of Pennsylvania, Philadelphia, PA

Meeting: ACR Convergence 2023

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Background/Purpose: Eosinophilic inflammation is a key pathophysiological mechanism of eosinophilic granulomatosis with polyangiitis (EGPA). Oral glucocorticoids (OGCs) and immunosuppressants remain the basis for the standard of care (SoC),but their long-term use is associated withsignificantadverse effects, and relapses are frequently seen. The MANDARA trial compared the efficacy and safety of benralizumab (a monoclonal antibody against the IL-5 receptor) and mepolizumab (an anti-IL-5 agent, and the only approved drug for EGPA) in patients with EGPA receiving SoC.

Methods: MANDARA was a randomized, active-controlled, parallel-group, multicenter, 52-week double-blind with open-label extension, Phase III non-inferiority study (NCT04157348). Patients (≥18 years) with documented EGPA based on asthma and blood eosinophilia plus ≥2 additional features of EGPA, and a history of relapsing/refractory disease requiring stable OGCs (≥7.5 mg prednisone/prednisolone daily) ± stable immunosuppressive therapy for ≥4 weeks before randomization, were included. Benralizumab 1 x 30 mg or mepolizumab 3 x 100 mg were administered by subcutaneous injection every 4 weeks for 52 weeks, and OGC was tapered if disease was controlled. The primary endpoint was the proportion of patients achieving remission (defined as Birmingham Vasculitis Activity Score [BVAS] = 0 and OGC dose ≤4 mg/day) at both Weeks 36 and 48. Secondary endpoints included accrued and maintained remission, OGC use, other clinical benefits, time to first relapse, and safety.

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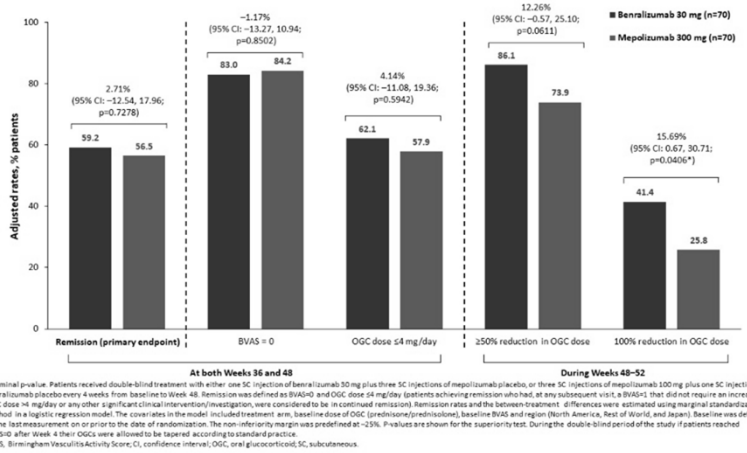
Conclusion: This study demonstrated non-inferiority of benralizumab vs mepolizumab over 52 weeks in patients with relapsing/refractory EGPA receiving SoC and provides evidence for the efficacy and utility of benralizumab, with more benralizumab-treated patients being fully tapered off OGC. Both study drugs were well tolerated with a similar proportion of patients reporting AEs.



*Nominal p-value. Patients received double-blind treatment with either one SC injection of benralizumab 30 mg plus three SC injections of mepolizumab placebo, or three SC injections of mepolizumab 100 mg plus one SC injection of benralizumab placebo every 4 weeks from baseline to Week 48. Remission was defined as BVAS=0 and OGC dose ≤4 mg/day (patients achieving remission who had, at any subsequent visit, a BVAS=1 that did not require an increase in OGC dose >4 mg/day or any other significant clinical intervention/investigation, were considered to be in continued remission). Remission rates and the between-treatment differences were estimated using marginal standardization method in a logistic regression model. The covariates in the model included treatment arm, baseline dose of OGC (prednisone/prednisolone), baseline BVAS and region (North America, Rest of World, and Japan). Baseline was defined as the last measurement on or prior to the date of randomization. The non-inferiority margin was predefined at −25%. P-values are shown for the superiority test. During the double-blind period of the study if patients reached BVAS=0 after Week 4 their OGCs were allowed to be tapered according to standard practice.
BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; OGC, oral glucocorticoid; SC, subcutaneous.

