Current Therapies for ANCA-Associated Vasculitis

Lindsay Lally and Robert Spiera

Department of Medicine/Division of Rheumatology, Hospital for Special Surgery, New York, NY 10021; email: lallyl@hss.edu, spierar@hss.edu

Annu. Rev. Med. 2015. 66:227–40

First published online as a Review in Advance on October 17, 2014

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi: 10.1146/annurev-med-011514-023051

Keywords

granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis (Churg-Strauss), biologics

Abstract

The ANCA-associated vasculitides, granulomatosis with polyangiitis (GPA, formerly Wegener's), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss), are a group of multisystem autoimmune diseases characterized by necrotizing small- to medium-vessel vasculitis and the presence of anti-neutrophil cytoplasmic antibodies. Current therapeutic strategies consist of glucocorticoids in conjunction with either conventional or biologic agents for both induction of remission and remission maintenance. Treatment goals include reducing toxicity of induction therapy, preventing disease relapse, and limiting overall accrual of both disease-related damage and treatment-related morbidity. Future research directions include investigation of the optimal duration and frequency of maintenance therapy as well as development of targeted therapeutic agents, which is enhanced by emerging insights into disease pathogenesis.

INTRODUCTION

GPA: granulomatosis with polyangiitis

MPA: microscopic polyangiitis

ANCA: antineutrophil cytoplasmic autoantibody

AAV: ANCA-associated vasculitide

PR3: proteinase-3

MPO: myeloperoxidase

MTX: methotrexate

AZA: azathioprine

RTX: rituximab

Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) comprise the antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitides (AAVs), a group of systemic vasculitides characterized by pauci-immune necrotizing inflammation of small- to medium-sized blood vessels. AAVs are multisystem diseases affecting a variety of organ systems, with glomerulonephritis and pulmonary involvement being common manifestations. As the name implies, AAVs are associated with serologically detectable ANCAs in the majority of cases. ANCAs specifically directed against proteinase-3 (PR3) or myeloperoxidase (MPO) are associated with GPA and MPA, respectively, in >80% of cases (1). Conversely, only half of patients with EGPA are ANCA positive; when present, ANCAs are directed against MPO in 75% of cases (2). GPA and MPA share several clinical phenotypes and similar treatment responses, but unlike MPA, GPA is associated with extravascular granulomatous inflammation with a predilection for the upper and lower airways. Because of differences in clinical manifestations such as eosinophilia and asthma, disease course, and serologic positivity, EGPA is discussed separately at the end of this review.

In the past three decades, there have been several major advances in the treatment of AAV (**Table 1**). Although most of the observational data reflect the experience of physicians at the National Institutes of Health caring for GPA patients, similar trends are evident in MPA. Recognition of the efficacy of remission-induction regimens consisting of daily oral cyclophosphamide (CYC) and high-dose corticosteroids transformed this disease from uniformly fatal to a chronic-relapsing disease with mortality of 25% at five years (3). Although CYC is effective in inducing remission in the majority of patients, there is significant morbidity associated with CYC use (4). The efforts to minimize CYC-related toxicity led to adoption of the concept of inducing remission with CYC and maintaining it with less potent but safer immunosuppressives such as methotrexate (MTX) or azathioprine (AZA). Subsequently, stratification of AAV by disease severity led to the understanding that patients with limited disease, defined as no organ or life-threatening involvement, could be successfully treated with CYC-free regimens (5). The last major recent advance in AAV treatment was born out of the search for more targeted therapy. Targeting of B cells, known to be important in disease pathogenesis, with rituximab (RTX), the monoclonal anti-CD20 antibody, has been demonstrated to be effective for both remission induction and maintenance in severe AAV (6, 7). In 2011, RTX became the first therapy for GPA and MPA to be approved by the US Food and Drug Administration (FDA).

As AAV therapies continue to evolve, several treatment principles remain paramount. Treatment should be tailored to severity of disease. Ideally, therapy should be further individualized according to a patient's history, co-morbidities, and pattern of organ involvement. The treatment course should be conceptualized as consisting of two components, namely induction of remission followed by institution of maintenance therapy. Relapse is common in AAV, especially after discontinuation of immunosuppression; the risk of prolonged immunosuppression must be balanced with the risk of relapse and varies from patient to patient. End-organ damage, which can be the sequela of both previous disease activity and treatment-related toxicity, occurs frequently in AAV. Treatment should be directed to avoid accrual of permanent damage while ensuring immunosuppressive therapy is aimed only at manifestations of active disease, not those reflecting prior damage.

