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

Supplementary File

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METHODS

The recommendations were drafted according to the 2014 update of the EULAR standardised operating procedures (SOPs) for the development of EULAR-endorsed recommendations[7] and the updated version of the Appraisal of Guidelines for Research & Evaluation (AGREE II) instrument,[8] where applicable.

Task Force & Steering Committee

After approval by the EULAR Executive Committee, the Convenor (BH) and the methodologist (RL) assembled a task force including 27 members. The task force consisted of 20 clinical experts including rheumatologists (MC, BH, JH, OK, RL, AJM, CM, JM, PM, GT, DV), internists (AM,DB, BT) and nephrologists (AK, ML, MS, OT, AV, DJ), from 15 European countries, and the USA (PM), two methodologists (RL; GT), convenor (BH) and co-convenor (DJ), two delegates of the EULAR young rheumatologists' network EMEUNET (AB, SM), two fellows (BA, JS), one health professional (NH) and two patient representatives (PV, FPK). All task force members disclosed their potential conflicts of interest to the EULAR executive committee before the start of the project.

Systematic Literature Research

Research questions were defined by a 3-step Delphi via email. First, the steering committee reviewed the topics of the 2016 update released call among the task force members asking for proposal for new topics. Then, proposed topics were grouped and the task force was asked to rank the importance of topics. Based on this ranking, the SC selected the topics with highest priority and formulated 14 research questions according to PICO format (Population, Intervention, Control, Outcome) which are displayed in **Table S3**.

The SLRs obtained for the 2016 update[6] served as a starting point and a systematic analysis of the literature published between February 1st 2015 and February 2022 was performed. For new domains and drugs not included in last update the search was unrestricted. The SLR was restricted to English language articles and focused on randomized controlled clinical trials (RCTs) and observational studies with < 50 patients for GPA/MPA and < 20 for EGPA that included a control group. Recent congress abstracts of RCTs were also included (ACR/EULAR/Intl. Vasculitis Workshop). The following databases were used: PubMed, EMBASE and Cochrane Library.

Summary of findings tables (SoF) were created. Risk of bias (RoB) in individual studies was systematically assessed at study level using the Cochrane revised tool for assessing risk of bias for RCTs (RoB2), the ROBINS-1 tool for observational studies, QUADAS II for studies on accuracy of diagnostic tests and AMSTAR II for meta-analyses. As per EULAR SOP, each article was assigned a level of evidence (LoE) according to the standards of the Oxford Centre for Evidence-Based Medicine (2009).[7] The assessment was done independently by the two fellows. Differing assessments were discussed until consensus was reached. Detailed methods and results of the SLR are published separately.[9, 10] The steering committee discussed the results of the SLRs thoroughly and formulated proposals for an update of the recommendations based on this information.

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Consensus finding

During a face-to-face meeting, the SoF-tables derived from the SLRs were presented and formed the basis for the generation of the recommendations. After discussion, task force members independently voted on each recommendation. Only the recommendations (**Table 3**) were formally voted on during the face-to-face meeting, but not the subsequent paragraphs. For a change of an existing overarching principle or recommendation or a new overarching principle or recommendation to be accepted for the final document, a majority of ≥75% of the votes was required in the first ballot, which was achieved for all recommendations. After the meeting, participants were asked via email to anonymously report their level of agreement on each recommendation and on the overarching principles on a scale of 0-10 (10 meaning full agreement, 0 meaning no agreement whatsoever); the mean values of these votes are presented (**Table 3**). During the meeting, notes were taken that captured the contents of the discussions and the reasoning behind each decision and these are presented in the comments accompanying the individual overarching principles and recommendations. A research agenda was formulated from the gaps in the evidence and any controversial issues (**Table 5**). We submitted the manuscript to the EULAR Executive Committee for review and approval.

