Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Stand: November 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Mepolizumab
[Eosinophile Granulomatose mit Polyangiitis]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Als nicht-medikamentöse Behandlung kommt im vorliegenden Anwendungsgebiet eine Plasmapherese in Betracht.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Mepolizumab Nucala ®	Nucala ist angezeigt als Zusatzbehandlung für Patienten ab 6 Jahren mit schubförmig remittierender oder refraktärer eosinophiler Granulomatose mit Polyangiitis (EGPA).
Dapson J04BA02 Dapson-Fatol®	Einzelbefunde über positive Behandlungsergebnisse liegen vor bei Vaskulitiden und bei Arteriitis temporalis, wenn Kortikoide allein nicht ausreichend wirksam sind. (FI Stand Januar 2015)
Glucokortikoide	
Prednisolon H02AB06 Generisch Tab.	Decortin H 1 mg/5 mg/10 mg/20 mg/50 mg Tabletten sind angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad (Dosierungsschemata (DS: a bis d) s. Abschnitt 4.2. Dosierung): Decortin H wird angewendet bei Erwachsenen, Kindern aller Altersgruppen und Jugendlichen. <u>Rheumatologie</u> - […] - *Churg-Strauss-Syndrom*: Initialtherapie (DS: a-b), bei Organmanifestationen und schweren Verläufen in Kombination mit Immunsuppressiva, Remissionserhaltung (DS: d) <u>Dermatologie</u> Erkrankungen der Haut und Schleimhäute, die aufgrund ihres Schweregrades und/oder Ausdehnung bzw. Systembeteiligung nicht oder nicht ausreichend mit topischen Glucocorticoiden behandelt werden können. Dazu gehören: -[…] -*Vaskulitiden*: z. B. Vasculitis allergica, Polyarteriitis nodosa (DS b bis a) […] <u>Gefäßerkrankungen</u> Hypertonie, Erhöhung des Arteriosklerose- und Thromboserisikos, *Vaskulitis* (auch als Entzugssyndrom nach Langzeittherapie).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	(FI Decortin H Stand Juli 2017)
Prednisolon H02AB06 Generisch i.v.	[…] <u>Rheumatologie</u> ‑ Schwer verlaufende/lebensbedrohliche Situationen bei folgenden rheumatischen Erkrankungen: Rheumatoide Arthritis und Still-Syndrom, Felty-Syndrom, Polymyalgia rheumatica, systemische juvenile idiopathische Arthritis (z. B. Morbus Still, seropositive Polyarthritis), Kollagenosen, *Vaskulitiden*, rheumatisches Fieber […] Prednisolut wird angewendet bei Erwachsenen, Kindern und Säuglingen. (FI Prednisolut Stand März 2020)
Prednison H02AB07 Generisch Tab.	Cutason ist angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad (Dosierungsschemata (DS: a bis d) s. Abschnitt 4.2. Dosierung): Cutason wird angewendet bei Erwachsenen, Kindern aller Altersgruppen und Jugendlichen. <u>Rheumatologie</u> –Aktive Phasen von Systemvaskulitiden (DS a, b): […] -*Churg-Strauss-Syndrom*: Initialtherapie (DS: a ‑ b), bei Organmanifestationen und schweren Verläufen in Kombination mit Immunsuppressiva, Remissionserhaltung (DS: d) <u>Dermatologie</u> Erkrankungen der Haut und Schleimhäute, die aufgrund ihres Schweregrades und/ oder Ausdehnung bzw. Systembeteiligung nicht oder nicht ausreichend mit topischen Glucocorticoiden behandelt werden können. Dazu gehören: -[…] -Granulomatöse Erkrankungen: z. B. Sarkoidose, Cheilitis granulomatosa (monosymptomatisches Melkersson-Rosenthal-Syndrom) (DS b bis a) -*Vaskulitiden*: z. B. Vasculitis allergica, Polyarteriitis nodosa (DS b bis a) […] <u>Gefäßerkrankungen</u> Hypertonie, Erhöhung des Arteriosklerose- und Thromboserisikos, *Vaskulitis* (auch als Entzugssyndrom nach Langzeittherapie) (FI Decortin Stand September 2017)

II. Zugelassene Arzneimittel im Anwendungsgebiet

Methylprednisolon H02AB04 generisch	Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad zum Beispiel: <u>Hauterkrankungen</u> Erkrankungen der Haut und Schleimhäute, die aufgrund ihres Schweregrades und/ oder Ausdehnung bzw. Systembeteiligung nicht oder nicht ausreichend mit topischen Glucocorticoiden behandelt werden können. Dazu gehören: […] - *Vaskulitiden*, z. B. Vasculitis allergica, Polyarteriitis nodosa […] Dosierung: Für Erwachsene […], für Kinder […] (FI Methylprednisolon acis, Stand Februar 2020)

Quellen: AMIS-Datenbank, Fachinformationen, Lauer-Fischer-Taxe

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-287 (Mepolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. Oktober 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AAV	ANCA-associated vasculitis
ANCA	Antineutrophil cytoplasmic antibody
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azathioprine
BVAS	Birmingham Vasculitis Activity Score
CBC	Complete blood count
CYC	Cyclophosphamide
ECRI	ECRI Guidelines Trust
EGPA	Eosinophilic GPA
ENT	Ear, Nose and Throat
ESRD	End-stage renal disease
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss
GC	Glucocorticoids
GIN	Guidelines International Network
GoR	Grade of Recommendations
GPA	Granulomatosis with polyangiitis
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	Intravenous
KI	Konfidenzintervall
LoE	Level of Evidence
MMF	Mycophenolate mofetil
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio

PR3	Proteinase 3
RoB	Risk of Bias
RR	Relatives Risiko
RTX	Rituximab
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Add-on-Therapie für Patienten ab 6 Jahren mit Eosinophiler Granulomatose mit Polyangiitis (EGPA).

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Eosinophile Granulomatose mit Polyangiitis* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.10.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 211 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 6 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse / IQWiG-Berichte

Es wurden kein relevanten G-BA-Beschlüsse / IQWiG-Berichte identifiziert.

3.2 Cochrane Reviews

Es wurden kein relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Es wurden keine relevanten Systematischen Reviews identifiziert.

3.4 Leitlinien

Tieu J et al., 2020 [5].

Rituximab for maintenance of remission in ANCA-associated vasculitis: expert consensus guidelines

Zielsetzung/Fragestellung

We present guidelines developed through a modified Delphi exercise on the use of RTX in the maintenance of remission in adult AAV patients, with additional focus on adjunct therapies, the use of RTX in the maintenance of remission in adult AAV patients, with additional focus on adjunct therapies adverse effects and use of prophylaxis

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz, hinsichtlich der Fragestellung und zugelassener Arzneimittel zur Therapie für Patienten mit Eosinophiler Granulomatose mit Polyangiitis (EGPA), wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium (11 nephrologists, eight rheumatologists and one paediatric rheumatologist; keine Patienten eingeschlossen)
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt (keine Angaben);
- Systematische Suche der Literatur (ohne Datumangabe), Auswahl (Studies including
- at least 20 patients receiving at least two infusions of
- RTX were included) und Bewertung der Evidenz (Oxford Centre for Evidence-Based Medicine);
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt (A final vote determined the level of agreement; a level of 80% was prespecified for inclusion in these guidelines.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert (keine Angaben).

Recherche/Suchzeitraum:

- Unterschiedliche Datenbanken (u.a. PubMed, Embase, Medline); keine Angaben zum Suchzeitraum

LoE & GoR

- Oxford Centre for Evidence-Based Medicine

Sonstige methodische Hinweise

- Es liegt nicht für alle genannten Wirkstoffe eine Zulassung für das vorliegende Anwendungsgebiet vor.
- Keine Angaben zum Recherchezeitraum
- Keine Angaben über den Einschluss von Patienten für die Empfehlungen

- Keine Regelmäßige Überprüfung der Aktualität

Empfehlung

1. When should RTX be used for the maintenance of remission in AAV?

1.1. GPA/MPA—new and relapsing patients

We recommend the use of RTX for the maintenance of remission in patients with GPA and MPA following RTX induction. RTX maintenance can also be considered after cyclophosphamide induction.

Level of evidence: 1b (following cyclophosphamide induction), 2b (following RTX induction).

Grade of recommendation: A (following cyclophosphamide induction), B (following RTX induction).

Vote: 18/18 (100%).

Two randomized controlled trials (RCT) have evaluated the efficacy of RTX for the maintenance of remission in AAV [15, 16]. The MAINRITSAN trial randomized 115 patients with newly diagnosed (80%) or relapsing (20%) AAV (excluding EGPA) to receive a RTX or azathioprine based maintenance regimen following remission induction with cyclophosphamide [15]. The RTX regimen was two 500mg doses of RTX a fortnight apart after remission induction followed by 500mg every 6 months until month 18 (i.e. three further doses). After 28 months, fewer major relapses occurred in patients who received RTX compared with azathioprine (5% vs 29%, hazard ratio 6.61; 95% CI: 1.56, 27.96; P ¼ 0.002), resulting in a number needed to treat of four patients to prevent one major relapse [15]. The superiority of RTX over azathioprine in relapse prevention persisted at 60 months' follow-up [17].

MAINRITSAN2 compared the fixed-schedule RTX dosing from the MAINRITSAN trial with an individually tailored RTX maintenance regimen, where after an initial maintenance infusion of 500mg RTX 2, further 500mg doses were administered based on 3-monthly measures of ANCA and B cells [16]. In this trial, RTX induction was used in 37% of patients. At 28 months after the first maintenance RTX infusion, eight (9.9%) patients receiving fixed-schedule RTX had relapsed (three major) compared with 13 (16.0%) patients experiencing 14 relapses (six major) in the tailored infusion arm.

One ongoing RCT, RITAZAREM (NCT01697267), compares 4-monthly 1000mg RTX dosing with azathioprine for the maintenance of remission following RTX induction in patients with a relapse of AAV [18].

Several observational studies, with follow-up to 7.6 years, provide further evidence on the safety and efficacy of RTX for the maintenance of remission in patients with new, relapsing and refractory AAV [19–26]. Reflecting current practice patterns, these studies have largely used RTX to maintain remission after successful RTX induction.

Referenzen aus Leitlinien

15 Guillevin L, Pagnoux C, Karras A et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.
16 Charles P, Terrier B, Perrodeau E et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77:1143–9.
17 Terrier B, Pagnoux C, Perrodeau E et al. Long-term efficacy of remission-maintenance regimens for ANCAassociated vasculitides. Ann Rheum Dis 2018;77:1150–6.
18 Gopaluni S, Smith RM, Lewin M et al. Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibodyassociated vasculitis (RITAZAREM): study protocol for a randomized controlled trial. Trials 2017;18:112.
19 Pendergraft WF 3rd, Cortazar FB, Wenger J et al. Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis. Clin J Am Soc Nephrol 2014;9:736–44.
20 Cartin-Ceba R, Golbin JM, Keogh KA et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum 2012;64:3770–8.
21 Smith RM, Jones RB, Guerry MJ, Laurino S et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3760–9.
22 Alberici F, Smith RM, Jones RB et al. Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. Rheumatology (Oxford) 2015;54:1153–60.
23 Calich AL, Puechal X, Pugnet G et al. Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients. J Autoimmun 2014;50:135–41.
24 Roubaud-Baudron C, Pagnoux C, Meaux-Ruault N et al. Rituximab maintenance therapy for granulomatosis with polyangiitis and microscopic polyangiitis. J Rheumatol 2012;39:125–30.
25 Charles P, Neel A, Tieulie N et al. Rituximab for induction and maintenance treatment of ANCAassociated vasculitides: a multicentre retrospective study on 80 patients. Rheumatology (Oxford) 2014;53:532–9.
26 Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. Rheumatology (Oxford) 2013;52:2041–7.

1.2. EGPA patients

Despite limited evidence regarding the use of RTX for the maintenance of remission in EGPA, we advise a similar approach to use in GPA and MPA. Overall treatment responses to RTX may differ from GPA and MPA, and steroid withdrawal may be more challenging.

Level of evidence: 4

Grade of recommendation: C

Vote: 15/18 (83%)

EGPA is a relatively understudied subgroup of AAV, owing to phenotypic differences from GPA and MPA, and relative rarity of disease. Published trials of RTX for induction and maintenance of remission in AAV have not included patients with EGPA. One multicentre retrospective case series of 41 patients with predominantly refractory or relapsing EGPA reported a clinical improvement in 83% by 6 months, with 34% achieving complete remission [27]. Prednisolone cessation was possible in only two patients at 12 months. In a single centre study including 69 patients with EGPA, similar remission rates were identified (34% at 6 months and 49% at 12 months) [28]. Median prednisolone doses were 7.25 mg/day at 12 months and 5 mg/day at 24 months. Relapse was common, with 54% of patients relapsing, predominantly due to uncontrolled asthma or other respiratory manifestations. In both studies, patients who were ANCA positive were more likely to achieve remission. An ongoing RCT, MAINRITSEG (NCT02807103), is evaluating RTX in patients with EGPA for maintenance of remission [29].

Referenzen aus Leitlinien

27 Mohammad AJ, Hot A, Arndt F et al. Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Ann Rheum Dis 2016;75:396–401.
28 Teixeira V, Mohammad AJ, Jones RB, Smith R, Jayne D. Efficacy and safety of rituximab in the treatment of eosinophilic granulomatosis with polyangiitis. RMD Open 2019;5:e000905.
29 Rituximab in Eosinophilic Granulomatosis with Polyangiitis (REOVAS). 2018. https://ClinicalTrials.gov/show/NCT02807103.

2. What RTX maintenance regimen should be used for AAV?

2.1. Dose and dosing intervals

We recommend fixed interval dosing with RTX, either 500 mg or 1000 mg administered every 6 months for a period of 2 years. There is ongoing relapse risk after RTX withdrawal and patients should be monitored accordingly.