INDUCTION THERAPY

Severe Disease

Severe AAV is defined as organ- or life-threatening disease manifestations and encompasses most patients presenting with pulmonary-renal syndrome as well as those with scleritis, central nervous

Table 1 Induction and maintenance therapies for GPA/MPA

Therapy	Use	Data	Additional considerations
Cyclophosphamide	Induction in severe GPA/MPA	CR achieved in >75%, no difference in time to remission or mortality between PO or IV CYC, higher relapse rate with PO (4, 9, 10)	Concerns about toxicity (gonadal failure, bone marrow failure, malignancy) limit prolonged use
Rituximab	Induction in severe GPA/MPA maintenance	Noninferior to CYC for induction (6, 7)	Dosing frequency for maintenance under investigation, may have role for granulomatous ENT manifestations in GPA (50)
Methotrexate	Induction in limited GPA/MPA maintenance	Similar remission rates when compared to PO CYC with longer time to remission and more relapses (5, 15)	Caution in patients with renal insufficiency
Azathioprine	Maintenance	No difference in relapse rates compared to PO CYC (19), compared to MTX for maintenance no difference in relapse rate or adverse events (20)	
Leflunomide	Maintenance	Lower rate of major relapses compared to MTX (21)	In trial, high rates of drug discontinuation due to gastrointestinal side effects on high-dose leflunomide
Trimethoprim-sulfamethoxazole	Maintenance in limited GPA	Reduced relative risk of relapse compared to placebo (28)	Can consider as monotherapy for mild localized ENT or in combination with immunosuppressives
Mycophenolate mofetil	Maintenance	Higher rate of relapse compared to AZA (23)	Not generally used as first-line therapy for maintenance, may have role for induction in MPA (24, 25)

Abbreviations: AZA, azathioprine; CR, complete remission; CYC, cyclophosphamide; ENT, ear, nose, throat; GPA, granulomatosis with polyangiitis; IV, intravenous; MPA, microscopic polyangiitis; MTX, methotrexate; PO, oral.

system (CNS) involvement, and mesenteric ischemia (8). As mentioned above, CYC in combination with high-dose glucocorticoids was long considered the standard of care for remission induction therapy in severe AAV. Complete remission is attainable in more than three-quarters of patients treated with oral CYC at doses of 2 mg/kg/day (with dose reductions for older age and renal insufficiency); however, nearly half of patients historically treated with daily oral CYC developed serious treatment-related morbidity, including hemorrhagic cystitis, malignancy, and infertility (4). In an effort to minimize toxicity of oral CYC, use of pulse intravenous CYC (IV-CYC) was investigated. In a head-to-head study comparing daily oral to pulse IV-CYC in newly diagnosed AAV with renal involvement, there was no difference in time to remission or remission rates between the two groups (9). Patients treated with IV-CYC received lower cumulative doses of CYC and had one-third fewer occurrences of leukopenia. Although this initial study was not powered to detect a difference in relapse rates, long-term follow-up of study participants suggested an increased rate of relapse in those treated with IV-CYC (10). The possibly higher relapse rates in IV-CYC must be balanced with higher rates of leukopenia and potential infection in daily oral regimens (11). The selection of oral or IV-CYC needs to be an individualized decision between the patient and the treating physician. Regardless of the CYC regimen, all patients receiving CYC should be monitored serially for leukopenia, and prophylaxis against *Pneumocystis jirovecii* should

be administered, as patients with AAV have been demonstrated to have higher rates of *P. jirovecii* pneumonia compared to other patients with autoimmune disease on similar immunosuppressive regimens (12, 13).

B lymphocytes are implicated in the pathogenesis of AAV by giving rise to autoantibody-producing plasma cells, contributing to local cytokine production, acting as antigen-presenting cells, and enabling T cell costimulation. It had long been recognized that CYC in the doses used to treat AAV had profound suppressive effects on B lymphocytes (14). Specific targeting of B lymphocytes with RTX has been shown to be an effective treatment strategy in severe AAV. Two randomized trials including patients with both newly diagnosed and relapsing severe AAV demonstrated that RTX was noninferior to CYC for remission induction (6, 7). In the double-blind, double-dummy randomized controlled Rituximab in ANCA-Associated Vasculitis (RAVE) trial, a single course of rituximab (375 mg/m^2 per week for four weeks) was compared to CYC followed by AZA in 197 AAV patients. Patients with serum creatinine greater than 4 mg/dl or alveolar hemorrhage requiring mechanical ventilatory support were excluded from RAVE. The primary endpoint, namely complete remission and tapering of prednisone at six months, was achieved by 64% of patients receiving RTX compared to 53% of those receiving CYC, meeting the criteria for noninferiority. In the subset of patients with relapsing disease at trial enrollment, RTX appeared to be superior to CYC in inducing remission. There were similar rates of flares and serious adverse events in both treatment groups.

Published concurrent to RAVE, the Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis (RITUXIVAS) study was an open-label trial in which patients with newly diagnosed AAV with renal involvement were randomized 3:1 to receive RTX plus two doses of IV-CYC or pulse IV-CYC (7). Patients in both arms received similar high-dose corticosteroids. At 12 months, 76% of patients in the RTX-CYC group and 82% of the CYC-only patients had achieved sustained remission. Similarly, there were no differences between the two groups in incidence of severe adverse events. Paralleling the results from RAVE, RITUXIVAS concluded that an RTX-based regimen was noninferior to a standard CYC induction regimen with similar rates of adverse events. Thus, with the results of these two studies showing efficacy of RTX in inducing remission, there has been increasing use of RTX as initial therapy in AAV, especially in patients with concerns about infertility or malignancy. Because patients with severe renal dysfunction and respiratory failure were excluded from RAVE, and RITUXIVAS used RTX in combination with CYC, the efficacy of RTX-only regimens in these critically ill patients is not well studied.

