

Treatment Updates in Antineutrophil Cytoplasmic Autoantibodies (ANCA) Vasculitis

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Abstract

ANCA vasculitis is a small-vessel vasculitis (SVV) resulting in inflammation of small- and medium-sized blood vessels. Since the initial description of SVV, there have been tremendous advances in our understanding of its pathogenesis. Over the last decade, we have made significant progress in understanding the pathogenesis and improving the treatment and prognosis of patients with ANCA vasculitis. Patient and renal survival has improved, and treatment is moving toward individualizing care, minimizing severe adverse events, and preventing relapse. This review focuses on treatment updates in ANCA vasculitis, duration of therapy, and management of relapses. We also describe the existing treatment protocols used at our institution.

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Introduction

ANCA vasculitides are a group of rare disorders occurring predominantly in the sixth and seventh decades of life. ANCA vasculitides can present phenotypically as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic GPA, and renal-limited vasculitis with pauci-immune necrotizing and crescentic GN on review of the renal biopsy specimen. Serologically, patients may exhibit autoantibodies to myeloperoxidase (MPO-ANCA) or proteinase 3 (PR3-ANCA), with a small proportion remaining ANCA negative.

The estimated annual incidence of ANCA vasculitis is 10–20 per million (1). In the United States, the incidence and prevalence rate of GPA is 13 and 218 per million (2), compared with 8.6 and 95 per million in Australia (3), and 9.7 and 62.9 per million in the United Kingdom (4), respectively. Overall, the prevalence in people of European ancestry is twice as high as those of non-European ancestry (104.7 versus 52.5 per million) (5).

Geographically, GPA and PR3-ANCA are more prevalent in Northern Europe compared with Southern Europe and Asia, where MPA is more common (6). ANCA vasculitis is more common in White people. Patients who are Black are more likely to have MPO-ANCA and are younger at presentation. One study found no difference in treatment response, development of ESKD, renal relapse, and death rates between Black and White individuals (7).

Numerous factors have been implicated in the pathogenesis of ANCA vasculitis. Recent studies suggest ANCAs themselves are pathogenic, especially MPO-ANCAs (8–10). Genetic susceptibility and environmental triggers, such as silica, drug exposure, and infections, have been associated with the development

of ANCA vasculitis (11–13). Drugs commonly implicated are levamisole-adulterated cocaine, hydralazine, and propylthiouracil (14). There is potential association of minocycline, allopurinol, methimazole, penicillamine, and sulfasalazine with drug-induced vasculitis (14).

Management of ANCA vasculitis consists of remission induction, maintenance, and relapse therapy. Here we focus on these components and discuss recent treatment updates.

Induction of Remission Corticosteroids

Optimal glucocorticoid dosing and duration in ANCA vasculitis remains controversial. Traditionally, for life- or organ-threatening ANCA vasculitis, 1–3 g of intravenous (IV) methylprednisolone has been used, followed by 1 mg/kg per day oral prednisone. The Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial successfully tapered prednisone by 5 months (15), with other trials maintaining a dosage of 5 mg/d beyond 6 months (15,16).

Recent studies have focused on reducing cumulative glucocorticoid dose and other steroid-sparing therapies. The Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis (PEXIVAS) trial compared standard-dose or reduced-dose oral glucocorticoid regimens in severe ANCA vasculitis (17). At 6 months, the reduced-dose group had 60% less glucocorticoid exposure. Although both groups remained on 5 mg through week 52, reduced dosing was noninferior to standard dosing with regards to all-cause mortality and ESKD (17). Among 49 patients who received a combination cyclophosphamide-rituximab infusion, rapid glucocorticoid withdrawal (between 1 and 2

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weeks) reduced severe adverse events (SAEs) with effective remission induction compared with matched previous European Vasculitis Society (EUVAS) trials (18). Additionally, retrospective analysis of 114 patients showed no benefit of adding IV methylprednisolone, and higher incidence of diabetes and infection was noted (19). Currently, a low-dose prednisolone (0.5 mg/kg per day) versus high-dose prednisolone (1 mg/kg per day) plus rituximab trial is underway to assess its relapse and safety profile (20).

Corticosteroid-Sparing Strategies

Corticosteroid reduction may be further achieved with complement-based therapy, although these have not yet been approved. Avacopan (CCX168), an oral C5a receptor antagonist, in addition to cyclophosphamide or rituximab, successfully replaced corticosteroids in the phase 2 randomized controlled trial (RCT) CLEAR (21). Preliminary results from the ADVOCATE study show similar remission achievement in 166 patients treated with avacopan compared with 164 patients treated with glucocorticoids at 26 weeks (72% versus 70%) (22,23). Avacopan was superior to prednisone at 52 weeks in sustaining remission (23). IFX-1 (anti-C5a antibody) is currently being studied in phase 2 trials, although the steroid dose is not reduced (NCT03712345, NCT03895801).

We recommend a reduced-dose corticosteroid regimen, with tapering and discontinuation for most patients by 16 weeks.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that inhibits nuclear DNA replication, potently affecting rapidly dividing cell populations (24). Cyclophosphamide has been used for induction therapy since the first published case series in 1971 in GPA (25).

Risks of cyclophosphamide include infertility; urotoxicity, including cystitis and transitional-cell carcinoma of the bladder; hematologic toxicity; and infections (26,27). The pulse versus continuous cyclophosphamide for induction of remission (CYCLOPS) trial compared IV cyclophosphamide to daily oral cyclophosphamide with no difference in time to remission (hazard ratio [HR], 1.10; 95% CI, 0.78 to 1.55). Pulse cyclophosphamide therapy led to a lower cumulative dose (8.2 versus 15.9 g) and lower rate of leukopenia (HR, 0.41; 95% CI, 0.23 to 0.71) as compared with oral cyclophosphamide (28). In long-term follow-up of patients from CYCLOPS, Harper *et al.* (29) found a higher relapse risk with pulse cyclophosphamide, but no difference in survival and renal function. Both groups received azathioprine for maintenance, which is associated with higher relapse rates than rituximab (30). The French Vasculitis Study Group demonstrated fewer SAEs in patients ≥ 65 years with fixed, low-dose, IV cyclophosphamide compared with conventional cyclophosphamide dosing (500 mg/m² every 2–3 weeks). The overall mortality was approximately 20%, with no significant difference between the two groups (31). Older age has been associated with increased mortality (32).

We recommend using monthly IV cyclophosphamide (0.35–0.75 gm/m²) with lower dosing for patients who are older (≥ 65 years) or have markedly reduced kidney function (eGFR <30 ml/min per 1.73 m²).

Rituximab

Rituximab is an anti-CD20 chimeric mAb. A decade ago, two groundbreaking RCTs revolutionized the treatment of ANCA vasculitis (15,16). The RAVE trial found rituximab noninferior to oral cyclophosphamide for remission induction in 197 patients with newly diagnosed or flaring GPA or MPA. Rituximab was more efficacious in relapsing disease (odds ratio, 1.40; 95% CI, 1.03 to 1.91) (15). *Post hoc* analysis showed a higher complete remission rate for patients with PR3-ANCA treated with rituximab compared with cyclophosphamide at 6, 12, and 18 months (33). Although patients with serum creatinine >4 mg/dl were excluded from this study, the eGFR-based remission rates between the two groups were not different (34).

The Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis (RITUXVAS) trial compared a combination of rituximab with two IV cyclophosphamide doses against IV cyclophosphamide for 3–6 months, followed by azathioprine. As opposed to RAVE, the RITUXVAS trial did include patients with severe renal disease (median eGFR, 18 ml/min per 1.73 m²). The two groups had similar high rates of remission induction at 12 months (76% rituximab versus 82% cyclophosphamide) and SAEs (16). At 2 years, the composite outcome of death, ESKD, and relapse was similar between the two groups (35). A retrospective study of 225 patients with severe renal involvement (eGFR <30 ml/min per 1.73 m²) noted no significant difference between cyclophosphamide and rituximab for induction (36).

We advise use of rituximab over cyclophosphamide in patients ≥ 65 years who have high hematologic toxicity risk and younger patients who desire to preserve fertility. We also recommend rituximab in patients with significant past exposure to cyclophosphamide, relapsing disease, and PR3-ANCA vasculitis.

Combination of Cyclophosphamide and Rituximab

RITUXVAS paved the way for other studies that have shown success with combination cyclophosphamide and rituximab (18,37,38), allowing for rapid tapering of corticosteroids.

Combined induction with corticosteroids, rituximab, and low-dose IV cyclophosphamide was studied in a cohort of 66 patients with biopsy specimen–proven renal ANCA vasculitis (37). Compared with propensity-matched patients in EUVAS trials, 94% of patients achieved remission in 6 months. Additionally, the combination treatment had lower death rates (HR, 0.29; 95% CI, 0.125 to 0.675), progression to ESKD (HR, 0.20; 95% CI, 0.06 to 0.65), and relapse rates (HR, 0.49; 95% CI, 0.25 to 0.97) (37).

To reduce cyclophosphamide exposure, we recommend using IV cyclophosphamide and rituximab for induction in ANCA vasculitis, especially with severe renal involvement (eGFR <30 ml/min per 1.73 m² or diffuse crescentic GN) or severe pulmonary hemorrhage (requiring supplemental oxygen or mechanical ventilation). We suggest using cyclophosphamide and combination cyclophosphamide-rituximab–based regimens to help achieve earlier withdrawal of steroids.

Plasma Exchange

The role of plasma exchange (PLEX) remains uncertain in the treatment of ANCA vasculitis. The Plasma Exchange or High-Dosage Methylprednisolone (MEPEX) trial compared the addition of PLEX in 137 patients with newly diagnosed ANCA vasculitis on renal biopsy and serum creatinine >5.8 mg/dl (39). Both groups received oral corticosteroids and cyclophosphamide; one group received IV methylprednisolone and the other PLEX. Renal biopsy-specimen characteristics were similar in both groups. No difference in adverse events and survival at 1 year was observed. However, PLEX was associated with lower progression to ESKD over 12 months (HR, 0.47; 95% CI, 0.24 to 0.91) (39). A meta-analysis also showed potential reduction in the composite end point of ESKD and death in patients with ANCA vasculitis treated with PLEX (40).

Long-term follow-up of MEPEX patients showed no difference in all-cause mortality. The risk of progression to ESKD was not statistically significant, with a potential trend toward benefit (HR, 0.64; 95% CI, 0.40 to 1.05) (41). In PEXIVAS, PLEX did not reduce the primary composite outcome of all-cause mortality and ESKD (HR, 0.86; 95% CI, 0.65 to 1.13) in patients with severe ANCA vasculitis, defined as an eGFR of <50 ml/min per 1.73 m² or pulmonary hemorrhage (17). One limitation of PEXIVAS was the wide range of renal injury without a kidney biopsy to assess interstitial fibrosis and tubular atrophy. Furthermore, in subgroup analyses of patients with pulmonary hemorrhage, PLEX showed a trend for benefiting the primary composite outcome, although not statistically significant (17). PLEX may have a potential role in severe acute renal damage without chronic changes. Although another retrospective study of 251 patients showed no benefit with PLEX (36), the updated American Society of Apheresis guidelines still support the use of PLEX in a subset of patients with severe acute kidney failure and pulmonary hemorrhage (42).

We recommend limiting PLEX use for ANCA vasculitis to patients with severe AKI (eGFR <30 ml/min per 1.73 m² without significant interstitial fibrosis) and lung hemorrhage (requiring supplemental oxygen or mechanical ventilation). We also recommend kidney biopsy when indicated and safe to assess underlying chronicity and rule out concomitant disease (e.g., anti-glomerular basement membrane disease).

Mycophenolate

Various reports exist regarding the success of mycophenolate induction in patients with ANCA vasculitis (43–45). In a retrospective study, 67 patients were treated with mycophenolate mofetil (MMF) for remission maintenance, 29 of whom received MMF for remission induction as well. MMF was comparable to cyclophosphamide for induction (45).

Jones *et al.* (43) randomized 140 patients (132 adult and eight pediatric) with newly diagnosed, active ANCA vasculitis to receive either MMF or pulse cyclophosphamide, followed by azathioprine for remission maintenance. Patients with life-threatening vasculitis, an eGFR of <15 ml/min/m², or rapidly declining kidney function were excluded. Although MMF was noninferior to cyclophosphamide in inducing remission (67% versus 61%), more relapses

were seen in the MMF group (33% versus 19%), with similar serious infectious risk (43). In another RCT with 84 patients, fewer participants attained sustained remission with MMF as compared with cyclophosphamide (66% versus 81%) (44). Thus, MMF may have a role in nonlife-threatening vasculitis.

Remission Maintenance

Over the past two decades, considerable progress has been made in maintaining remission in patients with ANCA vasculitis using a variety of medications, including rituximab, azathioprine, mycophenolate, methotrexate, and glucocorticoids.

The cyclophosphamide or azathioprine as a remission therapy for vasculitis (CYCAZAREM) trial demonstrated that azathioprine could safely replace oral cyclophosphamide for maintenance without increasing the relapse rate (46). The International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial compared MMF with azathioprine in maintaining remission after cyclophosphamide induction. Although both treatment arms had similar adverse events, MMF had a higher relapse rate (HR, 1.69; 95% CI, 1.06 to 2.70) (47). The Wegener's Granulomatosis–Entretien (WEGENT) trial was designed to compare the safety of azathioprine with methotrexate. Among 126 patients in remission, there was no difference in safety or relapse between the two groups (48). Other trials have found methotrexate to be a safe alternate to cyclophosphamide in maintaining remission (49). Methotrexate can be used in patients without significant kidney dysfunction who are unable to receive azathioprine or rituximab.