Figure 1. Efficacy outcomes and between-treatment differences in rates during the double-blind treatment period

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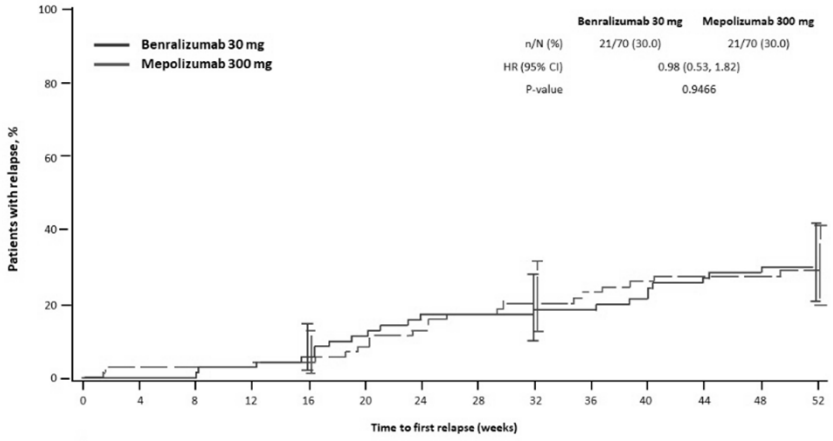

Relapse was defined as worsening or persistence of active disease characterized by: active vasculitis (BVAS >0), or active symptoms and/or signs of asthma with a corresponding worsening in ACQ-6 score, or active nasal and/or sinus disease with a corresponding worsening in at least one of the sino-nasal symptom questions; warranting: an increase of OGCs, or an increased dose or addition of an immunosuppressive agent, or hospitalization related to worsening of EGPA. The HR (benralizumab vs mepolizumab) and 95% CIs were estimated using a Cox regression model with Efron method to control for ties. The covariates in the model included treatment arm, baseline dose of OGC (prednisone/prednisolone), baseline BVAS, and region. P-value was calculated using unstratified log-rank test.
ACQ-6, 6-item Asthma Control Questionnaire; BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; EGPA, eosinophilic granulomatosis with polyangiitis; HR, hazard ratio; OGC, oral glucocorticoids.

Figure 2. Time to first relapse

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	Treatment	Patients with accrued remission duration up to Week 52, n (%)					Comparison between groups	
		0 weeks	> 0 to < 12 weeks	12 to < 24 weeks	24 to <36 weeks	≥36 weeks	OR (95% CI)	P value
Accrued remission up to Week 52								
Remission	Benralizumab (n=70)	9 (12.9)	12 (17.1)	8 (11.4)	21 (30.0)	20 (28.6)	1.36 (0.75, 2.48)	0.3142
	Mepolizumab (n=70)	15 (21.4)	10 (14.3)	8 (11.4)	19 (27.1)	18 (25.7)		
Achieved remission by Week 24 and maintained remission until Week 52								
		Patients, n (%)			Adjusted remission rates, %		Difference in remission rates (95% CI)	P value
Remission	Benralizumab (n=70)	28 (40.0)			42.1		5.54 (–9.30, 20.37)	0.4643
	Mepolizumab (n=70)	27 (38.6)			36.5			
Achieved clinical benefit								
		Patients, n (%)			Adjusted response rates, %		Difference in response rates (95% CI)	P value
Clinical benefit (OGC dose ≤4 mg/day threshold)	Benralizumab (n=70)	66 (94.3)			94.4		4.60 (–4.22, 13.41)	0.3068
	Mepolizumab (n=70)	63 (90.0)			89.8			
Clinical benefit (OGC dose ≤7.5 mg/day threshold)	Benralizumab (n=70)	68 (97.1)			97.3		–1.13 (–5.85, 3.59)	0.6390
	Mepolizumab (n=70)	69 (98.6)			98.5			
Achieved complete response								
		Patients, n (%)			Adjusted response rates, %		Difference in response rates (95% CI)	P value
Complete response (OGC dose ≤4 mg/day threshold)	Benralizumab (n=70)	43 (61.4)			62.5		7.90 (–7.32, 23.12)	0.3088
	Mepolizumab (n=70)	39 (55.7)			54.6			
Complete response (OGC dose ≤7.5 mg/day threshold)	Benralizumab (n=70)	45 (64.3)			64.9		6.93 (–8.42, 22.28)	0.3762
	Mepolizumab (n=70)	41 (58.6)			57.9			