Level of evidence: 1b.

Grade of recommendation: B.

Vote: 18/18 (100%).

This regimen is recommended following the completion of induction therapy. The treatment regimen should be individualized, particularly in post-pubertal adolescents and older individuals with comorbidities where concerns regarding adverse effects exist. There are limited data for the use of RTX in children. No direct comparisons have been made between the two most commonly used doses of RTX—500 and 1000 mg. Both published RCTs have used 500mg doses of RTX while observational studies have largely used 1000mg doses and this dose is being used in the ongoing RITAZAREM trial [15, 16, 19, 21–23]. While observational cohorts include a greater proportion of patients with relapsing or refractory disease than RCTs, it is unknown if the dose of RTX influences clinical outcomes in these patients.

There are two main approaches to RTX dosing intervals: fixed interval dosing and biomarker guided dosing. As detailed above, the MAINRITSAN2 trial compared fixed 6-monthly RTX infusions with dosing based on 3- monthly assessments for ANCA return or increase and B cell return [16]. At 28 months' follow-up, no difference in relapse rate was identified between the two groups (P = 0.22); 8/81 (9.9%) patients receiving fixed interval dosing had experienced eight relapses including three major relapses, whereas 13/81 (16.0%) patients with repeat dosing determined by biomarker changes had experienced 14 relapses including six major. No difference in serious adverse events related to infection was identified, with 16 individuals receiving fixed interval RTX having 18 infections and nine individuals with tailored dosing having 18 infections.

The role of biomarker guided RTX dosing has not been proven and requires further study, including the evaluation of long-term outcomes. Relapses in spite of ANCA negativity and B cell depletion have been observed in both RCTs and observational studies [15–17, 21–23, 26, 30]. Fixed interval dosing has therefore been recommended. As discussed below, in selected patients, biomarker fluctuations, comorbidities and adverse effects may necessitate a more individualized approach to RTX dose and dosing intervals.

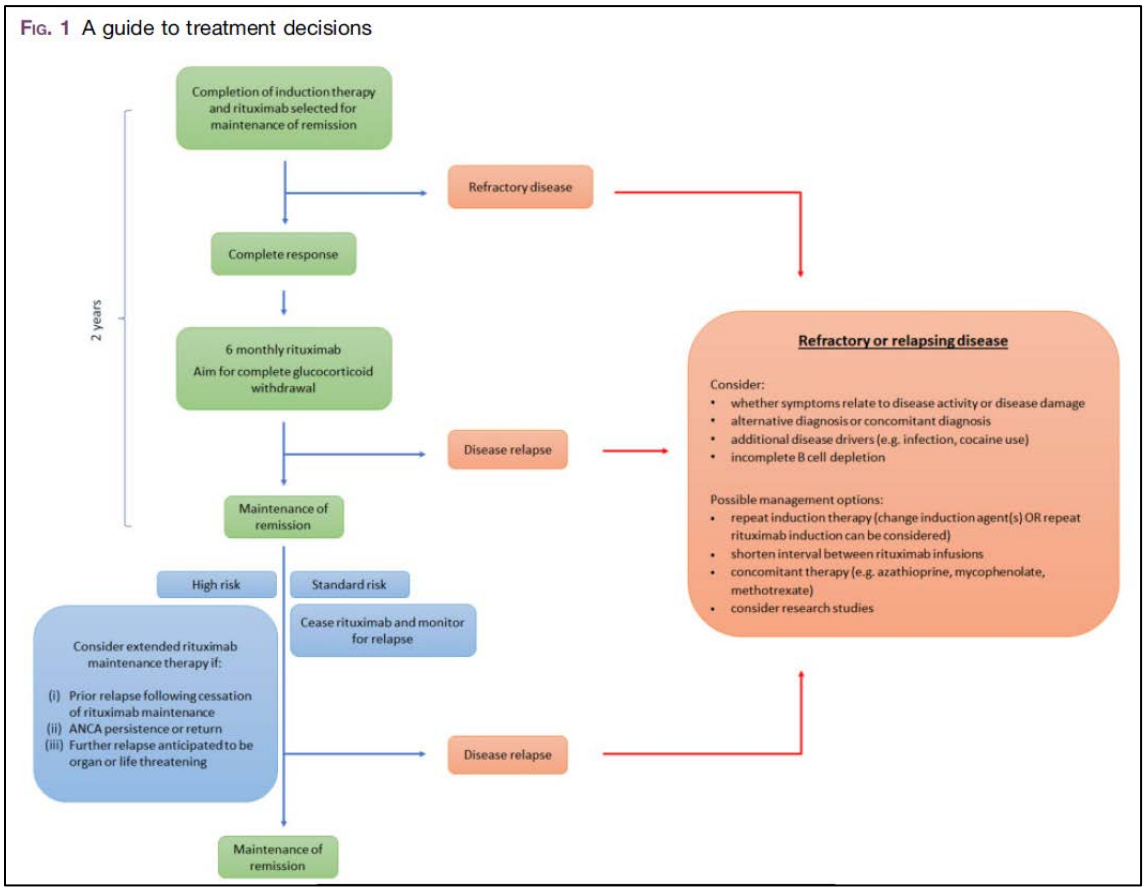
Referenzen aus Leitlinien

15 Guillevin L, Pagnoux C, Karras A et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.
16 Charles P, Terrier B, Perrodeau E et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77:1143–9.
17 Terrier B, Pagnoux C, Perrodeau E et al. Long-term efficacy of remission-maintenance regimens for ANCAassociated vasculitides. Ann Rheum Dis 2018;77:1150–6.
19 Pendergraft WF 3rd, Cortazar FB, Wenger J et al. Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis. Clin J Am Soc Nephrol 2014;9:736–44.
21 Smith RM, Jones RB, Guerry MJ, Laurino S et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3760–9.
22 Alberici F, Smith RM, Jones RB et al. Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. Rheumatology (Oxford) 2015;54:1153–60.
23 Calich AL, Puechal X, Pugnet G et al. Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegener's). Results of a single-center cohort study on 66 patients. J Autoimmun 2014;50:135–41.
26 Besada E, Koldingsnes W, Nossent JC. Long-term efficacy and safety of pre-emptive maintenance therapy with rituximab in granulomatosis with polyangiitis: results from a single centre. Rheumatology (Oxford) 2013;52:2041–7.
30 Cartin-Ceba R, Fervenza FC, Specks U. Treatment of antineutrophil cytoplasmic antibody-associated vasculitis with rituximab. Curr Opin Rheumatol 2012;24

2.2 Management of relapse despite maintenance RTX

Changes to treatment in refractory disease or relapse despite induction and RTX maintenance therapy should be determined according to severity of disease activity and organ involvement. A guide to treatment decisions is presented (Fig. 1).

FIG. 1 A guide to treatment decisions



Level of evidence: 4.

Grade of recommendation: C.

Vote: 18/18 (100%).

In view of the rarity of refractory disease or relapse on RTX maintenance therapy, there are no studies specifically evaluating treatment approaches. Various strategies have been adopted in specialized centres and described in RCTs and observational studies [15, 16, 19, 21, 22].

Referral to a specialized centre is advised. Assessment requires careful consideration of the relative contribution of disease damage and activity to patient symptoms, alternative diagnoses, and potential disease drivers including infection, nasal carriage of Staphylococcus aureus and cocaine use. Treatment of disease activity should depend on its severity, including consideration of major organ involvement and whether any benefit from RTX has been derived. For example, major organ involvement typically necessitates re-induction therapy. Shortened interval dosing is considered where disease activity emerges shortly prior to scheduled infusions, and the addition of concomitant immunosuppression could be considered where, despite a response to RTX, there is mild persistent disease activity without major organ manifestations. Concomitant therapy includes traditional maintenance agents (e.g. azathioprine, methotrexate or mycophenolate), or low dose glucocorticoids (≤ 5mg/day prednisolone, or equivalent). In the event of RTX failure, alternative maintenance strategies should be considered.

Referenzen aus Leitlinien

15 Guillevin L, Pagnoux C, Karras A et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.
16 Charles P, Terrier B, Perrodeau E et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). Ann Rheum Dis 2018;77:1143–9.
19 Pendergraft WF 3rd, Cortazar FB, Wenger J et al. Long-term maintenance therapy using rituximab-induced continuous B-cell depletion in patients with ANCA vasculitis. Clin J Am Soc Nephrol 2014;9:736–44.
21 Smith RM, Jones RB, Guerry MJ, Laurino S et al. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2012;64:3760–9.
22 Alberici F, Smith RM, Jones RB et al. Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. Rheumatology (Oxford) 2015;54:1153–60.

2.3. Extended RTX maintenance therapy

In selected patients, relapse risk remains high after 2 years of maintenance therapy, and extended duration therapy could be considered. This includes patients who relapse after a prior course of RTX maintenance, with persistent elevation or return of ANCA, or where the consequence of relapse would be organ or life threatening. Optimal treatment approaches beyond 2 years are yet to be determined in these patients. RTX 500-1000 mg every 6-12 months for up to 5 years could be considered. In patients with prior relapse after maintenance RTX cessation, this could be adjusted based on time from treatment cessation to disease relapse.

Level of evidence: 5.

Grade of recommendation: D.

Vote: 17/18 (94.4%).

Long term follow-up data from the MAINRITSAN trial highlight the risk of relapse after RTX cessation [17]. Until 28 months' follow-up, 10months after the last RTX infusion, only three (5%) patients experienced a major relapse. Over the subsequent 22months, without further scheduled RTX infusions, an additional 13 (23%) patients experienced a major relapse. Consistent with this, RTX maintenance cohorts demonstrate a progressive reduction in relapse-free survival after RTX cessation [22, 23]. An ongoing RCT (MAINRITSAN3) compares the effects of extended RTX maintenance with standard duration therapy (NCT02433522) [31].

Optimal regimens for extended RTX maintenance require further study. Extended treatment to 5 years is proposed in patients at high risk of relapse or its consequences. The dosing strategy presented (Fig. 1) is a guide, derived by expert consensus. Individualization of any extended treatment regimen is emphasized, based on the patient's wishes, comorbidities, age, and the history of their AAV.

Identifying patients at greatest risk of relapse after RTX treatment remains challenging. Patients who have relapsed after a previous course of RTX are considered empirically to be at greater risk of further relapse. Patients who are ANCA positive, either through persistent positivity or return, are likely to have a greater risk of relapse. Notably, in the MAINRITSAN trial, the risk of relapse for patients who were ANCA positive at each follow-up visit increased over time [17]. Following RTX cessation, one cohort reported that switching from negative to positive ANCA status was predictive of subsequent relapse [22]. This is consistent with findings from the REMAIN trial, which randomized patients who had completed 18–24 months of treatment to continue or withdraw maintenance azathioprine and glucocorticoid [32]. The withdrawal of azathioprine maintenance therapy and ANCA positivity at randomization (i.e. 18–24 months after commencement of treatment) increased the risk of relapse.

The highlighted factors should be considered in each patient's individual context, and the risk of relapse must be balanced against potential adverse effects of ongoing RTX. Traditional risk factors for relapse such as PR3-ANCA-associated disease, GPA phenotype and the absence of renal involvement should also be considered in assessing the overall risk of relapse [15, 33, 34]. Observational cohorts of patients with AAV have not identified a clear association between cumulative RTX dose and infection or chronic hypogammaglobulinaemia [35, 36]. Long term prospective data are required, and ongoing vigilance is recommended.

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3. Concomitant therapy

3.1. Concomitant immunosuppressive agents/disease disease modifying anti-rheumatic drugs (DMARD)

Where RTX is commenced in a patient already receiving a DMARD for remission maintenance (e.g. azathioprine, methotrexate or mycophenolate), we suggest that the existing DMARD(s) be withdrawn.

Level of evidence: 4.

Grade of recommendation: C.

Vote: 15/18 (83.3%).

Concomitant therapy refers to concurrent use of another non-glucocorticoid immunosuppressive or DMARD with RTX.

In clinical trials of RTX for the maintenance of remission in AAV, concomitant therapy has not been used. In observational cohorts, in which patients are already receiving a non-glucocorticoid immunosuppressive agent as maintenance therapy and RTX has been added, there has usually been withdrawal of this medication [19–22]. Owing to the potential for increased adverse effects, the routine use of concomitant therapy has not been recommended.

There is limited evidence from small numbers of patients receiving RTX maintenance treatment with refractory or relapsing disease described in observational studies, suggesting concomitant therapy may be efficacious in this setting [19, 22]. Rare cases of persistent disease activity despite ongoing RTX maintenance therapy may benefit from the addition of a concomitant immunosuppressive agent.

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3.2. Glucocorticoids

Glucocorticoid tapering strategies should aim for complete cessation 6–12 months after RTX commencement.

Level of evidence: 5.

Strength of recommendation: D.

Vote: 17/18 (94.4%).

Glucocorticoid-free remission remains ideal in view of known, predictable adverse effects. In long term followup of patients enrolled in European RCTs, prolonged glucocorticoid use was associated with greater disease damage, after adjusting for number of relapses during follow-up, age, baseline disease activity and renal involvement [38].

Shorter glucocorticoid tapering strategies are possible in many patients with AAV. One RCT that randomized patients to RTX induction or cyclophosphamide followed by azathioprine maintenance provided a standardized glucocorticoid taper to cessation at 6 months to patients in both arms [39]. Glucocorticoid-free remission was achieved in 64% of the RTX treated patients and 53% of those who received cyclophosphamide. Completed RCTs of RTX for the maintenance of remission have used glucocorticoid protocols allowing for glucocorticoid reduction in the first 6–12 months, but typically continue at low dose until at least 18 months following induction therapy [15, 16]. In uncontrolled settings, earlier prednisolone dose reduction and cessation is well documented with RTX maintenance therapy [20–22]. In practice, patients with EGPA have greater difficulty with glucocorticoid withdrawal, often resulting in incomplete control of asthma symptoms [27]. Adrenal insufficiency may also prohibit complete cessation of glucocorticoids [40, 41].

