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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/m^2 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/m^2) with lower dosing for patients who are older (≥65 years) or have markedly reduced kidney function (eGFR <30 ml/min per 1.73 m^2).

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 m^2). 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 m^2) 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 m^2 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 m^2 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 m^2 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/m^2, 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 m^2; 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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