Use of rituximab for remission was evaluated by the Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis (MAINRITSAN) trial that compared low-dose rituximab (500 mg on days 0 and 14, and then months 6, 12, and 18) with azathioprine (until 22 months) after induction with cyclophosphamide. Rituximab was superior to azathioprine in maintaining remission at 28 months, but azathioprine was tapered earlier than is typical (30). Long-term follow-up showed higher relapse-free survival for the rituximab group at 60 months (50).

Optimal maintenance therapy after rituximab has been evaluated in the rituximab versus azathioprine in remission maintenance (RITAZAREM) trial which enrolled patients who achieved remission with rituximab after experiencing a relapse. Patients received 1000 mg rituximab every 4 months for five doses, or 2 mg/kg per day of azathioprine for 24 months (51). Although the final analyses of the maintenance phase has yet to be published, 170 patients were randomized and 18% of patients in the rituximab arm versus 38% in the azathioprine arm experienced a relapse. Fewer SAEs occurred in the rituximab group (52).

Dosing, Relapses, and Duration of Treatment

MAINRITSAN2 examined dosing of rituximab for remission. Participants in remission either received a fixed 500 mg rituximab infusion on days 0 and 14, and then 6, 12, and 18 months, or tailored therapy. The tailored group received 500 mg rituximab at randomization and were redosed on the basis of CD19+ B lymphocytes or ANCA titer (53).

Relapses were similar in both groups at 28 months (17% versus 10%), but the tailored group received fewer infusions (median of three versus five infusions) (53).

The optimal duration of maintenance therapy is unknown. Patients with PR3-ANCA (compared with MPO-ANCA) and upper respiratory or lung involvement are more likely to relapse (54,55). Although they may require longer treatment, it is controversial when and if immunosuppression can be discontinued.

The prolonged remission-maintenance therapy in systemic vasculitis (REMAIN) trial compared azathioprine/prednisolone maintenance for 24 versus 48 months after cyclophosphamide induction (56). Whereas the 48-month therapy had fewer relapses (22% versus 63%), although higher than other rituximab trials (51), and lower ESKD rate (zero versus four cases), more frequent SAEs were noted in this group (nine versus three events) (56).

In the Glomerular Disease Collaborative Network (GDCN) registry, we analyzed 427 patients, of whom 277 (65%) stopped therapy at a median of 20 months postinduction. These patients remained off immunosuppression for a median of 36 months (interquartile range, 13–88 months) (57). A total of 63 patients were off therapy for ≥ 5 years, with 13 (21%) patients relapsing after 5 years. Patients were more likely to come off treatment if they were women, had MPO-ANCA, and renal-limited disease (57).

Recently, MAINRITSAN3 studied the effect of extended maintenance rituximab therapy on relapse and death (58). MAINRITSAN3 included patients from MAINRITSAN2 who were in remission at month 28. Participants (97) either received placebo or rituximab (500 mg biannually) for an additional 18 months (58). At 28 months, 96% receiving rituximab versus 74% receiving placebo were relapse free (HR, 7.5; 95% CI, 1.67 to 33.7). The number of SAEs was similar between the two groups, although the mean γ -globulin was lower in the rituximab group (58). Although extended rituximab therapy may be safe and benefit some patients, especially those with frequent relapses, MAINRITSAN3 did select patients who previously tolerated rituximab successfully. Furthermore, none of the patients with ANCA and undetectable CD19+ B cells relapsed (58).

For remission maintenance with rituximab, we suggest a 500 mg dose tailored to CD19+ B-lymphocyte count. Additionally, because long-term remission (≥ 2 years off therapy) is possible (57,59), risk of hypogammaglobulinemia with long-term rituximab exists (60–62), and reinduction for relapse is quite successful (57), we highly recommend discontinuing maintenance therapy in those with long-term remission.

Alternative Therapies

Mepolizumab, an IL-5 mAb, is approved by the Food and Drug Administration for treating eosinophilic GPA after studies showing efficacy and acceptable safety (63,64). IV Ig has been used successfully as adjunctive therapy in both MPO- and PR3-ANCA vasculitis for refractory or relapsing disease (65–68). IV Ig is usually considered in patients with hypogammaglobulinemia, especially with recurrent infections, either as Ig replacement therapy or in addition to ongoing immunosuppression (68,69). In patients unable to receive blood products or cyclophosphamide, eculizumab

along with rituximab and steroids has been used successfully in case reports (70).

Belimumab, an anti-B-lymphocyte stimulator mAb, did not reduce relapses when used as adjunctive therapy to azathioprine and glucocorticoids in remission maintenance (71). Similarly, alemtuzumab, an anti-CD52 mAb, and antithymocyte globulin have been investigated, but concerns exist regarding toxicity (72,73).

Management in the Dialysis Population

Management of ANCA vasculitis in patients with severe kidney dysfunction is challenging due to poor renal and patient prognosis (32). A study of 100 patients who underwent diagnostic kidney biopsy at study entry found fibrous crescents predicted dialysis requirement at presentation (74). Age, tubular atrophy, and intraepithelial infiltrates were all predictors of dialysis at 12 months (74).

A time-limited trial of immunosuppression may be worthwhile in patients initially presenting with dialysis needs. We retrospectively examined 155 patients in the GDCN registry with a median eGFR of 7.1 ml/min per 1.73 m²; 87% requiring hemodialysis. Cyclophosphamide therapy and treatment response within 4 months of kidney biopsy were associated with improved renal and patient survival (75). Of these patients, 51% responded to treatment within 4 months, and 50% remained dialysis free at 12 months. As expected, treatment response was lower in patients with severe renal scarring (75). Another retrospective study noted patients were more likely to come off dialysis within 3 months of immunosuppression. However, 12 out of 156 patients became dialysis independent after 3 months (76).

Renal Transplant and ANCA Vasculitis

Per United States Renal Data System data, kidney transplants decrease all-cause mortality by 70% in patients with ESKD from GPA (77). In the European Renal Association–European Dialysis and Transplant Association Registry, the 10-year patient and transplant survival after first kidney transplant was 75% and 64%, respectively, for patients with ANCA vasculitis (78). Numerous studies have highlighted benefits of kidney transplantation in ANCA vasculitides (79–83). One study noted a higher risk of graft failure in patients with MPA compared with GPA (84).

Appropriate timing of kidney transplants in patients with ANCA vasculitis is unclear. A 2009 study showed higher risk of graft loss due to death if transplanted within 12 months of remission (85). Therefore, the Kidney Disease Improving Global Outcomes recommends waiting at least 1 year after clinical remission before transplantation (86).

Presence of positive ANCA titers should not preclude transplantation. However, presence of PR3-ANCA does carry a higher risk of relapse post-transplant (87), and these patients require closer follow-up. The relapse rate post-transplantation can vary from 5% to 17% over 44–66 months post-transplant (79,85). Treatment of ANCA vasculitis flares post-transplant is similar to pretransplant, taking patient characteristics and severity of flare into consideration.