Secondary endpoints are not multiplicity-protected. All p-values are nominal. ORs and 95% CIs for benralizumab versus mepolizumab were estimated using a proportional odds model, with covariates including treatment arm, baseline OGC dose, baseline BVAS, and region. Rates and the difference in rates (benralizumab minus mepolizumab) and 95% CIs, were estimated using marginal standardization method from a logistic regression model, with covariates including treatment arm, baseline OGC dose, baseline BVAS, and region. Remission was defined as BVAS=0 and OGC dose ≤4 mg/day (patients achieving remission who had, at any subsequent visit, a BVAS>1 that did not require an increase in OGC dose >4 mg/day or any other significant clinical intervention/investigation, were considered to be in continued remission). Daily dose of OGCs: Baseline is defined as the last measurement on or prior to the date of randomization. Clinical benefit was defined as any of the following: remission (BVAS=0 and OGC dose ≤4 mg/day or ≤7.5 mg/day) at any time during the double-blind treatment period; ≥50% reduction in average daily OGC dose during Weeks 48 through 52; relapse free during the double-blind treatment period. Complete response was defined as all of the following: remission (BVAS=0 and OGC dose ≤4 mg/day or ≤7.5 mg/day) at any time during the double-blind treatment period; ≥50% reduction in average daily OGC dose during Weeks 48 through 52; relapse free during the double-blind treatment period.
BVAS, Birmingham Vasculitis Activity Score; CI, confidence interval; OGC, oral glucocorticoids; OR, odds ratio.

Table 1. Secondary endpoints during the double-blind treatment period

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What is the impact of MANDARA on treatment of EGPA and future research in EGPA?

- **Benralizumab will quite likely be approved for use in EGPA**
  - **Then there will be two options for IL-5 inhibition for EGPA**
- **Additional ancillary studies from data in MANDARA will be done**
- **Trials and interest in expanding use of IL-5 inhibition in EGPA**
- **Analyses of real-world and cohort data on utility of anti-IL5 therapies is underway**
- **Several new agents with new mechanisms of action will soon be tested for EGPA**

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Treatment of Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

- **Level of evidence for almost all treatments is low (except anti-IL5)**
- **Treatment may include glucocorticoids only**
- **Proper treatment of asthma is *essential***
- **Commonly need chronic low-dose glucocorticoids**
- **Severe disease: cyclophosphamide or rituximab**
- **Maintenance of remission:**
  - **Although azathioprine, methotrexate, and mycophenolate are used → poor data supporting this practice**
- **Anti-IL-5 agents: Now 2 RCTs**
  - **Effective for airway disease/non-severe disease**
  - **Rapid, substantial uptake in use in countries with access to these agents**
  - **Glucocorticoid-sparing effect is important**
  - **Need data on effectiveness for severe manifestations of disease**

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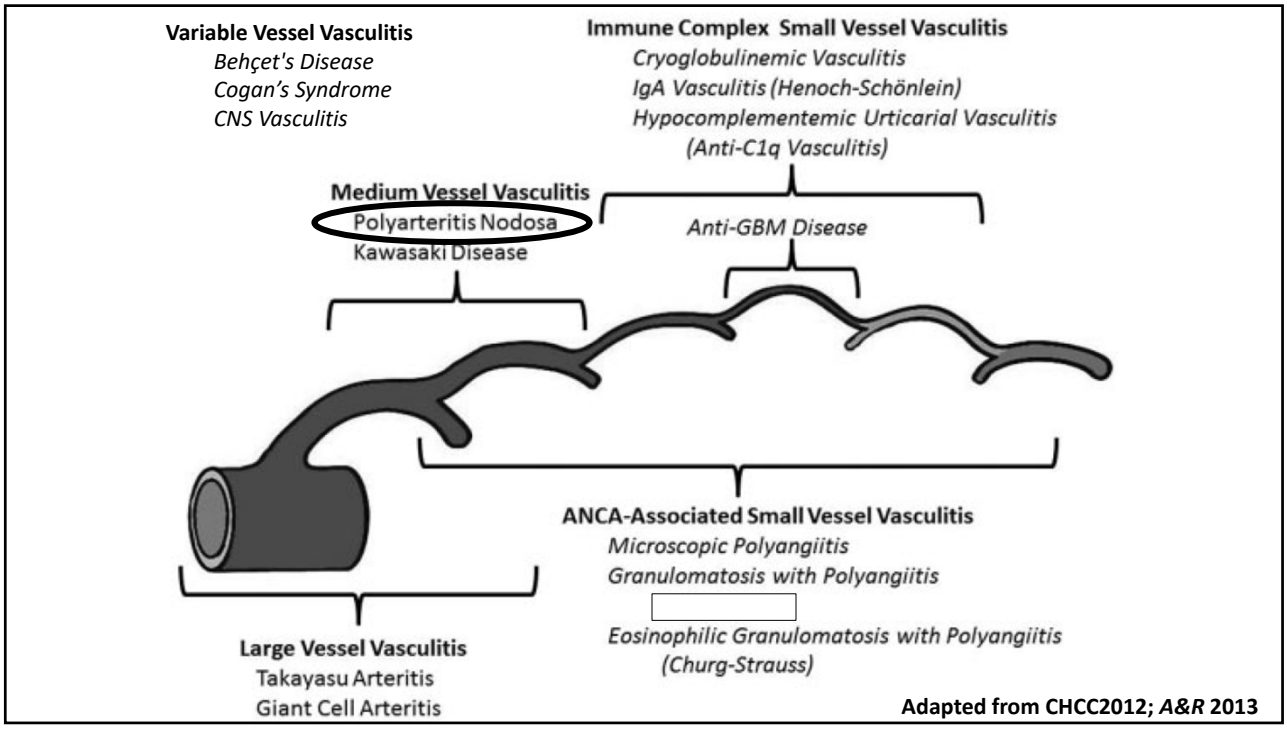