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Supplementary Table S1. Protocols for treatment of granulomatosis with polyangiitis and microscopic polyangiitis

Protocol	Disease and activity stage	Dosing	Level of evidence[+]	References
Cyclophosphamide-Pulse* (CYCLOPS)	Life-/organ-threatening; remission induction	15 mg/kg** intravenously weeks 0, 2 and 4, then every 3 weeks until remission; maximum of 10 pulses	I-b	224
Rituximab* (RAVE)	Life-/organ-threatening; remission induction	375 mg/m^2 intravenously weeks 0, 1, 2, 3	I-b	81
Rituximab*,#	Life-/organ-threatening; remission induction	1000 mg intravenously days 1 and 15	4	92
Rituximab (MAINRITSAN)	Remission maintenance	500 mg intravenously every 6 months for 18-36 months	I-b	136 138 139
Rituximab# (RITAZAREM)	Remission maintenance	1000 mg intravenously every 4 months	1-b	137
Methotrexate#	Not life-/organ-threatening for remission induction*,& and all severity stages for maintenance	15-25 mg once weekly orally or sub-cutaneously	1b	106 147 148
Mycophenolate Mofetil*,#	Not life-/organ-threatening for remission induction* and all severity stages for maintenance	2000-3000 mg/day (remission induction); 2000 mg/day (remission maintenance)	1-b	21 149
Azathioprine	maintenance (all severity stages)	2 mg/kg/day; maximum of 200 mg/day	1-b	136 147 228
Leflunomide#	maintenance (all severity stages), GPA only	20-(30) mg/day	1-b	148
Intravenous immunoglobulins#	Refractory disease	Single course (2 grams/kg) added to standard induction therapy	1-b	135

* Plus prednisolone, for details on dosing see Table no. 4, avacopan 30 mg twice daily can be used as an alternative to prednisolone (see Statement No. 5);

** Maximum dose per pulse is 1200 mg, reduce dose in case of impaired kidney function and age > 65 years (see www.euvas.org for details) and daily oral treatment (2 mg/kg) can be considered as an alternative if intravenous pulse therapy is not feasible (see www.euvas.org for details);

Not formally approved for use in AAV in the European Union;

& GPA only

+ Based on studies with the highest level of evidence according to EULAR standard operating procedures for EULAR recommendations.[7]

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Supplementary Table S2. Protocols for treatment of eosinophilic granulomatosis with polyangiitis

Protocol	Disease and activity stage	Dosing	Level of evidence[+]	References
Cyclophosphamide-Pulse*,#	Life-/organ-threatening (FFS≥1); remission induction	600 mg/m^2 days 1, 15 and 29, then 500 mg on days 50, 71, 92, 113, 134, and 155	2-b	77
Rituximab*,#	Life-/organ-threatening (FFS≥1); remission induction	1 g days 1 and 15	2-b	77
Mepolizumab*	No active life-/organ-threatening manifestation (FFS=0)+ relapsing or refractory disease; remission induction and maintenance	300 mg every 4 weeks s.c.	I-b; 4**	78
Azathioprine*,§	Not life-/organ-threatening (FFS=0) for remission induction and all severity stages for maintenance	2 mg/kg/day, maximum 200 mg/day)	2-b§ (for lack of efficacy)	173 184
Methotrexate*,#	Not life-/organ-threatening (FFS=0) for remission induction and all severity stages for maintenance	15-25 mg once weekly orally or sub-cutaneously	2b	186,189
Mycophenolate Mofetil*,#	Not life-/organ-threatening (FFS=0) for remission induction and all severity stages for maintenance)	2000-3000 mg/day	4	185
Prednisolone monotherapy	Not life-/organ-threatening (FFS=0) for remission induction and all severity stages for maintenance)	1 mg/kg/day for 3 weeks (maximum 80 mg/day), reduction by 7.5 mg every two weeks until 0.25 mg/kg/day after 3 months, then by 5 mg every 2 weeks until 10 mg/day, then by 1 mg every 3 weeks to the lowest effective dose	2-b§	173

*Prednisolone as described under prednisolone monotherapy in table, consider lower starting dose and/or faster tapering depending on individual disease severity/course; ** remission maintenance for patients after remission induction for life-/organ-threatening manifestations

Not formally approved for use in eosinophilic granulomatosis with polyangiitis in the European Union;

+ Based on studies with the highest level of evidence according to EULAR standard operating procedures for EULAR recommendations;[7]

§ randomized controlled study with heterogenous population.