Conclusions

In the last decade, we have made significant advancements in the field of ANCA vasculitis. We have been successful in improving patient prognosis, with earlier remissions and lower relapse rates. However, many questions remain unanswered including optimal timing of treatments, and, more importantly, when to withdraw therapy. Rituximab has gained popularity as a single agent and in combination, and there are new trials underway that may again change the landscape in the next decade. Our understanding of the pathogenesis continues to expand and reveals the complexity of the disease. We need targeted therapies to tailor treatment on the basis of patient preference, comorbidities, relapse risk, and ANCA type.

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References

- Ntatsaki E, Watts RA, Scott DG: Epidemiology of ANCA-associated vasculitis. *Rheum Dis Clin North Am* 36: 447–461, 2010 <https://doi.org/10.1016/j.rdc.2010.04.002>
- Panupattanapong S, Stwalley DL, White AJ, Olsen MA, French AR, Hartman ME: Epidemiology and outcomes of granulomatosis with polyangiitis in pediatric and working-age adult populations in the United States: Analysis of a large national claims database. *Arthritis Rheumatol* 70: 2067–2076, 2018 <https://doi.org/10.1002/art.40577>
- Ormerod AS, Cook MC: Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. *Intern Med J* 38: 816–823, 2008 <https://doi.org/10.1111/j.1445-5994.2008.01672.x>
- Watts RA, Lane SE, Bentham G, Scott DG: Epidemiology of systemic vasculitis: A ten-year study in the United Kingdom. *Arthritis Rheum* 43: 414–419, 2000 [https://doi.org/10.1002/1529-0131\(200002\)43:2<414::AID-ANR23>3.0.CO;2-0](https://doi.org/10.1002/1529-0131(200002)43:2<414::AID-ANR23>3.0.CO;2-0)
- Mahr A, Guillevin L, Poissonnet M, Aymé S: Prevalences of polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis, and Churg-Strauss syndrome in a French urban multiethnic population in 2000: A capture-recapture estimate. *Arthritis Rheum* 51: 92–99, 2004 <https://doi.org/10.1002/art.20077>
- Scott DGI, Watts RA: Epidemiology and clinical features of systemic vasculitis. *Clin Exp Nephrol* 17: 607–610, 2013 <https://doi.org/10.1007/s10157-013-0830-8>
- Geetha D, Poulton CJ, Hu Y, Seo P, McGregor JA, Falk RJ, Hogan SL: Clinical characteristics and outcome of pauci-immune glomerulonephritis in African Americans. *Semin Arthritis Rheum* 43: 778–783, 2014 <https://doi.org/10.1016/j.semarthrit.2013.11.011>
- Jennette JC, Falk RJ: Pathogenesis of antineutrophil cytoplasmic autoantibody-mediated disease. *Nat Rev Rheumatol* 10: 463–473, 2014 <https://doi.org/10.1038/nrrheum.2014.103>
- Roth AJ, Ooi JD, Hess JJ, van Timmeren MM, Berg EA, Poulton CE, McGregor J, Burkart M, Hogan SL, Hu Y, Winnik W, Nachman PH, Stegeman CA, Niles J, Heeringa P, Kitching AR, Holdsworth S, Jennette JC, Preston GA, Falk RJ: Epitope specificity determines pathogenicity and detectability in ANCA-associated vasculitis. *J Clin Invest* 123: 1773–1783, 2013 <https://doi.org/10.1172/JCI65292>
- Little MA, Al-Ani B, Ren S, Al-Nuaimi H, Leite M Jr, Alpers CE, Savage CO, Duffield JS: Anti-proteinase 3 anti-neutrophil cytoplasm autoantibodies recapitulate systemic vasculitis in mice with a humanized immune system. *PLoS One* 7: e28626, 2012 <https://doi.org/10.1371/journal.pone.0028626>
- Hogan SL, Cooper GS, Savitz DA, Nylander-French LA, Parks CG, Chin H, Jennette CE, Lionaki S, Jennette JC, Falk RJ: Association of silica exposure with anti-neutrophil cytoplasmic autoantibody small-vessel vasculitis: A population-based, case-control study. *Clin J Am Soc Nephrol* 2: 290–299, 2007 <https://doi.org/10.2215/CJN.03501006>
- Gómez-Puerta JA, Gedmintas L, Costenbader KH: The association between silica exposure and development of ANCA-associated vasculitis: Systematic review and meta-analysis. *Autoimmun Rev* 12: 1129–1135, 2013 <https://doi.org/10.1016/j.autrev.2013.06.016>
- Stegeman CA, Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG: Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. *Ann Intern Med* 120: 12–17, 1994 <https://doi.org/10.7326/0003-4819-120-1-199401010-00003>
- Hogan JJ, Markowitz GS, Radhakrishnan J: Drug-induced glomerular disease: Immune-mediated injury. *Clin J Am Soc Nephrol* 10: 1300–1310, 2015 <https://doi.org/10.2215/CJN.01910215>
- Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CGM, St Clair EW, Turkiewicz A, Tchao NK, Webber L, Ding L, Sejismundo LP, Mieras K, Weitzkamp D, Ikle D, Seyfert-Margolis V, Mueller M, Brunetta P, Allen NB, Ferrenza FC, Geetha D, Keogh KA, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Specks U; RAVE-ITN Research Group: Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 363: 221–232, 2010 <https://doi.org/10.1056/NEJMoa0909905>
- Jones RB, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh D, Walsh M, Westman K, Jayne DR; European Vasculitis Study Group: Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 363: 211–220, 2010 <https://doi.org/10.1056/NEJMoa0909169>
- Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, Hawley CM, Khalidi N, Floßmann O, Wald R, Girard LP, Levin A, Gregorini G, Harper L, Clark WF, Pagnoux C, Specks U, Smyth L, Tesar V, Ito-Ihara T, de Zoysa JR, Szczeklik W, Flores-Suárez LF, Carette S, Guillevin L, Pusey CD, Casian AL, Brezina B, Mazzetti A, McAlear CA, Broadhurst E, Reidlinger D, Mehta S, Ives N, Jayne DRW; PEXIVAS Investigators: Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. *N Engl J Med* 382: 622–631, 2020 <https://doi.org/10.1056/NEJMoa1803537>
- Pepper RJ, McAdoo SP, Moran SM, Kelly D, Scott J, Hamour S, Burns A, Griffith M, Galliford J, Levy JB, Cairns TD, Gopaluni S, Jones RB, Jayne D, Little MA, Pusey CD, Salama AD: A novel glucocorticoid-free maintenance regimen for anti-neutrophil cytoplasm antibody-associated vasculitis. *Rheumatology (Oxford)* 58: 260–268, 2019
- Chanouzas D, McGregor JAG, Nightingale P, Salama AD, Szpirt WM, Basu N, Morgan MD, Poulton CJ, Draibe JB, Krarup E, Dospinescu P, Dale JA, Pendergraft WF, Lee K, Egfjord M, Hogan SL, Harper L: Intravenous pulse methylprednisolone for induction of remission in severe ANCA associated vasculitis: A multi-center retrospective cohort study. *BMC Nephrol* 20: 58, 2019 <https://doi.org/10.1186/s12882-019-1226-0>
- Furuta S, Sugiyama T, Umibe T, Kaneko Y, Amano K, Kurasawa K, Nakagomi D, Hiraguri M, Hanaoka H, Sato Y, Ikeda K, Nakajima H; LoVAS Trial study investigators: Low-dose glucocorticoids plus rituximab versus high-dose glucocorticoids plus rituximab for remission induction in ANCA-associated vasculitis (LoVAS): Protocol for a multicentre, open-label, randomised controlled trial [published correction appears in *BMJ Open* 8: e018748corr1, 2018 10.1136/bmjopen-2017-018748corr1].