Limited Disease

Methotrexate (MTX), administered either orally or parenterally at doses of 20–25 mg weekly, can be used to induce remission in limited AAV. An open-label, randomized trial comparing MTX to CYC for remission induction in AAV patients demonstrated that MTX could be used instead of CYC in those without critical organ manifestations (5). In this study, which included patients with mild renal involvement, 90% of MTX-treated patients and 94% of CYC-treated patients had achieved remission at six months. Patients receiving MTX took a longer time to achieve remission. At 18 months, higher rates of relapse were seen in those who had been treated with MTX compared to CYC, although the majority of relapses occurred after therapy had been tapered off. This observation of high relapse rates after discontinuation of therapies has led to the standard continuation of maintenance immunosuppression for longer than 12 months in most patients. Follow-up of these patients at a median of six years following induction therapy revealed that patients initially treated with MTX had lower rates of relapse-free survival and were treated with immunosuppressive therapy for a longer period of time than those in the CYC group (15). Nonetheless, MTX remains a proven induction therapy for limited AAV.

MAINTENANCE THERAPY

Due to the toxicity and side-effect profile of long-term CYC treatment, the treatment paradigm in AAV has been to induce remission with CYC and then switch to an alternative immunosuppressive therapy after three to six months. Many alternatives, both conventional immunosuppressives and biologic agents, have been investigated as maintenance therapies following CYC induction. In patients receiving RTX or MTX as initial induction therapy, these same therapies can often be continued to maintain remission. Relapses are common in AAV, with the majority occurring after discontinuation of maintenance therapy. The optimal duration of maintenance therapy is unknown. Ideally, duration of maintenance therapy should be individualized and balance the patient's risk of relapse with treatment morbidity. Several factors associated with relapsing disease, including presence of PR3, prior relapse, and lung or upper-airway involvement, have been identified (16–18). Additionally, patients with GPA are at higher risk for relapse than those with MPA. Generally, longer duration of maintenance therapy should be considered in patients at high risk for relapsing disease.

Glucocorticoids remain part of most treatment regimens in active or relapsing disease and are usually tapered once remission is attained. Some patients are maintained on low-dose glucocorticoids during the maintenance period, though at most centers, the aim is for complete discontinuation of glucocorticoids after remission induction. The optimal tapering regimen and duration of glucocorticoid treatment are not established.

CONVENTIONAL IMMUNOSUPPRESSIVES

Azathioprine

In 2003, Jayne et al. published the CYCAZAREM trial, which randomized 155 patients with newly diagnosed AAV who had achieved remission on oral CYC to continue treatment with CYC at a lower dose or to switch to AZA at a dose of 2 mg/kg/day (19). All patients were placed on AZA at 12 months. The primary endpoint of this study was relapse rate at 18 months, which was not significantly different between the two treatment groups, nor was there a difference in adverse events observed between the groups. AZA is an effective and safe alternative to CYC in remission maintenance.

Methotrexate

Just as MTX has proven efficacy for remission induction in limited AAV, MTX can also be used as maintenance therapy. When MTX is used for both induction and maintenance therapy, it should generally be continued for at least 18 months to prevent relapse. Switching from CYC to MTX is also an established maintenance option. MTX and AZA for maintainence therapy were compared in a prospective, open-label trial of 159 AAV patients, all of whom received IV-CYC for induction (20). The primary endpoint of this trial was adverse events requiring discontinuation of therapy, and the hypothesis was that MTX would be less toxic than AZA. Rates of adverse events and relapse rates were similar in both groups of patients; echoing previous results, the majority of relapses in this trial occurred after discontinuation of maintenance therapy. Thus, MTX and AZA appear to be comparably efficacious and safe maintenance agents in AAV. In patients with permanent renal damage and reduced creatinine clearance, MTX should not be used because of its renal clearance, and AZA is likely a safer option. MTX is also a known teratogen, making AZA a better option for women of child-bearing potential.

Leflunomide

MMF: mycophenolate mofetil

Leflunomide was compared to MTX for remission maintenance in 54 patients following induction with CYC (21). Leflunomide was dosed at 30 mg daily, a dose higher than is typically used in clinical practice. This trial was terminated early owing to a higher incidence of major relapse in the MTX arm. However, patients treated with leflunomide experienced a significantly higher rate of adverse events. High rates of adverse events and discontinuation of therapy due to intolerability limit the use of leflunomide as first-line maintenance therapy. An uncontrolled study did show effectiveness of combination MTX and leflunomide in patients relapsing on either MTX or leflunomide monotherapy; however, 35% of patients discontinued the combination therapy owing to adverse events, most of which were gastrointestinal intolerance (22).

Mycophenolate Mofetil

With the widespread replacement of AZA with mycophenolate mofetil (MMF) in renal transplantation antirejection regimens, investigators considered the use of MMF in AAV maintenance, hypothesizing MMF would be more effective than AZA in preventing relapse. After CYC induction, 154 newly diagnosed AAV patients were randomized in an open-label study comparing MMF (dosed at 2000 mg/day) and AZA (23). At a median follow-up of 36 months, relapse rates were higher in the MMF treatment arm with a hazard ratio of 1.69. No differences in serious adverse events were observed. There have been no head-to-head comparisons of MMF and MTX. As MMF appears to be less efficacious than AZA in preventing relapse, it is not routinely used as a first-line maintenance therapy in AAV, although it may have a role in treating patients with refractory disease or those intolerant of other agents. Of note, small open-label pilot studies have shown MMF may be used as induction therapy in MPA patients with mild renal disease, although a controlled study comparing MMF to CYC was underpowered and ultimately inconclusive (24–26).

