We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

5,800
Open access books available

142,000
International authors and editors

180M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Treatment of ANCA-Associated Vasculitis in Adults

Aurore Fifi-Mah and Cheryl Barnabe

Additional information is available at the end of the chapter

1. Introduction

Vasculitis is the general term used to describe diseases associated with inflammation of the blood vessels. This inflammation results in end-organ ischemia and damage with life-threatening consequences. Treatment is tailored to the type of vasculitis the patient has, prognostic features and disease severity. Two main treatment phases are recognized: induction of remission, and maintenance of remission. In this chapter we will focus on the treatment of ANCA-associated vasculitis (AAV), namely: Granulomatosis with polyangiitis (GPA), formerly Wegener's Granulomatosis; Eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss Syndrome, and Microscopic Polyangiitis (MPA). Patients with Polyarteritis nodosa (PAN) were included in the initial therapeutic trials of these diseases, therefore some of the studies results have been applied to that population as well.

We introduce first the historical use of glucocorticoids, which are uniformly incorporated in the treatment protocols of therapeutic trials. Cyclophosphamide is recommended for the induction of remission in AAV, and in particular for generalized and severe disease. CYCLOPS, a trial of oral versus intravenous cyclophosphamide, demonstrated that intravenous dosing was as effective in inducing remission with a reduced cumulative dose, and with fewer episodes of leucopenia, but in long-term follow-up relapse was more common in the intravenous treatment group. NORAM compared the use of methotrexate compared to oral cyclophosphamide for induction of remission in patients with limited GPA, and concluded that methotrexate was nearly as effective as cyclosphosphamide in achieving remission, but in long-term follow-up more corticosteroids and further immunosuppressive agents were required. More recently, rituximab use for the induction of remission was studied in the RAVE and RITUXVAS clinical trials. Rituximab was proven to be effective as cyclophosphamide, but without a reduction in the rate of infection as had been expected. Plasma exchange in combination with oral cyclophosphamide for patients with severe renal involvement significantly decreases the risk of end-stage renal disease compared to intravenous steroids and oral cyclophosphamide, but without a significant difference in patient survival.

Maintenance of remission is typically with oral cyclophosphamide, azathioprine or metho-trexate, with demonstrated efficacy in the CYCAZAREM and WEGENT studies. Leflunomide is also effective, and mycophenolate mofetil is less effective than azathioprine but is an alternative agent should the others not be tolerated. Etanercept therapy does not have a role in maintenance therapy given its inefficacy and toxicity in patients exposed to cyclophospha-mide. Other anti-TNF agents, rituximab, Intravenous Immunoglobulin (IVIg), 15-Deoxysper-gualin, antithymocyte globulin and alemtuzumab (CAMPATH-1H) have shown some benefit for refractory or relapsing disease and require further evaluation.

We conclude the chapter by discussing the use of trimethoprim-sulfamethoxazole (T/S) use in localized disease, as well as a specific focus on the treatment evidence in EGPA with and without poor prognostic factors.

2. ANCA-associated vasculitis (AAV)

AAV refers to primary forms of vasculitis targeting the small and medium sized arteries. These were initially differentiated on the basis of clinical features in the 1990 American College of Rheumatology (ACR) classification [1-4]. Further refinements to the classification criteria and new nomenclature have evolved from the initial classification criteria. In 1994, the Chapel Hill Consensus Conference group incorporated vessel size and pathological features to define the different primary vasculitides. They also introduced the use of antibodies to discriminate between vasculitis of the small vessels [5]. Anti-neutrophil cytoplasmic antibodies (ANCA) were initially described in 1985 in patients with segmental necrotizing and crescentic glomer-ulonephritis [6] but were later identified in patients with GPA, EGPA and MPA, and are associated with these conditions with high sensitivity and specificity [7].

There are two major types of ANCA recognized by indirect immunofluorescence (IIF). The perinuclear pattern, or P-ANCA, is characterized by immunofluorescence seen at the periph-ery of the nucleus of alcohol-fixed neutrophils. The cytoplasmic pattern, or C-ANCA, is characterized by diffuse staining of the cytoplasm. C-ANCA has a specificity for proteinase 3 (PR3), most frequently associated with GPA. P-ANCA has a specificity for myeloperoxidase (MPO), and is most commonly seen in MPA and EGPA.

Although the etiopathogenesis of AAV is not yet well understood, immune system dysregu-lation and abnormal inflammatory responses ensue. Therapies which alter immune system signaling and response are used to halt perpetuation of the inflammatory response to prevent end-organ damage and suppress disease activity.

3. Outcomes without treatment and determining prognosis

Because these diseases have a high mortality rate (82% of mortality in GPA at one year without treatment) [8] and relapse frequently (38% of patients with AAV will experience

a relapse within 5 years despite treatment) [9] treatment protocols have reflected the need to obtain rapid control of disease activity and maintain long-term immunosuppression while reducing drug toxicity. This is the basis for an induction phase of treatment to achieve remission followed by a maintenance phase to reduce the risk of relapse. Guillevin et al. developed the Five Factor Score [10] to identify factors associated with poor prognosis at the time of diagnosis. They initially analysed 342 patients with MPA, EGPA and PAN, and the five factors associated with increased mortality were: renal failure with creatinine greater than 140 µmol/L, proteinuria greater than 1 gram/day, cardiac involvement, central nervous system involvement, or severe gastro-intestinal involvement. In patients with none of these features, the 5 year survival rate was 88.1%. With 1 of these features, the 5 year survival rate declined to 74.1%, and with 2 or more of these features the survival rate was only 54.1%. The analysis of a larger group of 1108 patients with GPA, MPA, EGPA and PAN in 2009 [11] resulted in the identification of new prognosis factors associated with an increase in 5-year mortality rate. These include age > 65 years, cardiac involvement, gastro-intestinal involvement, and renal failure with creatinine >150 µmol/L. The presence of ear, nose and throat symptoms in patients with GPA and EGPA is associated with a lower relative risk of death.

4. Categorization of disease severity to guide initial treatment agent

As reflected in the European League Against Rheumatism (EULAR) treatment guidelines [12] the initial immunosuppressive agent choice is dictated by the extent and severity of the disease. The European Vasculitis Study (EUVAS) disease categorisation [13] separates disease severity into localized disease, early systemic disease, generalized, severe and refractory disease.