Referenzen aus Leitlinien
15 Guillevin L, Pagnoux C, Karras A et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. N Engl J Med 2014;371:1771–80.
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5. Adverse effects

5.1. Hypogammaglobulinaemia

(i) In the setting of RTX maintenance therapy: a. Immunoglobulins should be monitored in all patients b. Further investigation is recommended if recurrent or atypical infections occur, or IgG <3 g/L (in paediatric age ranges, IgG less than age appropriate lower limit of normal should be used).

Level of evidence: 2a (part a), 5 (part b).

Grade of recommendation: B (part a), D (part b).

Vote: 18/18 (100%).

Despite stable IgG levels reported by RCTs of RTX maintenance therapy, hypogammaglobulinaemia has been consistently observed in observational cohorts of patients receiving RTX [15, 16, 35, 36]. Conflicting results are likely a result of multiple factors; observational cohorts include a greater proportion of patients with a higher burden of prior immunosuppression for refractory or relapsing disease, and hypogammaglobulinaemia is variably defined, is transient in some and can be a late complication. While long term data are limited, the primary concern with persistent hypogammaglobulinaemia is recurrent, chronic and/or atypical infections.

It is not known whether RTX should be withheld for low or falling IgG levels and in clinical trials a threshold of 3 g/l has been used [18]. The possibility that continued RTX will exacerbate hypogammaglobulinaemia should be considered.

Patients with an established pattern of recurrent or atypical infections and hypogammaglobulinaemia may benefit from interventions including prophylactic antimicrobial therapy and/or immunoglobulin replacement. This should be considered in these subgroups of patients in accordance with local guidelines. Consistent with other recently published guidelines, while patients with persistent IgG <3 g/l without infections may not require further intervention, their infection profile and vaccination responses should be reviewed, in conjunction with Clinical Immunology services [48, 49]. For patients in paediatric age ranges, the long-term implications of hypogammaglobulinaemia are of greater concern and Clinical Immunology review should be sought when IgG levels fall below age-adjusted norms.

Referenzen aus Leitlinien
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(ii) Parallel administration of RTX and immunoglobulin replacement could be considered in patients with hypogammaglobulinaemia and a clinically important response to RTX is anticipated.

Level of evidence: 5.

Grade of recommendation: C.

Vote: 18/18 (100%).

In rare circumstances, relapse of AAV occurs in patients receiving immunoglobulin replacement therapy for hypogammaglobulinaemia. Uncontrolled disease typically necessitates further immunosuppression despite an established immunodeficient state. The additive effect of RTX associated hypogammaglobulinaemia with other immunosuppressive agents, thereby targeting multiple immune pathways, is unclear. Decisions on co-administration of RTX and immunoglobulin replacement, and the timing of these agents should be in conjunction with Clinical Immunology.

5.2. Late onset neutropenia

Clinicians and patients should be aware of the possibility of late onset neutropenia with RTX use. A history of uncomplicated late onset neutropenia does not prohibit future RTX use.

Level of evidence: 4.

Grade of recommendation: C.

Vote: 16/18 (88.9%).

In patients with a history of late onset neutropenia, there should be greater clinician and patient vigilance of infective symptoms after future RTX administration. Late onset neutropenia is incompletely understood but postulated to result from arrest of granulopoiesis in favour of B cell lymphopoiesis [50]. Late onset neutropenia has been identified in patients in RTX maintenance cohorts and RCTs [16, 19, 22, 23, 51, 52]. Owing to the unpredictable timing of late onset neutropenia, regular evaluation for neutropenia is not routine. The neutropenia is often asymptomatic, typically short-lived and, in the absence of routine testing, therefore likely underrecognized. Late onset neutropenia often recovers without therapy, with granulocyte colony stimulating factor (G-CSF) used in symptomatic patients with prolonged neutropenia, or with infective symptoms in conjunction with antimicrobial therapy. Moreover, reports of recurrence in patients treated for autoimmune disease, including AAV, are uncommon [53, 54]. In patients with a history of neutropenia complicated by severe infection, there is limited experience in repeat RTX administration.

Referenzen aus Leitlinien

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Mendel A et al., 2020 [3].

CanVasc consensus recommendations for the management of antineutrophil cytoplasm antibody-associated vasculitis: 2020 update zu 2016

Zielsetzung/Fragestellung

In 2015, the Canadian Vasculitis Research Network (CanVasc) created recommendations for the management of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV) in Canada. The current update aimed to revise existing recommendations and create additional recommendations, as needed, based on a review of new available evidence.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz, hinsichtlich der Fragestellung und zugelassener Arzneimittel zur Therapie für Patienten mit Eosinophiler Granulomatose mit Polyangiitis (EGPA), wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: keine Beteiligung von Patientenorganisationen im Gremium, aber externer Review durch Patientenorganisation;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche beschrieben; Auswahl und Bewertung der Evidenz nicht beschrieben;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Systematic literature review (publications spanning May 2014-September 2019) - Medline, Embase, and Cochrane.

LoE

Category of Evidence	Evidence Available
1A	From meta-analysis of randomized controlled trials.
1B	From at least 1 randomized controlled trial.
2A	From at least 1 controlled study without randomization.
2B	From at least 1 quasi-experimental study.
3	From descriptive studies, such as comparative studies, correlation studies, or case-control studies.
4	From expert committee reports or opinions and/or clinical experience of respected authorities.

GoR

Strength of Recommendation	Directly based on (level of evidence)
A	Category 1 evidence
B	Category 2 evidence or extrapolated recommendations from category 1 evidence.
C	Category 3 evidence or extrapolated recommendations from category 1 or 2 evidence.
D	Category 4 evidence or extrapolated recommendations from category 2 or 3 evidence.

Sonstige methodische Hinweise

- Auswahl und Bewertung der Evidenz nicht beschrieben.
- Es liegt nicht für alle genannten Wirkstoffe eine Zulassung für das vorliegende Anwendungsgebiet vor.

Empfehlung

Update: Eleven new and 16 revised recommendations were created, and 12 original (2015) recommendations were retained. New and revised recommendations are discussed in detail within this document. Five original recommendations were removed, of which 4 were incorporated into the explanatory text.

C. Updated Recommendations for the Treatment of EGPA

20. An initial dose of 1 mg/kg/day prednisone equivalent (no greater than 80 mg/day) is recommended for remission induction in patients with severe EGPA (Category 2A Strength C). b. Pulse IV methylprednisolone can be considered in severe, organ or lifethreatening EGPA, but lacks proven efficacy and carries a potential risk of adverse effects (Category 3, Strength D)

In a trial of EGPA patients with poor-prognosis factors (ie, Five Factor Score [FFS] ≥ 1), IV MP pulses were given to 72% of patients (43). There are no studies comparing the efficacy of pulse versus no pulse MP for induction of severe EGPA. Until such data are available, recommendations are extrapolated from GPA and MPA (Recommendation 5).

21. A GC tapering protocol should be initiated within 2-4 weeks of induction therapy in EGPA (Category 4, Strength D)

The EGPA Consensus Task Force (44) recommends tapering prednisone after 2-3 weeks, to approximately 20 mg/day by 3 months. Unlike in GPA and MPA, a reduced-dose GC taper has not been evaluated in EGPA.

22. We recommend remission induction therapy with a combination of GC and CYC in patients with severe newly diagnosed EGPA (Category 2A, Strength B)

In a prospective trial of patients with EGPA and FFS ≥ 1, IV CYC pulses led to complete remission in 89%(43). Extrapolating from GPA and MPA data (34, 37, 38), CYC induction should be followed by either AZA or MTX maintenance (with LEF or MMF as alternatives) for a minimum of two years.

23. Patients with non-severe EGPA without major organ involvement or poor prognostic factors may be treated with GC alone for initial induction therapy (Category 1B, Strength A).

CHUSPAN2 compared AZA plus GC to GC alone for induction in non-severe (FFS=0), newly diagnosed EGPA (n=51), MPA (n=25), or polyarteritis nodosa (n=19) (45). Within the EGPA subset at 2 and 5 years, relapse-free survival did not differ between groups (46). Although there is no evidence that adding immunosuppressants to initial induction is superior to GC alone, conventional immunosuppressants are often justified if vasculitic disease manifestations, such as mononeuritis multiplex, progress (47). Until further data is available, any of the conventional immunosuppressants (AZA, MTX, LEF, MMF, or even CYC in some cases) should be promptly added in patients with progressive vasculitic manifestations of EGPA for whom the FFS remains 0.

24. Mepolizumab 300 mg SC monthly can be considered in non-severe, glucocorticoiddependent refractory or relapsing EGPA (Category 1B, Strength A).

MIRRA (48) compared mepolizumab (300mg subcutaneously [SC] every 4 weeks) to placebo in 136 patients with refractory, relapsing, or GC-dependent EGPA (new diagnosis and severe disease excluded). The primary endpoint of remission (BVAS=0) at week 36 and 48 occurred more often in the mepolizumab group (OR 16.74, 95% CI 3.6-77.6) (48). Relapse rates were reduced but remained high overall (56% vs 82% with placebo), with no difference in serious adverse events (48). However, MIRRA was unable to determine the efficacy of mepolizumab for acute vasculitic manifestations or myocarditis (48). As of yet, no anti-IL-5 studies have been completed in patients without relapsing or refractory, GC-dependent EGPA.

25. Consideration of other (off-label) therapies for EGPA should be made in collaboration with centres of expertise (Category 4, Strength D).

Case series have suggested benefit of RTX for patients with relapsing or refractory EGPA (49, 50). Response or median time to remission may be better in ANCA positive patients (50). A retrospective study comparing 14 RTX-recipients to 14 CYC-recipients found similar remission (36% vs 29%) and relapse-free survival rates between groups (51). While two RCTs will evaluate RTX for EGPA induction (NCT02807103) and maintenance (NCT03164473), currently RTX should be reserved for patients who have failed conventional therapies and should be discussed with a centre of expertise.

Referenzen aus Leitlinien

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De Graeff N et al., 2019 [1].

European consensus-based recommendations for the diagnosis and treatment of rare paediatric vasculitides - the SHARE initiative

Zielsetzung/Fragestellung

The European initiative Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) aimed to optimize care for children with rheumatic diseases. Systemic vasculitides are very rare in children. Consequently, despite recent advances, paediatric-specific information is sparse. The lack of evidence-based recommendations is an important, unmet need. This study aimed to provide recommendations for diagnosing and treating children with rare forms of childhood systemic vasculitis.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz, hinsichtlich der Fragestellung und zugelassener Arzneimittel zur Therapie für Patienten mit Eosinophiler Granulomatose mit Polyangiitis (EGPA), wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: keine Beteiligung von Betroffenen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse; externes Begutachtungsverfahren nicht berichtet;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität nicht berichtet.

Recherche/Suchzeitraum:

- PubMed/MEDLINE, EMBASE and Cochrane databases were systematically searched on 20 June 2013

LoE

	For diagnostic/observational studies	For treatment studies
1A	Meta-analysis of cohort studies	Meta-analysis of randomized controlled trials
1B	Meta-analysis of case-control studies	Randomized controlled trial
2A	Cohort studies	Controlled study without randomisation
2B	Case-control studies	Quasi-experimental study
3	Non-comparative descriptive studies	Descriptive study
4	Expert opinion	Expert opinion

GoR

- Strength of recommendation

A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendations from category I or II evidence
D	Category IV evidence or extrapolated recommendations from category II or III evidence

Sonstige methodische Hinweise

- Externes Begutachtungsverfahren nicht berichtet.
- Regelmäßige Überprüfung der Aktualität nicht berichtet.
- Es liegt nicht für alle genannten Wirkstoffe eine Zulassung für das vorliegende Anwendungsgebiet vor.

Empfehlungen

Cross-cutting recommendations on treatment of rare paediatric vasculitides

No.	Recommendation	*LoE* [16]	*SoR* [12]
1.	The treatment of severe systemic vasculitis (organ- or potentially life-threatening disease), requires a period of intense treatment (induction therapy) followed by a period of less intense maintenance therapy.	4	D
2.	While limited data prevent specific recommendations on induction therapy for vasculitic syndromes, a general approach for severe vasculitis may include treatment with: Corticosteroids (methylprednisolone or prednisolone) IV CYC Therapeutic plasma exchange	3	C
3.	IV CYC is preferred to oral CYC due to lower toxicity and comparable efficacy, as well as ensured adherence to treatment.	3	C
4.	The following immunomodulatory agents should be considered for first-line maintenance:AZA; MTX; MMF; RTX (for AAV)	3	C
5.	Second or third line therapeutic agents for induction and/or maintenance that may be considered are: MMF, MTX, RTX, anti-TNF agents, IVIG, and/or Tocilizumab	3	C
6.	In case of relapse or failed primary induction therapy, increased dose of corticosteroids (oral or IV) are usually warranted, and a change in disease modifying agent should be considered after exclusion of non-compliance.	4	D
7.	There is no high-level evidence about how to stop maintenance therapy. However, treatment may be withdrawn slowly over at least 6 months if a patient has been in remission for at least 12 months on maintenance therapy	4	D
8.	A general outline for treatment of severe systemic vasculitis is outlined in Fig. 1. This outline can be followed for treatment of severe systemic vasculitis.	4	D
9.	A general outline for treatment of crescentic glomerulonephritis/rapidly progressive glomerulonephritis is outlined in Fig. 2. This outline can be followed for treatment of crescentic glomerulonephritis/rapidly progressive glomerulonephritis.	4	D
10.	During immunomodulatory treatment, other important aspects of management that should be considered are: Antiplatelet agents Antibiotic prophylaxis (specifically against PJP) Osteoporosis prophylaxis Gastric protection (PPI)	4	D
11.	CYC should be administered with MESNA unless there is hypersensitivity to the latter.	4	D
12.	Sperm cryopreservation may be considered for all post-pubertal males prior to receiving CYC.	4	D
13.	IV epoprostenol should be administered in case of incipient gangrene or other critically severe ischaemic complications.	4	D

AAV: ANCA associated vasculitis; IV: intravenous; PJP: *Pneumocystis jiroveci* pneumonia; PPI: proton pump inhibitor; MESNA: 2-mercaptoethane sulfonate Na (Na = sodium); LoE: level of evidence; RTX: rituximab; 1A: meta-analysis of randomized controlled trial; 1B: randomized controlled study; 2A: controlled study without randomization; 2B: quasi-experimental study; 3: descriptive study; 4 expert opinion [17]; SoR: strength of recommendation; A: based on level 1 evidence; B: based on level 2 or extrapolated from level 1; C: based on level 3 or extrapolated from level 1 or 2; D: based on level 4 or extrapolated from level 3 or 4 expert opinion [12].

