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1. DACH ANCA VASKULITIS FORUM 2023
12. & 13. MAI 2023

Aktuelle Evidenz zu neuen Therapieansätzen in der AAV

Prof. Dr. Sabine Adler

Aarau

AT-AVA-2300036
DE-AVA-2300048

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Aktuelle Evidenz zu neuen Therapieansätzen bei AAV

1st DACH ANCA Vaskulitis Forum 2023
12. Mai 2023

Sabine Adler
Klinik für Rheumatologie und Immunologie
Kantonsspital Aarau

Überblick aktuelle Evidenz AAV

- Rückblick
- Plasmaseparation
- Glucocorticoid "low-dose"
- Rituximab (versus Cyclosphospamid)
- Avacopan
- "what else"? Ausblick...

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Rückblick


Annals of Internal Medicine

Short Papers | 1 June 1987

Wegener Granulomatosis and Trimethoprim-Sulfamethoxazole

Complete Remission After a Twenty-Year Course

BURTON C. WEST, M.D., JOHN R. TODD, M.D., JOHN W. KING, M.D.

Author, Article, and Disclosure Information

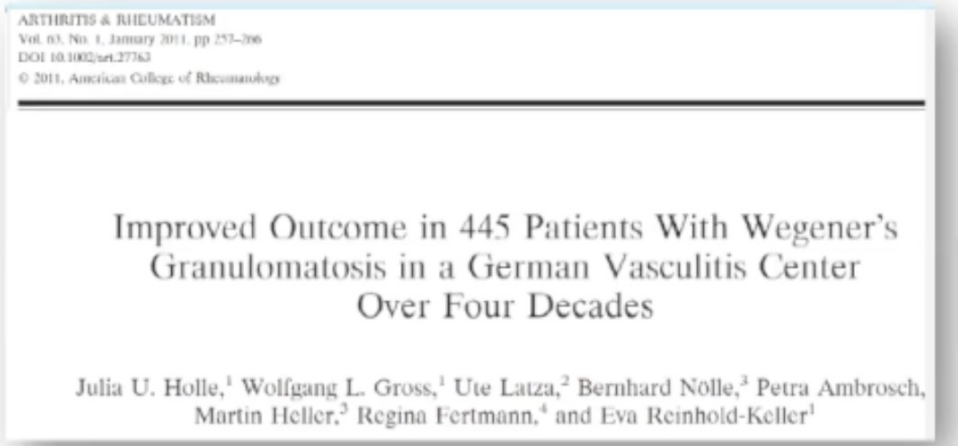
https://doi.org/10.7326/0003-4819-106-6-840

1965: 42 jährige Frau mit GPA

- AZA / Glucocorticoide=> Progression
- ***1969*** Cyclophosphamid kurz => relapse
- Dauertherapie mit Cyc
- ***1984*** Wechsel auf TMP/SMX
- => komplette Remission nach 22 Jahren

West BC, et al:
Ann Int Med 1987 June 1,
doi.org/10.7326/0003-4819-106-6-840

Rückblick



ARTHRITIS & RHEUMATISM
Vol. 63, No. 1, January 2011, pp 257–266
DOI 10.1002/art.27763

Improved Outcome in 445 Patients With Wegener's Granulomatosis in a German Vasculitis Center Over Four Decades

Julia U. Holle,[1] Wolfgang L. Gross,[1] Ute Latza,[2] Bernhard Nölle,[3] Petra Ambrosch, Martin Heller,[3] Regina Fertmann,[4] and Eva Reinhold-Keller[1]

- 290 GPA Patienten
- 1966 – 2002: 3 Kohorten
- unterschiedliche Therapieregime
- outcome / Nebenwirkungen

Holle JU, et al:
Arthritis Rheumatism, 2011;63(1):257-266

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Rückblick

Improved Outcome in 445 Patients With Wegener's Granulomatosis in a German Vasculitis Center Over Four Decades

	Cohort 1, 1966–1993 (n = 155)	Cohort 2, 1994–1998 (n = 123)	Cohort 3, 1999–2002 (n = 167)	P†
Therapy regimen				
CYC	142 (91.6)	110 (89.4)	142 (85.0)	0.154
Cumulative dose, median (range) gm	67 (0–378)	36 (0–200)	24 (0–136)	<0.001‡
MTX, induction	8(5.2)	32 (26)	33 (19.8)	<0.001
MTX, maintenance	37 (23.9)	63 (51.2)	71 (42.5)	<0.001
AZA, maintenance	16 (10.3)	51 (41.5)	50 (29.9)	<0.001
LEF, maintenance	1 (0.6)	35 (28.5)	47 (28.1)	<0.001
TNF antagonists	0 (0.0)	5 (4.1)	26 (15.6)	<0.001
Rituximab	0 (0.0)	1 (0.8)	6 (3.6)	0.026

Holle JU, et al:
Arthritis Rheumatism, 2011;63(1):257-266

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Rituximab	0 (0.0)	1 (0.8)	6 (3.6)	0.026
Outcome				
Complete remission	83 (53.5)	86 (69.9)	123 (73.7)	<0.001§
Worsening	0 (0.0)	1 (0.8)	0 (0.0)	–
"Response" (stabilization/improvement)	72 (46.5)	36 (29.3)	44 (26.3)	–
Relapse	99 (63.9)	63 (51.2)	59 (35.3)	0.028‡
Relapse in those with >5 years of followup	86/112 (76.8)	59/102 (57.8)	20/40 (50)	–
Malignancy	8 (5.2)	2 (1.6)	8 (4.8)	0.233
MDS	11 (7.1)	12 (9.8)	7 (4.2)	0.171
CYC-induced cystitis	17 (11.0)	13 (10.6)	10 (6.0)	0.228
Infections	41 (26)	31 (25.2)	33 (19.8)	0.326

