

Supplementary file 1: Treatment SLR GPA / MPA

**Online supplementary material**

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## Supplementary file 1: Treatment SLR GPA / MPA

**1. Research questions in PICO format addressing treatment of GPA and MPA**

Fourteen research questions were developed. The PICO questions addressing treatment of GPA and MPA (#3 to #10) are addressed in this article, research questions addressing diagnostic procedures, follow-up testing, and treatment of EGPA as well as a search for areas of general management are addressed in a second SLR article.

PICO #	PICO question
	<b>Remission induction (immunosuppressive drug treatment)</b>
<b>PICO # 3</b>	<p><b>In patients with <i>new-onset</i> 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)?</b></p> <ul style="list-style-type: none"> <li>- 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</li> <li>- Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole.</li> </ul>
<b>PICO # 4</b>	<p><b>In patients with <i>new-onset non-organ-threatening</i> 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 (O1) and treatment-related adverse events (O2)?</b></p> <ul style="list-style-type: none"> <li>- 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</li> <li>- Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole.</li> </ul>
<b>PICO # 5</b>	<p><b>In patients with <i>relapsing</i> 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 (O1) and treatment-related adverse events (O2)?</b></p> <ul style="list-style-type: none"> <li>- 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</li> <li>- Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole.</li> </ul>

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<b>PICO # 6</b>	<p><b>In patients with <i>relapsing non</i>-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 (O1) and treatment-related adverse events (O2)?</b></p> <ul style="list-style-type: none"> <li>- 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</li> <li>- Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole.</li> </ul>
<b>Glucocorticoid dosing</b>	
<b>PICO # 7</b>	<p><b>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)?</b></p> <ul style="list-style-type: none"> <li>- 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)</li> <li>- 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</li> </ul>
<b>Avacopan</b>	
<b>PICO # 8</b>	<p><b>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)?</b></p> <ul style="list-style-type: none"> <li>- 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)</li> </ul>
<b>Plasma exchange</b>	
<b>PICO # 9</b>	<p><b>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)?</b></p> <ul style="list-style-type: none"> <li>- 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</li> </ul>

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	Maintenance treatment
<b>PICO # 10</b>	<p><b>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)?</b></p> <ul style="list-style-type: none"><li>- 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)</li><li>- Interventions and comparators to consider: Cyclophosphamide (oral and intravenous), Rituximab, mycophenolate mofetil, IVIG, azathioprine, methotrexate, leflunomide, belimumab, cotrimoxazole.</li></ul>

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**2. Search strategies****2.1. Search strategy treatment PubMed**

((("Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis"[Mesh]) OR („ANCA associated vasculiti\*“ [tiab]) OR ("churg-strauss" [tiab]) OR ("wegener" [tiab]) OR ((("granulomatosis"[tiab]) OR ("microscopic"[tiab])) AND ("polyangiitis"[tiab])) OR (((("ANCA"[tiab]) OR ("Antibodies, Antineutrophil Cytoplasmic"[Mesh]) OR ("antineutrophil cytoplasmic antibod\*" [tiab])) AND ("vasculitis"[tiab]) OR ("glomerulonephritis"[tiab]) OR ("renal"[tiab])))