Category	Definition
Localised	Upper and/or lower respiratory tract disease without any other systemic involvement or constitutional symptoms
Early Systemic	Any, without organ-threatening or life-threatening disease
Generalised	Renal or other organ threatening disease, serum creatinine <500 µmol/liter (5.6 mg/dl)
Severe	Renal or other vital organ failure, serum creatinine "/>500 µmol/litre (5.6 mg/dl)
Refractory	Progressive disease unresponsive to glucocorticoids and cyclophosphamide

Table 1. Categorization of disease severity to guide initial treatment in anti-neutrophilic cytoplasmic antibodies (ANCA)-associated vasculitis [13]

We will now review in detail the evidence for the agents recommended in these treatment guidelines, as well as new evidence arising since their development.

5. Induction of remission

5.1. Glucocorticoids

Efficacy: Glucocorticoids are the first line treatment to rapidly control inflammation and prevent further organ damage in patients with active AAV. There is no trial evidence to support the use, dose or route of steroids traditionally used in AAV but certainly experience has solidified their clinical use. In all the randomized trials glucocorticoids were used in combination with immunosuppressants and is it not possible to know their effect alone. A report in 1957 of 17 patients with PAN revealed that the use of glucocorticoids alone lead to 80% survival at 12 months compared to 64% in an untreated group [14]. However the superiority of cortisone was not maintained at 3 years [14, 15].

In randomized controlled studies of remission induction, prednisone is started at 1 mg/kg then tapered to a low dose (e.g. 5 mg at 18 months in CYCLOPS) [16] or completely stopped at 12 months (NORAM) [17] or even 6 months (WGET [18], RAVE [19]). The complete weaning of steroids is not necessarily desirable as shown by a meta-analysis done by Walsh et al [20]. Continuation of low dose prednisone (5-7.5 mg/day) was associated with a lower relapse rate of 14% (95%CI 10-19%) compared to a relapse rate of 43% (95%CI 33-52%) in those with complete glucocorticoid discontinuation.

The European Vasculitis Study group (EUVAS) guidelines for the treatment of AAV [12] indicate that high dose prednisolone or prednisone at 1 mg/kg be used for the first month, then tapered to no less than 15 mg at 3 months and 10 mg or lower during the maintenance phase of treatment. In instances where rapid control of disease is necessary, parenteral methylprednisolone (1 g daily for 3 days) should be used in addition to oral glucocorticoids.

A clinical trial currently in progress named 'plasma exchange and glucocorticoid dosing in the treatment of ANCA-associated vasculitis' (PEXIVAS) (ClinicalTrials.gov Identifier: NCT00987389) will address the question of dose and tapering schedule of glucocorticoids. The trial design will compare the standard dosing of glucocorticoids (similar to the recommendations of EUVAS) compared to a reduced dose regimen. All patients will receive between 1 and 3 g of intravenous methylprednisolone over 1 to 3 days, then daily oral glucocorticoid, which may consist of prednisone or prednisolone and administered through a weight-based protocol. Based on body weight, all participants will receive either 50, 60 or 75 mg/day of oral glucocorticoid for 7 days. Participants in the standard-dose group will continue at 50, 60 or 75 mg/day for 7 additional days and taper to between 12.5 and 20 mg/day at 3 months and 5 mg/day at 6 months. Participants in the low-dose group will continue at 25, 30 or 40 mg/day for 7 days and taper to between 6 and 10 mg/day by 3 months and 5 mg/day by 6 months.
All patients will receive 5 mg/day from 6 months to 12 months after randomisation.

Safety: Multiple adverse consequences of steroid therapy are recognized, including weight gain and fat redistribution, fluid retention and hypertension, irritability and difficulty sleeping, cataracts and glaucoma, elevated blood sugars and skin thinning. It is critical to minimize steroid exposure while suppressing disease activity. It is common practice to prescribe therapy to reduce the risk of glucocorticoid-induced osteoporosis. Vitamin D supplementation and

Calcium intake should fall in line with local treatment recommendations, and bisphosphonates are typically necessary for patients as they will be exposed to prolonged steroid use. Additional considerations are prophylaxis against opportunistic infections such as *Pneumocystis jiroveci* with Trimethoprim/Sulfamethoxazole (T/S), and stress-dose steroids for critical illness.

5.2. Induction of remission in generalized and severe AAV

5.2.1. Cyclophosphamide

Efficacy: Cyclophosphamide is typically reserved for patients with severe or generalized AAV, or if a poor prognostic factor is present. In 1973, Fauci and Wolff published their experience of treating 18 patients with GPA and systemic involvement with oral cyclophosphamide [21]. Twelve patients achieved remission, and 6 were able to discontinue immunosuppression after several months. They later reported on a larger cohort of 85 patients with GPA treated with a protocol of oral cyclophosphamide of 2 mg/kg/day and high dose prednisone of 1 mg/kg /day [22]. They were followed prospectively over 21 years with 93% achieving complete remission and a mean survival of 48 months although 29% relapsed. This work also highlighted the toxicity of this drug, such as gonadal failure, cystitis in 34% of patients, and 1 patient developing lymphoma.

In an effort to reduce the toxicity associated with the prolonged used of cyclophosphamide, Hoffman et al [23] designed a protocol of intravenous pulses, similar to the National Institute of Health (NIH) study of treatment of severe lupus nephritis [24]. Fourteen patients with GPA, 12 with relapsing disease previously treated with daily oral cyclophosphamide, received monthly pulses of $1g/m^2$ of cyclophosphamide for 6 months along with high dose oral glucocorticoids. If remission was achieved the pulses were reduced in frequency to every 2 months for 6 months then every 3 months for a total of 1.5 years. Glucocorticoids were tapered and stopped over this time period. Unfortunately, although 93% improved initially, only 21% had sustained remission. Thirty six percent (4 patients) had experienced toxicity, mostly attributable to infections, but confounded by the concomitant use of high doses of prednisone.