Trimethoprim-Sulfamethoxazole

Bacterial colonization, such as nasal carriage of *Staphylococcus aureus*, has been hypothesized to play a role in induction of autoimmunity and disease relapse in GPA patients (27). As such, the role of antistaphylococcal therapy with trimethoprim-sulfamethoxazole (TMP-SMX) was investigated as an adjunctive remission maintenance agent in GPA. In a double-blind study, 81 GPA patients, stratified by renal involvement, were randomized to receive TMP-SMX (800 mg/160 mg twice daily) or placebo (28). At 24 months, 82% of TMP-SMX treated patients were in remission compared to 60% of the placebo group with a relative risk of relapse for TMP-SMX of 0.4; however, 20% of the TMP-SMX group discontinued the medication owing to side effects. The benefit of TMP-SMX seemed most apparent in GPA patients with upper-airway involvement. Treatment doses of TMP-SMX can be considered an alternative maintenance therapy for GPA patients with mild, localized upper-airway disease or an adjunctive therapy in those on other immunosuppressive agents to reduce risk of relapse.

BIOLOGIC THERAPIES

Rituximab

A recently published follow-up of RAVE reported that among patients receiving the single course of RTX, 48% and 39% remained in complete remission at 12 and 18 months, respectively, compared to 39% and 33% of those in the CYC group, again meeting the criteria for noninferiority.

RTX again seemed superior in those with relapsing disease with no difference in adverse events between the groups (29). These data suggest that, given the prolonged duration of its biologic effects, a single course of RTX has comparable safety and efficacy to continuous conventional immunosuppressive therapy in remission induction and maintenance out to 18 months.

The ideal dosing frequency of RTX maintenance remains unknown. An observational study reporting the Mayo Clinic's decade-long experience with repeated RTX treatment for refractory GPA suggests utility in the combination of B lymphocyte reconstitution and ANCA level in predicting relapse (30). In this cohort of chronically relapsing patients, all observed relapses occurred after B cell reconstitution and were temporally accompanied by an increase in PR3 levels (except in one patient who was ANCA negative), suggesting that RTX retreatment can be individualized based on return of B lymphocytes and rising ANCA titers. Other investigators have demonstrated effectiveness of pre-emptive retreatment with RTX (31, 32). Smith et al. compared patients treated with RTX maintenance at a fixed dose and interval of 1 g every six months to those treated at time of relapse and found reduced relapse rates and longer periods of remission in the RTX retreatment group without an increase in infection or adverse events (31). A trial comparing these two RTX-based maintenance regimens, one based on reconstitution of B lymphocytes and rising ANCA and the other on a strategy of fixed-interval retreatment every six months, is currently ongoing. There is also an ongoing trial comparing RTX to AZA as maintenance therapy for relapsing AAV after remission induction with RTX. Hypogammaglobulinemia and neutropenia can be a consequence of repeated RTX administration and may predispose patients to infection. Belimumab, an approved therapy for systemic lupus erythematosus that targets B lymphocytes by inhibiting the critical B lymphocyte survival factor BLyS, is also being studied as a potential therapy for AAV.

Etanercept

Based on the known role of tumor necrosis factor α (TNFα) in granuloma formation and experimental data suggesting that TNFα may be an important inflammatory mediator in GPA, the Wegener's Granulomatosis Etanercept Trial (WGET) was conducted more than a decade ago (33). It was the first clinical trial in which a biologic was evaluated as a treatment for vasculitis. WGET randomized 180 GPA patients to receive either the TNFα blocker etanercept or placebo in addition to standard therapy for remission maintenance. Patients with limited disease at enrollment received MTX as standard therapy and those with severe disease were given CYC. There was no difference in rates of sustained remission in those receiving etanercept compared to placebo, and flares were common in both groups. WGET concluded etanercept is not effective for remission maintenance in GPA. Furthermore, six patients in the etanercept group developed solid malignancies whereas no patients in the control group developed malignancy. All of the patients who developed malignancy had received CYC prior to etanercept; whether TNFα blockade had an additive effect on malignancy risk in AAV is unknown. However, given the findings in WGET, anti-TNFα therapy does not have a routine role in treatment of AAV.

ADJUNCTIVE THERAPIES FOR REFRACTORY DISEASE

Plasma Exchange for Severe Renal Disease and Alveolar Hemorrhage

Because ANCAs are believed to play a role in disease pathogenesis, removal of the circulating pathogenic antibodies with plasma exchange has been utilized as adjunctive therapy in severe AAV. Plasma exchange, used in conjunction with standard induction therapy in patients with active glomerulonephritis, may improve renal recovery in dialysis-dependent patients and in those with