AND

(((((("Drug Therapy"[Mesh]) OR ("therapy"[tiab]) OR ("treatment" [tiab]) OR ("Glucocorticoids" [Pharmacological Action]) OR ("Glucocorticoid" [tiab]) OR ("steroid" [tiab]) OR ("corticosteroid" [tiab]) OR ("prednisone"[tiab]) OR ("prednisolone"[tiab]) OR ("methylprednisolone"[tiab]) OR ("dexamethasone"[tiab]) OR ("Cyclophosphamide"[Mesh]) OR ("Cyclophosphamide" [tiab]) OR ("rituximab" [tiab]) OR ("methotrexate" [tiab]) OR ("azathioprine" [tiab]) OR ("immunosuppress\*" [tiab]) OR ("leflunomide" [tiab]) OR („cyclosporine“ [tiab]) OR ("Mycophenol\*" [tiab]) OR ("Trimethoprim" [tiab]) OR ("Sulfamethoxazole" [tiab]) OR ("Cotrim" [tiab]) OR ("Immunoglobulins, Intravenous"[Mesh]) OR („immunoglobulin\*" [tiab]) OR (("biologic\*" [tiab]) AND ("agent" [tiab]) OR ("therapy" [tiab]))) OR ("plasmapheresis" [Mesh]) OR ("plasmapheresis" [tiab]) OR ("plasma exchange" [tiab]) OR ("trial"[tiab]) OR ("random\*" [tiab]) OR ("Randomized Controlled Trial" [Publication Type]) OR ("Controlled Clinical Trial" [Publication Type])) AND ("2015/02/01"[Date - Publication] : "3000"[Date - Publication])) OR ((("mepolizumab" [tiab]) OR ("reslizumab" [tiab]) OR ("benralizumab" [tiab]) OR ("interleukin 5" [tiab]) OR ("omalizumab" [tiab]) OR ("avacopan" [tiab]) OR ("CCX168" [tiab]) OR ("belimumab" [tiab]) OR ("abatacept" [tiab]) OR ("Janus Kinase Inhibitors"[Mesh]) OR ("Janus kinase inhibitor\*" [tiab]) OR ("tofacitinib" [tiab]) OR ("baricitinib" [tiab]) OR ("upadacitinib" [tiab]) OR ("filgotinib" [tiab])))

NOT

("Case reports" [Publication Type])

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## 2.2. Search strategy treatment EMBASE

('ANCA associated vasculitis'/exp OR 'ANCA associated vasculiti\*':ab,ti OR 'churg-strauss':ab,ti OR wegener:ab,ti OR ((granulomatosis:ab,ti OR microscopic:ab,ti) AND polyangiitis:ab,ti) OR ((ANCA:ab,ti OR 'neutrophil cytoplasmic antibody'/exp OR 'antineutrophil cytoplasmic antibod\*':ab,ti) AND (vasculitis:ab,ti OR glomerulonephritis:ab,ti OR renal:ab,ti)))

AND

((('drug therapy'/exp OR therapy:ab,ti OR treatment:ab,ti OR 'glucocorticoid'/exp OR glucocorticoid:ab,ti OR steroid:ab,ti OR corticosteroid:ab,ti OR prednisone:ab,ti OR prednisolone:ab,ti OR methylprednisolone:ab,ti OR dexamethasone:ab,ti OR 'cyclophosphamide'/exp OR cyclophosphamide:ab,ti OR rituximab:ab,ti OR methotrexate:ab,ti OR azathioprine:ab,ti OR immunosuppress\*:ab,ti OR leflunomide:ab,ti OR cyclosporine:ab,ti OR Mycophenol\*:ab,ti OR trimethoprim:ab,ti OR Sulfamethoxazole:ab,ti OR Cotrim:ab,ti OR 'immunoglobulin'/exp OR immunoglobulin\*:ab,ti OR (biologic\*:ab,ti AND (agent:ab,ti OR therapy:ab,ti)) OR 'plasmapheresis'/exp OR plasmapheresis:ab,ti OR 'plasma exchange':ab,ti OR trial:ab,ti OR random\*:ab,ti OR 'Controlled Clinical Trial'/exp) AND [01-02-2015]/sd) OR (mepolizumab:ab,ti OR reslizumab:ab,ti OR benralizumab:ab,ti OR 'interleukin 5':ab,ti OR omalizumab:ab,ti OR avacopan:ab,ti OR CCX168:ab,ti OR belimumab:ab,ti OR abatacept:ab,ti OR 'janus kinase inhibitor'/exp OR 'janus kinase inhibitor\*':ab,ti OR tofacitinib:ab,ti OR baricitinib:ab,ti OR upadacitinib:ab,ti OR filgotinib:ab,ti))

AND

([article]/lim OR [article in press]/lim OR [review]/lim)