Disease-specific recommendations on treatment of rare paediatric vasculitides

No.	Recommendation	*LoE* [16]	*SoR* [12]
GPA and MPA			
1.	Considering the lack of evidence in children and the high level of evidence in adult studies for AAV, the EULAR recommendations on adult-onset AAV (2013) can be used in paediatric AAV patients.	4	D
2.	Treatment with a biological agent may be indicated in AAV patients with critical organ or life-threatening disease that has failed to respond to standard vasculitis therapy, or in patients in whom concerns exist regarding CYC toxicity.	1b	B
3.	In case of treatment with a biological agent, B-cell depleting therapy should be the treatment of first choice.	1b	B
4.	Cotrimoxazole is recommended to be added to treatment for AAV to help prevent bacterial infection, PJP, and to help prevent upper respiratory tract relapses in GPA.	1b	B
5.	Clinical trials/studies involving paediatric AAV patients are warranted; given the rarity of this disease in the paediatric population, inclusion of children in adult trials may be acceptable depending on the trial design/therapeutic agent under consideration.	4	D
EGPA			
1.	No disease-specific recommendations have been noted for EGPA. For general treatment guidelines, see the section: 'Cross-cutting recommendations on treatment of rare paediatric systemic vasculitides'.	4	D

Treatment of ANCA-associated vasculitis: GPA and MPA

In view of the lack of robust evidence in children and the high level of evidence in adult studies for AAV, it was recommended that EULAR recommendations for managing adult-onset AAV (first published in 2009 [68], updated in 2016 [65]), should also be followed for children. An important caveat to this was the aforementioned use of RTX as a maintenance agent in children with AAV. As clinical trials/studies involving paediatric AAV patients are clearly warranted, the panel agreed that given the rarity of this disease in the paediatric population, including children in adult-focused trials may be acceptable depending on the trial design and therapeutic agent under consideration. One example of this is the MYCYC trial [57]. Use of biological agents, including RTX as an alternative to, or to limit exposure to CYC was recommended for paediatric AAV patients with critical organ or life-threatening disease failing to respond to standard vasculitis therapy, or in patients with concerns exist regarding CYC toxicity. Specific attention was also given to considering the use of prophylactic co-trimoxazole, since in addition to preventing P. jiroveci pneumonia; it might help prevent upper respiratory tract relapses in GPA [69].

Treatment of EGPA:

There was no specific high-level evidence underpinning disease-specific recommendations for paediatric EGPA. Hence, recommendations were based on descriptive studies [37, 38] and/or expert opinion. Thus, the general treatment approach outlined in Fig. 1 was considered appropriate.

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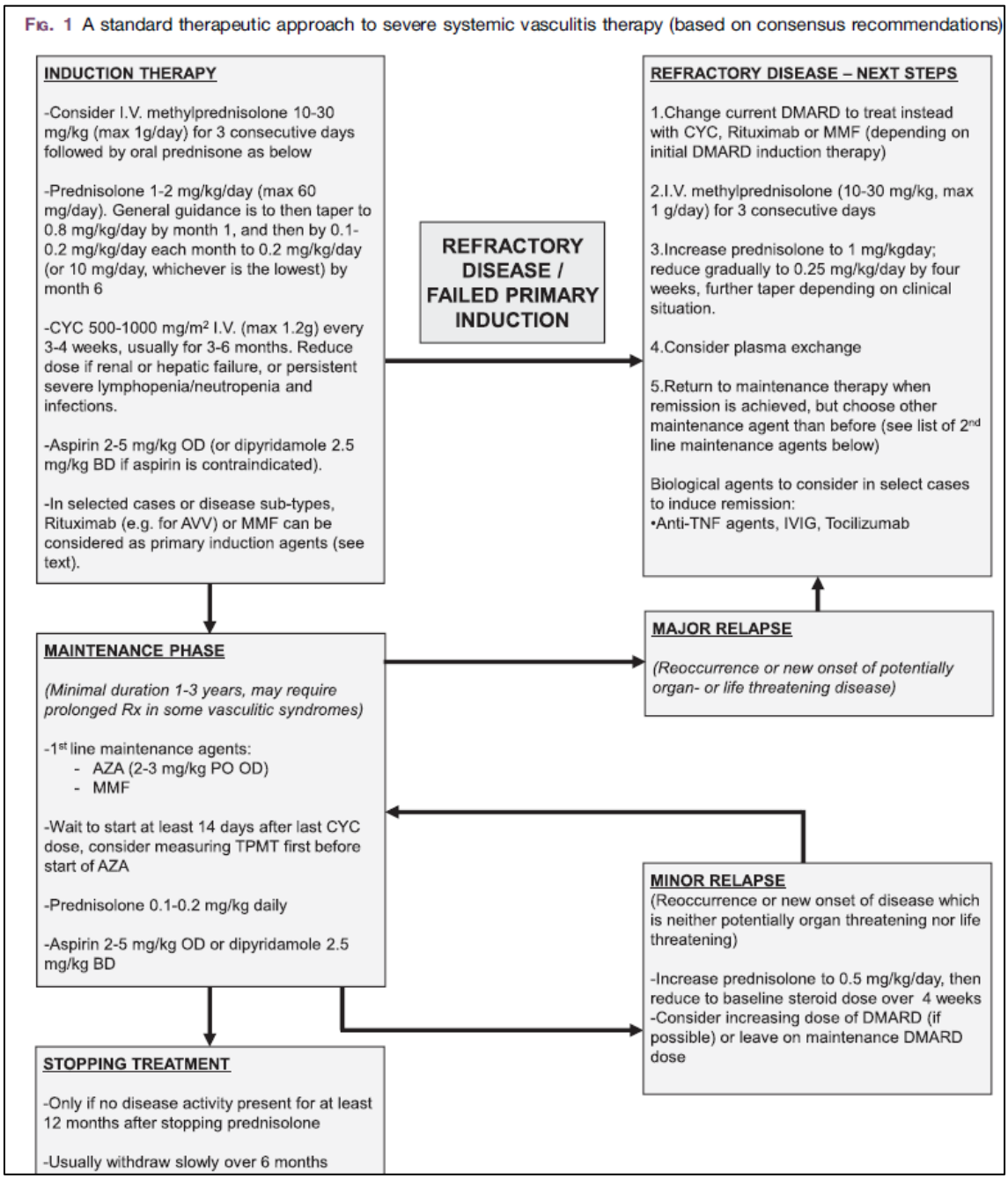


Second line maintenance agents include: MMF or AZA (if not used as first line maintenance treatment), MTX, RTX (for AAV - seek expert advice), and TNF blockade (seek expert advice). Other biological agents to consider in select individuals who fail to respond to standard induction therapy should be given under expert paediatric rheumatology or nephrology supervision only. Consider epoprostenol IV continuous infusion for incipient gangrene, seek expert advice regarding dose and duration. AAV: ANCA associated vasculitides; BD: bi-daily; OD: once daily; Rx: treatment; TPMT: thiopurine methyltransferase; RTX: rituximab.

Yates M et al., 2016 [6].

European League against Rheumatism (EULAR), European Renal Association - European Dialysis and Transplant Association (ERA-EDTA)

EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis

Siehe auch: Sznajd, J et al., 2016 [4], HO C et al., 2018 [2].

Zielsetzung/Fragestellung

In 2009 we published the European League Against Rheumatism (EULAR) recommendations for managing primary systemic vasculitis which included the management of AAV (10). The publication of 1691 papers on primary systemic vasculitis in the past 5 years in internal medicine, rheumatology and nephrology journals, as well as the licensing of rituximab for AAV, make this an opportune time to update the guidelines with an AAV focus.

This paper reassesses standard therapy, including the use of biologic agents, the prognostic value of histopathology and management of long-term complications, integrating these into treatment algorithms.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz, hinsichtlich der Fragestellung und zugelassener Arzneimittel zur Therapie für Patienten mit Eosinophiler Granulomatose mit Polyangiitis (EGPA), wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte dargelegt, keine Informationen zur finanziellen Unabhängigkeit identifiziert;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse dargelegt, externes Begutachtungsverfahren nicht beschrieben;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität wahrscheinlich gesichert.

Recherche/Suchzeitraum:

- EMBASE, CINAHL PLUS and CENTRAL up to February 2015

LoE

- Categorisation of evidence according to EULAR SOP

Category	Evidence
1A	From meta-analysis of randomised controlled trials (RCTs)
1B	From at least one randomised controlled trial (RCT)
2A	From at least one controlled study without randomisation
2B	From at least one type of quasi-experimental study
3	From descriptive studies, such as comparative studies, correlation studies, or case-control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities

GoR

- Strength of recommendations according to EULAR SOP

Strength	Directly based on
A	Category 1 evidence
B	Category 2 evidence or extrapolated recommendations from category 1 evidence
C	Category 3 evidence or extrapolated recommendation from category 1 or 2 evidence
D	Category 4 evidence or extrapolated recommendation from category 2 or 3 evidence

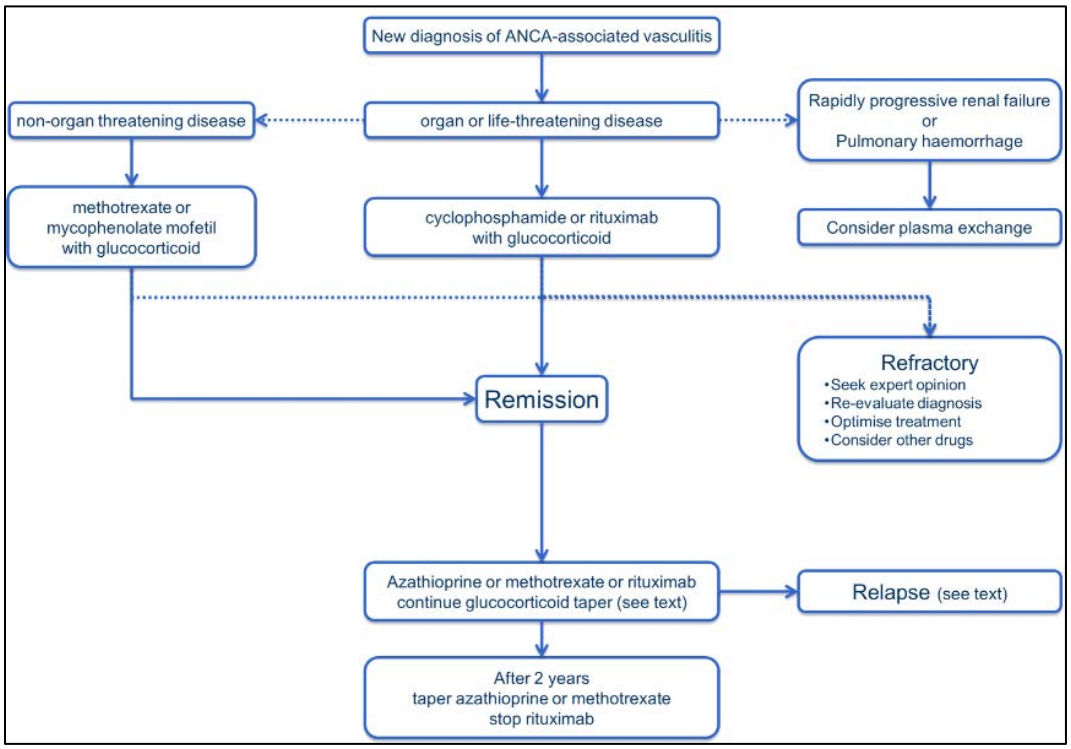
Expert opinion approach – for recommendation statements which are not derived from clinical trials, consensus was based on clinical recommendations of the taskforce committee; these have a default strength of D.

Sonstige methodische Hinweise

- Es liegt nicht für alle genannten Wirkstoffe eine Zulassung für das vorliegende Anwendungsgebiet vor.

Empfehlungen

Algorithm to describe the management of new antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Dashed lines indicate alternative or supplementary action to consider.



Statement Three

For remission-induction of new-onset organ or life-threatening ANCA-associated vasculitis we recommend treatment with a combination of glucocorticoids and either cyclophosphamide OR rituximab.

- cyclophosphamide (CYC)

- level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 100%.
- level of evidence 3 for **EGPA**; grade of recommendation C; strength of vote 88%.

- rituximab (RTX)
  - level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 100%.
  - level of evidence 3 for **EGPA**; grade of recommendation C; strength of vote 59%.

EGPA

The grade of evidence for cyclophosphamide use in EGPA is lower than for GPA/MPA as no randomised controlled trials (RCTs) for the treatment of EGPA have been published. One study did compare cyclophosphamide doses: cyclophosphamide (0.6 mg/m2) was used initially every two weeks for a month then every four weeks (55). The intervention arm was given six pulses in total; whilst the control arm received 12 pulses. Complete remission was achieved in both groups at a similar rate (21/23 in intervention arm, 21/25 in control arm).