severe renal disease (defined as serum creatinine >5.8 mg/dl), but it does not appear to improve overall survival (34). The Methylprednisolone versus Plasma Exchange (MEPEX) trial was an open-label study of 1 g pulse methylprednisolone daily for three days compared to seven sessions of plasma exchange for newly diagnosed AAV with severe renal disease (35). All patients, 69% of whom were on dialysis at time of enrollment, were treated with oral corticosteroids and CYC. At three months, 69% of those treated with plasma exchange compared to 49% of those treated with methylprednisolone were alive and dialysis independent; similarly, plasma exchange–treated patients were less likely to progress to end-stage renal disease at one year. There have been no controlled trials of plasma exchange to treat diffuse alveolar hemorrhage, although retrospective data suggest there may be a benefit (36). To answer questions about the role of plasma exchange in AAV with alveolar hemorrhage and/or severe renal disease, the Plasma Exchange and Glucocorticoids for the Treatment of ANCA-associated Vasculitis, a randomized controlled international study evaluating adjunctive plasma exchange and two oral glucocorticoid regimens, is ongoing (37). By comparing a lower dose (0.5 mg/kg daily of prednisone) to the standard prednisone dose (1 mg/kg daily) for induction therapy, investigators hope to also determine the effectiveness of a treatment strategy employing a reduced initial and cumulative dose of glucocorticoids in addition to studying the role of plasma exchange in severe renal disease and alveolar hemorrhage.

Intravenous Immunoglobulin

Administration of pooled immunoglobulin has a variety of immunomodulatory effects, which are proposed to be modulated by effects on Fc receptors, downregulation of B and T lymphocytes, and inflammatory cytokine blockade (38). Intravenous immunoglobulin (IVIg) has been used in the treatment of refractory AAV. In the only controlled trial of IVIg in AAV, 34 patients with persistent disease activity on immunosuppressive therapy (CYC or AZA) were randomized to receive adjunctive IVIg (2 g/kg) or placebo (39). More patients in the IVIg group experienced a reduction in disease activity, but this difference was not maintained after three months. Several small, uncontrolled experiences with IVIg in relapsing or persistent disease yielded conflicting results; one study suggested benefit, with 13 of 22 patients in complete remission at nine months, whereas another reported that 0 of 15 patients achieved complete remission after repeated cycles of IVIg (40, 41). The discrepancy may in part be related to differences in IVIg dose and frequency of administration. Some authors have speculated that IVIg might have a synergistic effect when given in combination with RTX, as has been done in management of other immune-mediated diseases (42), but there are currently no data supporting this approach in AAV.

Gusperimus

Gusperimus (15-deoxyspergualin) is a synthetic molecule with potent immunosuppressive effects whose mechanism of action is poorly understood but believed to involve modulation of B cells, T cells, and antigen-presenting cells (43). Two small open-label studies have demonstrated safety and efficacy of gusperimus (administered subcutaneously for 21 days) in patients with refractory GPA (44, 45). Reversible leukopenia was commonly observed in gusperimus-treated patients; thus, serial monitoring of white blood cell count is recommended during treatment. A randomized controlled trial comparing gusperimus to conventional therapy in GPA is under way.

Rituximab for Limited Disease Manifestations

Although the efficacy of RTX for induction and maintenance in severe AAV has been demonstrated, there are no controlled studies of RTX expressly for limited disease manifestations. In

GPA, the most common limited manifestations occur in the upper airway and otolaryngologic domain, with granulomatous extravascular lesions present in >90% of GPA patients (4). As noted above, upper-airway involvement is an independent risk factor for disease relapse (17, 18). In addition to frequent relapse, persistent, grumbling otolaryngologic disease is common and can lead to accrual of permanent damage such as nasal bridge collapse, hearing loss, and subglottic stenosis. The efficacy of RTX for the granulomatous compared to vasculitic manifestations of GPA is debated, with several case series offering conflicting results (46–50). Failure of several of these studies to demonstrate efficacy of RTX for granulomatous GPA was driven mostly by failure to improve orbital disease. This is a notoriously refractory disease feature, and radiographic differentiation between active disease and necrosis can be difficult. Recently, in the largest reported experience of RTX solely for otolaryngologic manifestations of GPA, patients receiving RTX for active ENT (ear, nose, and throat) disease were >10 times less likely to have active ENT disease compared to patients being treated with other therapies (50). Results of this retrospective study suggest RTX may be a useful therapy for granulomatous otolaryngologic disease in GPA.

FUTURE TREATMENT STRATEGIES

Future treatment strategies will likely focus on agents targeting elements of the innate and adaptive immune response thought to be involved in disease pathogenesis. Complement activation, particularly through the alternative pathway, has been implicated in pathogenesis of AAV, with murine and human studies suggesting the common pathway component C5a plays a key role (51–53). In murine models of MPO-induced glomerulonephritis, C5a knockouts or treatment with a C5a receptor inhibitor abrogated disease development (54). A small-molecule oral inhibitor of human C5a receptor, CCX168, is currently being investigated in patients with AAV and active renal involvement.

Although the role of B cells in AAV pathogenesis has long been appreciated, there is increasing focus on T cell dysregulation in AAV. T cells are known to be the predominant effector cells present in inflammatory tissue infiltrates, with evidence that presence of T cell tubulitis is a predictor of poor renal outcome (55). Abnormally activated T cells can be detected in the sera of AAV patients during periods of disease activity, and remission and signature of $CD8^+$ T cells may identify a group of AAV patients more likely to relapse, which could allow for a more tailored approach to maintenance therapy (56, 57). Therapeutic strategies targeting T cells are under investigation. Blocking T cell costimulation with abatacept, CTLA4-Ig, has recently been investigated in AAV (58). In an open-label study of 20 GPA patients with nonsevere relapsing disease, the addition of intravenous abatacept to maintenance therapy (MTX, AZA, or MMF) resulted in clinical remission in 80% of patients. Abatacept, however, was ultimately discontinued in six patients due to increasing disease activity. A double-blind placebo-controlled trial to evaluate efficacy of abatacept in relapsing GPA is planned. Lymphocyte depletion with alemtuzumab, an anti-CD52 monoclonal antibody, has demonstrated effectiveness in inducing sustained remission in refractory AAV in a single-center retrospective analysis; however, high rates of infection, adverse events, and death were reported in long-term follow-up (59).