FFS= Five Factor Score (age > 65 years, cardiac symptoms, gastrointestinal manifestations, chronic kidney disease defined as stable maximum serum creatinine ≥150 µmol/L are factors of bad prognosis, ear, nose, and throat manifestations is a factor of good prognosis for GPA and EGPA).

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Supplementary Table S3. Research Questions

Diagnostic testing

1. **In patients with GPA/MPA (P1) or EGPA (P2), what is the impact of a positive tissue biopsies (I) vs obtaining no biopsy/negative biopsy (C) to confirm a clinical diagnosis of AAV (0)?**

2. **In patients with GPA/MPA (P1) or EGPA (P2), what is the impact of a positive ANCA vs a negative ANCA (C) to confirm a clinical diagnosis of AAV (0)?**

Treatment: remission induction GPA/MPA

3. **In patients with *new-onset* organ-threatening or life-threatening GPA/MPA (P), what is the impact of cyclophosphamide or other immunosuppressive drugs (I) vs. comparator immunosuppressive drugs such as rituximab (C1), mycophenolate mofetil (C2) or other drugs (C3) on disease-related outcomes (O1) and treatment-related adverse events (O2)?**
   - Outcomes to consider: disease activity, disease damage, relapse, death, recovery of renal function, health-related quality of life and other patient-related outcomes, infection, malignancy including bladder cancer, serious adverse events, hypogammaglobulinemia, cytopenia, toxicity leading to discontinuation
   - Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole.

4. **In patients with *new-onset* non-organ-threatening or life-threatening GPA/MPA (P), what is the impact of cyclophosphamide (I) vs. comparator immunosuppressive drugs such as rituximab (C1), mycophenolate mofetil (C2), methotrexate (C3) or other drugs (C4) on disease-related outcomes (01) and treatment-related adverse events (O2)?**
   - Outcomes to consider: disease activity, disease damage, relapse, death, recovery of renal function, health-related quality of life and other patient-related outcomes infection, malignancy including bladder cancer, serious adverse events, hypogammaglobulinemia, toxicity leading to discontinuation
   - Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole.

5. **In patients with *relapsing* organ-threatening or life-threatening GPA/MPA (P), what is the impact of cyclophosphamide (I) vs. comparator immunosuppressive drugs such as rituximab (C1), mycophenolate mofetil (C2) or other drugs (C3,…) on disease-related outcomes (01) and treatment-related adverse events (O2)?**
   - Outcomes to consider: disease activity, disease damage, relapse, death, recovery of renal function, health-related quality of life and other patient-related outcomes infection, malignancy including bladder cancer, serious adverse events, hypogammaglobulinemia, cytopenia, toxicity leading to discontinuation

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- Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole, 15-desoxyspergualin.

6. **In patients with *relapsing* non-organ-threatening or life-threatening GPA/MPA (P), what is the impact of cyclophosphamide (I) vs. comparator immunosuppressive drugs such as rituximab (C1), mycophenolate mofetil (C2) or other drugs (C3) on disease-related outcomes (01) and treatment-related adverse events (O2)?**
   - Outcomes to consider: disease activity, disease damage, relapse, death, recovery of renal function, health-related quality of life and other patient-related outcomes infection, malignancy including bladder cancer, serious adverse events, hypogammaglobulinemia, cytopenia, toxicity leading to discontinuation
   - Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole, 15-desoxyspergualin.

7. **In patients with active GPA/MPA (P), what is the impact of using a standard glucocorticoids protocol for remission induction (I) vs control glucocorticoids protocols (e.g. faster taper vs standard taper, i.v. MP vs oral) (C) on disease-related outcomes and treatment-related adverse events (O)?**
   - Outcomes to consider: disease activity, disease damage, relapse, death, renal function, health-related quality of life and other patient-related outcomes infection, serious adverse events, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)
   - Interventions to consider: “standard taper” oral high dose GC protocol, “rapid taper/reduced dose” oral high dose GC protocol, i.v. GC pulse treatment, medium dose oral GC protocol