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Clinical Characteristics and Outcomes of Polyarteritis Nodosa – an International Study

O. Karadâg, E. Bolek, G. Ayan…P. Merkel

Arthritis & Rheumatism (In Press)

- **First large cohort study of PAN in decades and first since Chapel Hill Consensus Conference definitions stated ANCA positivity is inconsistent with PAN**
- **International collaboration: 9 countries across Europe, Japan, and North America**
- **Combination of prospectively and retrospectively collected data**
- **Subsets/modifiers:**
  - **Systemic PAN (sPAN)**
  - **Cutaneous PAN (cPAN)**
  - **Adult-onset vs. Pediatric-onset**
  - **DADA2, FMF, and HBV**
  - **We did not identify patients with VEXAS genotype**

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Clinical Characteristics and Outcomes of Polyarteritis Nodosa – an International Study

O. Karadâg, E. Bolek, G. Ayan…P. Merkel

Arthritis & Rheumatism (In Press)

- **Proper classification and clinically-relevant subsets are important**
  - **Consider monogenic causes: DADA2, FMF**
  - **Always rule out HBV**
  - **Look for VEXAS**
- **Look hard for disease manifestations**
- **Relapses happen → Keep following patients!**

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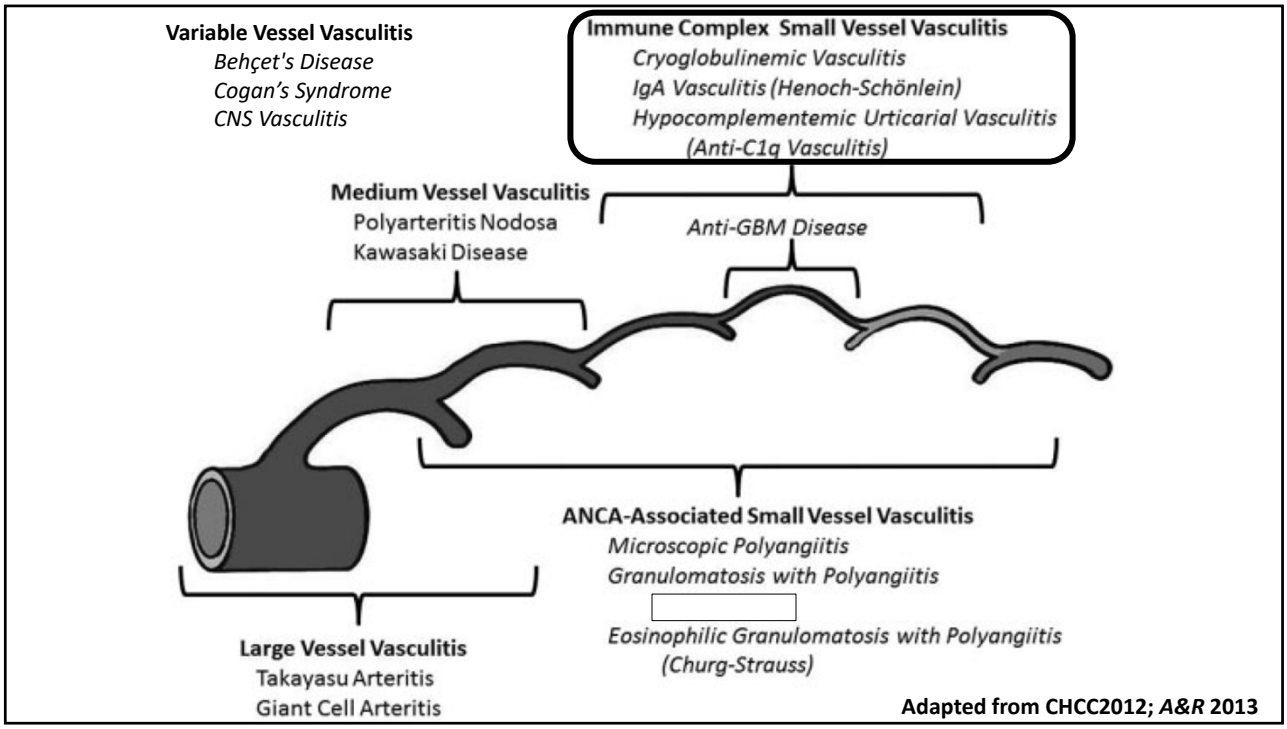