EGPA

Eosinophilic granulomatosis with polyangiitis (EGPA) commonly presents with asthma/allergic rhinitis, pulmonary infiltrates, and peripheral eosinophilia. Asthma is a cardinal feature of EGPA, and development of asthma and atopy often precede frank vasculitic manifestations by several years. The vasculitic phase of EGPA, which most commonly affects the skin and peripheral

nervous system (with mononeuritis multiplex occurring in up to 75% of patients in some cohorts), represents a distinct phase of disease (60). Renal involvement with glomerulonephritis occurs in approximately one-quarter of patients and is more common in those with serologically detectable ANCA (61).

Treatment of EGPA is largely driven by the affected organ systems and severity of vasculitic disease. The French Vasculitis Study Group has devised a scoring system, the five-factor score (FFS), to quantify disease activity and severity in EGPA and guide initial management decisions (62). In its first iteration, one point was given for presence of each of these five factors: cardiac involvement, gastrointestinal ischemia, renal insufficiency, proteinuria, and CNS disease. Patients with more than two of these manifestations are given a score of 2. A more recent version of the FFS included age over 65 and absence of otolaryngologic disease as features indicating a poor prognosis, and proteinuria and CNS disease were removed from the score (63). The FFS has important treatment and prognostic implications.

Glucocorticoids are the mainstay of therapy for EGPA. The initial dose and tapering schedule are not standardized and are based on individual presentation. In patients with nonsevere disease (FFS 0), glucocorticoids alone can be used. An open-label study of 72 EGPA patients without poor-prognostic factors demonstrated that 93% of patients achieved remission on systemic glucocorticoids alone; however, one-third of patients relapsed and required additional immunosuppressive agents, and 80% of patients required low doses of steroids to maintain remission (64).

CYC in addition to glucocorticoids is recommended for patients with severe disease manifestations (FFS 2 or FFS 1 with CNS or cardiac involvement). Some experts also advocate using CYC as the initial treatment when there is aggressive vasculitic involvement of peripheral nervous system, such as a mononeuritis multiplex. Treatment with CYC substantially reduces mortality in these patients with poor-prognostic features (65). There are no studies of oral versus IV CYC in EGPA or data on optimal duration of CYC treatment, so practice is usually extrapolated from management of the other AAVs. Similarly, AZA or MTX can be used as induction therapy in place of CYC in patients with mild to moderate disease severity, although there are limited data in EGPA to support this practice. Observational cohorts also support the use of AZA as maintenance therapy or in those with relapsing disease. In general, the approach to EGPA treatment parallels the management of GPA and MPA in that initial treatment choice should be tailored to disease severity, pattern of organ involvement, and patient comorbidities, with a step down to less potent immunosuppressives once remission has been induced. Small series have been reported in which refractory EGPA was treated with RTX with improvement in disease activity in both ANCA-positive and ANCA-negative patients, although no controlled data exist (66).

Promising future therapies for EGPA target pathways involved in disease pathogenesis. A Th2 immune response has been implicated in disease pathogenesis, with high levels of IL-5 driving the obligatory eosinophilia in EGPA (67). A monoclonal antibody antagonizing IL-5, mepolizumab, which has been used in hypereosinophilic syndromes, has been investigated in EGPA. Open-label experience with mepolizumab in EGPA suggests safety and a steroid-sparing effect (68, 69). A large controlled trial of mepolizumab in EGPA is ongoing.

CONCLUSION

The current therapeutic armamentarium for AAVs includes agents with proven efficacy for remission induction and/or maintenance. Current treatments are limited by high rates of relapse, treatment-related toxicity, and comorbidity. Emerging therapeutics will target pathways implicated in AAV disease pathogenesis and may provide additional therapeutic options.

DISCLOSURE STATEMENT

Dr. Lally is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. Dr. Spiera has received grant funding for research from Roche-Genetech. This has included support for investigator initiated clinical trials.