Holle JU, et al:
Arthritis Rheumatism, 2011;63(1):257-266

Überblick aktuelle Evidenz AAV

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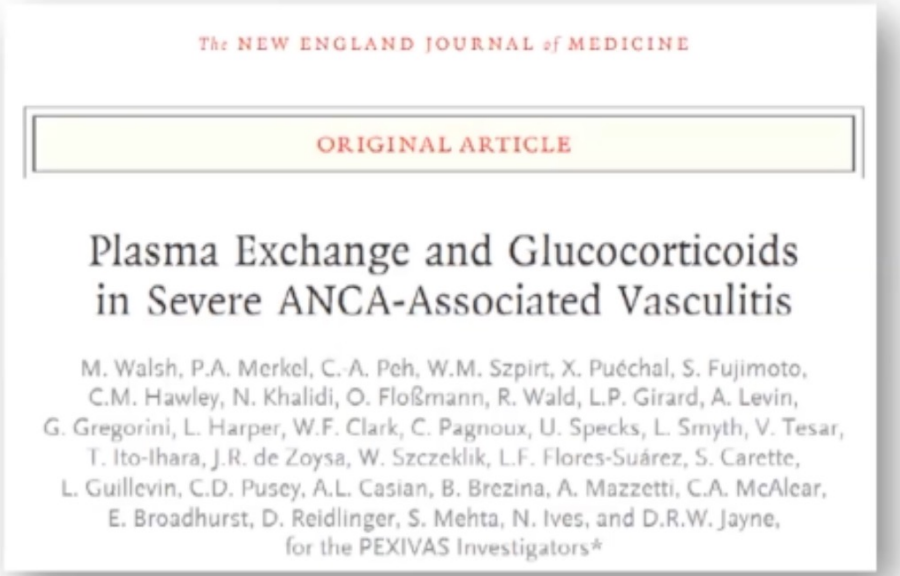
AAV Plasmaseparation "PEXIVAS"



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*

- RCT: Nutzen der Plasmaseparation (PS) bei AAV
- eGFR < 50ml/min oder pulmonale Hämorrhagie
- Induktion: Rituximab *oder* Cyclophosphamid
- PS 7x inn. 14 Tagen *versus* keine PS
- Standard GC Dosis *versus* reduzierte GC Dosis
- 7 Jahre follow-up:
  Versterben oder terminales Nierenversagen

Walsh M, et al
NEJM 2020:382:662-631.

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AAV Plasmaseparation

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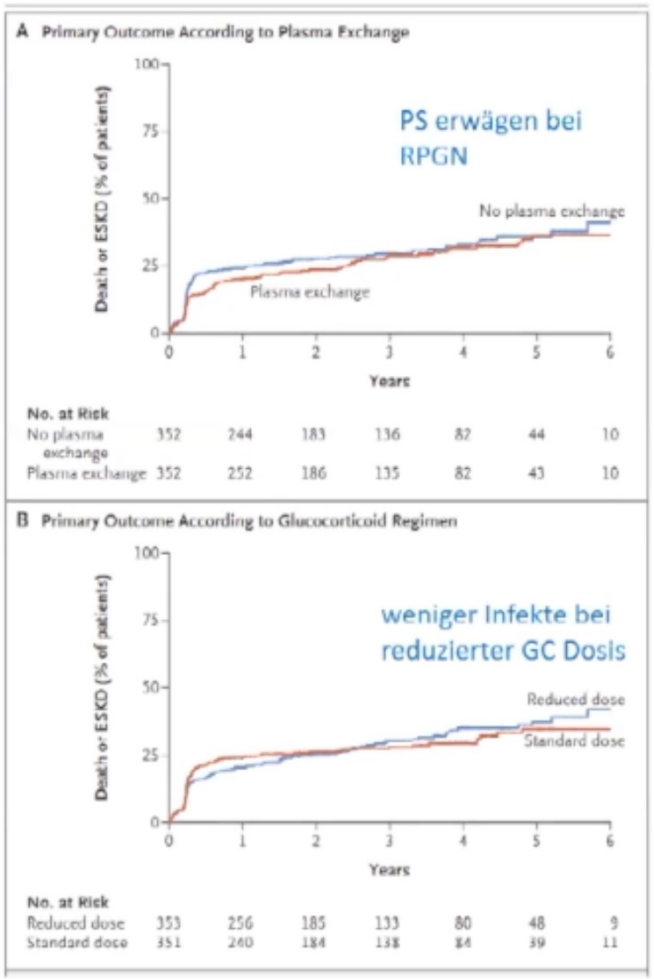

NB: KEIN Unterschied zwischen Cyc und RTX

Walsh M, et al
NEJM 2020;382:662-631.

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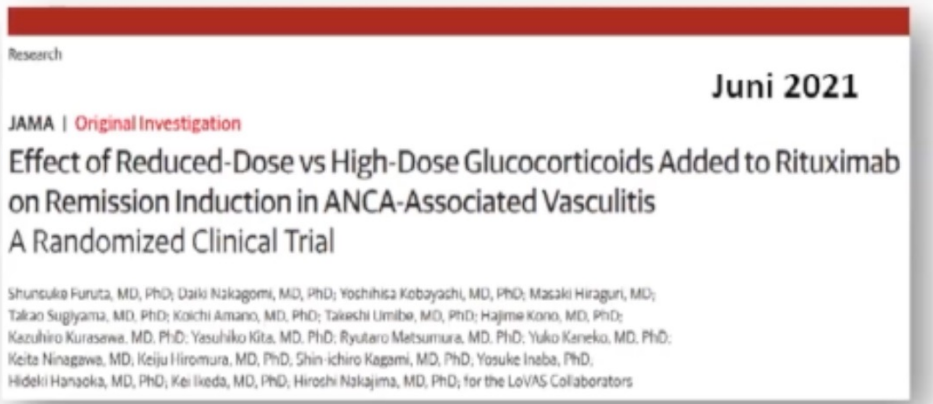
AAV RTX und reduzierte GC Dosis



