Treatment updates in Antineutrophil Cytoplasmic Autoantibodies (ANCA) vasculitis

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Abstract

Anti-neutrophil cytoplasmic autoantibody (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 the 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 towards 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 utilized at our institution.

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 Granulomatosis with Polyangiitis (EGPA), and renal-limited vasculitis (RLV) with pauci-immune necrotizing and crescentic glomerulonephritis on renal biopsy. 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 United States, the incidence and prevalence rate of GPA is 13 and 218 per million,2 compared to 8.6 and 95 per million in Australia,3 and 9.7 and 62.9 per million in the UK,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 to Southern Europe and Asia where MPA is more common.6 ANCA vasculitis is more common in Caucasians.
Patients of African descent are more likely to have MPO-ANCA and are younger at presentation. One study found no difference in treatment response, development of end-stage kidney disease (ESKD), renal relapse and death rates between African Americans and Caucasians.\textsuperscript{7}

Numerous factors have been implicated in the pathogenesis of ANCA vasculitis. Recent studies suggest ANCAs themselves are pathogenic, especially MPO-ANCA autoantibodies.\textsuperscript{8-10} Genetic susceptibility, environmental triggers such as silica, drug exposure and infections have been associated with the development of ANCA vasculitis.\textsuperscript{11-13} Drugs commonly implicated are levamisole-adulterated cocaine, hydralazine and propylthiouracil.\textsuperscript{14} There is potential association of minocycline, allopurinol, methimazole, penicillamine and sulfasalazine with drug-induced vasculitis.\textsuperscript{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, intravenous (IV) methylprednisolone 1-3 g has been used, followed by oral prednisone 1mg/kg/day. The Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis (RAVE) trial successfully tapered prednisone by 5 months\textsuperscript{15} with other trials maintaining 5mg/day dose beyond six months.\textsuperscript{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.\textsuperscript{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 non-inferior to standard-dosing with regards to all-cause mortality and ESKD. Among 49 patients who received combination cyclophosphamide-rituximab infusion, rapid glucocorticoid withdrawal (between 1-2 weeks) reduced severe adverse events (SAEs) with effective remission induction compared to matched previous European Vasculitis Society (EUVAS) trials. Additionally, retrospective analysis of 114 patients showed no benefit of adding IV methylprednisolone, and higher incidence of diabetes and infection was noted. Currently, a low-dose prednisolone (0.5 mg/kg/day) versus high-dose prednisolone (1mg/kg/day) plus rituximab trial is underway to assess relapse and safety profile.

Corticosteroid Sparing Strategies

Corticosteroid reduction may be further achieved with complement-based therapy, although these have not yet been approved. Avacopan (CCX168), oral C5a receptor (C5aR) antagonist, in addition to cyclophosphamide or rituximab successfully replaced corticosteroids in a phase 2 RCT (CLEAR). Preliminary results from the ADVOCATE study show similar remission achievement in 166 avacopan-treated patients compared to 164 glucocorticoid-treated at 26 weeks (72.3% versus 70.1%). Avacopan was superior to prednisone at 52 weeks in sustaining remission. 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.\textsuperscript{24} Cyclophosphamide has been used for induction therapy since the first published case series in 1971 in GPA.\textsuperscript{25}

Risks of cyclophosphamide include infertility, urotoxicity including cystitis and transitional-cell carcinoma of the bladder, hematologic toxicity, and infections.\textsuperscript{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 (HR 1.098, 95\% CI:0.78-1.55). Pulse cyclophosphamide therapy led to lower cumulative dose (8.2 g versus 15.9 g) and lower rate of leukopenia (HR 0.41, 95\% CI:0.23-0.71) as compared to oral cyclophosphamide.\textsuperscript{28} In long-term follow-up of patients from CYCLOPS, Harper et. al. found a higher relapse risk with pulse cyclophosphamide, but no difference in survival and renal function.\textsuperscript{29} Both groups received azathioprine for maintenance which is associated with higher relapse rates than rituximab.\textsuperscript{30} The French Vasculitis Study Group demonstrated fewer SAEs in patients ≥65 years with fixed low-dose intravenous cyclophosphamide compared with conventional cyclophosphamide dosing (500mg/m\textsuperscript{2} every 2-3 weeks). The overall mortality was approximately 20\% with no significant difference between the two groups.\textsuperscript{31} Older age has been associated with increased mortality.\textsuperscript{32}

\textbf{We recommend utilizing monthly IV cyclophosphamide (0.35gm-0.75gm/m\textsuperscript{2}) with lower dosing for patients who are older (≥65years) or have markedly reduced kidney function (eGFR<30ml/min/1.73m\textsuperscript{2}).}