Antiemetic therapy should be routinely administered with intravenous cyclophosphamide. Cyclophosphamide metabolites are toxic to the urothelium and can cause haemorrhagic cystitis in the short term and malignancy in the long term (26, 56, 57). Patients should be encouraged to drink plenty of fluids and if thought necessary, given intravenous fluids on the day of the infusion to dilute the metabolites in the urine. Patients receiving pulse cyclophosphamide may also be given oral or intravenous 2-mercaptoethanesulfonate sodium (MESNA) which binds to acrolein, a toxic metabolite of cyclophosphamide, rendering it non-toxic (24). MESNA also retards the degradation of 4-hydroxymetabolites, further reducing the toxic acrolein products in the urine. MESNA may also be beneficial in patients receiving continuous oral cyclophosphamide (23, 24, 58).

Monitoring of patients receiving cyclophosphamide should follow standard protocols (59). In both modalities of administration, dose changes or discontinuation of cyclophosphamide may be necessary in the event of an acute leucopoenia or a gradual fall over time. In the event of a stable leucopoenia, it may be possible to maintain the immunosuppression with stringent blood monitoring. We encourage prophylaxis against infection with Pneumocystis jirovecii with trimethoprim/sulphamethoxazole (800/160 mg on alternate days or 400/80 mg daily) in all patients being treated with cyclophosphamide where not contraindicated (60-62). The use of inhaled monthly pentamidine in the event of an adverse reaction or contraindication to trimethoprim/sulphamethoxazole may be useful but is not cost-effective and not routinely indicated (60). Other alternatives include dapsone and atovaquone.

[…]

The grade of evidence for the use of rituximab in patients with EGPA is lower than for GPA/MPA. A retrospective analysis of 41 patients with EGPA who received differing regimens of rituximab found that 34% achieved complete remission at six months and 49% at 12 months (65). In total, 19/41 patients received a single course of rituximab. Re-treatment was given for 22/41 at six months and 17/22 were re-treated again at 12 months. Two received their first re-treatment at 12 months. The initial treatment schedule was 375 mg/m2/week for four weeks (n=10) or two doses of 1000 mg given two weeks apart (n=30). One patient received two doses of 800 mg at a two-week interval. Subsequent rituximab courses and doses were 375 mg/m2/week for four weeks (three patients), two doses of 1000 mg two weeks apart (two patients), 1000 mg single dose (16 patients), and a single dose of 600 mg rituximab (one patient) (65).

[…]

The taskforce considered appropriate a target of between 7.5 mg to 10 mg of prednisolone (or equivalent) after three months (12 weeks) of treatment. A review of the prednisolone protocol reduction regimens published for the key trials illustrated that on average a dose of 10mg was achieved after 19 weeks, and a dose of 7.5mg after 21 weeks (Figure 2) (49, 63, 64, 72-77). Therefore although a target prednisolone dose of 7.5mg to 10mg is desirable by 3 months, in practice it may be 5 months before this is achieved.

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Statement Four

For remission-induction of non organ-threatening ANCA-associated vasculitis we recommend treatment with a combination of glucocorticoids and either methotrexate or mycophenolate mofetil.

- MTX
  - Level of evidence 1B; grade of recommendation B; strength of vote 77%.
- MMF
  - Level of evidence 1B; grade of recommendation C; strength of vote 65%.

The taskforce was keen to stress that the use of methotrexate or mycophenolate mofetil should not be used for remission induction in the following scenarios:

- Meningeal involvement
- Retro-orbital disease
- Cardiac involvement
- Mesenteric involvement
- Acute-onset mononeuritis multiplex
- Pulmonary haemorrhage of any severity

Methotrexate (20–25 mg/week, oral or parenteral) can be used as an alternative to cyclophosphamide in patients with less severe disease and in those with normal renal function (23, 74, 78-85). There have been trials using either methotrexate or mycophenolate mofetil as the remission induction agent in patients with AAV. The NORAM study, a RCT, was the largest of these and recruited 95 participants with AAV (89 with GPA and 6 with MPA) (74). The exclusion criteria for the NORAM study were those with organ or life-threatening manifestations (severe haemoptysis associated with bilateral infiltrates, cerebral infarction due to vasculitis, rapidly progressive neuropathy, orbital pseudo-tumour, massive gastrointestinal bleeding, heart failure due to pericarditis or myocarditis) or serum creatinine >150 µmol/L, urinary red cell casts, or proteinuria >1.0 g/day. Therefore methotrexate use should be restricted to those individuals with less severe disease manifestations of AAV. Oral methotrexate (15 mg/wk given, escalating to a maximum of 20 to 25 mg/wk by week 12) was compared to oral cyclophosphamide 2 mg/kg/day (maximum 150 mg/day) until remission (minimum three months, maximum six months). Both treatments were tapered from month 10 and were stopped by month 12. Long-term follow-up of NORAM revealed that although there were no differences in major events (serious infection, end-stage renal failure or death) between the two groups, the methotrexate group was less effective at controlling disease and required other immunosuppressive agents for longer periods than the cyclophosphamide group. (86). Methotrexate should therefore be considered only for non organ-threatening disease. Examples include the following in the absence of renal involvement

- *Nasal and paranasal disease without bony involvement (erosion) or cartilage collapse or olfactory dysfunction or deafness*
- *Skin involvement without ulceration*

- *Myositis (skeletal muscle only)*
- *Non-cavitating pulmonary nodules/infiltrate without haemoptysis*
- *When cyclophosphamide or rituximab are not available or contraindicated or patient choice.*

The induction trials involving methotrexate are generally larger and of higher evidence grade than those using mycophenolate mofetil. The previous recommendations from EULAR made reference to two trials using mycophenolate mofetil (MMF) at a dose of 2g/day for remission induction (10). (72, 87). The first study was a retrospective analysis of a case series of patients with AAV treated with MMF: of 22 patients receiving MMF for active disease, 86.4% achieved remission, however 9 (47.4%) relapsed (87). The other study was also an uncontrolled study and recruited 32 patients with AAV (29 with GPA and 3 with MPA) who could not be treated with cyclophosphamide (72). Complete remission (Birmingham Vasculitis Activity Score - BVAS <1 (88)) was achieved in 25 patients (78%) after a median duration of 2.2 months. Nine (36%) patients relapsed within a year (72).

Following these uncontrolled studies, RCTs have been published (89, 90). The first was published in 2008 and compared MMF 2 g/day (1.5 g per day for those <50 kg in weight) to cyclophosphamide 0.75 to 1.0 g/m2 body surface area (89). There were 35 participants recruited with active AAV with renal involvement (34 MPA, 1 GPA). Important exclusions were severe renal failure, with serum creatinine ≥500 µmol/L or renal replacement treatment for more than two weeks, or life-threatening organ manifestations (lung hemorrhage, central nervous system involvement). There is therefore little evidence for the use of MMF in such scenarios.

The outcome was measured as complete remission (BVAS <1) at six months. In the intent-to-treatment analysis, 14 of 18 patients (77.8%) treated with MMF and 8 of 17 patients (47.1%) receiving cyclophosphamide (although four participants were lost to follow-up) had complete remission (89). The other RCT was published in 2011 and involved 41 Chinese participants, all of whom had MPA (90). It compared MMF 1 g/day (1.5 g/day in those weighing >70 kg) against cyclophosphamide monthly 1 g per pulses (0.8 g per pulse in those weighing <50 kg). This trial also included those with severe renal failure as defined by a serum creatinine of >500 µmol/L (5/22 participants in the cyclophosphamide group and 4/19 in the MMF group). Important exclusions were: severe lung haemorrhage (haemoptysis >300 ml/24 h or with hypoxemia) or central nervous system involvement and other life-threatening situations or age >70 years, which prevents the generalisability of the findings to other more severe presentations of AAV.

The outcome was measured as complete remission (BVAS <1 and dose of prednisolone <7.5 mg/day) at six months; this was achieved in 63.6% of the cyclophosphamide group and 78.9% of the MMF group (90). To date, the two RCTs using MMF mainly have been conducted primarily in patients with MPA (of the 76 participants 75 had MPA). MPA often affects renal function and in such situations methotrexate would not be indicated. The MYCYC trial compared MMF (2 to 3 g daily) to pulsed cyclophosphamide (15 mg/kg for 6 to 10 pulses); preliminary results have been published in abstract form but full publication is awaited (91). The remission end point (absence of disease activity for four weeks or longer whilst on prednisolone at six months) was achieved in 66% (MMF) and 69% (cyclophosphamide) of patients (91). No data are yet available on the numbers of participants with GPA or MPA recruited to this trial.

Statement Five

For a major relapse of organ- or life-threatening disease in ANCA-associated vasculitis we recommend treatment as per new disease with a combination of glucocorticoids and either cyclophosphamide OR rituximab.

- RTX
    - level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%.
    - level of evidence 4 for **EGPA**; grade of recommendation D; strength of vote 100%.
- CYC

- level of evidence 1A for GPA and MPA; grade of recommendation A; strength of vote 88%.
- level of evidence 3 for **EGPA**; grade of recommendation C; strength of vote 88%.

Most trials published on remission induction in AAV make no distinction between those participants treated for a new or relapsing presentation of their disease. It is for these reasons that the trial evidence for new or relapsing disease is often from the same studies. However, some studies have distinguished between those participants with new and relapsing disease and have stratified by this factor when randomising patients.

The largest RCT to investigate the use of rituximab for remission induction in AAV (RAVE) stratified participants by new or relapsing disease; those with relapsing disease treated with rituximab were more likely to be in disease remission at the 6 and 12 month time points but not the 18 month follow-up visit (64).

The cumulative dose of cyclophosphamide is related to toxicity and is a particular concern with prolonged oral dosing, where cumulative doses are higher (92). For this reason the taskforce has favoured a greater strength of recommendation for rituximab over cyclophosphamide for relapsing disease.

Further analysis of the RAVE trial data has revealed some important insights with respect to minor relapses. There were 44 participants with a non-severe relapse (BVAS for Wegener's Granulomatosis (BVAS/WG) (93) <4 and absence of a major item). These patients were more likely to be PR3-ANCA positive (82%), diagnosed with GPA (91%) and have a history of relapsing disease at baseline (64%) (94). An increase in the prednisolone dosage led to remission in 35 (80%) cases, but 31 had a second relapse (14 severe) (94). The mean time to second relapse was 9.4 months. A similar percentage of patients achieved and maintained remission when treated with high-dose prednisolone (≥20 mg/day) as opposed to low-dose prednisolone (<20 mg/day). Seventy-seven percent of patients with relapsing disease who were treated with high-dose prednisolone achieved remission, and 23% of those patients maintained those remissions for the remainder of follow-up. In comparison, 82% of the patients with relapsing disease who were treated with low-dose prednisolone achieved remission, and 36% maintained those remissions (94). In conclusion, treatment of non-severe relapses in AAV with a temporary increase in the glucocorticoid dose restores disease remission in most patients but recurrent relapses within a relatively short time period remain common. Given these data, alternative approaches to the treatment of non-severe relapses must be considered, especially if relapses are frequent. We therefore recommend treatment with intensification or modification of the immunosuppressive remission maintenance regimen.

Statement Six

Plasma exchange should be considered for patients with ANCA-associated vasculitis and a serum creatinine level of greater than 500 µmol/L (5.7 mg/dL) due to rapidly progressive glomerulonephritis in the setting of new or relapsing disease. Level of evidence 1B; grade of recommendation B; strength of vote 77%.

Plasma exchange can also be considered for the treatment of severe diffuse alveolar haemorrhage. Level of evidence 3; grade of recommendation C; strength of vote 88%.

Plasma exchange (PLEX) use is usually reserved for patients with either severe renal impairment or those with diffuse alveolar haemorrhage (95-97). The largest trial published to date is MEPEX which recruited those individuals with either a serum creatinine >500µmol/L (5.7 mg/dL) or those requiring dialysis (77). Long-term follow-up and analysis of this trial has also been published (98). In this trial 137 participants with AAV were recruited and received cyclophosphamide and glucocorticoids in addition to either PLEX or pulsed IV methylprednisolone (up to 3g). The primary end point was end-stage renal disease (ESRD) or death at three months. Of those treated with IV methylprednisolone, 33 (49%) were alive and dialysis-independent at three months, compared with 48 (69%) in the PLEX group (95% confidence interval for the difference 18 to 35%; P = 0.02) (77). However, a long-term follow-up study revealed no statistically significant benefit for the PLEX group when comparing a composite outcome of ESRD or death (99). Prior to the publication of this long-term follow-up data, a meta-analysis had concluded that plasma exchange may decrease the composite end point of ESRD or death in patients with renal vasculitis (100). However most trials of PLEX did not restrict use to individuals with a serum creatinine >500 µmol/L (5.7 mg/dL). One RCT with long-term follow-up that has tested whether PLEX may benefit individuals with a serum creatinine of <500 µmol/L (5.7 mg/dL) (101). This trial recruited 32 participants with GPA and compared the effects of PLEX versus no PLEX and of oral cyclophosphamide (100 or 150 mg daily for 3 to 12 months) versus cyclosporine A (5 mg/kg) with a Latin square design (101). Elevated serum creatinine at enrolment was noted in 22 of the 32 participants who were equally allocated amongst the four groups. After 1 month, none of the PLEX participants required haemodialysis (HD) or had worsening renal function compared with six with declining renal function and five on HD in the reference group (p < 0.05) (101).