NOT

'case report'/exp

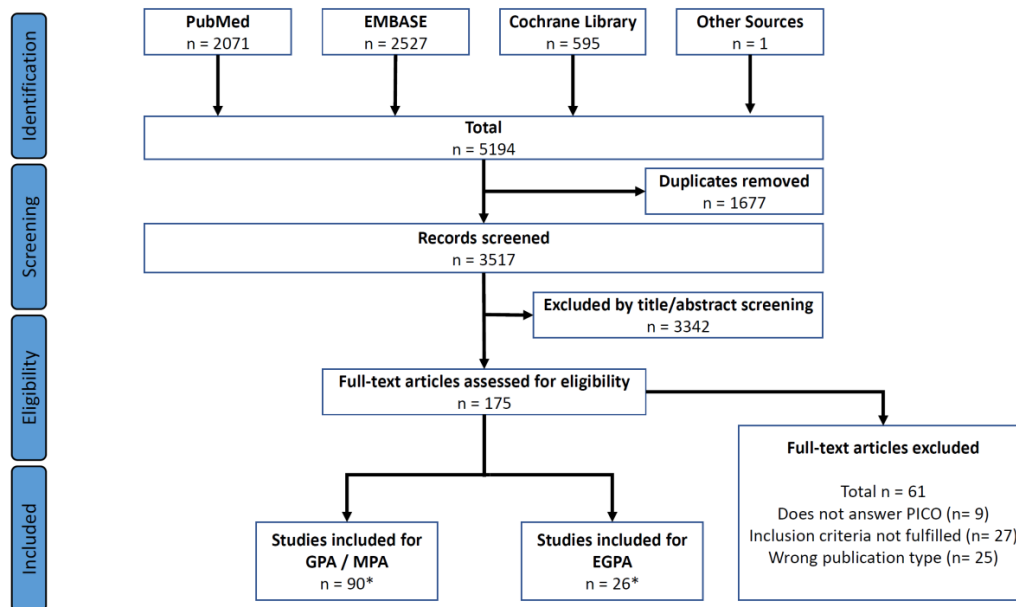
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**2.3. Search strategy treatment Cochrane Library**

ID	Search
#1	MeSH descriptor: [Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis] explode all trees
#2	(ANCA associated vasculiti* OR churg-strauss OR wegener):ti,ab,kw (Word variations have been searched)
#3	(granulomatosis OR microscopic):ti,ab,kw (Word variations have been searched)
#4	(polyangiitis):ti,ab,kw (Word variations have been searched)
#5	#3 AND #4
#6	MeSH descriptor: [Antibodies, Antineutrophil Cytoplasmic] explode all trees
#7	(antineutrophil cytoplasmic antibod* OR ANCA):ti,ab,kw (Word variations have been searched)
#8	#6 OR #7
#9	(vasculitis OR glomerulonephritis OR renal):ti,ab,kw (Word variations have been searched)
#10	#8 AND #9
#11	#1 OR #2 OR #5 OR #10
#12	MeSH descriptor: [Drug Therapy] explode all trees
#13	MeSH descriptor: [Glucocorticoids] explode all trees
#14	MeSH descriptor: [Cyclophosphamide] explode all trees
#15	MeSH descriptor: [Immunoglobulins, Intravenous] explode all trees
#16	MeSH descriptor: [Plasmapheresis] explode all trees
#17	("randomized controlled trial"):pt
#18	("controlled clinical trial"):pt
#19	(biologic):ti,ab,kw (Word variations have been searched)
#20	(agent OR therapy):ti,ab,kw (Word variations have been searched)
#21	#19 AND #20
#22	(therapy OR treatment OR Glucocorticoid OR steroid OR corticosteroid OR prednisone OR prednisolone OR methylprednisolone OR dexamethasone OR cyclophosphamide OR rituximab OR methotrexate OR azathioprine OR immunosuppress* OR leflunomide OR cyclosporine OR mycophenol* OR Trimethoprim OR Sulfamethoxazole OR Cotrim OR immunoglobulin* OR plasmapheresis OR plasma exchange OR trial OR random*):ti,ab,kw (Word variations have been searched)
#23	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #21 OR #22 with Cochrane Library publication date Between Feb 2015 and Feb 2022
#24	MeSH descriptor: [Janus Kinase Inhibitors] explode all trees
#25	(mepolizumab OR reslizumab OR benralizumab OR interleukin 5 OR omalizumab OR avacopan OR CCX168 OR belimumab OR abatacept OR Janus kinase inhibitor* OR tofacitinib OR baricitinib OR upadacitinib OR filgotinib):ti,ab,kw (Word variations have been searched)
#26	#24 OR #25
#27	#23 OR #26
#28	#11 AND #27

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## 3. PRISMA diagram



\* 2 RCTs included in both evidence syntheses