Research

Juni 2021

JAMA | Original Investigation

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

Shunsuke Furuta, MD, PhD; Daiki Nakagomi, MD, PhD; Yoshihisa Kobayashi, MD, PhD; Masaki Hiraguri, MD; Takao Sugiyama, MD, PhD; Koichi Amano, MD, PhD; Takeshi Umibe, MD, PhD; Hajime Kono, MD, PhD; Kazuhiro Kurasawa, MD, PhD; Yasuhiko Kita, MD, PhD; Ryutaro Matsumura, MD, PhD; Yuko Kaneko, MD, PhD; Keita Ninagawa, MD; Keiju Hiromura, MD, PhD; Shin-ichiro Kagami, MD, PhD; Yosuke Inaba, PhD; Hideki Hanaoka, MD, PhD; Kei Ikeda, MD, PhD; Hiroshi Nakajima, MD, PhD; for the LoVAS Collaborators

- AAV de novo
- RTX Remissionsinduktion
- 140 Patienten 1:1
- eGRF 52-55 ml/min/qm KÖF
- GC 0.5 mg/kgKG vs 1.0 mg/kg KG

- Ziele:
- Remission nach 6 Monaten
- nicht-Unterlegenheit (20% marge)

Furuta S et al
JAMA. 2021;325(21):2178-2187.

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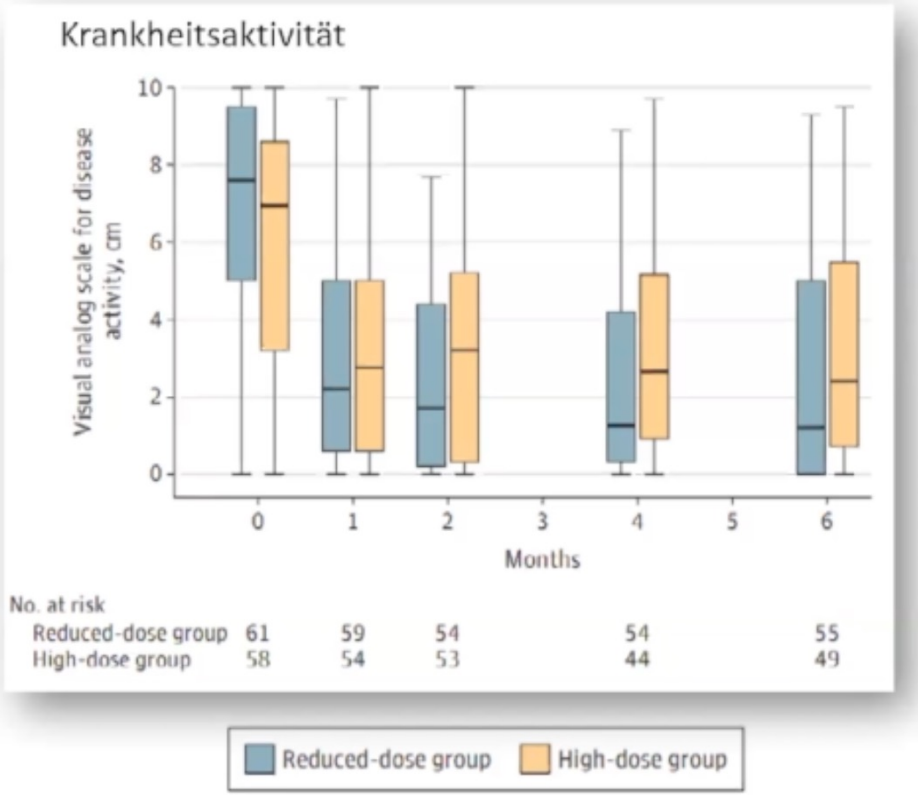
AAV RTX und reduzierte GC Dosis



- 65/67 Pat "low-dose" vs "high-dose"

Remission	71	69.2%
Relapse	4.3	0%
eGFR Differenz	3.2ml	
ESRD	0	1.5%
GC	1318	4515 mg
SAE	18.8	36.9%

Furuta S et al
JAMA. 2021;325(21):2178-2187.

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Überblick aktuelle Evidenz AAV

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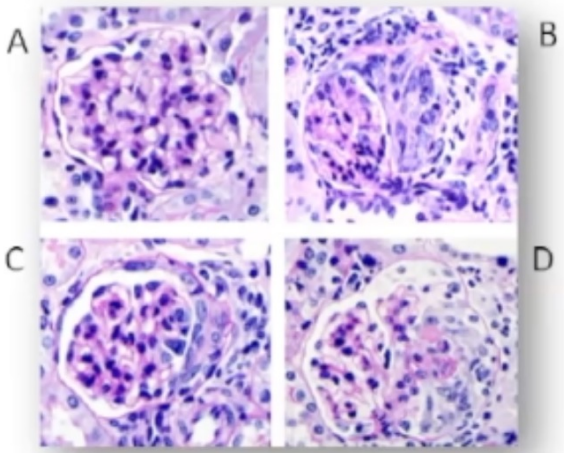
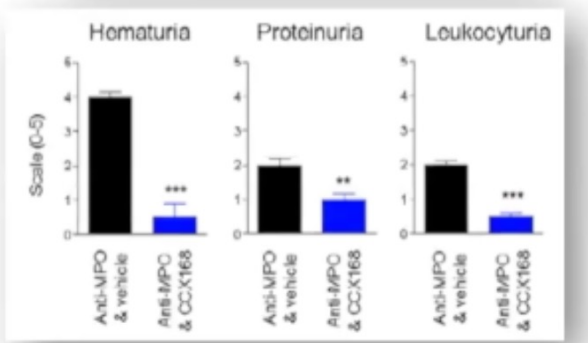
AAV Anti MPO und C5a Blockade -Mausmodell-