Despite the improvements in renal function, there were no differences in all-cause mortality between the PLEX and reference groups after five years of follow-up (101). PEXIVAS is a global trial that is currently recruiting with a target of 700 participants with moderate renal impairment (eGFR <50 ml/min) and aims to provide definitive answers regarding the use of PLEX in AAV, especially regarding the cut-off of serum creatinine of 500 µmol/L (5.66 mg/dL). The PEXIVAS trial uses the following protocol for PLEX (102):

- *Seven plasma exchanges of 60 mL/kg, either with centrifugation or filter separation according to local practice and availability.*
- *Anticoagulation by heparinisation or citrate according to local practice.*
- *Replacement fluid with human serum albumin (3-5% depending on local availability). Albumin may be combined with crystalloid (e.g. saline).*
- *Patients with active bleeding to receive supplemental plasma to replace clotting factors according to local practice.*

All participants in the PEXIVAS trial will also receive IV methylprednisolone (1000 mg pulses for 1 to 3 days) with standard induction therapy either pulsed cyclophosphamide or rituximab. The trial investigators suggest waiting 48 hours after RTX is given prior to undertaking a session of PLEX.

There is also potential benefit for PLEX in patients with AAV who are also anti-GBM antibody positive, particularly those in whom there is linear staining of IgG on the glomerular basement membrane, and PLEX should be performed early in such patients to improve outcome (97, 103).

Statement Seven

<u>For remission-maintenance of ANCA-associated vasculitis we recommend treatment with a combination of low-dose glucocorticoids and either azathioprine, rituximab, methotrexate, or mycophenolate mofetil.</u>

- **GPA/MPA**
  - • AZA: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 94%.
  - RTX: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 59%.
  - MTX: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 53%
  - MMF: Level of evidence 1B for GPA and MPA; grade of recommendation A; strength of vote 53%
- **EGPA**
  - AZA: Level of evidence 3 for EGPA; grade of recommendation C; strength of vote 77%.

Long-term therapy with cyclophosphamide has been used to maintain remission in patients with AAV (23). However the toxicity of long-term cyclophosphamide makes it an unattractive option (26, 56, 57). Azathioprine (2 mg/kg/day) is safer than oral cyclophosphamide but as effective at 18 months in preventing relapse (76, 104). Methotrexate (20–25 mg/kg/week) has been effectively used for maintenance therapy after induction of remission with cyclophosphamide (if the serum creatinine is >130 µmol/L or 1.5 mg/dL) (105, 106). Leflunomide (20–30 mg/day) may be more effective than methotrexate in remission maintenance but is associated with more adverse effects (107). Therefore Leflunomide is considered for second-line treatment in cases of intolerance to AZA, MTX, MMF or RTX. Early cessation of therapy is associated with an increased risk of relapse (74).

Long-term follow-up of the CYCAZAREM study which recruited 155 participants with AAV (95 GPA, 60 MPA) was published in 2014 (108). Participants received remission induction therapy with oral cyclophosphamide (2 mg/kg per day) with prednisolone (initially 1 mg/kg reducing to 0.25 mg/kg per day by 12 weeks) and 93% were in remission by six months (76). Those patients in whom remission had been achieved by three months, or between three and six months, were randomly assigned to treatment with azathioprine as a substitute for cyclophosphamide (azathioprine group) or to continued cyclophosphamide

therapy (cyclophosphamide group). Twelve months after study entry, the patients in the cyclophosphamide group were switched to the same azathioprine regimen as the azathioprine group was receiving and continued to receive this regimen until the end of the study, 18 months after entry. The initial paper concluded there was no difference in relapse rate at 18 months between the two groups. Long-term follow-up revealed no statistical significance differences for outcome between the two groups (108).

The WEGENT trial compared methotrexate to azathioprine and recruited 126 participants with AAV (GPA 96 and MPA 30) (109). Participants received pulsed cyclophosphamide and prednisolone for remission induction. The first three cyclophosphamide pulses were given two weeks apart, following which the interval was increased to every three weeks for the next three pulses. Prednisolone target dose at six months was 12.5mg/day with withdrawal after 24 months (109). Methotrexate (0.3 mg/kg increasing in 2.5 mg increments weekly to maximum 25 mg per week) or azathioprine (2 mg/kg/day) were started after the sixth pulse of cyclophosphamide and both were withdrawn over a period of three months after 24 months (109). 24 months after randomisation, relapse-free survival rates were 71.8% (95% CI, 59.7% to 83.8%) in the azathioprine group and 74.5% (95% CI, 62.7% to 86.4%) in the MTX group. The hazard ratio for the risk of relapse among MTX vs AZA was 0.92 (95% CI, 0.52 to 1.65; P = 0.78).

The MAINRITSAN trial compared rituximab to azathioprine for remission maintenance (110). This trial recruited 115 participants with AAV (87 GPA, 23 MPA and five with renal limited vasculitis) all of whom were treated with pulsed cyclophosphamide (initially 0.6 g/m2 every 2 weeks for three pulses then 0.7 g/m2 every three weeks for a further three to six pulses) and prednisolone for remission induction. During the month after the last cyclophosphamide pulse, patients in the rituximab group received intravenous rituximab (at a fixed 500 mg dose) on days 0 and 14 after randomisation, and then at months 6, 12, and 18 after the first infusion. Patients in the azathioprine group took azathioprine at a dosage of 2 mg/kg/day for 12 months, and then 1.5 mg/kg/day for 6 months and 1 mg/kg/day for 4 months. In addition, prednisolone treatment was further tapered and kept at a low dose (approximately 5 mg/day) for at least 18 months after randomisation. Prednisolone dose tapering and the decision to stop prednisolone treatment after 18 months were left to each site investigator's discretion (110). Rituximab was superior to azathioprine at preventing relapse. At month 28, major relapses had occurred: 17 in the azathioprine group (eight occurred within 12 months of treatment, two when dosage of AZA was between 1.5 and 1 mg/kg/day and the rest once AZA stopped), 3 in the rituximab group (at months 8, 22 and 24). Renal relapses occurred in 8/17 major relapses in the AZA group and 0/3 in the RTX group (110).

Azathioprine (AZA) is preferred over mycophenolate mofetil (MMF) for remission maintenance, primarily because of the results from the IMPROVE trial (111). This study recruited 156 participants with AAV (GPA 100, MPA 56), who were treated initially with cyclophosphamide induction and randomised to receive either azathioprine (2 mg/kg per day, n=80) or MMF (2 g daily, n=76). In both groups the remission maintenance agent was reduced at two time points (after 12 and 18 months) and withdrawn after 42 months. Prednisolone was given as part of remission reduction with the regimen taper resulting in withdrawal after 24 months (111). The primary end point was relapse-free survival from the time remission was first achieved. Relapses were noted in 42 participants treated with MMF (55.3%; 18 major and 24 minor) and in 30 participants in the AZA group (37.5%; 10 major and 20 minor, p <0.01).

The addition of trimethoprim/sulphamethoxazole (800/160 mg twice daily) to standard remission maintenance can reduce the risk of relapse in GPA (112).

Although trimethoprim/sulphamethoxazole has been used as the sole remission maintenance agent in half the patients of one RCT, trimethoprim/sulphamethoxazole monotherapy may not be effective for maintenance of remission (112, 113). In patients with nasal disease, treatment with topical antibiotics such as mupirocin may be considered in the presence of chronic carriage of nasal Staphylococcus aureus (114).

Statement Eight

We recommend that remission-maintenance therapy for ANCA-associated vasculitis be continued for at least 24 months following induction of sustained remission. Level of evidence

4; grade of recommendation D; strength of vote 75% for MPO persistent disease, 62% for MPO negative disease, 100% for PR3 persistent disease and 92% for PR3 negative disease.

No published RCTs have directly compared duration of maintenance therapy regimens. Early cessation of therapy is associated with an increased risk of relapse (74). Most of the data regarding relapse risk are derived from a combination of observational cohort data and long-term follow-up from clinical trials. There are however important differences in the make-up of the participants from these sources, with many more patients with GPA likely to be present in observational cohort studies (115). A meta-analysis of 13 studies (eight RCTs and five observational studies with 983 participants) examining the effect of duration of glucocorticoids on relapse rate concluded that continuing glucocorticoids is associated with fewer relapses (116). The pooled total estimate for the proportion of patients suffering with a relapse recruited to RCTs was 36% (95% confidence interval 25% to 47%) but only 14% for those studies which continued glucocorticoids. In patients with AAV with renal involvement, worse prognosis is associated with those who have MPO-ANCA, even after adjustment for baseline factors such as age, sex and serum creatinine (117). Furthermore, patients with MPO-ANCA have more severe tubulointerstitial inflammation and both CD3(+) T cell tubulitis and tubular atrophy are independently associated with eGFR at 12 months (118). In addition, kidney biopsies displaying sclerosis are associated with worse outcomes in AAV (119). However, patients with PR3-ANCA and those with cardiovascular or lung involvement are more likely to relapse (43, 120). The resultant grade for the strength of recommendation of the taskforce reflects the lack of data for this area. It should be noted that there was a trend to increase the duration of therapy in patients who are PR3-ANCA positive and this was reflected with median of the vote for 36 months of maintenance therapy in this particular scenario.

Statement Nine

For patients with ANCA-associated vasculitis refractory to remission-induction therapy we recommend switching from cyclophosphamide to rituximab or from rituximab to cyclophosphamide. These patients should be managed in close conjunction with, or referred to, an expert centre for further evaluation and potential enrolment in clinical trials. Level of evidence 3; grade of recommendation C; strength of vote 71%.

Refractory disease is defined by EULAR as (45):

- *Unchanged or increased disease activity in acute AAV after 4 weeks of treatment with standard therapy in acute AAV, or*
- *Lack of response, defined as <50% reduction in the disease activity score (e.g. BVAS or BVAS/WG), after 6 weeks of treatment, or*
- *Chronic, persistent disease defined as presence of at least one major or three minor items on the disease activity score after >12 weeks of treatment.*

It is important to consider why a particular patient may have refractory disease and what it is that is driving the conclusion that they have refractory disease. Items to consider are:

- *Re-evaluate the primary diagnosis are they truly refractory – do they have AAV?*
- *Has the treatment regimen been optimised i.e. have target dosages for therapy been reached?*
- *Is this active disease or could it be damage?*
- *Is the present disease due to AAV or could it be due to an infection or other co-morbidity or possible malignancy?*

Rituximab has proven useful in patients with refractory disease, particularly those who have been previously treated with cyclophosphamide. Patients with refractory renal disease have the greatest chance of improvement, while those with retro-orbital disease pose a particular challenge (44, 65, 121, 122). Based on the results of an additional analysis of the WEGENT trial, the taskforce suggested a switch from pulsed to oral cyclophosphamide as a potential strategy under the guidance of an expert centre when rituximab is unavailable (123).

Additional analysis of the 52% of patients enrolled into the RAVE trial who had renal involvement (biopsy proven pauci-immune glomerulonephritis, red blood cell casts in the urine, and / or a rise in serum creatinine concentration attributed to vasculitis) revealed no difference in remission rates at 6, 12 or 18 month between the two groups (124). However, when the 47 (24%) of the participants who failed to achieve the primary end point were treated with blinded crossover or according to best medical judgment by the trial physician, this led to disease control in the majority (125). Of the participants with uncontrolled disease or who experienced a severe relapse, 91% had proteinase 3 (PR3)-ANCA. Re-analysis of 37 of these 47 participants (excluding the 10 (5%) with uncontrolled disease) revealed treatment with rituximab was better than cyclophosphamide for those participants who were PR3-ANCA positive had fewer flares (8 of 59 [14%] versus 20 of 62 [32%]; P = 0.02) (125).

For patients who fail to achieve remission and have persistent low activity, adjunctive therapy with intravenous immunoglobulin may help patients achieve remission (126-128). Prior to therapy, serum immunoglobulin levels must be measured because patients with selective IgA deficiency may develop an anaphylactic reaction on receiving intravenous immunoglobulin (IVIG) or a preexisting hyperglobulinemia may become aggravated leading to a hyperviscosity state.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2020) am 13.10.2020

#	Suchfrage
1	MeSH descriptor: [Granulomatosis with Polyangiitis] explode all trees
2	MeSH descriptor: [Churg-Strauss Syndrome] explode all trees
3	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] this term only
4	MeSH descriptor: [Systemic Vasculitis] this term only
5	((eosinophil* OR granulomato*) AND (polyangiiti* OR vasculiti*)):ti,ab,kw
6	(Wegener* OR Churg* OR EGPA):ti,ab,kw
7	(allergic AND (angiiti* OR granulomato*)):ti,ab,kw
8	((ANCA OR (pauci NEXT immune)) AND vasculiti*):ti,ab,kw
9	(systemic NEAR/5 vasculiti*):ti,ab,kw
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	#10 with Cochrane Library publication date from Oct 2015 to present

Systematic Reviews in Medline (PubMed) am 13.10.2020

#	Suchfrage
1	“Granulomatosis with Polyangiitis”[MeSH Terms]
2	“Churg-Strauss Syndrome”[MeSH Terms]
3	Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis[Mesh:NoExp]
4	Systemic Vasculitis[Mesh:NoExp]
5	(eosinophil*[Title/Abstract] OR granulomato*[Title/Abstract]) AND (polyangiiti*[Title/Abstract] OR vasculiti*[Title/Abstract])
6	Wegener*[Title/Abstract] OR Churg*[Title/Abstract] OR EGPA[Title/Abstract]
7	allergic[Title/Abstract] AND (angiiti*[Title/Abstract] OR granulomato*[Title/Abstract])
8	(ANCA[Title/Abstract] OR pauci-immune[Title/Abstract]) AND vasculiti*[Title/Abstract]
9	systemic[Title] AND vasculiti*[Title]
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	(#10) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR

	search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
12	(#11) AND ("2015/10/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 13.10.2020

#	**Suchfrage**
1	“Granulomatosis with Polyangiitis”[MeSH Terms]
2	“Churg-Strauss Syndrome”[MeSH Terms]
3	Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis[Mesh:NoExp]
4	Systemic Vasculitis[Mesh:NoExp]
5	(eosinophil*[Title/Abstract] OR granulomato*[Title/Abstract]) AND (polyangiiti*[Title/Abstract] OR vasculiti*[Title/Abstract])
6	Wegener*[Title/Abstract] OR Churg*[Title/Abstract] OR EGPA[Title/Abstract]
7	allergic[Title/Abstract] AND (angiiti*[Title/Abstract] OR granulomato*[Title/Abstract])
8	(ANCA[Title/Abstract] OR pauci-immune[Title/Abstract]) AND vasculiti*[Title/Abstract]
9	systemic[Title] AND vasculiti*[Title]
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	(#10) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
12	(#11) AND ("2015/10/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT (retracted publication [pt] OR retraction of publication [pt])

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2020-B-287

Kontaktdaten

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Indikation gemäß Beratungsantrag

Add-on-Therapie für Patienten ab 6 Jahren mit Eosinophiler Granulomatose mit Polyangiitis (EGPA)

1. Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei einer Add-on-Therapie für Patienten ab 6 Jahren mit Eosinophiler Granulomatose mit Polyangiitis (EGPA)? Wie sieht die Versorgungspraxis in Deutschland aus?