\textit{Rituximab}

Rituximab is an anti-CD20 chimeric monoclonal antibody. A decade ago, two groundbreaking RCTs revolutionized the treatment of ANCA vasculitis.\textsuperscript{15,16} RAVE trial found rituximab non-inferior to oral
cyclophosphamide for remission induction in 197 patients with newly-diagnosed or flaring GPA or MPA. Rituximab was more efficacious in relapsing disease (OR 1.40, 95% CI:1.03-1.91). Post-hoc analysis showed a higher complete remission rate for PR3-ANCA patients with rituximab compared to cyclophosphamide at 6-, 12- and 18-months. Although patients with serum creatinine >4 mg/dL were excluded from this study, remission rates between two groups based on the estimated glomerular filtration rates (eGFR) were not different.

Rituximab versus Cyclophosphamide in the 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/1.73 m²). The two groups had similar high remission induction rates at 12 months (76% rituximab versus 82% cyclophosphamide) and SAEs. At 2-years, the composite outcome of death, ESKD, and relapse was similar between the two groups. A retrospective study of 225 patients with severe renal involvement (eGFR<30 ml/min/1.73m²) noted no significant difference between cyclophosphamide and rituximab for induction.

We advise use of rituximab over cyclophosphamide in patients ≥65years 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 showing success with combination cyclophosphamide and rituximab, allowing rapid tapering of corticosteroids.
Combined induction with corticosteroids, rituximab, and low-dose intravenous cyclophosphamide was studied in a cohort of 66 patients with biopsy-proven renal ANCA vasculitis.\textsuperscript{37} Compared to 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:0.125-0.675), progression to ESKD (HR 0.20, 95% CI:0.06-0.65), and relapse rates (HR 0.49, 95% CI:0.25-0.97).\textsuperscript{37}

To reduce cyclophosphamide exposure, we recommend using intravenous cyclophosphamide and rituximab for induction in ANCA vasculitis, especially with severe renal involvement (eGFR<30ml/min/1.73m\textsuperscript{2} or diffuse crescentic glomerulonephritis) 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 (PLEX)**

Role of 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.\textsuperscript{39} Both groups received oral corticosteroids and cyclophosphamide; one group received intravenous methylprednisolone and the other PLEX. Renal biopsy characteristics were similar in both groups. No difference in adverse events and survival at one year was observed. However, PLEX was associated with lower progression to ESKD over 12 months (HR 0.47, 95% CI:0.24-0.91).\textsuperscript{39} A meta-analysis also showed potential reduction in the composite endpoint of ESKD and death in patients with ANCA vasculitis treated with PLEX.\textsuperscript{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 towards benefit (HR 0.64;
95% CI:0.40-1.05). In PEXIVAS, PLEX did not reduce the primary composite outcome of all-cause mortality and ESKD (HR 0.86, 95% CI:0.65-1.13) in patients with severe ANCA vasculitis, defined as eGFR<50 mL/min/1.73m² or pulmonary hemorrhage. 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. 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, the updated American Society of Apheresis guidelines still supports use of PLEX in a subset of patients with severe acute kidney failure and pulmonary hemorrhage.

**We recommend limiting PLEX use for ANCA vasculitis to patients with severe acute kidney injury (eGFR<30ml/min/1.73m² 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. In a retrospective study, 29 of 67 patients treated with mycophenolate mofetil (MMF) received MMF for remission induction. MMF was comparable to cyclophosphamide for induction. Jones et. al. randomized 140 newly diagnosed active ANCA vasculitis patients (132 adult and 8 pediatric) to receive either MMF or pulse cyclophosphamide, followed by azathioprine for remission maintenance. Patients with life-threatening vasculitis, eGFR<15 mL/min/m² or rapidly declining kidney
function were excluded. While MMF was non-inferior to cyclophosphamide in inducing remission (67% vs. 61%), more relapses were seen in the MMF group (33% vs. 19%) with similar serious infectious risk.\textsuperscript{43} In another RCT with 84 patients, fewer participants attained sustained remission with MMF as compared to cyclophosphamide (66% vs. 81%).\textsuperscript{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 with a variety of medications including rituximab, azathioprine, mycophenolate, methotrexate, and glucocorticoids.