- Anti MPO induzierte AAV-GN in Mäusen

Halbmondbildung

- C5aR -/- Maus (A) ↓
- C5L2 -/- Maus (B) ↑
- C6 -/- Maus (C) ↑
- hC5aR Maus (D) ↑

- + Placebo / + CCX 168 (C5a Inhibitor)
- => "C5a Rezeptor Blockade schützt vor MPO-ANCA Glomerulonephritis"

Xiao H et al 2014;25:225-231

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AAV Avacopan CLEAR Studie

CLINICAL RESEARCH www.jasn.org 2017

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis

David R.W. Jayne,* Annette N. Bruchfeld,† Lorraine Harper,‡ Matthias Schaier,§ Michael C. Venning,‖ Patrick Hamilton,‖ Volker Burst,¶ Franziska Grundmann,¶ Michel Jadoul,** István Szombati,†† Vladimir Tesar,‡‡ Mårten Segelmark,§§ Antonia Potarca,‖‖ Thomas J. Schall,‖‖ and Pirow Bekker,‖‖ for the CLEAR Study Group

*Department of Medicine, Addenbrooke's Hospital, Cambridge, United Kingdom; †Department of Renal Medicine, Karolinska University Hospital, Huddinge, Stockholm, Sweden; ‡Department of Nephrology, University of Birmingham Research Laboratories, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham, United Kingdom; §Renal Centre, University of Heidelberg, Heidelberg, Germany; ‖Department of Renal Medicine, Manchester Royal Infirmary, Manchester, United Kingdom; ¶Department of Nephrology, Rheumatology, Diabetology and General Internal Medicine, Uniklinik Cologne, Cologne, Germany; **Service de Nephrologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium; ††Budai Irgalmasrendi Korhaz, Budapest, Hungary; ‡‡Department of Nephrology, Charles University, Prague, Czech Republic; §§Department of Nephrology, Linköping University, Linköping, Sweden; and ‖‖ChemoCentryx, Inc., Mountain View, California

The CLEAR Study Group members are provided in the Supplemental Material.

- AAV de novo oder relapse
- RTX oder CYC (standard of care SOC)
- 1:1:1
- Placebo + Pred 60mg/d
- Avacopan 2x30mg/d + Pred 20mg/d
- Avacopan 2x30mg/d + Pred 0

- Ziel: ≥ 50% Reduktion BVAS in 12 Wochen

Jayne D, et al
J Am Soc Nephrol 28: 2756–2767, 2017

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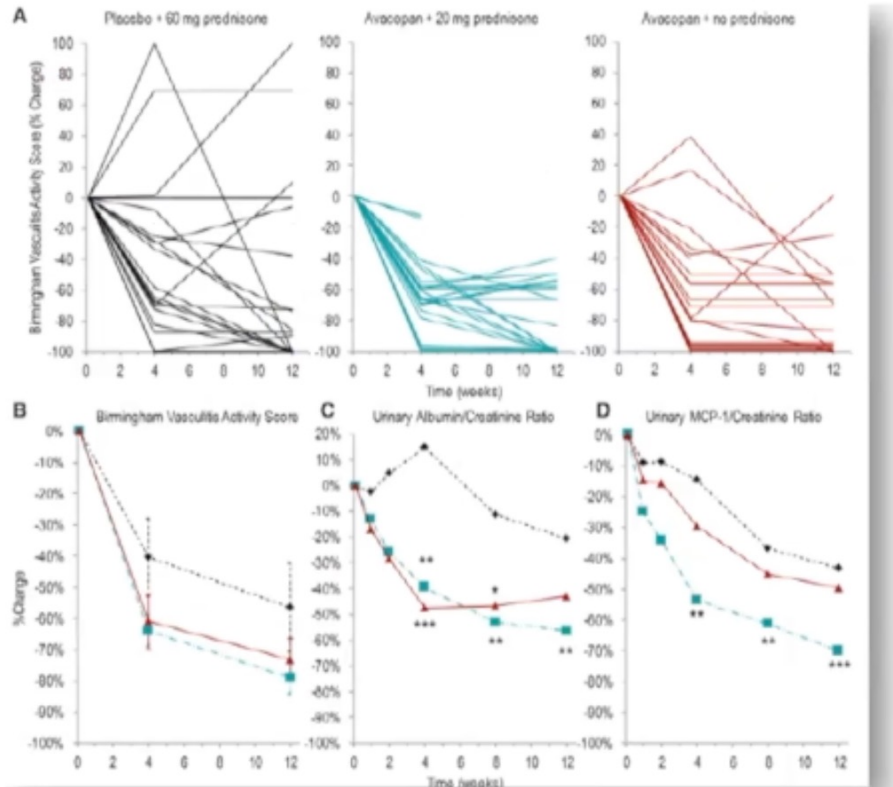
AAV Avacopan CLEAR Studie



MCP-1:
monocyte-chemoattractant protein-1

	Plac /Av20/Av0
• eGFR initial [ml/min]	47 / 53 / 55
• renal response [%]:	40 / 56 / 33