A subsequent 18 month European open-label randomized controlled multicenter clinical trial, CYCLOPS [16], of pulse versus daily oral cyclophosphamide in 149 newly diagnosed patients with AAV (including GPA, MPA and renal limited vasculitis) with renal involvement and a creatinine between 150 and 500 umol/L was performed. Patients in the intravenous pulse group received cyclophosphamide 15 mg/kg every 2 weeks for the first 3 pulses then continued either intravenous pulse (15 mg/kg) or oral pulse (5 mg/kg for 3 consecutive days), every 3 weeks afterwards until remission and then for another 3 months. The oral cyclophosphamide group received 2 mg/kg daily until remission then 1.5 mg/kg for another 3 months. Remission maintenance was with azathioprine at a dose of 2 mg/kg for 18 months. The cyclophosphamide doses were adjusted for renal function and age, as well as leukocyte count, with a maximum dose of 1.2 g in the pulse group and 200 mg in the daily oral group. Both groups were also treated with oral glucocorticoids during induction, with initially 1 mg/kg (maximum 80 mg) used, but with progressive tapering to 12.5 mg at 3 months and 5 mg at 18 months.

The administration route of cyclophosphamide did not affect the remission rate, with 88% of subjects randomized to pulse therapy and 88% of subjects randomized to daily oral therapy in remission at 9 months. Both groups had a median time to remission of 3 months (range of 0.5 to 8 months in the pulse group and 1 to 7.5 months in the daily oral group). The cumulative dose in the oral group was higher than the pulse group (median 15.9 g vs. 8.2 g) with a lower rate of leukopenia in the pulse group.

The long-term follow-up of these studies was recently reported [25]. Retrospective chart information was available for 134 out of 148 patients, and 1 patient was subsequently excluded as their diagnosis was changed to EGPA. The median follow-up was 4.3 years. An increased relapse rate was observed in the pulse group compared to the daily oral group. Fifteen (20.8%) of the daily oral group and 30 (39.5%) of the pulse group had at least one relapse. However there was no difference in survival, renal function nor adverse events between groups. The presence of PR3-ANCA was independently associated with an increase risk of relapse (hazard ratio 2.47 (95%CI 1.32-4.59, p=0.004).

A meta-analysis [26] of randomized trials [27-29] comparing daily oral versus intravenous pulse of cyclophosphamide concluded that pulse therapy was significantly less likely to fail in remission induction (odds ratio (OR) 0.29 (95% CI 0.12-0.73) and had a significantly lower risk of infection (OR: 0.45 (95% CI 0.23-0.89)) and leucopenia (OR 0.36 (95% CI 0.17-0.78)). There was a non-significant increase in the relapse odds in the pulse cyclophosphamide group (OR 1.79 (95%CI 0.85-3.75).

Safety: Although cyclophosphamide has been the mainstay of treatment for generalized and severe forms of AAV, there are several limitations to its use. First, there are significant adverse events associated with this drug even at the lower cumulative dose achieved through pulse therapy. Infertility is a concern in individuals of childbearing age, and bladder toxicity and malignancy are associated with increased morbidity and mortality [30-32]. The development of leukopenia significantly increases the risk of bacterial infection, and renders the patient susceptible to opportunistic infections. Table 2 provides dose adjustment recommendations based on the patient's age, renal function and leukocyte nadir to reduce the risk of toxicity.

5.2.2. Rituximab

Efficacy: The use of Rituximab, an anti-CD20 monoclonal antibody depleting B lymphocytes, has been reported in several case series and case reports to be effective in patients with generalized, severe and refractory disease [33]. This was subsequently confirmed by 2 randomized controlled trials published in 2010, "Rituximab in ANCA-associated Vasculitis" (RAVE) [19] and "Randomised Trial of Rituximab Versus Cyclophosphamide for Generalized ANCA-Associated Vasculitis" (RITUXVAS) [34]. In these two studies rituximab was non-inferior and/or equivalent to cyclophosphamide in inducing remission in AAV. Rituximab was superior to cyclophosphamide in relapsing patients.

RAVE [19] was a North American multicentre, randomized, double blind, controlled thera-peutic trial where 197 patients with new or relapsing ANCA positive GPA and MPA without severe renal disease (creatinine less than 354 umol/L) or severe alveolar hemorrhage (not

	Age	Creatinine	Leukocyte nadir (10-14 days)	Leukocyte count
IV cyclosphamide: 15 mg/kg Max dose: 1.2 g	>60: reduce dose by 2.5 mg/kg per pulse >70: reduce dose by 5 mg/kg per pulse	300 to 500 µmol/L (3.4 to 5.7 mg/dL) reduce pulse by 2.5 mg/kg	2 to 3 x10^9/L reduce dose of subsequent pulse by 20% 1 to 2 x10^9/L reduce dose of subsequent pulse by 40%	
Daily Oral cyclophosphamide 2 mg/kg Max dose: 200 mg	>60 reduce dose by 25% >70 reduce dose by 50%			< 4x10^9/L stop drug until >4 reduce dose by 25% <1x10^9/L restart at 50 mg then increase weekly as tolerated

Table 2. Adjusted cyclophosphamide dose according to age, renal function and leukocyte count [16]

requiring a ventilator). The study was designed as a non-inferiority trial comparing intravenous rituximab (375 mg/m^2 of body surface weekly for 4 weeks) to daily oral cyclophosphamide (2mg/kg). Both groups received methylprednisolone 1 g for one to three pulses, followed by prednisone 1 mg/kg. The primary end point was defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) [35] of 0 and the complete discontinuation of prednisone at 6 months. Once remission was achieved by 3 to 6 months, maintenance therapy was initiated in the cyclophosphamide group with azathioprine (2 mg/kg), however the Rituximab group did not receive maintenance therapy. There was no difference in the primary outcome at 6 months between the 2 groups. Sixty-three of the 99 patients in the rituximab group (64%) reached the primary end point, as compared with 52 of 98 in the control group (53%), and met the criterion for non-inferiority (P<0.001). However, among patients with relapsing disease at baseline, rituximab was more efficacious than cyclophosphamide, with 34 of 51 patients in the rituximab group (67%) reaching the primary end point, as compared with only 21 of 50 in the control group (42%) (p=0.01). In an oral presentation at the American College of Rheumatology Annual Meeting in November 2011, the extended follow-up to 18 months was reported. One single course of rituximab without maintenance therapy was as effective as 18 months of induction and maintenance therapy with cyclophosphamide followed by azathioprine. Complete remission was achieved and sustained at 6, 12, and 18 months in 64%, 47%, and 39% of subjects in the rituximab arm, comparable at 53%, 39%, and 33% of subjects in the cyclophosphamide/azathioprine arm, respectively. Disease flares in the two treatment arms did not differ in number or severity, and no unexpected safety issues were detected. Patients at highest risk for flare had GPA, were PR3 positive, were without major renal disease, and had relapsing disease at baseline. Disease flares in the rituximab treated subjects occurred only after the return of detectable levels of B cells.