8. **In patients with organ-threatening or life-threatening GPA/MPA (P), what is the impact of using avacopan + cyclophosphamide/rituximab (I) vs. cyclophosphamide/rituximab + steroids alone (C) on disease-related outcomes and treatment-related adverse events (O)?**
   - Outcomes to consider: disease activity, disease damage, relapse, death, renal function, infection, health-related quality of life and other patient-related outcomes serious adverse events, toxicity leading to discontinuation (e.g., hyperglycemia, decreased bone mineral density)

9. **In patients with organ-threatening or life-threatening GPA/MPA (P), what is the impact of using plasma exchange + cyclophosphamide/rituximab + glucocorticoids (I) vs. cyclophosphamide/rituximab + glucocorticoids alone (C) on disease-related outcomes and treatment-related adverse events (O)?**
   - Outcomes to consider: disease activity, disease damage, relapse, death, renal function, infection, health-related quality of life and other patient-related outcomes, serious adverse events, toxicity leading to discontinuation

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Treatment: remission maintenance GPA/MPA

10. **In patients with GPA/MPA in remission after induction therapy (P), what is the impact of using azathioprine (I) vs. comparator immunosuppressive drugs (including MTX, rituximab and MMF)) (C) on disease-related outcomes and treatment-related adverse events (O)?**
    - Outcomes to consider: relapse (minor and major), time to first relapse, death, disease damage, renal function, infection, health-related quality of life and other patient-related outcomes, serious adverse events, toxicity leading to discontinuation, glucocorticoid use (cumulative dose)
    - Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole, 15-desoxyspergualin.

Treatment: remission induction EGPA

11. **In patients with new-onset and/or relapsing active organ-threatening or life-threatening EGPA (P), what is the impact of cyclophosphamide or other immunosuppressive drugs (I) vs. comparator immunosuppressive drugs such as rituximab (C1), or other drugs (C2) on disease-related outcomes (01) and treatment-related adverse events (O2)?**
    - Outcomes to consider: disease activity, disease damage, relapse, death, recovery of renal function, control of asthma symptoms, control of rhino-sinusitis symptoms, health-related quality of life and other patient-related outcomes, infection, malignancy including bladder cancer, cytopenia serious adverse events, hypogammaglobulinemia, toxicity leading to discontinuation
    - Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, mepolizumab, benralizumab, reslizumab, omalizumab.

12. **In patients with new-onset and/or relapsing active non-organ-threatening or life-threatening EGPA (P), what is the impact of mepolizumab or immunosuppressive drugs (I) vs. comparator immunosuppressive drugs such as rituximab or GC monotherapy (C1), or other drugs (C2) on disease-related outcomes (01) and treatment-related adverse events (O2)?**
    - Outcomes to consider: disease activity, disease damage, relapse, death, recovery of renal function, control of asthma symptoms, control of rhino-sinusitis symptoms, health-related quality of life and other patient-related outcomes, infection, malignancy including bladder cancer, serious adverse events, hypogammaglobulinemia, toxicity leading to discontinuation
    - Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, mepolizumab, benralizumab, reslizumab, omalizumab.

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Treatment: remission maintenance EGPA

13. **In patients with EGPA in remission after induction therapy (P), what is the impact of using azathioprine (I) vs. comparator immunosuppressive drugs (including MTX, mepolizumab, rituximab and MMF)) (C) on disease-related outcomes and treatment-related adverse events (O)?**
    - Outcomes to consider: relapse (minor and major), time to first relapse, death, disease damage, renal function, infection, health-related quality of life and other patient-related outcomes, serious adverse events, toxicity leading to discontinuation, glucocorticoid use (cumulative dose)
    - Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, mepolizumab, benralizumab, reslizumab, omalizumab.

Patient Follow-Up and Monitoring

14. **In patients with AAV (P), what is the impact of measurement of which clinical parameters, tests and biomarkers (I) vs. not measuring these (C) on disease-related outcomes and treatment-related adverse events (O)?**
    Outcomes to consider: relapse (minor and major), time to first relapse, death, disease damage, renal function, infection, health-related quality of life and other patient-related outcomes, serious adverse events, toxicity leading to discontinuation

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