- BMJ Open* 7: e018748, 2017 <https://doi.org/10.1136/bmjopen-2017-018748>
21. Jayne DRW, Bruchfeld AN, Harper L, Schaier M, Venning MC, Hamilton P, Burst V, Grundmann F, Jadoul M, Szombati I, Tesar V, Segelmark M, Potarca A, Schall TJ, Bekker P; CLEAR Study Group: Randomized trial of C5a receptor inhibitor avacopan in ANCA-associated vasculitis. *J Am Soc Nephrol* 28: 2756–2767, 2017 <https://doi.org/10.1681/ASN.2016111179>
 22. Merkel PA, Jayne DR, Wang C, Hillson J, Bekker P: Evaluation of the safety and efficacy of avacopan, a C5a receptor inhibitor, in patients with antineutrophil cytoplasmic antibody-associated vasculitis treated concomitantly with rituximab or cyclophosphamide/azathioprine: Protocol for a randomized, double-blind, active-controlled, phase 3 trial. *JMIR Res Protoc* 9: e16664, 2020 <https://doi.org/10.2196/16664>
 23. Merkel PA, Jayne D, Yue H, Schall T, Kelleher C, Bekker P; on behalf of the ADVOCATE Study Group: OP0011 A randomized, double-blind, active-controlled study of avacopan in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Ann Rheum Dis* 79: 8, 2020 <https://doi.org/10.1136/annrheumdis-2020-eular.1073>
 24. Shand FL: The immunopharmacology of cyclophosphamide. *Int J Immunopharmacol* 1: 165–171, 1979 [https://doi.org/10.1016/0192-0561\(79\)90038-9](https://doi.org/10.1016/0192-0561(79)90038-9)
 25. Novack SN, Pearson CM: Cyclophosphamide therapy in Wegener's granulomatosis. *N Engl J Med* 284: 938–942, 1971 <https://doi.org/10.1056/NEJM197104292841703>
 26. Talar-Williams C, Hijazi YM, Walthers MM, Linehan WM, Hallahan CW, Lubensky I, Kerr GS, Hoffman GS, Fauci AS, Sneller MC: Cyclophosphamide-induced cystitis and bladder cancer in patients with Wegener granulomatosis. *Ann Intern Med* 124: 477–484, 1996 <https://doi.org/10.7326/0003-4819-124-5-199603010-00003>
 27. Bergsagel DE, Robertson GL, Hasselback R: Effect of cyclophosphamide on advanced lung cancer and the hematological toxicity of large, intermittent intravenous doses. *Can Med Assoc J* 98: 532–538, 1968
 28. de Groot K, Harper L, Jayne DRW, Flores Suarez LF, Gregorini G, Gross WL, Luqmani R, Pusey CD, Rasmussen N, Sinico RA, Tesar V, Vanhille P, Westman K, Savage COS; EUVAS (European Vasculitis Study Group): Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial. *Ann Intern Med* 150: 670–680, 2009 <https://doi.org/10.7326/0003-4819-150-10-200905190-00004>
 29. Harper L, Morgan MD, Walsh M, Högglund P, Westman K, Flossmann O, Tesar V, Vanhille P, de Groot K, Luqmani R, Flores-Suarez LF, Watts R, Pusey C, Bruchfeld A, Rasmussen N, Blockmans D, Savage CO, Jayne D; EUVAS investigators: Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: Long-term follow-up. *Ann Rheum Dis* 71: 955–960, 2012 <https://doi.org/10.1136/annrheumdis-2011-200477>
 30. Guillevin L, Pagnoux C, Karras A, Khouatra C, Aumaitre O, Cohen P, Maurier F, Decaux O, Ninet J, Gobert P, Quéméneur T, Blanchard-Delaunay C, Godmer P, Puéchal X, Carron PL, Hatron PY, Limal N, Hamidou M, Ducret M, Daugas E, Papo T, Bonnotte B, Mahr A, Ravaud P, Mouthon L; French Vasculitis Study Group: Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med* 371: 1771–1780, 2014 <https://doi.org/10.1056/NEJMoa1404231>
 31. Pagnoux C, Quéméneur T, Ninet J, Diot E, Kyndt X, de Wazières B, Reny JL, Puéchal X, le Berruyer PY, Lidove O, Vanhille P, Godmer P, Fain O, Blockmans D, Bienvenu B, Rollet F, Ait el Ghaz-Poignant S, Mahr A, Cohen A, Mouthon L, Perrudeau E, Ravaud P, Guillevin L; French Vasculitis Study Group: Treatment of systemic necrotizing vasculitides in patients aged sixty-five years or older: Results of a multicenter, open-label, randomized controlled trial of corticosteroid and cyclophosphamide-based induction therapy. *Arthritis Rheumatol* 67: 1117–1127, 2015 <https://doi.org/10.1002/art.39011>