RITUXVAS [34] was a European multicenter, open label, randomized trial of rituximab compared to intravenous cyclophosphamide in 44 patients with newly diagnosed ANCA-associated vasculitis with renal involvement [34]. Subjects in the rituximab group received both

rituximab (375 mg/m^2 per week for 4 consecutive weeks) and intravenous cyclophosphamide (15 mg/kg) with the first and third rituximab infusions. They did not receive any maintenance therapy. If they had progressive disease within the first 6 months, a third dose of intravenous cyclophosphamide was permitted. Subjects in the control group received intravenous cyclophosphamide (15 mg/kg), every 2 weeks for the first three doses then every 3 weeks for 3 to 6 months until remission, followed by azathioprine for maintenance. Both treatment arms received 1 g of intravenous methylprednisolone and then oral prednisone at 1 mg/kg per day initially, with a reduction to 5 mg per day at the end of 6 months. The primary outcome was sustained remission and rates of serious adverse events at 12 months. Thirty-three subjects were enrolled in the rituximab group and 11 in the control group. Sustained remission was observed in 25 of 33 patients in the rituximab group (76%) and 9 of 11 patients in the control group (82%) (p=0.68). Six of the 33 subjects in the rituximab group (18%) and 2 of the 11 patients in the control group (18%) died. Among the survivors, sustained remission rates at 12 months were equal, and observed in 93% of the rituximab group and 90% of the control group (p = 0.80). The median time to remission was 90 days (interquartile range, 79 to 112) in the rituximab group and 94 days (interquartile range, 91 to 100) in the control group (p=0.87). At 12 months of follow-up, 4 of 27 subjects in the rituximab group (15%) and 1 of 10 subjects in the control group (10%) suffered a relapse (p=0.70). This study also demonstrated efficacy in serious renal disease. Among the 9 subjects who were on dialysis at study entry, 6 of the 8 subjects randomized to the rituximab group attained sustained remission, and 5 no longer required dialysis.

Safety: Unfortunately, rituximab use was not associated with a lower rate of serious adverse events in either study, although there were more episodes of leukopenia in subjects randomized to cyclophosphamide. In the RAVE study, there were no significant differences between the treatment groups in the numbers of total adverse events, serious adverse events, or non−disease related adverse events. During the first 6 months of the trial, solid malignant tumors were diagnosed in 1 patient in each group; 2 patients in the control group and 1 in the rituximab group died. Six malignant conditions developed in 5 additional patients after 6 months. Four of those patients had been assigned initially to rituximab and one had been assigned to cyclophosphamide. Among patients with exposure to rituximab during the trial, malignant conditions developed in 6 of 124 (5%), as compared with 1 of 73 patients without exposure to rituximab (1%, p=0.26). In RITUXVAS, severe adverse events were similar between groups (rituximab group 42% and 36% in the standard care group). Infection rates were similar (rituximab group incidence rate 0.66/patient year vs 0.60/patient year in the standard care group). Dialysis patients were particular prone to adverse events, with 3 of the 9 dying, and 7 of 9 with at least one serious adverse event.

5.2.3. Plasma exchange

The rationale for the physical removal of ANCA by plasma exchange is based on the demonstration of the pathogenic role of ANCA in animal models of AAV [36, 37]. Corticosteroids and cyclophosphamide are used concomitantly to suppress inflammation and autoantibody production.

A study of patients with severe renal involvement of GPA and MPA causing rapidly progressive glomerulonephritis was designed to compare intravenous (IV) methylprednisolone and plasma exchange [38]. One hundred and thirty-seven patients with creatinine >500 umol/l were enrolled in this open label, randomized trial and 69% were on dialysis for less than 2 weeks at study entry. Both groups received oral cyclophosphamide (2.5 mg/kg/day reduced to 1.5 mg/kg/day at 3 months and stopped at 6 months), followed by azathioprine (2 mg/kg/day). Oral prednisolone was tapered from 1 mg/kg/day at entry to 0.25 mg/kg/day by week 10,15 mg/day at 3 months and10mg/day from 5 to12 months. The IV methylprednisolone group (n=67) received 1000 mg/day for three consecutive days, and the subjects in the plasma exchange group (n=70) underwent a total of seven plasma exchanges within 14 days of study entry, with a plasma exchange volume of 60 ml/kg on each occasion and volume replacement with 5% albumin mandated in the protocol. The primary outcome measure was renal recovery at 3 months, defined by patient survival, dialysis independence, and serum creatinine <500 umol/l (5.8 mg/dl).

There was a significant decrease in the risk of end-stage renal disease in the plasma exchange group compared to IV methylprednisolone but there was no significant difference in patient survival at 12 months. By 3 months, renal recovery had occurred in 33 (49%) of 67 of the IV methylprednisolone group and 48 (69%) of 70 of the plasma exchange group (95%CI for the difference 18 to 35%; p = 0.02). This effect was sustained to 12 months from entry with only two from each group progressing to end stage renal disease after initial recovery, with a risk reduction of 24% (95%CI 6.1 to 41) at 12 months. At 12 months, 43% of subjects in the IV methylprednisolone group and 59% of subjects in the plasma exchange group remained alive and independent of dialysis (p = 0.008). The hazard ratio for end stage renal disease over 12 months for plasma exchange versus IV methylprednisolone was 0.47 (95%CI 0.24 to 0.91; p = 0.03). Subject survival at 3 and 12 months respectively was 84% and 76% in the IV methylprednisolone group and 84% and 73% in the plasma exchange group (log rank test p = 0.68). Mortality was 25.5% at 12 months, and the major causes of death were infection (n = 19), pulmonary hemorrhage (n = 6), and cardiovascular disease (n = 4). Most deaths occurred during the first 3 months, when corticosteroid dosages were highest and vasculitis was most active. After 3 months, there was a higher mortality in those who had failed to recover renal function.