The cyclophosphamide or azathioprine as a remission therapy for vasculitis (CYCAZEREM) trial demonstrated that azathioprine could safely replace oral cyclophosphamide for maintenance without increasing the relapse rate.\textsuperscript{46} The International Mycophenolate Mofetil Protocol to Reduce Outbreaks of Vasculitides (IMPROVE) trial compared MMF to azathioprine in maintaining remission after cyclophosphamide induction. While both treatment arms had similar adverse events, MMF had a higher relapse rate (HR 1.69, 95% CI:1.06-2.70).\textsuperscript{47} The Wegener's Granulomatosis–Entretien (WEGENT) trial was designed to compare the safety of azathioprine to methotrexate. Among 126 patients in remission, there was no difference in the safety or relapse between the two groups.\textsuperscript{48} Other trials have found methotrexate to be a safe alternate to cyclophosphamide in maintaining remission.\textsuperscript{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 trial (MAINRITSAN) which compared low-dose rituximab
(500mg on days 0 and 14, 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 typical. Long-term follow-up showed higher relapse-free survival for the rituximab group at 60 months.

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 1000mg rituximab every 4 months for 5 doses or 2mg/kg/day of azathioprine for 24 months. While 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.

Dosing, Relapses and Duration of Treatment

MAINRITSAN2 examined dosing of rituximab for remission. Participants in remission either received fixed 500mg rituximab infusion on days 0 and 14, then 6, 12 and 18 months or tailored therapy. The tailored group received 500mg rituximab at randomization and re-dosed based on CD19+ B-lymphocytes or ANCA titer. Relapses were similar in both groups at 28 months (17.3% versus 9.9%), but the tailored group received fewer infusions (median 3 versus 5).

Optimal duration of maintenance therapy is unknown. Patients with PR3-ANCA (compared to MPO-ANCA), upper respiratory or lung involvement are more likely to relapse. While 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. While the 48-month therapy had fewer relapses (22% versus 63%), although higher than other rituximab
trials, and lower ESKD rate (0 versus 4 cases), more frequent SAEs were noted in this group (9 versus 3 events).  

In the Glomerular Disease Collaborative Network (GDCN) registry, we analyzed 427 patients, of whom 277 (65%) stopped therapy at a median of 20 months post-induction. These patients remained off immunosuppression for a median of 36 months (IQR 13-88). Sixty-three patients were off therapy for five or more years, with 13 (20.6%) patients relapsing after five years. Patients were more likely to come off treatment if they were women, had MPO-ANCA and renal-limited disease.

Recently, MAINRITSAN3 studied the effect of extended maintenance rituximab therapy on relapse and death. MAINRITSAN3 included patients from MAINRITSAN2 who were in remission at month 28. Ninety-seven participants either received placebo or rituximab (500mg biannually) for an additional 18 months. At 28 months, 96% receiving rituximab versus 74% receiving placebo were relapse-free (HR 7.5, 95% CI:1.67-33.7). The number of SAEs were similar between the two groups, although the mean gamma globulin was lower in the rituximab group. While 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.

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

Alternative Therapies
Mepolizimab, an interleukin-5 monoclonal antibody, is approved by the Food and Drug Administration for treating EGPA following studies showing efficacy and acceptable safety. Intravenous immunoglobulin (IVIG) has been utilized successfully as adjunctive therapy in both MPO- and PR3-ANCA vasculitis for refractory or relapsing disease. IVIG is usually considered in patients with hypogammaglobulinemia, especially with recurrent infections, either as immunoglobulin replacement therapy or in addition to ongoing immunosuppression. In patients unable to receive blood products or cyclophosphamide, eculizumab along with rituximab and steroids has been used successfully in case reports.

Belimumab, an anti-B-lymphocyte stimulator monoclonal antibody, did not reduce relapses when used as adjunctive therapy to azathioprine and glucocorticoids in remission maintenance. Similarly, Alemtuzumab, an anti-CD52 monoclonal antibody, and anti-thymocyte globulin have been investigated, but concerns exist regarding toxicity.

Management in the Dialysis Population

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

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 7.1mL/min/1.73m²; 87% requiring hemodialysis. Cyclophosphamide therapy and treatment response within 4 months of kidney biopsy were associated with improved renal and patient survival. Fifty-one percent 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. 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.

**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. In the European Renal Association-European Dialysis and Transplant Association registry, the 10-year patient and transplant survival after first kidney transplant was 74.8% and 63.7%, respectively, for patients with ANCA vasculitis. Numerous studies have highlighted benefits of kidney transplantation in ANCA vasculitides. One study noted a higher risk of graft failure in MPA compared to GPA patients.

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

Presence of positive ANCA titers should not preclude transplantation. However, presence of PR3-ANCA does carry a higher risk of relapse post-transplant, and these patients require closer follow-up. Relapse rate post-transplantation can vary from 4.7% to 17.3% over 44-66 months post-transplant. Treatment of ANCA-vasculitis flares post-transplant is similar to pre-transplant, taking patient characteristics and severity of flare into consideration.

**Conclusion**

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 based on patient preference, comorbidities, relapse risk, and ANCA type.

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