Jayne D, et al
J Am Soc Nephrol 28: 2756–2767, 2017

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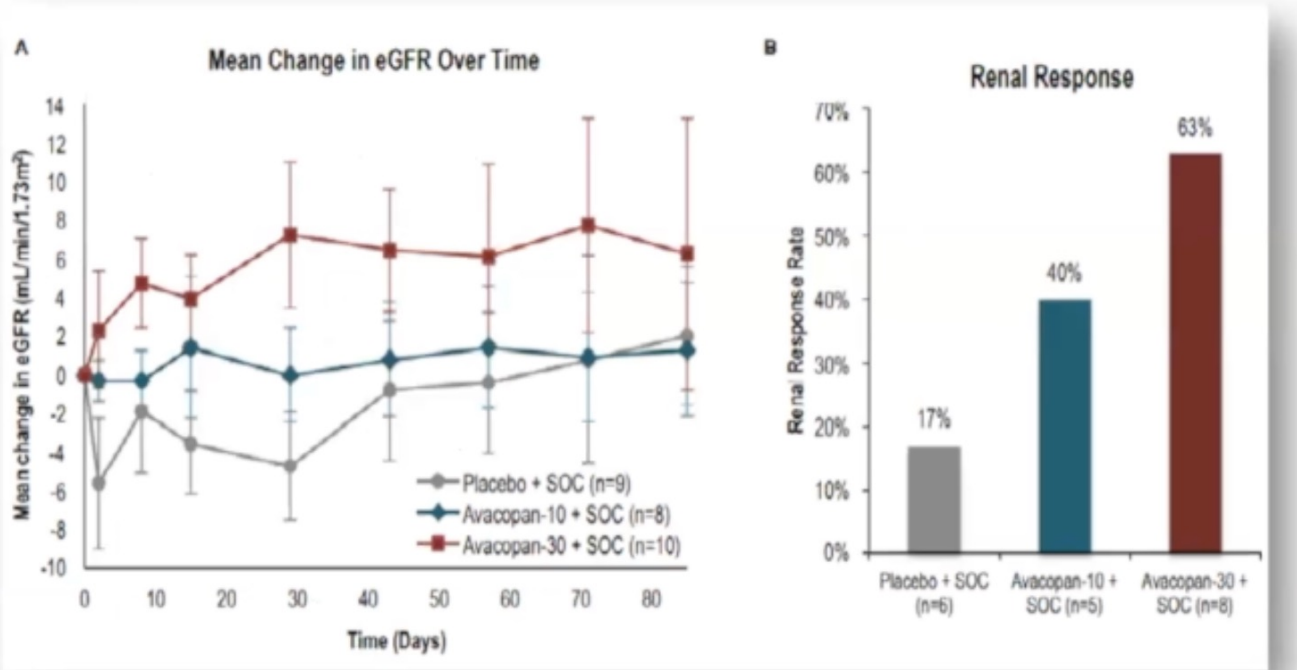
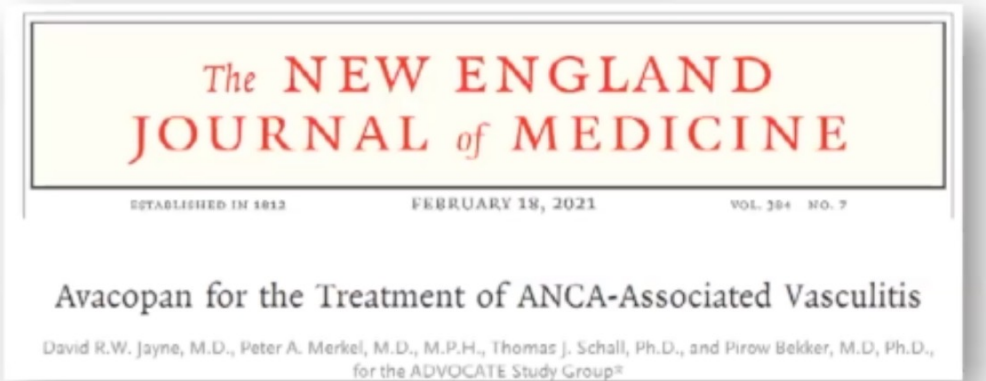
AAV Avacopan CLASSIC Studie



Merkel P, et al. ACR Open Rheumatology 2020;11:662-671

CSL Vifor

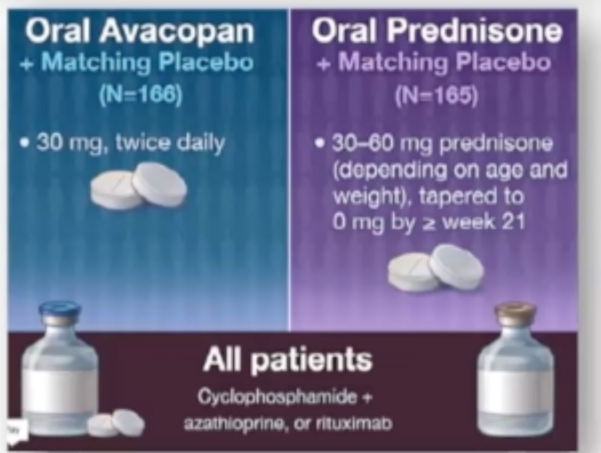
AAV Avacopan


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2021 VOL. 384 NO. 7

Avacopan for the Treatment of ANCA-Associated Vasculitis

David R.W. Jayne, M.D., Peter A. Merkel, M.D., M.P.H., Thomas J. Schall, Ph.D., and Pirow Bekker, M.D, Ph.D., for the ADVOCATE Study Group*



ADVOCATE Studie

nicht-Unterlegenheitsstudie

- RCT, Phase III
- NB: 81% Nierenbeteiligung
- initial Cyc => AZA oder RTX

- Ausschluss:
  - GFR < 15ml/min/1.73qm KÖF
  - GC Dosis > 3g iv in 4Wochen oder - 10mg/d in 6 Wochen vorher