 32. Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid MC, Cohen-Tervaert JW, Gross WL, Guillevin L, Jayne D, Mahr A, Merkel PA, Raspe H, Scott D, Witter J, Yazici H, Luqmani RA; European Vasculitis Study Group (EUVAS): Outcomes from studies of antineutrophil cytoplasmic antibody associated vasculitis: A systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis* 67: 1004–1010, 2008 <https://doi.org/10.1136/ard.2007.071936>
 33. Unizony S, Villarreal M, Miloslavsky EM, Lu N, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, Kallenberg CM, St Clair EW, Ikle D, Tchao NK, Ding L, Brunetta P, Choi HK, Monach PA, Fervenza F, Stone JH, Specks U; RAVE-ITN Research Group: Clinical outcomes of treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis based on ANCA type. *Ann Rheum Dis* 75: 1166–1169, 2016 <https://doi.org/10.1136/annrheumdis-2015-208073>
 34. Geetha D, Specks U, Stone JH, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, Kallenberg CG, St Clair EW, Fessler BJ, Ding L, Tchao NK, Ikle D, Jepsen B, Brunetta P, Fervenza FC; Rituximab for ANCA-Associated Vasculitis Immune Tolerance Network Research Group: Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol* 26: 976–985, 2015 <https://doi.org/10.1681/ASN.2014010046>
 35. Jones RB, Furuta S, Tervaert JW, Hauser T, Luqmani R, Morgan MD, Peh CA, Savage CO, Segelmark M, Tesar V, van Paassen P, Walsh M, Westman K, Jayne DR; European Vasculitis Society (EUVAS): Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. *Ann Rheum Dis* 74: 1178–1182, 2015 <https://doi.org/10.1136/annrheumdis-2014-206404>
 36. Casal Moura M, Irazabal MV, Eirin A, Zand L, Sethi S, Borah BJ, Winters JL, Moriarty JP, Cartin-Ceba R, Berti A, Baqir M, Thompson GE, Makol A, Warrington KJ, Thao V, Specks U, Fervenza FC: Efficacy of rituximab and plasma exchange in antineutrophil cytoplasmic antibody-associated vasculitis with severe kidney disease. *J Am Soc Nephrol* 31: 2688–2704, 2020 <https://doi.org/10.1681/ASN.2019111197>
 37. McAdoo SP, Medjeral-Thomas N, Gopaluni S, Tanna A, Mansfield N, Galliford J, Griffith M, Levy J, Cairns TD, Jayne D, Salama AD, Pusey CD: Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis [published correction appears in *Nephrol Dial Transplant* 33: 899, 2018 10.1093/ndt/gfy075]. *Nephrol Dial Transplant* 34: 63–73, 2019 <https://doi.org/10.1093/ndt/gfx378>
 38. Cortazar FB, Muhsin SA, Pendergraft WF III, Wallace ZS, Dunbar C, Laliberte K, Niles JL: Combination therapy with rituximab and cyclophosphamide for remission induction in ANCA vasculitis. *Kidney Int Rep* 3: 394–402, 2017 <https://doi.org/10.1016/j.ekir.2017.11.004>
 39. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, Mirapeix E, Savage CO, Sinico RA, Stegeman CA, Westman KW, van der Woude FJ, de Lind van Wijngaarden RA, Pusey CD; European Vasculitis Study Group: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 18: 2180–2188, 2007 <https://doi.org/10.1681/ASN.2007010090>
 40. Walsh M, Catapano F, Szpirt W, Thorlund K, Bruchfeld A, Guillevin L, Haubitz M, Merkel PA, Peh CA, Pusey C, Jayne D: Plasma exchange for renal vasculitis and idiopathic rapidly progressive glomerulonephritis: A meta-analysis. *Am J Kidney Dis* 57: 566–574, 2011 <https://doi.org/10.1053/j.ajkd.2010.10.049>
 41. Walsh M, Casian A, Flossmann O, Westman K, Högglund P, Pusey C, Jayne DR; European Vasculitis Study Group (EUVAS): Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int* 84: 397–402, 2013 <https://doi.org/10.1038/ki.2013.131>
 42. Balogun RA, Sanchez AP, Klingel R, Witt V, Aqui N, Meyer E, Padmanabhan A, Pham HP, Schneiderman J, Schwartz J, Wu Y, Zantek ND, Connelly-Smith L, Dunbar NM: Update to the ASFA guidelines on the use of therapeutic apheresis in ANCA-associated vasculitis. *J Clin Apher* 35: 493–499, 2020 <https://doi.org/10.1002/jca.21820>
 43. Jones RB, Hiemstra TF, Ballarin J, Blockmans DE, Brogan P, Bruchfeld A, Cid MC, Dahlsveen K, de Zoysa J, Espigol-Frigolé G, Lanyon P, Peh CA, Tesar V, Vaglio A, Walsh M, Walsh D, Walters