5.3. Induction of remission in early systemic disease

5.3.1. Methotrexate

The treatment of AAV with cyclophosphamide is associated with significant toxicity and morbidity as previously discussed. Alternative immunosuppression to reduce this risk have been studied. The "Non-Renal Wegener's Granulomatosis Treated Alternatively with Methotrexate" (NORAM) [17] trial was designed to test the hypothesis than methotrexate could replace cyclophosphamide for remission induction. NORAM was a non-inferiority, unblinded, prospective, randomized, controlled trial in early systemic GPA and MPA, without organ-threatening or life-threatening disease and a creatinine of less than 150 umol/

L. More than 90% of patients had GPA. In total, 49 subjects were treated with methotrexate (15 mg/week orally escalating to a maximum of 20–25 mg/week by 12 weeks), which was then maintained until month 10 and then tapered and discontinued by month 12. A total of 46 subjects received oral cyclophosphamide (2 mg/kg/day (maximum 150 mg/day) until remission), for a minimum of 3 and a maximum of 6 months. Dose alterations were made for subjects >60 years of age, and the drug was withdrawn if the total white blood cell count fell below 4 $\times10^9$/liter. At remission, cyclophosphamide was reduced to 1.5 mg/kg/day until month 10, when it was tapered and discontinued by month 12. Both treatment groups received oral prednisolone 1 mg/kg/day, tapered to 15 mg/day at 12 weeks and 7.5 mg/day by 6 months, and discontinued by 12 months. The primary end point was induction of remission within 6 months. Between month 12 to 18, patients received no immunosuppressant agents.

At 6 months, 90% of subjects randomized to methotrexate and 94% of subjects randomized to cyclophosphamide achieved remission (p=0.041). The median time to remission was 3 months (range 1–9) in the methotrexate group and 2 months (range 1–5) in the cyclophosphamide group (p=0.19 log rank test). Of the subjects who achieved remission during the treatment period, 70% of the subjects randomized to methotrexate and 47% of subjects randomized to cyclophosphamide had a relapse, with the time to relapse being significantly longer in the cyclophosphamide group (median 15 months, range 4-17) compared to the methotrexate group (median 13 months, range 2-17) (P =0.023 log rank test). Leukopenia was more common in the cyclophosphamide group and liver dysfunction was more common in the methotrexate group.

The long term follow-up of patients treated in the NORAM study was recently reported [39]. Data was obtained on all 95 original subjects with a median duration of follow-up of 6 years. Subjects in the methotrexate group required a longer duration of corticosteroid therapy during the trial period of 18 months (median 15 months, interquartile range (IQR) 12-18) compared to 12 months (IQR 12-15) in the cyclophosphamide group, p=0.005). During subsequent follow-up, the median duration of corticosteroid therapy during months 19-60 was 3.0 years in the methotrexate group and only 1.5 years in the cyclophosphamide group (p=0.004). After the trial period of 18 months, patients' treatment was left at the discretion of their physicians. Physicians were asked to provide information regarding drugs used to manage disease flare such as cyclophosphamide, methotrexate, azathioprine and mycophenolate mofetil. Exposure to cyclophosphamide and these other agents was also longer in the methotrexate group (p=0.037; and p=0.031, respectively).

Overall, the cumulative relapse-free survival from the time of first remission was 69% after 1 year, 32% after 3 years, and 24% after 5 years of follow-up, demonstrating a trend to being higher in the cyclophosphamide group (p=0.056, logrank test). The cumulative overall survival did not differ between treatment arms (p=0.88, log-rank test) and was 98% after 1 year, 93% after 3 years, and 89% after 5 years. The number of serious infections did not differ between treatment groups. The authors have concluded that methotrexate therapy was associated with less effective long-term disease control as compared to cyclophosphamide.

6. Maintenance of remission

The relapse rate of AAV is high, as demonstrated by the different induction trials, and occur frequently during a drug withdrawal period [32, 39]. Therefore it is important to maintain long-term immunosuppression, while limiting drug toxicity. When a standardized treatment of induction of remission followed by maintenance therapy is applied, the relapse rate in GPA can be reduced from 76.8% (in cohorts treated before 1993) to 50% (in cohorts treated after 1999) over 5 years follow-up [40]. Several studies have provided different drug alternatives for maintenance of remission.

6.1. Azathioprine

An 18 month prospective open label study (CYCAZAREM) compared the use of oral cyclophosphamide to azathioprine in the maintenance phase, with 155 subjects with GPA, MPA and renal limited vasculitis recruited from 39 hospitals in 11 European countries [41]. All subjects had received the same remission-induction therapy, consisting of daily oral cyclophosphamide (2 mg/kg) and prednisolone (initially 1 mg/kg/day, with the dose tapered to 0.25 mg/kg/day by 12 weeks). Renal vasculitis was the most common form of organ involvement, occurring in 94 percent of the patients in the study. Patients attaining remission by 3 months, and those attaining remission between 3 and 6 months, were randomly assigned to treatment with azathioprine (2 mg/kg/day) or to continue cyclophosphamide therapy at a lower dose (1.5 mg/kg/day). Both treatment groups continued to receive prednisolone 10 mg daily. At 12 months after study entry, both groups received azathioprine at a dose of 1.5 mg/kg/day and prednisolone 7.5 mg daily. The primary end point was relapse, either major (threatened function of the kidney, lung, brain, eye, motor nerve or gut) or minor (affecting at least three other items in the Birmingham Vasculitis Activity Score (BVAS)) [42].