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Summary of this update on small-vessel vasculitis and polyarteritis nodosa

- **We continue to make substantive progress in understanding and developing effective treatments for these complex diseases**
- **There is a *lot* of research being conducted on all forms of small-vessel vasculitis**
- **So…stay tuned for new updates!**

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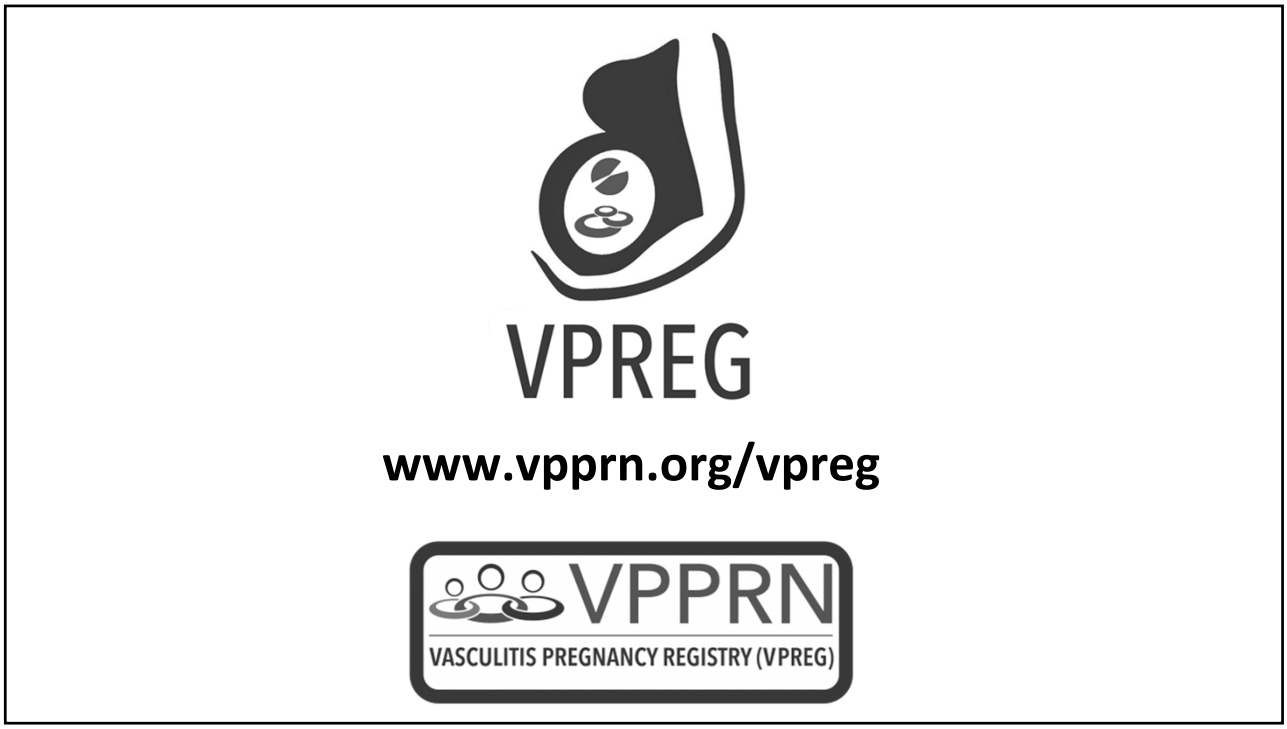
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