Definition der EGPA: Die Eosinophile Granulomatose mit Polyangiitis (EGPA) ist gemäss der Chapel-Hill Konsensuskonferenz zur Nomenklatur der Vaskulitiden definiert als eine Systemerkankung mit eosinophilenreicher und nekrotisierender granulomatöser Entzündung, die häufig die Atemwege betrifft und als nekrotisierende Vaskulitis, die prädominant kleine bis mittelgroße Gefäße betrifft und assoziiert ist mit Asthma und einer Eosinophilie (1). Autoantikörper gegen neutrophile cytoplasmatische Antigene (ANCA) finden sich bei etwa 30 % aller Patienten und treten häufiger auf, wenn eine Glomerulonephritis vorhanden ist (1, 2). ANCA sind die immunserologischen Marker der Granulomatose mit Polyangiitis (GPA) und der mikroskopischen Polyangiitis (MPA) (3, 4). Diese Vaskulitiden kleiner Gefäße werden daher zusammen mit der EGPA unter dem Begriff ANCA-assoziierten Vaskulitiden (AAV) in der Chapel-Hill Nomenklatur von anderen systemischen Vaskulitiden mit prädominantem Befall kleiner Gefäße abgegrenzt (1). Die in der Vergangenheit oft verwendeten Klassifikationskriterien des American College of Rheumatologie (ACR) von 1990 (5) werden derzeit aktualisiert, sind aber noch nicht final publiziert.

Da eine systemische Vaskulitis nicht bei allen Patienten vor Beginn einer Therapie auftritt, kam in aktuellen klinischen Studien u.a. zu Mepolizumab und Benralizumab eine modifizierte Definition der EGPA zur Anwendung, welche auch Patienten mit Blut+ Organeosinophile ohne Vaskulitis inkludiert. Gemäß den in der Studie zu Mepolizumab verwendeten MIRRA-Kriterien ist die EGPA wie folgt definiert (6): Asthma + Blut-Eosinophilie von mindestens 10 % (oder mehr als 1000 Eosinophilie/cmm^2) + zwei oder mehr der folgenden Kriterien: histologischer Nachweis einer eosinophilen Vaskulitis, perivaskuläre eosinophile Infiltration oder eosinophilen-reiche granulomatöse Entzündung; Neuropathie; pulmonale Infiltrate; Sinunasale Abnormalität (Sinutisitis); Glomerulonephritis; alveoläre Hämorrhagie, palpable Purpura, ANCA-Positivität.

Wissenschaftliche Grundlage des Behandlungsstandards: Die EGPA ist mit einer Inzidenz von ca. 1 Neuerkrankungen/1 Mio. Einwohner / Jahr eine sehr seltene Erkrankung (7). Aufgrund ihrer Seltenheit liegen zur Therapie der EGPA nur wenige höherwertige prospektive Studien vor, die teils auch Patienten mit anderen Vaskulitisformen wie der MPA oder Polyarteriitis nodosa (PAN) enthielten. In Deutschland ist derzeit lediglich Prednisolon zur Therapie der EGPA formal zugelassen. Für Cyclophosphamid liegt eine Zulassung zur Therapie „systemischer Vaskulitiden“ vor, was die EGPA aber einschließt. Bei allen anderen in der Folge beschriebenen Therapieverfahren handelt es sich somit formal um off-Label-Therapien. Der Bedarf an wirksamen und zugelassenen Therapieverfahren für die EGPA ist daher hoch.

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Die aktuell gültigen Prinzipien der Therapie der EGPA unterscheiden sich nur in einigen Details von dem Vorgehen bei der GPA und MPA. Die nationalen Empfehlungen zur Therapie der EGPA sind daher in den Ende 2017 publizierten ersten *Leitlinie zu Diagnose und Therapie der AAV* gemeinsam mit den Empfehlungen zur MPA und GPA enthalten (8). Die systematische Literatursuche zur S1-Leitlinie der Deutschen Gesellschaft für Rheumatologie (DGRh) umfasste einen Zeitraum bis März 2016. Die Empfehlungen der European League against Rheumatism (EULAR), der British Society of Rheumatology (BSR) und des Canadian Vasculitis Research Network (CanVasc) basieren ebenfalls auf einer mehr als 3 Jahre alten Datenbasis (9-12). Nach März 2016 publizierte Studiendaten zur EGPA die ein Abweichen von den Empfehlungen der deutschen S1-Leitlinie begründen und ein Neubewertung der Leitlinienempfehlungen im Falle einer zukünftigen Überarbeitung erwarten lassen (13) werden im folgenden Text gesondert kommentiert.

Kategorisierung und Therapiestratifizierung nach Krankheitsschwere: Die Behandlung der AAV im Allgemeinen und der EGPA im Spezielle richtet sich wesentlich nach der Krankheitsschwere und -ausdehnung sowie dem Therapiestadium (aktive Erkrankung vs. Rezidiv). Patienten mit aktiver EGPA (Neuerkrankung oder Rezidiv) sollten bezüglich ihrer Krankheitsschwere kategorisiert werden . Dabei werden Patienten mit schwerem Organbefall bzw. drohendem Organverlust (z.B. kardiale Beteiligung) von Patienten mit fehlender Bedrohung der Organfunktion (z.B. Purpura, Arthritis, Episkleritis) unterschieden. In der S1-Leitlinie (8) wird die Verwendung der EUVAS/EULAR-Einteilung in 5 Krankheitsstadien (lokalisiert, frühsystemisch, generalisiert, schwer, refraktär) empfohlen (14), da viele der relevanten Studien in Europa unter Verwendung dieser Einteilung durchgeführt wurden. In aktuellen Studien kommt häufig auch eine vereinfachtere Einteilung (Lebens-/Organbedrohlich versus nicht Lebens-/Organbedrohlich) zur Anwendung. Bei Erstdiagnose und auch im weiteren Krankheitsverlauf sollten aktive Krankheitsmanifestationen sowie Endorganschäden als Folge der AAV oder deren Therapie systematisch erfasst werden. Zu diesem Zweck stehen als validierte Instrumente der Birmingham Vasculitis Activity Score (BVAS) und der Vasculitis Damage Index (VDI) zur Verfügung (15). Spezielle für die EGPA ist zudem der Five-Factor Score etabliert, der fünf prognostisch relevante Faktoren umfasst (16, 17). Bei einem FFS von 1 oder mehr ist die Mortalität erhöht, es besteht somit eine potentiell organ- oder lebensbedrohliche Manifestation und somit eine Indikation für ein aggressiveres therapeutisches Vorgehen (18-20).

Therapie

Therapiestrategie: Bei aktiver Erkrankung (Neuerkrankung oder Rezidiv) erfolgt eine in der Regel intensivere immunsuppressive Therapie (**Remissionsinduktion**, s.u.). Da es auch nach erfolgreicher remissionsinduzierender Therapie nach Beendigung dieser Therapie häufig zu Rezidiven kommt (20) schießt sich an die remissionsinduzierende Therapie in der Regel eine weniger aggressive immunsuppressive Therapie an (**Remissionserhaltung**, s,.u.) (8).

Remissionsinduktion

Add-On-Therapie zur Remissionsinduktion bei potentiell organ- oder lebensbedrohliche Manifestationen:

Therapie der ersten Wahl: Die Standardtherapie zur Remissionsinduktion einer AAV mit potentiell Organ- oder lebensbedrohlicher Manifestation besteht in einer Kombination aus hochdosierten Glukokortikoiden (GC) und einer add-on-Gabe von Cyclophosphamid (CYC) (8, 9, 21, 22).

Glukokortikoide (GC): Im Rahmen der Remissionsinduktion wird die GC Therapie in der Regel mit einer Dosis von 1 mg/kg (maximal 80 mg/Tag) begonnen (8, 23, 24). Bei kritischem Organbefall empfehlen die DGRh und CANVASC Leitlinien (8, 11) die Gabe von Methylprednisolon (250 bis 1000 mg über 3 Tage). In den ersten größeren multizentrischen AAV-Studien wurden die GC eher langsam auf eine Dosis um 15

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mg nach 3 Monaten reduziert (25, 26). In diesen Kohorten stellten dann aber auch Infektionen die häufigste Todesursache in den ersten 12 Monaten der Behandlung dar (27), was sicherlich auch wesentlich durch die hohen GC-Dosierungen bedingt sein dürfte. EULAR und DGRh empfehlen daher heute Zieldosierungen im Bereich der Cushing-Schwellendosis nach 3 Monaten.

CYC: Die Empfehlungen zum Einsatz von CYC als first-Line add-on-Therapie bei der EGPA mit schlechter Prognose leiten sich aus prospektiven Studien der französischen Vaskulitistudiengruppe ab (28-30). In einer prospektiven multizentrischen Studie führte die Gabe von 12 CYC Pulsen zu signifikant weniger Rezidiven als die Gabe von 6 Pulsen (28). Head-to-Head-Studien von CYC im Vergleich zu einer GC-Monotherapie oder anderen add-on-Therapie liegen für die EGPA mit schlechter Prognose nicht vor. Gemäß den Empfehlungen von EULAR/ERA, DGRh und BSR wird CYC in Europa als intravenöse Pulstherapie nach dem CYCLOPS-Protokoll verabreicht, da diese im Vergleich zur vergleichbar wirksamen oralen Dauertherapie eine 50 % geringere kumulative CYC-Dosis benötigt (31), was im Hinblick auf potentielle CYC-induzierte Langzeitschäden vorteilhaft erscheint. Um das Risiko von Langzeitschäden zu begrenzen sollte die kumulative CYC-Dosis möglichst niedrig gehalten werden. Eine valide Datenbasis zur Empfehlung einer maximalen kumulativen Dosis existiert nicht. BSR und CANVASC nennen eine Höchstmenge von 25 g CYC kumulativ die nicht überschritten werden sollte (10, 11). Zur Induktionstherapie mit Rituximab ist in Deutschland das sogenannte „Lymphomschema“ (375 mg/m^2 Woche 0,1,2,3) zugelassen.

Alternativtherapien: Während zur Therapie der MPA und EGPA auch Rituximab (RTX) zugelassen ist, liegen Ergebnisse aus prospektiven kontrollierten Studien zur Therapie der EGPA mit RTX noch nicht vor. Daten aus retrospektiven Kohortenstudien bzw. Fallserien zeigen jedoch Hinweise auf eine mögliche Wirksamkeit von RTX auch bei der EGPA, insbesondere bei MPO-ANCA-positiven Patienten (32, 33). Eine Add-on-Therapie mit Plasmapheresen zeigten in einer prospektiven Therapiestudie bei Patienten mit EGPA oder PAN und ungünstigen Prognosefaktoren keinen Vorteil im Vergleich zu einer alleinigen Therapie mit CYC und GC (30).

Add-On-Therapie zur Remissionsinduktion bei Patienten ohne Organ- oder Lebensbedrohliche Manifestationen

Bei EGPA-Patienten ohne Organ- oder Lebensbedrohliche Manifestationen kann in der Regel durch eine Gabe mittel- hochdosierter Glukokortikoide eine Remission induziert werden. Allerdings kommt es nach Reduktion der Glukokortikoiddosis im Verlauf der Erkrankung gehäuft zu Rezidiven (29, 34, 35). Die deutsche S1-Leitlinie empfiehlt daher basierend auf Ergebnissen von Kohortenstudien (35, 36), daß bei der EGPA bei fehlender gravierender Organbeteiligung und unzureichendem Ansprechen auf eine alleinige GC Therapie zusätzlich Azathioprin oder **Methotrexat** zur Remissionsinduktion eingesetzt werden sollten (8). Nach Veröffentlichung der S1-Leitlinie publizierte Ergebnisse einer prospektiven Placebo-kontrollierten Studie an 55 EGPA Patienten ohne ungünstige prognostische Faktoren (FFS=0) zeigten allerdings, dass eine Therapie mit **Azathioprin** zusätzlich zu Glukokortikoiden im Vergleich zu einer Glukokortikoidmonotherapie keinen Einfluss auf das Rezidivrisiko, den kumulativen Glukokortikoidbedarf und die Rate von Asthma- und Siniusitisexazerbationen hat (37). Aktuelle Studienergebnisse zeigen zudem, dass unter einer Kombinationstherapie mit Azathioprin und Glukokortikoiden innerhalb von 5 Jahren 43 % aller Patienten ein Rezidiv erleiden (38). Zum Einsatz von Methotrexat oder anderen mittelpotenten Immunsuppressiva wie Mycophenolat-Mofetil oder Leflunomid bei der EGPA liegen keine kontrollierten Studien vor. Zusammenfassend ist die Evidenz für eine add-on-Therapie bei ohne Organ- oder Lebensbedrohliche Manifestationen unklar bzw. negativ (Azathioprin).