- G, Harper L, Jayne D; European Vasculitis Study Group (EUVAS): Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: A randomised, non-inferiority trial. *Ann Rheum Dis* 78: 399–405, 2019 <https://doi.org/10.1136/annrheumdis-2018-214245>
44. Tuin J, Stassen PM, Bogdan DI, Broekroelofs J, van Paassen P, Cohen Tervaert JW, Sanders JS, Stegeman CA: Mycophenolate mofetil versus cyclophosphamide for the induction of remission in nonlife-threatening relapses of antineutrophil cytoplasmic antibody-associated vasculitis: Randomized, controlled trial. *Clin J Am Soc Nephrol* 14: 1021–1028, 2019 <https://doi.org/10.2215/CJN.11801018>
 45. Draibe J, Poveda R, Fulladosa X, Vidaller A, Zurberti C, Gomà M, Pujol R, Ripoll È, Torras J, Grinyó JM: Use of mycophenolate in ANCA-associated renal vasculitis: 13 years of experience at a university hospital. *Nephrol Dial Transplant* 30: i132–i137, 2015 <https://doi.org/10.1093/ndt/gfv061>
 46. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadonienė J, Ekstrand A, Gaskin G, Gregorini G, de Groot K, Gross W, Hagen EC, Mirapeix E, Pettersson E, Siegert C, Sinico A, Tesar V, Westman K, Pusey C; European Vasculitis Study Group: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 349: 36–44, 2003 <https://doi.org/10.1056/NEJMoa020286>
 47. Hiemstra TF, Walsh M, Mahr A, Savage CO, de Groot K, Harper L, Hauser T, Neumann I, Tesar V, Wissing K-M, Pagnoux C, Schmitt W, Jayne DRW; European Vasculitis Study Group (EUVAS): Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled trial. *JAMA* 304: 2381–2388, 2010 <https://doi.org/10.1001/jama.2010.1658>
 48. Pagnoux C, Mahr A, Hamidou MA, Boffa JJ, Ruivard M, Ducroix JP, Kyndt X, Lifermann F, Papo T, Lambert M, Le Noach J, Khellaf M, Merrien D, Puéchal X, Vinzio S, Cohen P, Mouthon L, Cordier JF, Guillevin L; French Vasculitis Study Group: Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N Engl J Med* 359: 2790–2803, 2008 <https://doi.org/10.1056/NEJMoa0802311>
 49. Maritati F, Alberici F, Oliva E, Urban ML, Palmisano A, Santarsia F, Andrulli S, Pavone L, Pesci A, Grasselli C, Santi R, Tumiati B, Manenti L, Buzio C, Vaglio A: Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial. *PLoS One* 12: e0185880, 2017 <https://doi.org/10.1371/journal.pone.0185880>
 50. Terrier B, Pagnoux C, Perrodeau É, Karras A, Khouatra C, Aumaitre O, Cohen P, Decaux O, Desmurs-Clavel H, Maurier F, Gobert P, Quémener T, Blanchard-Delaunay C, Bonnotte B, Carron PL, Daugas E, Ducret M, Godmer P, Hamidou M, Lidove O, Limal N, Puéchal X, Mouthon L, Ravaud P, Guillevin L; French Vasculitis Study Group: Long-term efficacy of remission-maintenance regimens for ANCA-associated vasculitides. *Ann Rheum Dis* 77: 1150–1156, 2018 <https://doi.org/10.1136/annrheumdis-2017-212768>
 51. Gopaluni S, Smith RM, Lewin M, McAlear CA, Mynard K, Jones RB, Specks U, Merkel PA, Jayne DR; RITAZAREM Investigators: Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasmic antibody-associated vasculitis (RITAZAREM): Study protocol for a randomized controlled trial. *Trials* 18: 112, 2017 <https://doi.org/10.1186/s13063-017-1857-z>
 52. Smith R, Jayne D, Merkel PA: OP0026 A randomized, controlled trial of rituximab versus azathioprine after induction of remission with rituximab for patients with ANCA-associated vasculitis and relapsing disease. *Ann Rheum Dis* 79: 19–20, 2020
 53. Charles P, Terrier B, Perrodeau É, Cohen P, Faguer S, Huart A, Hamidou M, Agard C, Bonnotte B, Samson M, Karras A, Jourde-Chiche N, Lifermann F, Gobert P, Hanrotel-Saliou C, Godmer P, Martin-Silva N, Pugnet G, Matignon M, Aumaitre O, Viallard JF, Maurier F, Meaux-Ruault N, Rivière S, Sibilia J, Puéchal X, Ravaud P, Mouthon L, Guillevin L; French Vasculitis Study Group: 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) [published correction appears in *Ann Rheum Dis* 78: e101, 2019 <https://doi.org/10.1136/annrheumdis-2017-212878>]. *Ann Rheum Dis* 77: 1143–1149, 2018 <https://doi.org/10.1136/annrheumdis-2017-212878>
 54. Pagnoux C, Hogan SL, Chin H, Jettette JC, Falk RJ, Guillevin L, Nachman PH: Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: Comparison of two independent cohorts. *Arthritis Rheum* 58: 2908–2918, 2008 <https://doi.org/10.1002/art.23800>
 55. Hogan SL, Falk RJ, Chin H, Cai J, Jettette CE, Jettette JC, Nachman PH: Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med* 143: 621–631, 2005 <https://doi.org/10.7326/0003-4819-143-9-200511010-00005>
 56. Karras A, Pagnoux C, Haubitz M, Groot K, Puechal X, Tervaert JWC, Segelmark M, Guillevin L, Jayne D; European Vasculitis Society: Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis* 76: 1662–1668, 2017 <https://doi.org/10.1136/annrheumdis-2017-211123>
 57. Hogan SL, Nachman PH, Poulton CJ, Hu Y, Blazek LN, Free ME, Jettette JC, Falk RJ: Understanding long-term remission off therapy in antineutrophil cytoplasmic antibody-associated vasculitis. *Kidney Int Rep* 4: 551–560, 2019 <https://doi.org/10.1016/j.ekir.2019.01.004>
 58. Charles P, Perrodeau É, Samson M, Bonnotte B, Néel A, Agard C, Huart A, Karras A, Lifermann F, Godmer P, Cohen P, Hanrotel-Saliou C, Martin-Silva N, Pugnet G, Maurier F, Sibilia J, Carron PL, Gobert P, Meaux-Ruault N, Le Gallou T, Vinzio S, Viallard JF, Hachulla E, Vinter C, Puéchal X, Terrier B, Ravaud P, Mouthon L, Guillevin L: Long-term rituximab use to maintain remission of antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial. *Ann Intern Med* 173: 179–187, 2020 <https://doi.org/10.7326/M19-3827>
 59. Gapud EJ, Manno R, Seo P, Hanouneh M, Geetha D: Long-term clinical course of antineutrophil cytoplasmic antibody-associated vasculitis patients off maintenance therapy. *Cureus* 10: e2372, 2018 <https://doi.org/10.7759/cureus.2372>
 60. Besada E, Koldingsnes W, Nossent JC: Serum immunoglobulin levels and risk factors for hypogammaglobulinaemia during long-term maintenance therapy with rituximab in patients with granulomatosis with polyangiitis. *Rheumatology (Oxford)* 53: 1818–1824, 2014 <https://doi.org/10.1093/rheumatology/keu194>
 61. 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)* 52: 2041–2047, 2013 <https://doi.org/10.1093/rheumatology/ket257>
 62. Roberts DM, Jones RB, Smith RM, Alberici F, Kumaratne DS, Burns S, Jayne DR: Rituximab-associated hypogammaglobulinemia: Incidence, predictors and outcomes in patients with multi-system autoimmune disease. *J Autoimmun* 57: 60–65, 2015 <https://doi.org/10.1016/j.jaut.2014.11.009>
 63. Wechsler ME, Akuthota P, Jayne D, Khoury P, Klion A, Langford CA, Merkel PA, Moosig F, Specks U, Cid MC, Luqmani R, Brown J, Mallett S, Philipson R, Yancey SW, Steinfeld J, Weller PF, Gleich GJ; EGPA Mepolizumab Study Team: Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med* 376: 1921–1932, 2017 <https://doi.org/10.1056/NEJMoa1702079>
 64. Steinfeld J, Bradford ES, Brown J, Mallett S, Yancey SW, Akuthota P, Cid MC, Gleich GJ, Jayne D, Khoury P, Langford CA, Merkel PA, Moosig F, Specks U, Weller PF, Wechsler ME: Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis. *J Allergy Clin Immunol* 143: 2170–2177, 2019 <https://doi.org/10.1016/j.jaci.2018.11.041>
 65. Muso E, Ito-Ihara T, Ono T, Imai E, Yamagata K, Akamatsu A, Suzuki K: Intravenous immunoglobulin (IVIg) therapy in MPO-ANCA related polyangiitis with rapidly progressive glomerulonephritis in Japan. *Jpn J Infect Dis* 57: S17–S18, 2004
 66. Ito-Ihara T, Ono T, Nogaki F, Suyama K, Tanaka M, Yonemoto S, Fukatsu A, Kita T, Suzuki K, Muso E: Clinical efficacy of intravenous immunoglobulin for patients with MPO-ANCA-associated rapidly progressive glomerulonephritis. *Nephron Clin Pract* 102: c35–c42, 2006 <https://doi.org/10.1159/000088313>
 67. Martinez V, Cohen P, Pagnoux C, Vinzio S, Mahr A, Mouthon L, Sailler L, Delaunay C, Sadoun A, Guillevin L; French Vasculitis