Of the initial 155 subjects, clinical remission was achieved in 93% overall, with 77% reaching this target by 3 months and 16% between 3 and 6 months. These patients were randomly assigned to cyclophosphamide (73 patients) or azathioprine (71 patients). Azathioprine was demonstrated to be equivalent to cyclophosphamide for maintenance therapy. Sixteen percent in the azathioprine group had relapses, compared to 14% in the cyclophosphamide group (p=0.65). Five patients in each group had a major relapse. The most frequent adverse event was neutropenia (55% of patients, including the remission and maintenance phase), with 52% of infections occurring during an episode of neutropenia. There was no difference in renal outcomes between the groups, with renal failure occurring in only 3% of patients.

6.2. Methotrexate

A prospective, open-label, multicenter trial, comparing methotrexate and azathioprine for maintenance of remission in GPA and MPA (WEGENT) was designed to detect treatment tolerance [43]. Three-quarters of the patients had GPA. Sixty-three patients who had achieved remission with intravenous cyclophosphamide and corticosteroids received oral azathioprine (2 mg/kg/day) and 63 received methotrexate (initial 0.3 mg/kg/week, progressively increased to 25 mg per week) for 12 months. At the end of the scheduled maintenance therapy period,

azathioprine and methotrexate were withdrawn over a period of 3 months at the discretion of the treating physician. T/S was recommended for 2 additional years for patients with GPA after discontinuation of the maintenance immunosuppressive agents. The primary end point was an adverse event requiring discontinuation of the study drug or causing death.

At the censoring date for analysis, the mean follow-up after randomization was 29 months. Adverse events leading to the primary end point (i.e., discontinuation of the study drug or death) occurred in 11% of the azathioprine group and 19% in the methotrexate group (p=0.21). After starting maintenance therapy, 46% of azathioprine recipients had at least one adverse event as compared with 56% of methotrexate recipients (p= 0.29). Thirty-six percent of azathioprine subjects and 33% of methotrexate subjects had a relapse (p=0.71). In 73% of the patients the relapse occurred after discontinuation of the drugs. This study demonstrated that the two agents were equivalent in safety and also efficacy. There was a trend toward a higher risk of adverse events with methotrexate, with a hazard ratio of 1.65 (95%CI, 0.65-4.18).

6.3. Mycophenolate mofetil

Mycophenolate mofetil is a prodrug of mycophenolic acid, which is a reversible inhibitor of inosine monophosphate dehydrogenase in guanosine nucleotide synthesis, upon which T and B cells are dependent, and has cytostatic effects on lymphocytes [44]. It has been proposed as a less toxic alternative to azathioprine and has been evaluated in one randomized trial. The IMPROVE study was an open-label trial to assess whether mycophenolate mofetil reduces the risk of relapse compared with azathioprine in patients with AAV in remission [45]. All patients received cyclophosphamide (daily oral or intermittent intravenous doses for a maximum of 6 months) and glucocorticoids (up to 3 g of methylprednisolone over 3 days was allowed for severe disease, then 1 mg/kg/day (maximum 80 mg) of oral prednisolone) for induction of remission. Plasma exchange could also be used for severe disease. Oral steroids were reduced according to a standardized schedule to 15 mg/day at the start of the remission regimen, tapered to 5 mg/day after 12 months, and were withdrawn after 24 months. One hundred and fifty six patients with a new diagnosis of GPA and MPA were enrolled after remission was achieved. The azathioprine group (n=80) initially received 2 mg/kg/day (maximum 200 mg), with dose reductions to 1.5 mg/kg/day after 12 months and 1 mg/kg/day after 18 months, with drug withdrawal after 42 months. Seventy-six patients assigned to the mycophenolate mofetil group received 2 g/day, which was reduced to 1500 mg/day after 12 months, 1000 mg/day after 18 months, and withdrawn after 42 months. The primary end point was relapse-free survival, defined as the time from remission to the first relapse (major or minor), withdrawal, death or loss to follow-up, or the end of the follow-up period.

Median follow-up for both treatment groups from start of maintenance therapy was 39 months. Relapses were more common in the mycophenolate mofetil group. In total, 55% of the mycophenolate mofetil recipients experienced relapses (18 major, 24 minor), as compared to 38% of azathioprine recipients (10 major, 20 minor), with an unadjusted hazard ratio for mycophenolate mofetil use of 1.69 (95%CI, 1.06-2.70; p=0.03) at 4 years. The risk of severe adverse events was not significantly different between groups, with a hazard ratio of 0.53 (95%CI, 0.23-1.18, p=0.12). Therefore mycophenolate mofetil should not be considered as a first

choice for maintenance of remission in AAV, but could be used in situations of intolerance or contraindication to azathioprine.

6.4. Leflunomide

Leflunomide is a disease-modifying agent commonly used in the treatment of rheumatoid arthritis as an alternative to methotrexate. A prospective randomized controlled trial of leflunomide compared to methotrexate in patients with generalized GPA for maintenance of remission was conducted in 5 German rheumatology centres [46]. The study was powered to find equivalence between the 2 drugs. Patients achieving complete or partial remission with daily oral cyclophosphamide (2mg/kg) and prednisolone and maintained remission for at least 3 months were enrolled in the study. Partial remission was defined as partial improvement of the disease persisting for at least 3 months represented by a constant disease extent index and BVAS. Complete remission was defined as the absence of pathological findings in clinical, radiological and serological investigations, irrespective of the ANCA titre. Twenty-eight subjects received oral methotrexate starting at a dose of 7.5 mg/week, increased over 9 weeks to 20 mg/week. Folic acid 10 mg weekly was taken the day after methotrexate. Twenty-six patients received leflunomide with a loading dose of 100 mg daily for 3 days, followed by 20 mg daily and then increased to 30 mg daily after 4 weeks. Prednisone was allowed at a dose of 10mg/day or less, and was tapered by 2.5mg/month in the absence of disease activity until a dose of 5 mg was reached, and then by 1 mg/month thereafter. The primary efficacy outcome was the number of major and minor relapses.

In the leflunomide group, 23% of subjects experienced a relapse, compared to 46% of metho-trexate subjects (p=0.09), and the incidence of major relapses was significantly higher in the methotrexate group (p=0.037). The study was terminated prematurely in September 2003 after the advisory board had decided that the high rate of major relapses in the methotrexate group was not acceptable.