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Add-On-Therapie zur Induktionstherapie bei refraktärer Erkrankung

Mit den aktuell empfohlenen Induktionstherapieprotokollen kann bei Patienten mit einer EGPA in der Regel nach spätestens 3 Monaten eine Remission und eine Absenkung der GC-Dosis in den Zielbereich erreicht werden. Im Falle einer anhaltenden Symptomatik unter Standardtherapie sollte daher zunächst geprüft werden, ob tatsächlich eine refraktäre Therapiesituation vorliegt. Im Konsens empfehlen daher die aktuellen Leitlinien, Patienten mit vermeintlich refraktärer Erkrankung in Vaskulitis-Expertenzentren zu behandeln um sicher zu stellen, dass nicht terminale Endorganschäden oder Therapiekomplikationen wie opportunistische Infektionen als vermeintlich refraktäre Erkrankung fehlinterpretiert werden (8, 9). Eine Standardtherapie für tatsächlich refraktäre Fälle ist nicht definiert, die Behandlung wird individuell durch das Vaskulitis-erfahrene Zentrum festgelegt. In retrospektiven Fallserien und kleinen Kohortenstudien wurde bei EGPA-Patienten mit refraktärem Verlauf oder Rezidiv durch eine add-on-Therapie mit Interferon-alpha oder Rituximab eine Remission und eine Absenkung des Glukokortikoidbedarfs berichtet (39). Unter fortgesetzter Therapie mit **Interferon-Alpha** kommt es im weiteren Verlauf häufiger zur Rezidiven (39). Zudem schränken die schlechte Verträglichkeit (39) und fehlende Zulassung den Einsatz der Substanz ein. Eine add-on-Therapie mit **Rituximab** führt bei der Mehrzahl der EGPA-Patienten mit refraktärer oder rezidivierender zu einem Rückgang der entzündlichen Aktivität, die größere Subgruppe der ANCA-negativen EGPA-Patienten scheint aber deutlich schlechter anzusprechen (32, 33). In einer retrospektiven Untersuchung mehrerer europäischer Zentren wurde bei 63 von 147 erfassten Patienten mit Rezidiv oder refraktärem Verlauf einer EGPA Rituximab als off-label-Therapie eingesetzt (40). Unter Therapie mit Rituximab erreichten 40 % der Patienten eine Remission und 24 % eine Teilremission. Bei weiteren 24 % zeigte sich kein Therapieansprechen, 3 % brachen die Therapie aufgrund von Nebenwirkungen ab (40).

Mepolizumab ist ein monoklonaler Antikörper gegen Interleukin-5 (IL-5), der seit dem Jahr 2017 in einer dosis von 100 mg alle 4 Wochen s.c. zur Therapie des eosinophilen Asthma bronchiale zugelassenen ist. Die Wirksamkeit von Mepolizumab bei Patienten mit rezidivierender EGPA und erhöhtem GC-Bedarf wurde in 2 offenen einarmigen Pilotstudien und einer multizentrischen Phase-III-Studie untersucht (6, 41). In die randomisierte doppel-blinde Placebo-kontrollierte Phase-III-Studie wurden 126 Patienten mit Rezidiv oder refraktärem Verlauf einer EGPA (Diagnose nach den o.g. MIRRA-Kriterien) mit einer Krankheitsdauer von mindestens 6 Monaten und einer Prednisolondosis zwischen 7.5 und 50 mg pro Tag eingeschlossen. Die Patienten wurden 1:1 randomisiert: Fortsetzung der Standardtherapie oder Standardtherapie + Mepolizumab einer im Vergleich zur Asthmatherapie 3-fach höheren Dosis von 300 mg alle 4 Wochen s.c.. Die Prednisolondosis blieb 4 Wochen stabil und wurde dann sofern möglich reduziert. Co-primäre Endpunkte waren die Zahl der Wochen in Remission unter einer auf 4 mg reduzierten Prednisolondosis und der Anteil der Patienten in Remission in Woche 36 und 48. Die beiden co-primären Endpunkte der Studie wurden erreicht. Nur 3 % der Patienten im Placebo-Arm im Vergleich zu 28 % der Patienten im Mepolizumab-Arm erreichten eine für mindestens 24 Wochen stabile Remission (Odds Ratio 5.91; 95 % Konfidenzintervall 2.68-13.03; P>0.001). Zudem waren im Mepolizumab-Arm mehr Patienten in Woche 36 und 48 in Remission als im Placebo-Arm (32 % vs. 3 %; P<0.001). Der Unterschied blieb auch bei Anwendung der weniger stringenten EULAR-Remissionskriterien (BVAS=0, Prednisolon $\leq$ 7.5 mg statt 4 mg) bestehen (32 % vs. 9 %). Die Rezidivrate pro Jahr war mit 2.27 im Placebo-Arm doppelt so hoch wie im Mepolizumab-Arm (P<0.001). Auch die Rate schwere Rezidive war im Mepolizumab-Arm um 44 % reduziert (0.12 vs. 0.21). Vaskulitisrezidive traten bei unter Placebo (65 %)

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häufiger auf als unter Mepolizumab (43 %). Reine Vaskulitisrezidive traten aber seltener als reine Asthma- oder Sinusitis-Rezidive oder kombinierte Rezidive auf. Die durchschnittliche GC-Dosis lag in den letzten 4 Wochen der Studie im Mepolizumab-Arm signifikant unter der im Placebo-Arm (Odds-Ratio 0.2, P<0.001). Die mittlere Höhe der GC-Dosis während der gesamten Studie lag bei 9.5 mg im Mepolizumab-Arm und 13.5 mg im Placebo-Arm. Eine Zulassung von Mepolizumab zur Therapie der EGPA liegt in Deutschland nicht vor. Eine aktuelle retrospektive Befragung mehrerer europäischer Zentren ergab, dass bei 51 von 147 erfassten Patienten mit Rezidiv oder refraktärem Verlauf einer EGPA Mepolizumab als off-label-Therapie eingesetzt wurde (40). Die Remissionsraten nach 12 Monaten lagen bei 76 bzw. 82 % für die Dosierungen zu 100 mg bzw. 300 pro Monat.

Remissionserhaltende Therapie

Die Leitlinien der EULAR, DGRh, BSR und CANVASC empfehlen einheitlich, daß nach Erreichen einer Remission (Fehlen einer entzündlichen Aktivität der AAV) (14) und Erreichen einer GC-Dosis von 7.5-10 mg pro Tag eine mittelpotente immunsuppressive Therapie zur Remissionserhaltung über mindestens 18 bis 24 Monate durchgeführt werden sollte. Ergebnisse einer prospektiven Placebo-kontrollierten Studie an 55 EGPA Patienten ohne ungünstige prognostische Faktoren (FFS=0) zeigten, dass eine Therapie mit Azathioprin zusätzlich zu Glukokortikoiden im Vergleich zu einer Glukokortikoidmonotherapie keinen Einfluss auf das Rezidivrisiko, den kumulativen Glukokortikoidbedarf und die Rate von Asthma- und Sinusitisexazerbationen hat (37). Zu anderen Immunsuppressiva oder Biologika liegen keine Ergebnisse aus prospektiven Placebo-kontrollierten Studien zu einer add-on-Erhaltungstherapie vor.

2. Wie sieht die Versorgungspraxis in Deutschland aus?

Die EGPA ist mit einer Inzidenz von ca. 1 Neuerkrankungen/1 Mio. Einwohner / Jahr eine sehr seltene Erkrankung (7). Valide Zahlen zur Versorgungspraxis der EGPA in Deutschland liegen derzeit noch nicht vor. Ende 2019 wurde ein multizentrisches Register (GEVAS) für Patienten mit Vaskulitiden im deutschsprachigen Raum ins Leben gerufen. Im GEVAS-Register werden u.a. Versorgungsdaten von systemischen Vaskulitiden (inkl. der GPA und GPA) prospektiv erhoben und analysiert. Derzeit rekrutieren 7 Zentren (Lübeck, Dresden, Hamburg-Struenseehaus, Tübingen, Kirchheim-Teck, Mainz, Heidelberg) aktiv in das Register, der Einschluss weiterer Zentren ist in Vorbereitung. Erste Ergebnisse werden in 2021 erwartet.

3. Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von für Patienten ab 6 Jahren mit Eosinophiler Granulomatose mit Polyangiitis (EGPA) die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Im Kindes- und Jugendalter sind ANCA-assoziierte Vaskulitiden eine Rarität. Die Eosinophile Granulomatose mit Polyangiitis (EGPA) ist mit einer Prävalenz von 0,4/Mio {Hirano, 2019 #8} die seltenste Unterform der AAV in dieser Altersgruppe. Diagnostik und Therapieplanung erfordern Erfahrung, die nur in

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Indikation gemäß Beratungsantrag

Add-on-Therapie für Patienten ab 6 Jahren mit Eosinophiler Granulomatose mit Polyangiitis (EGPA)

einigen kinderrheumatologischen Zentren vorliegt. Die **Diagnose einer kindlichen EGPA (cEGPA) erfolgt nach den Kriterien der EULAR/PRINTO/PRES** (European League Against Rheumatism, Pediatric Rheumatology International Trial Organisation, Pediatric Rheumatology European Society {Ozen, 2010 #72}). Kindliche Manifestationen einer AAV unterscheiden sich von denen adulter AAVs in einigen Merkmalen deutlich {Iudici, 2018 #16}. Die cEGPA zeigt typischerweise ein relativ langes Prodromalstadium mit Asthma bronchiale, allergischer Rhinitis und nasaler Polyposis. Akut manifestiert sich die Erkrankung dann mit der typischen Eosinophilie im Blutbild, pulmonalen Infiltraten und Zeichen einer systemischen Vaskulitis. Die cEGPA hat vor allem kutane, neurologische, kardiale und gastrointestinale extrapulmonale Manifestationen. Die Nieren sind bei der cEGPA extrem selten miteinbezogen {Fina, 2018 #386;Gendelman, 2013 #417;Zwerina, 2009 #453}. Ein möglicher Zusammenhang des Auftretens einer cEGPA mit der Verwendung von Antileukotrien-Medikamenten ist nicht abschließend geklärt {Calapai, 2014 #404;Scadding, 2010 #436}

Zur Aktivitätsmessung wird der **Paediatric Vasculitis Activity Score (PVAS)** {Morishita, 2012 #121} mit einem Umfang von 0-63 Punkten (online Version mit Anleitung zur Anwendung unter http://www.mypan.org.uk/PVAS%20for%20MYPAN%20training%20presentation.pdf) empfohlen. Der PVAS umfasst 9 Organsysteme, erhoben werden müssen hierzu neben anamnestischen und klinischen Parametern auch der Gewichtsverlauf, Temperatur, RR und Pulse an allen 4 Extremitäten, Nierenfunktionsparameter, Urin- und Stuhldiagnostik, die Miteinbeziehung der Fachbereiche Augen, HNO, Pulmonologie, ggf. Neurologie, Bildgebung Lunge, Herz, ggf. HNO und ggf. die Durchführung einer Lungenbiopsie.

Aufgrund der Seltenheit der Erkrankungen im Kindes- und Jugendalter stehen keine Daten aus hochwertigen randomisierten und kontrollierten Therapiestudien zur Verfügung {Lee, 2019 #7}. Die Therapiestrategien orientieren sich daher an denen des Erwachsenenalters. So erfolgt zunächst eine intensive Induktionstherapie mit nachfolgender Erhaltungstherapie. Die Therapie findet daher nahezu ausschließlich als individuelle **„off-label“ Therapie** statt. Bei der Therapiewahl sind das Alter, der Entwicklungsstand und das Geschlecht des Patienten, die Therapiephase (Induktionstherapie vs. Erhaltungstherapie), die Krankheitsschwere (Lebens-/organbedrohlich vs. nicht Lebens-/organbedrohlich), der Therapieverlauf (Rezidive, Komplikationen der Therapie, Langzeitschäden) und Komorbiditäten (als Kontraindikation für bestimmte Therapieverfahren) zu berücksichtigen. Mit Ausnahme von Glucocorticoiden ist kein Medikament für die Therapie einer cEGPA im Kindesalter zugelassen. Glucocorticoide werden als Langzeittherapie bei nichtbedrohlichen Verläufen systemisch und inhalativ eingesetzt {Lee, 2019 #7;Yano, 2015 #406}. CYC wird in der Induktionstherapie der cEGPA bei schweren Verläufen empfohlen {Jariwala, 2020 #3}. Azathioprin (AZA) kann die Induktion einer Remission durch CYC additiv unterstützen (42). Hierzu liegen jedoch keine Daten bei Kindern vor. Die Rolle von Rituximab (RTX) in der Induktionstherapie bei der cEGPA ist unzureichend untersucht (43). In der Erhaltungstherapie wird der Einsatz von AZA favorisiert (44), obwohl hierfür keine evidentbasierten Studien vorliegen. Der erfolgreiche Einsatz von Mepolizumab wurde bislang bei der cEGPA nur in Einzelfällen berichtet (45, 46). Eine S1-Leitlinie zur Therapie kindlicher Vaskulitiden steht kurz vor der Einreichung bei der AWMF (Brunner J. et al., Manuskript in Vorbereitung). Zur Einschätzung der Krankheitsfolgen wird der **Paediatric Vasculitis Damage index (PVDI)** empfohlen (47).

Die zur Diagnostik und Therapie einer cEGPA notwendige interdisziplinäre Betreuungsstruktur unter Koordination eines Kinderrheumatologen ist bislang nur an wenigen Zentren möglich. Die Seltenheit der Erkrankung macht Zulassungsstudien in dieser Altersgruppe praktisch unmöglich. Die Übernahme extrapolierter Therapiestrategien aus dem Erwachsenenalter sollte jedoch in Registerstrukturen

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dokumentiert werden. Die strukturierte **Transition** der jungen Erwachsenen in Richtung Erwaschenenrheumatologie ist bei dieser lebenslangem Erkrankung besonders wichtig.

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