- Study Group: Intravenous immunoglobulins for relapses of systemic vasculitides associated with antineutrophil cytoplasmic autoantibodies: Results of a multicenter, prospective, open-label study of twenty-two patients. *Arthritis Rheum* 58: 308–317, 2008 <https://doi.org/10.1002/art.23147>
68. Crickx E, Machelart I, Lazaro E, Kahn JE, Cohen-Aubart F, Martin T, Mania A, Hatron PY, Hayem G, Blanchard-Delaunay C, de Moreuil C, Le Guenno G, Vandergheynst F, Maurier F, Crestani B, Dhote R, Silva NM, Ollivier Y, Mehdaoui A, Godeau B, Mariette X, Cadranet J, Cohen P, Puéchal X, Le Jeune C, Mouthon L, Guillemin L, Terrier B; French Vasculitis Study Group: Intravenous immunoglobulin as an immunomodulating agent in antineutrophil cytoplasmic antibody-associated vasculitides: A French nationwide study of ninety-two patients. *Arthritis Rheumatol* 68: 702–712, 2016 <https://doi.org/10.1002/art.39472>
 69. Kant S, Azar A, Gapud EJ, Antiochos B, Manno R, Seo P, Geetha D: Subcutaneous immunoglobulin for antibody deficiency in Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis. *Cureus* 11: e6367, 2019 <https://doi.org/10.7759/cureus.6367>
 70. Huizenga N, Zonozi R, Rosenthal J, Laliberte K, Niles JL, Cortazar FB: Treatment of aggressive antineutrophil cytoplasmic antibody-associated vasculitis with eculizumab. *Kidney Int Rep* 5: 542–545, 2019 <https://doi.org/10.1016/j.ekir.2019.11.021>
 71. Jayne D, Blockmans D, Luqmani R, Moiseev S, Ji B, Green Y, Hall L, Roth D, Henderson RB, Merkel PA; BREVAS Study Collaborators: Efficacy and safety of belimumab and azathioprine for maintenance of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized controlled study. *Arthritis Rheumatol* 71: 952–963, 2019 <https://doi.org/10.1002/art.40802>
 72. Schmitt WH, Hagen EC, Neumann I, Nowack R, Flores-Suárez LF, van der Woude FJ; European Vasculitis Study Group: Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): An open study in 15 patients. *Kidney Int* 65: 1440–1448, 2004 <https://doi.org/10.1111/j.1523-1755.2004.00534.x>
 73. Walsh M, Chaudhry A, Jayne D: Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). *Ann Rheum Dis* 67: 1322–1327, 2008 <https://doi.org/10.1136/ard.2007.081661>
 74. de Lind van Wijngaarden RAF, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, Noël LH, Ferrario F, Waldherr R, Hagen EC, Bruijn JA, Bajema IM: Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: A prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol* 17: 2264–2274, 2006 <https://doi.org/10.1681/ASN.2005080870>
 75. Lee T, Gasim A, Derebail VK, Chung Y, McGregor JG, Lionaki S, Poulton CJ, Hogan SL, Jennette JC, Falk RJ, Nachman PH: Predictors of treatment outcomes in ANCA-associated vasculitis with severe kidney failure. *Clin J Am Soc Nephrol* 9: 905–913, 2014 <https://doi.org/10.2215/CJN.08290813>
 76. Ma TT, Liu YR, Chen M, Zhao MH: Late restoration of renal function in patients with severe ANCA-associated glomerulonephritis who were dialysis-dependent at presentation. *Clin Rheumatol* 37: 2143–2150, 2018 <https://doi.org/10.1007/s10067-018-4100-8>
 77. Wallace ZS, Wallwork R, Zhang Y, Lu N, Cortazar F, Niles JL, Heher E, Stone JH, Choi HK: Improved survival with renal transplantation for end-stage renal disease due to granulomatosis with polyangiitis: Data from the United States Renal Data System. *Ann Rheum Dis* 77: 1333–1338, 2018 <https://doi.org/10.1136/annrheumdis-2018-213452>
 78. Hruskova Z, Stel VS, Jayne D, Aasarød K, De Meester J, Ekstrand A, Eller K, Heaf JG, Hoitsma A, Martos Jimenez C, Ravani P, Wanner C, Tesar V, Jager KJ: Characteristics and outcomes of granulomatosis with polyangiitis (Wegener) and microscopic polyangiitis requiring renal replacement therapy: Results from the European Renal Association–European Dialysis and Transplant Association Registry. *Am J Kidney Dis* 66: 613–620, 2015 <https://doi.org/10.1053/j.ajkd.2015.03.025>
 79. Nachman PH, Segelmark M, Westman K, Hogan SL, Satterly KK, Jennette JC, Falk R: Recurrent ANCA-associated small vessel vasculitis after transplantation: A pooled analysis. *Kidney Int* 56: 1544–1550, 1999 <https://doi.org/10.1046/j.1523-1755.1999.00666.x>
 80. Deegens JK, Artz MA, Hoitsma AJ, Wetzels JF: Outcome of renal transplantation in patients with pauci-immune small vessel vasculitis or anti-GBM disease. *Clin Nephrol* 59: 1–9, 2003 <https://doi.org/10.5414/CNP59001>
 81. Geetha D, Eirin A, True K, Valentina Irazabal M, Specks U, Seo P, Nachman P, Fervenza FC: Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: A multicenter experience. *Transplantation* 91: 1370–1375, 2011 <https://doi.org/10.1097/TP.0b013e31821ab9aa>
 82. Marco H, Mirapeix E, Arcos E, Comas J, Ara J, Gil-Vernet S, Puig J, Vinyas O, Perello M, Oppenheimer F, Poveda R, Ibernón M, Díaz M, Ballarin J; Catalan Study Group of Glomerular Diseases (GLOM-CAT): Long-term outcome of antineutrophil cytoplasmic antibody-associated small vessel vasculitis after renal transplantation. *Clin Transplant* 27: 338–347, 2013 <https://doi.org/10.1111/ctr.12084>
 83. Göçeroğlu A, Rahmattulla C, Berden AE, Reinders ME, Wolterbeek R, Steenbergen EJ, Hilbrands LB, Noorlander I, Berger SP, Peutz-Kootstra CJ, Christiaans MH, van Dijk MC, de Joode AA, Goldschmeding R, van Zuilen AD, Harper L, Little MA, Hagen EC, Bruijn JA, Bajema IM: The Dutch Transplantation in Vasculitis (DUTRAVAS) study: Outcome of renal transplantation in antineutrophil cytoplasmic antibody-associated glomerulonephritis. *Transplantation* 100: 916–924, 2016 <https://doi.org/10.1097/TP.0000000000000910>
 84. Tang W, Bose B, McDonald SP, Hawley CM, Badve SV, Boudville N, Brown FG, Clayton PA, Campbell SB, Peh CA, Johnson DW: The outcomes of patients with ESRD and ANCA-associated vasculitis in Australia and New Zealand. *Clin J Am Soc Nephrol* 8: 773–780, 2013 <https://doi.org/10.2215/CJN.08770812>
 85. Little MA, Hassan B, Jacques S, Game D, Salisbury E, Courtney AE, Brown C, Salama AD, Harper L: Renal transplantation in systemic vasculitis: When is it safe? *Nephrol Dial Transplant* 24: 3219–3225, 2009 <https://doi.org/10.1093/ndt/gfp347>
 86. Kidney Disease Improving Global Outcomes. <https://kdigo.org/guidelines/gd/> Accessed on February 17, 2021
 87. Geetha D, Lee SM, Shah S, Rahman HM: Relevance of ANCA positivity at the time of renal transplantation in ANCA associated vasculitis. *J Nephrol* 30: 147–153, 2017 <https://doi.org/10.1007/s40620-015-0253-6>

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