Jayne D et al 2021:NEJM 384:599-609

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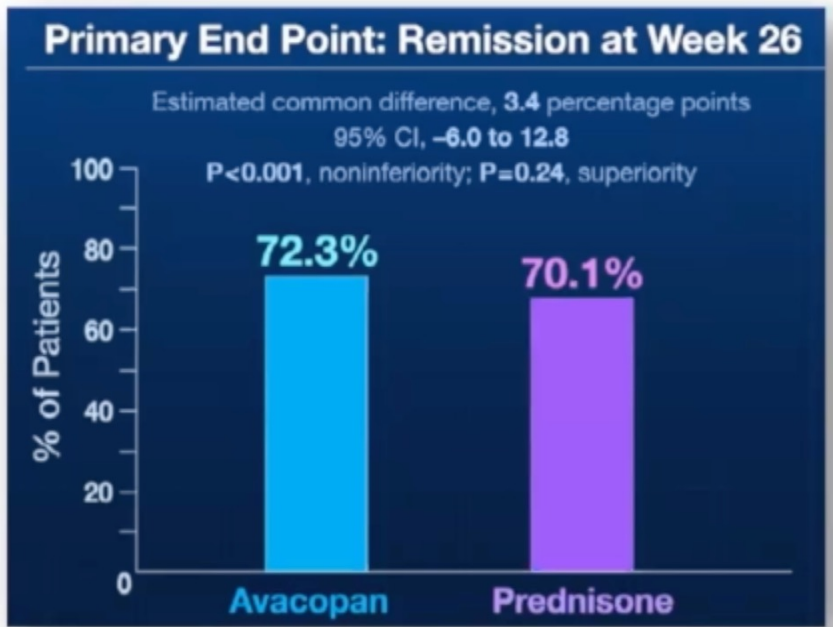
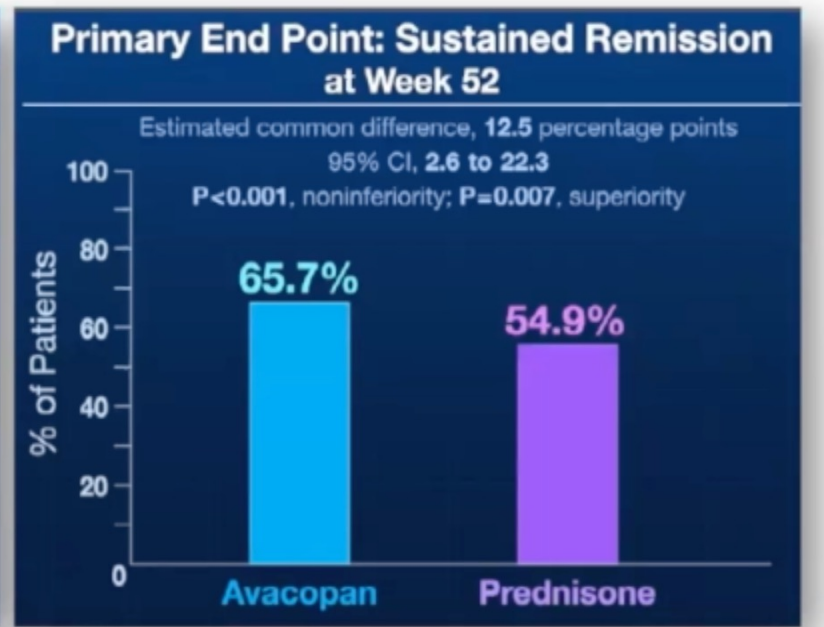
AAV Avacopan ADVOCATE Studie





SAE: 37.3% (Avacopan) vs 39% (Prednison)

Quick Take adaptiert aus
Jayne D et al 2021:NEJM 384:599-609

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ADVOCATE Studie eGFR Verlauf

	Avacopan N=166	Prednison N=164	Differenz 95% CI
eGFR — ml/min/1.73 m^2‡‡			
Baseline			
Patients evaluated	131	134	
Mean	44.6±2.4	45.6±2.4	
Change from baseline to wk 26			
Patients evaluated	121	127	
Least-squares mean	5.8±1.0	2.9±1.0	2.9 (0.1 to 5.8)
Change from baseline to wk 52			
Patients evaluated	119	125	
Least-squares mean	7.3±1.0	4.1±1.0	3.2 (0.3 to 6.1)

Jayne D et al 2021:NEJM 384:599-609

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ADVOCATE Studie

eGFR Verlauf Subanalyse

Renal Recovery for Patients with ANCA-Associated Vasculitis and Low eGFR in the ADVOCATE Trial of Avacopan

Frank B. Cortazar[1], John L. Niles[2], David R.W. Jayne[3], Peter A. Merkel[4], Annette Bruchfeld[5,6], Huibin Yue[6], Thomas J. Schall[6], Pirow Bekker[6] and on behalf of the ADVOCATE Study Group[7]

[1]New York Nephrology Vasculitis and Glomerular Center, Saint Peter's Hospital-Albany, Albany, New York, USA; [2]Nephrology Division, Massachusetts General Hospital, Boston, Massachusetts, USA; [3]Department of Medicine, University of Cambridge, Cambridge, UK; [4]Division of Rheumatology, Department of Medicine, Division of Epidemiology, Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania, USA; [5]Department of Renal Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; and [6]ChemoCentryx, Inc., San Carlos, California, USA

Patienten mit eGFR < 20 ml/min/1.73m²

	Avacopan	Placebo
Anzahl	27/166 [16%]	23/164 [14%]
SAE	13/27 [48%]	16/23 (70%)
eGFR [ml/min/1.73m²]	+ 16	+ 7.7