LITERATURE CITED

1. Finkielman JD, Lee AS, Hummel AM, et al. 2007. ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. *Am. J. Med.* 120(7):9–14
2. Sablé-Fourtassou R, Cohen P, Mahr A, et al. 2005. Antineutrophil cytoplasmic antibodies in the Churg-Strauss syndrome. *Ann. Intern. Med.* 143(9):632–38
3. Flossmann O, Berden A, de Groot K, et al. 2011. Long-term patient survival in ANCA-associated vasculitis. *Ann. Rheum. Dis.* 70(3):488–94
4. Hoffman GS, Kerr GS, Leavitt RY, et al. 1992. Wegener granulomatosis: an analysis of 158 patients. *Ann. Intern. Med.* 116(6):488–98
5. de Groot K, Rasmussen N, Bacon PA, et al. 2005. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 52(8):2461–89
6. Stone JH, Merkle PA, Spiera R, et al. 2010. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N. Engl. J. Med.* 363(3):221–32
7. Jones RB, Tervaert JW, Hauser T, et al. 2010. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N. Engl. J. Med.* 363(3):211–20
8. Stone JH, Wegener's Granulomatosis Etanercept Trial Research Group. 2003. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's granulomatosis etanercept trial. *Arthritis Rheum.* 48(8):2299–309
9. de Groot K, Harper L, Jayne DR, et al. 2009. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann. Intern. Med.* 150(10):670–80
10. Harper L, Morgan MD, Walsh M, et al. 2012. Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann. Rheum. Dis.* 71(6):955–60
11. de Groot K, Adu D, Savage CO, European Vasculitis Study Group (EUVAS). 2001. The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review. *Nephrol. Dial. Transplant.* 16(10):2018–27
12. Mukhtyar C, Guillevin L, Cid MC, et al. 2009. EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann. Rheum. Dis.* 68(3):310–17
13. Falagas ME, Manta KG, Betsi GI, Pappas G. 2007. Infection-related morbidity and mortality in patients with connective tissue diseases: a systematic review. *Clin. Rheumatol.* 26(5):663–70
14. Cupps TR, Edgar LC, Fauci AS. 1982. Suppression of human B lymphocyte function by cyclophosphamide. *J. Immunol.* 128(6):2453–57
15. Faurschou M, Westman K, Rasmussen N, et al. 2012. Brief report: long-term outcome of a randomized clinical trial comparing methotrexate to cyclophosphamide for remission induction in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 34(10):3472–77
16. Hogan SL, Falk RJ, Chin H, et al. 2005. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann. Intern. Med.* 143(9):621–31
17. Walsh M, Flossmann O, Berden A, et al. 2012. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 64(2):542–48
18. Pagnoux C, Hogan SL, Chin H, et al. 2008. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum.* 58(9):2908–18
19. Jayne D, Rasmussen N, Andrassy K, et al. 2003. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N. Engl. J. Med.* 349(1):36–44

20. Pagnoux C, Mahr A, Hamidou MA, et al. 2008. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N. Engl. J. Med.* 359(26):2790–803
21. Metzler C, Miehle N, Manger K, et al. 2007. Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. *Rheumatology* 46(7):1087–91
22. Bremer JP1, Ullrich S, Laudien M, et al. 2010. Methotrexate plus leflunomide for the treatment of relapsing Wegener's granulomatosis. A retrospective uncontrolled study. *Clin. Exp. Rheumatol.* 28 (1 Suppl. 57):67–71
23. Hiemstra TF, Walsh M, Mahr A, et al. 2010. Mycophenolate mofetil versus azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 304(21):2381–88
24. Silva F, Specks U, Kalra S, et al. 2010. Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement—a prospective, open-label pilot trial. *Clin. J. Am. Soc. Nephrol.* 5(3):445–53
25. Han F, Liu G, Zhang X, et al. 2011. Effects of mycophenolate mofetil combined with corticosteroids for induction therapy of microscopic polyangiitis. *Am. J. Nephrol.* 33(2):185–92
26. Alba MA, Flores-Suarez LF. 2013. Seven clinical conundrums in the treatment of ANCA-associated vasculitis. *Clin. Exp. Rheumatol.* 31(Suppl. 75):74–83
27. Tadema H, Heeringa P, Kallenberg CG. 2011. Bacterial infections in Wegener's granulomatosis: mechanisms potentially involved in autoimmune pathogenesis. *Curr. Opin. Rheumatol.* 23(4):366–71
28. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. 1996. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N. Engl. J. Med.* 335(1):16–20
29. Specks U, Merkle PA, Seo P, et al. 2013. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N. Engl. J. Med.* 369(5):417–27
30. Cartin-Ceba R, Golbin J, Keogh KA, et al. 2012. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): a single-center ten-year experience. *Arthritis Rheum.* 64(11):3770–78
31. Smith RM, Jones RB, Guerry M, et al. 2012. Rituximab for remission maintenance in relapsing antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* 64(11):3760–69
32. Calich AL, Puéchal X, Pugnet G, et al. 2014. Rituximab for induction and maintenance therapy in granulomatosis with polyangiitis (Wegeners). Results of a single-center cohort study on 66 patients. *J. Autoimmun.* 50:135–41
33. Wegener's Granulomatosis Etanercept Research Group. 2005. Etanercept plus standard therapy for Wegener's granulomatosis. *N. Engl. J. Med.* 352(4):351–61
34. Pusey CD, Rees AJ, Evans DJ, et al. 1991. Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. *Kidney Int.* 40(4):757–63
35. Jayne DR, Gaskin G, Rasmussen N, et al. 2007. Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J. Am. Soc. Nephrol.* 18(7):2180–88
36. Klemmer PJ, Chalermskulrat W, Reif MS, et al. 2003. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. *Am. J. Kidney Dis.* 42(6)1149–52
37. Walsh M, Merkle PA, Peh CA, et al. 2013. Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. *Trials* 14:73
38. Bayry J, Negi VS, Kayeri SV. 2011. Intravenous immunoglobulin therapy in rheumatic diseases. *Nat. Rev. Rheumatol.* 7(6):349–59
39. Jayne DR, Chapel H, Adu D, et al. 2000. Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM* 93(7):433–39
40. Martinez V, Cohen P, Pagnoux C, et al. 2008. 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(1):308–17
41. Richter C, Schnabel A, Csernok E, et al. 1995. Treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis with high-dose intravenous immunoglobulin. *Clin. Exp. Immunol.* 101(1):2–7