Safety: There was no significant difference in the number of adverse events between the groups. Thirty-four adverse events were observed in the leflunomide group and 17 in the methotrexate group (p=0.09). Leflunomide was stopped in two patients with intractable hypertension, one patient with peripheral neuropathy and one patient with leucopenia, whereas no patient stopped due to adverse events in the methotrexate group. Twenty-five infectious episodes, 13 in the leflunomide group and 12 in the methotrexate group were noted, all responding well to conventional antibiotic treatment on outpatient basis.

7. Refractory/relapsing disease

Some patients have disease that proves to be refractory to the therapies used for induction and maintenance of remission as above. Typically, patients with lung and upper airway involve-ment, positive PR3-ANCA and severe renal involvement have more resistant disease [47-49]. Relapse is also frequent in AAV, with an overall risk of 38% at 5 years seen in a large cohort of 535 patients from 70 European trial sites between 1995 and 2002 [32]. The presence of positive

PR3 ANCA, cardiac involvement and absence of severe renal disease at presentation was found to be a predictor of relapse in that group [9]. A variety of agents have been proposed to address these refractory cases.

7.1. Tumor necrosis factor inhibition

7.1.1. Etanercept

The "Wegener's Granulomatosis Etanercept Trial" (WGET) was a randomized, double blind, placebo controlled trial of etanercept as an adjunct to conventional therapy in patients with GPA [18]. The study enrolled 181 patients from 8 centres in the United States. Patients had newly diagnosed or relapsing GPA with a BVAS/WG of ≥3 and either limited or severe manifestations of their disease. Etanercept at the dose of 25 mg twice weekly subcutaneously or placebo was used simultaneously at the time of randomization with conventional therapy (corticosteroids along with methotrexate for limited disease and oral cyclophosphamide followed by methotrexate for severe disease induction and azathioprine for maintenance) and maintained as the conventional drugs were tapered over time. Prednisone was tapered by a specific protocol to be completely discontinued within six months, assuming that no relapse occurred.

The primary outcome measure was sustained disease remission, defined as a BVAS/WG of 0, for at least six months. The median duration of treatment was 25 months for etanercept and 19 months for placebo and the mean duration of follow-up was 27 months in the overall cohort. Seventy percent of subjects in the etanercept group met the primary outcome, as compared with 75% in the control group (p=0.39). There was no significant difference between groups in the time to sustained remission. The overall rate of sustained remission throughout follow-up was only 49.4%. Disease flares during treatment were not significantly different between the etanercept and control groups (relative risk, 0.89 (95%CI 0.62 to 1.28; p=0.54). The major concern arising from this study however was in the development of adverse events. Moderately severe to fatal infections occurred in 49% of subjects and were equal between treatment groups, however six solid cancers were identified during the trial, and all occurred in the etanercept group (standardized incidence ratio of 3.12 (95%CI 1.15–6.80, p=0.014)). An additional 3 other patients were subsequently diagnosed with a solid malignancy within 6 months of completion of the trial [50]. This study clearly demonstrated that etanercept was not effective, and the use of etanercept in combination with cyclophosphamide is associated with an increased risk of malignancy.

7.1.2. Infliximab and adalimumab

Infliximab has been studied as an adjuvant therapy for induction of remission in new, relapsing and refractory disease. A prospective, open label, multicenter study in the United Kingdom evaluated 2 small groups of patients with active disease [51]. In the new presentation or relapse group, infliximab (5 mg/kg) was given at 0, 2, 6 and 10 weeks as an adjuvant therapy to oral cyclophosphamide (2mg/kg/day) for 14 weeks and prednisolone. Once remission was achieved the cyclophosphamide was replaced by azathioprine (2 mg/kg/day, reduced to 1.5

mg/kg/day after 1 year) or mycophenolate mofetil if azathioprine wasn't tolerated. In patients with persistent disease despite the use of methotrexate, azathioprine, mycophenolate mofetil or T/S, infliximab (5 mg/kg) at 0, 2, 6 and 10 weeks was added. If remission was achieved infliximab was maintained every 6 weeks for 1 year. In both groups, 88% achieved remission (BVAS ≤1) within a mean of 6.4 weeks. During follow-up (mean 17 months), only 18% experienced a relapse of disease. Both groups were able to significantly reduce their glucocorticoid dose from a mean of 24 mg/day to 9 mg/day at week 14. There were 2 deaths in the newly diagnosed and relapsing group and 21% had severe infections. A second study has also examined infliximab use (5 mg/kg at 0, 2, 6 and 10 weeks) in addition to standard therapy and found no effect [52]. At 1 year, time to achieve remission, remission rates, adverse events, damage index scores, and relapse rates were similar between groups.

Adalimumab was used as an adjunctive therapy in a single centre, open label, prospective, uncontrolled study of newly diagnosed patients with GPA or MPA with renal involvement [53]. Seventy-nine percent of patients achieved remission (BVAS = 0) within the first 14 weeks of the study, and the mean oral prednisolone dose decreased from 37 to 8 mg/day, demonstrating potential efficacy but requiring further rigorous study.

7.2. Rituximab

Smith et al [54] reported a retrospective study of maintenance therapy with Rituximab in 73 patients with refractory or relapsing GPA and MPA. Twenty-eight received treatment with a single dose of rituximab (1000 mg) at the time of relapse. Of these, 19 were subsequently retreated at 6 months intervals. Another 45 patients were treated with rituximab (1000 mg twice at an interval of 2 weeks) and then received treatment (1000 mg) every 6 months for 24 months with ongoing follow-up for an additional 24 months. Of the patients treated with a single 1000 mg dose at relapse, 73% relapsed within 24 months. The frequency of relapse was lower in patients who received retreatment at 6 months at only 11% (p<0.001), and in those treated with the higher initial dose and ongoing retreatment at 12% (p<0.001). At 48 months, relapses had occurred in 81% of the single dose group, compared to 26% and 39% in the group with retreatment and the higher initial dose and retreatment. The median time to first relapse was 12 months (range 5-76) in the group receiving the single dose, compared to 29 months (range 5-48) in the group receiving retreatment and 34.5 months (range 5-53) in the group with the higher initial dose and retreatment. Retreatment was associated with a reduction in relapse rates compared to single rituximab courses and allowed early withdrawal of immunosuppression and glucocorticoid reduction or withdrawal. In this study B cell count and ANCA positivity didn't correlate with the time of relapse.