Adaptiert aus Cortazar FB, et al
Kidney Int Reports 2023:8:860-870

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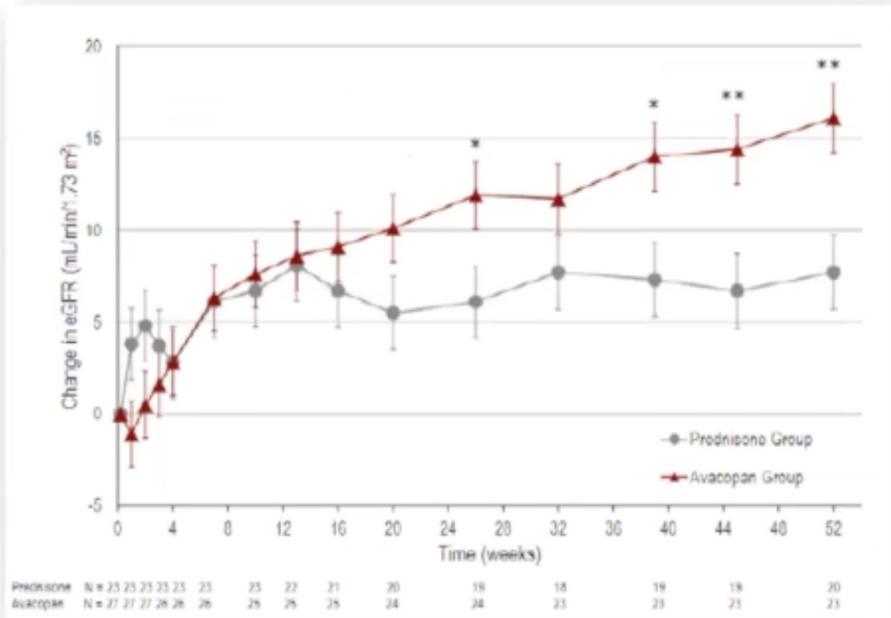
ADVOCATE Studie

eGFR Verlauf Subanalyse



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AAV Daratumumab

- Therapie-refraktäre AAV Situation
- "Ursache": long-lived plasma cells
- persistierende Auto-AK Produktion
- Suppression mittels anti-CD38 AK Daratumumab

Ostendorf L, et al:
RMD open 2023;9:e002742

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AAV Daratumumab

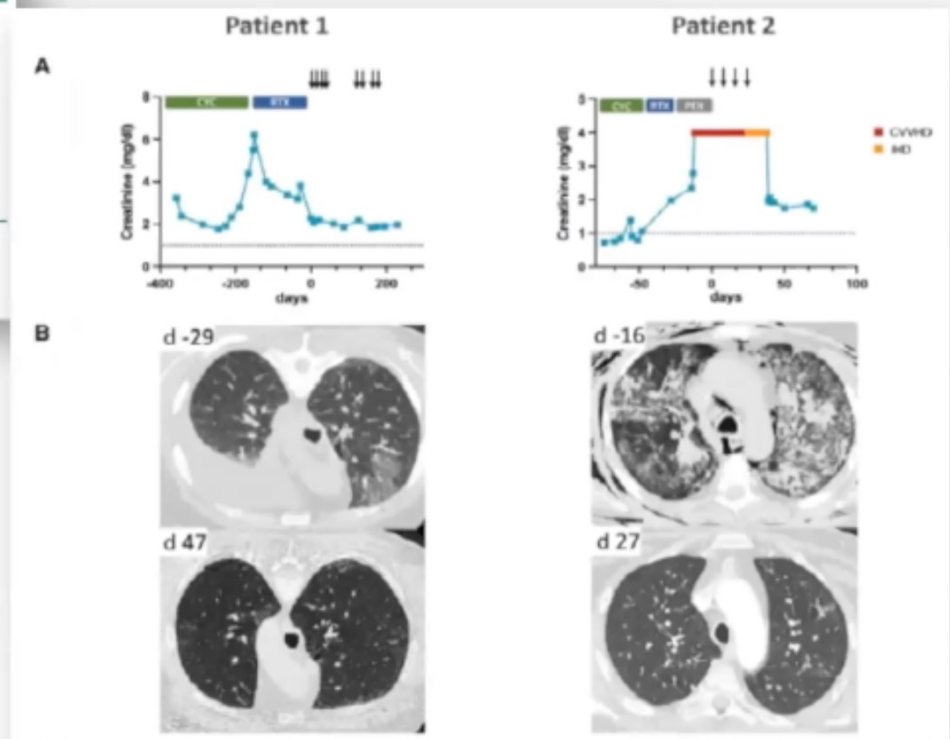
Vasculitis

RMD Open
Rheumatic & Musculoskeletal Diseases

SHORT REPORT

Daratumumab for the treatment of refractory ANCA-associated vasculitis

Lennard Ostendorf ,[1,2] Marie Burns,[2] Dimitrios Laurin Wagner,[3,4,5,6] Philipp Enghard,[1,2] Kerstin Amann,[7] Henrik Mei,[2] Kai-Uwe Eckardt,[1] Evelyn Seelow,[1] Adrian Schreiber [1,8]



Ostendorf L, et al:
RMD open 2023;9:e002742

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…take home…

AAV Therapie

• potente Induktionstherapie	(RTX versus Cyc)
• Glucocorticoide	reduzierte Dosis wählen
• Plasmaseparation	bei AAV-RPGN erwägen
• Avacopan	erweiterte Remissionsinduktion in Kombination mit RTX / CYC
• long-lived plasmacells	neues "target"

Liste der Referenzen

Aqeel F, et al. Immune checkpoint inhibitors as potential triggers for ANCA vasculitis. RMD Open 2022;8:e002500.

Banik P et al. et al. Outcomes of Methotrexate as an Initial Induction and Maintenance Regimen for Localized Granulomatosis with Polyangiitis: A Retrospective Review. Arthritis Rheumatol 2022;74(suppl 9):Abstract #1082-ACR Convergence 2022

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Die Fachpersonen können bei Vifor Pharma Switzerland AG eine vollständige Kopie des zitierten Prüfungsberichts anfordern.

Gekürzte Verschreibungsinformationen

Deutschland

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Dies ermöglicht eine schnelle Identifizierung neuer Sicherheitsdaten. Angehörige der Gesundheitsberufe werden gebeten, alle Verdachtsfälle von unerwünschten Wirkungen zu melden.