42. Aries PM, Hellmich B, Gross WL. 2005. Intravenous immunoglobulin therapy in vasculitis: speculation or evidence? *Clin. Rev. Allergy Immunol.* 29(3):237–45
43. Perenyei M, Jayne DR, Floßmann O. 2014. Gusperimus: immunological mechanism and clinical applications. *Rheumatology* 53:1732–41
44. Flossman O, Baslund B, Bruchfeld A, et al. 2009. Deoxyspergualin in relapsing and refractory Wegener's granulomatosis. *Ann. Rheum. Dis.* 68(7):1125–30
45. Schmitt WH, Birck R, Heinzel PA, et al. 2005. Prolonged treatment of refractory Wegener's granulomatosis with 15-deoxyspergualin: an open study in seven patients. *Nephrol. Dial. Transplant.* 20(6):1083–92
46. Holle J, Dubrau C, Herlyn K, et al. 2012. Rituximab for refractory granulomatosis with polyangiitis: comparison of efficacy in granulomatous versus vasculitic manifestation. *Ann. Rheum. Dis.* 71(3):327–33
47. Aries PM, Hellmich B, Voswinkel J, et al. 2006. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. *Ann. Rheum. Dis.* 65(7):853–85
48. Seo P, Specks U, Keogh KA. 2008. Efficacy of rituximab in limited Wegener's with refractory granulomatous manifestations. *J. Rheum.* 35(10):2017–23
49. Martinez DP, Chaudhry A, Jones RB, et al. 2009. B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study. *Clin. Otolaryngol.* 34(4):328–35
50. Lally L, Lebovic R, Huang WT, Spiera R. 2014. Effectiveness of rituximab for the otolaryngologic manifestations of granulomatosis with polyangiitis. *Arthritis Care Res.* 66:1403–9
51. Xiao H, Schreiber A, Heeringa P, et al. 2007. Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. *Am. J. Pathol.* 170(1):52–64
52. Schreiber A, Xiao H, Jeannette JC, et al. 2009. C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. *J. Am. Soc. Nephrol.* 20:289–98
53. Yuan J, Gou SJ, Huang J. 2012. C5a and its receptors in human anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. *Arthritis Res. Ther.* 14(3):R140–52
54. Xiao H, Dairaghi DJ, Powers JP, et al. 2014. C5a receptor (CD88) blockade protects against MPO-ANCA GN. *J. Am. Soc. Nephrol.* 25(2):225–31
55. Berden AE, Jones RB, Erasmus DD, et al. 2012. Tubular lesions predict renal outcome in antineutrophil cytoplasmic antibody associated glomerulonephritis after rituximab therapy. *J. Am. Soc. Nephrol.* 23(2):313–21
56. Wilde B, Thewissen M, Deamoiseaux J, et al. 2010. T cells in ANCA-associated vasculitis: What can we learn from lesional versus circulating T cells? *Arthritis Res. Ther.* 12(1):204–13
57. McKinney EF, Lyons PA, Carr EJ. 2010. A CD8+ T cell transcription signature predicts prognosis in autoimmune disease. *Nat. Med.* 16(5):586–91
58. Langford CA, Monarch PA, Specks U, et al. 2013. An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). *Ann. Rheum. Dis.* 73(7):1376–9
59. Walsh M, Chaudhry A, Jayne D. 2008. Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-IH). *Ann. Rheum. Dis.* 67(9):1322–27
60. Comarmond C, Pagnoux C, Khellaf M, et al. 2013. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): clinical characteristics and long-term followup of the 383 patients enrolled in the French Vasculitis Study Group cohort. *Arthritis Rheum.* 65(1):270–81
61. Sinico RA, Di Toma L, Maggiore U, et al. 2005. Renal involvement in Churg-Strauss syndrome. *Am. J. Kidney Dis.* 47(5):770–79
62. Guillevin L, Lhote F, Gayraud M, et al. 1996. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine* 75(1):17–28
63. Guillevin L, Pagnoux C, Seror R, et al. 2011. The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine* 90(1):19–27
64. Ribi C, Cohen P, Pagnoux C, et al. 2008. Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheum.* 58(2):586–94

65. Gayraud M, Guillevin L, le Toumelin P, et al. 2001. Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum.* 44(3):666–75
66. Thiel J, Hässler F, Salzer U, et al. 2013. Rituximab in the treatment of refractory or relapsing eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Arthritis Res. Ther.* 15(5):R133–42
67. Jakiela B, Szczeklik W, Plutecka H, et al. 2012. Increased production of IL-5 and dominant Th2-type response in airways of Churg-Strauss syndrome patients. *Rheumatology* 51(10):1887–93
68. Kim S, Marigowda G, Oren E, et al. 2010. Mepolizumab as a steroid-sparing treatment option in patients with Churg-Strauss syndrome. *J. Allergy Clin. Immunol.* 125(6):1336–43
69. Moosig F, Gross WL, Hermann K, et al. 2011. Targeting interleukin-5 in refractory and relapsing Churg-Strauss syndrome. *Ann. Intern. Med.* 155(5):341–34