TAVNEOS®▼ 10 mg Hartkapseln: Wirkstoff: Avacopan. **Zusammensetzung:** Jede Hartkapsel enthält 10 mg Avacopan. Sonstige Bestandteile mit bekannter Wirkung: 245 mg Macrogolglycerolhydroxystearat (Ph.Eur.). **Anwendungsgebiete:** Tavneos ist in Kombination mit einem Rituximab- oder Cyclophosphamid-Dosierungsschema indiziert zur Behandlung erwachsener Patienten mit schwerer aktiver Granulomatose mit Polyangiitis (GPA) oder mikroskopischer Polyangiitis (MPA). **Gegenanzeigen:** Überempfindlichkeit gegen den Wirkstoff oder einen der sonstigen Bestandteile. **Nebenwirkungen:** Sehr häufig: Übelkeit, Kopfschmerzen, erniedrigte Leukozytenzahl, Infektion der oberen Atemwege, Diarrhö, Erbrechen, Nasopharyngitis, erhöhte Werte in Leberfunktionstests. Häufig: Pneumonie, Rhinitis, Harnwegsinfektion, Sinusitis, Bronchitis, Gastroenteritis, Infektion der unteren Atemwege, Zellulitis, Herpes zoster, Influenza, Orale Candidose, Oraler Herpes, Otitis media, Neutropenie, Schmerzen im Oberbauch, erhöhte Kreatinphosphokinase im Blut. Gelegentlich: Angioödem. **VERSCHREIBUNGSPFLICHTIG. Fachinformation beachten. Pharmazeutischer Unternehmer:** Vifor Fresenius Medical Care Renal Pharma France, 100-101 Terrasse Boieldieu, Tour Franklin La Défense 8, 92042 Paris La Défense Cedex, Frankreich. **Stand der Information:** Februar 2022

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Tavneos® Fachkurzinformation: Tavneos®10mg Hartkapsel. **Zusammensetzung:** Jede Hartkapsel enthält 10 mg Avacopan. Sonstige Bestandteile mit bekannter Wirkung:245 mg Macrogolglycerolhydroxystearat(Ph.Eur). **Anwendungsgebiete**: Tavneos® ist in Kombination mit einem Rituximab- oder Cyclophopamid-Dosierungsschema indi- ziert zur Behandlung erwachsener Patienten mit schwerer aktiver Granulomatose mit Polyangiitis (GPA) oder mikroskopischer Polyangiitis (MPA). **Gegenanzeigen**: Überempfindlichkeit gegen den Wirkstoff oder einen der sonstigen Bestandteile. Pharmakotherapeutische Gruppe: L04AJ05 Complement Inhibitors **ATC-Code:** L04AJ05. **Inhaber der Zulassung:** Vifor France, 100-101 Terrasse Boieldieu Tour Franklin La Defense 8 92042 Paris La Defense Cedex, Frankreich. Rezept- und apothekenpflichtig. Weitere Angaben zu Warnhinweisen und Vorsichtsmaßnahmen für die Anwendung, Wechselwirkungen mit anderen Arzneimitteln oder sonstigen Wechselwirkungen, Schwangerschaft und Stillzeit und Nebenwirkungen sowie Gewöhnungseffekten sind der veröffentlichten Fachinformation zu entnehmen. Stand der Information: Letzter Stand Fachinformation

Schweiz

▼Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Für weitere Informationen, siehe Fachinformation TAVNEOS® auf www.swissmedicinfo.ch.

Tavneos®: Z: Avacopan. **I:** Tavneos, als ergänzende Therapie zu einer immunsuppressiven Standardbehandlung auf Basis von Rituximab oder Cyclophosphamid mit Glukokortikoiden, ist für die Behandlung erwachsener Patienten mit schwerer aktiver ANCA Vaskulitis (GPA/MPA) indiziert. **D:** Orale Einnahme morgens und abends 2x täglich 30 mg (3 Kapseln zu je 10 mg) mit Nahrung. **KI:** Überempfindlichkeit gegen den Wirkstoff oder einen der Hilfsstoffe. **VM:** Hepatotoxizität; Angioödem; Überwachung des Blutbildes (weisse Blutkörperchen); Schwere Infektionen; Reaktivierung des Hepatitis-B-Virus; Herzbeschwerden; Bösartige Tumore; Macroglycerinhydroxystearat. **S/S:** Eine Anwendung während der Schwangerschaft und bei Frauen im gebärfähigen Alter, die keine Verhütungsmethode anwenden, ist nicht empfohlen. Es ist nicht bekannt, ob Avacopan in die Muttermilch ausgeschieden wird. Der Nutzen des Stillens für das Kind sollte gegen den Nutzen der Behandlung für die Patientin abgewogen werden. **UW:** Sehr häufig: Infektion der oberen Atemwege, Nasopharyngitis; Kopfschmerzen; Erbrechen, Durchfall, Übelkeit; erhöhter Lebertest; verminderte Anzahl weisser Blutkörperchen. Häufig: Lungenentzündung, Infektion der unteren Atemwege, Influenza, Bronchitis, Zellulitis, Infektion der Harnwege, Herpes zoster, Sinusitis, orale Candidose, Herpes im Mundbereich, Otitis media, Rhinitis, Gastroenteritis; Neutropenie; Oberbauchschmerzen; Anstieg der Kreatinphosphokinase im Blut. Gelegentlich: Angioödeme. **IA:** Avacopan ist ein Substrat von CYP3A4. Die gleichzeitige Verabreichung von Induktoren oder Inhibitoren dieses Enzyms kann die Pharmakokinetik von Avacopan beeinflussen. Siehe Fachinformation. **P:** Tavneos 10 mg: 30 und 180 Hartkapseln. **Liste B**. Detaillierte Informationen**:** www.swissmedicinfo.ch. Stand der Information**:** September 2022. **Zulassungsinhaberin:** Vifor Fresenius Medical Care Renal Pharma Ltd., St. Gallen. **Vertrieb:** Vifor Pharma Switzerland AG, CH-1752 Villars-sur-Glâne | CH-AVA-2300011