7.3. Intravenous immunoglobulin (IVIg)

IVIg consists of intact IgG molecules, representing all IgG subclasses, from the pooled plasma of donors [55]. Small amounts of IgM, IgA, HLA and cytokines are also present in the preparation. As such, IVIg contains a broad range of immune antibodies against pathogens and foreign antigens. Proposed mechanisms of action include modulation of the expression and function of Fc receptors, interference with the activation of complement and the cytokine

network, provision of antiidiotypic antibodies (idiotypes are located in the variable region of autoantibodies in autoimmune conditions), and effects on the activation, differentiation and effector functions of both T and B cells [55]. In vasculitis, IVIG may reverse monocyte and neutrophil activation, reduce autoantibody production or effect the autoreactive T cell function [56]. In vitro, incubation of ANCA vasculitis patient sera with IVIg inhibited ANCA activity [57] which provided evidence to proceed with clinical use of this agent.

In the initial publication, 7 patients with long-standing ANCA vasculitis resistant to standard immunosuppressive therapy received IVIg at a dose of 0.4 g/kg/day for 5 days [58] with maintenance of steroids and cytotoxic drugs for at least 6 weeks following the infusions. All patients improved within 2 days to 3 weeks; 5 went into full remission, 1 had sustained improvement and 1 had a partial transient response within 8 weeks. Relapses occurred in 3 patients between 2 and 9 months after treatment, with no relapses documented in the others who were followed between 6 and 18 months. Other successful case reports, case series and open-label studies followed [59-64] describing positive treatment responses, however there is likely an element of publication bias and confounding due to the variety in disease presentations, prior and concomitant immunosuppressive therapies received, variable steroid doses and the lack of a control arm for comparison. Jayne et al reported on a prospective double-blind placebo-controlled multicentre randomized study targeting a reduction in the BVAS [65]. Patients had either GPA or MPA with active vasculitis despite 2 months of treatment with prednisolone and cyclophosphamide or azathioprine. The mean disease duration of subjects in this study was 52.5 months. Seventeen subjects were randomized to receive IVIg 0.4 g/kg/day for 5 days with no changes in immunosuppressive drugs for 3 months after the trial infusion, and 17 subjects were in the placebo arm. Patients were assessed 2 weeks following the infusion and then monthly until 12 months. A 50% reduction in the BVAS was observed in 14/17 of the IVIg group and 6/17 of the placebo group respectively (OR 8.56; 95%CI 1.74-42.2, p-0.015) and two subjects in the placebo group died within 3 months. The mean BVAS in the IVIg group at baseline was 6.1, with a BVAS reduction of 3.2 at 1 month and 4.1 at 3 months, compared to a baseline BVAS of 5.4 in the placebo group with reductions of 0.87 and 2.3 at 1 and 3 months. However, after 3 months there were no significant differences in the BVAS between groups or in the frequency of relapse (5/16 for IVIG and 4/15 for placebo), and no differences in the subsequent steroids or immunosuppressive doses in follow-up.

An open-label study enrolled 22 poor-prognosis patients experiencing a relapse of WG or MPA despite treatment or within 1 year of stopping corticosteroids and/or immunosuppressants (0.5 g/kg/day for 4 days) to monthly IVIg for 6 months [66]. Temporary increases in prednisone doses were allowed but other immunosuppressants had to be maintained during the 6 months of IVIg therapy but could then be reduced, discontinued or switched to maintenance agents if cyclophosphamide had been given. In this study, the mean disease duration was 27 months (range 7-109 months) and the median BVAS 2005 at study entry was 11 (range 3-25). All but 1 patient was receiving steroids and/or immunosuppressants. Between months 1 and 5, 21 subjects achieved remission, with complete remission in 73% at 6 months, partial remission in 9% and relapse in 14%. The effect seemed persistent, with 13/16 responders still in complete remission at 9 months, and with 12/16 in complete remission at month 24. In those achieving

complete remission at month 9, steroids were stopped in 4 and reduced in 9, with reductions in other immunosuppressants in 4 subjects. The median BVAS 2005 was 0 (range 0-13) at month 9 and 0 (range 0-12) at month 24. Moderate and transient effects of IVIg were reported including nausea, headaches, fever, arthralgias, and 1 patient developed renal insufficiency and was deemed a treatment failure.

IVIg is a safe agent for use in particular clinical situations, such as pregnancy, those with a potential infection mimicking vasculitis, and for patients with refractory persistent disease despite traditional immunsuppressive agents. Adverse effects included headaches, rise in creatinine, aseptic meningitis, backache and fever/chills. Theoretical adverse effects include the transmission of blood-borne pathogens, although extensive screening of blood donors occurs. Randomized clinical trials are lacking, and the role in new-onset disease or specific ANCA vasculitis entities is unexplored. The current evidence base is considered poor given the open-label nature of the literature with a lack of a control arm data or control over concomitant treatments received in addition of IVIg.

7.4. 15-deoxyspergualin (DSG; 1-amino-19-guanidino-11-hydroxy-4,9,12-triazanona-decane-10,1-3-dione; gusperimus)

DSG is a synthetic analogue of spergualin, a natural product of the bacterium *Bacillus laterosporus*, which possesses immunosuppressive properties [67, 68]. DSG has effects on B cell differentiation, blocks kappa light-chain expression at the transcriptional level and acts on T effector cells. A pilot study of DSG (0.5 mg/kg daily subcutaneously to target a leukocyte nadir of 3000/μ, 6 cycles with 2 week recovery periods) was performed in 20 subjects with refractory WG or MPA [68]. Steroids were dosed at the discretion of the treating physician but no other immunosuppressives were allowed. The primary endpoint was remission (either complete remission with no signs of disease activity, or partial remission defined as no new activity but with minor persistent activity) after 6 cycles of DSG. Response was noted in 14 subjects (6 complete, 8 partial, with the mean BVAS improving from 11 (SD 5.8) to 4 (2.9) in responders, and a reduction of oral steroids from 30 mg per day to 7.5 mg/day. Response was maintained out to 6 months for 11/14 of the responders. Side effects were largely infectious in nature, with diarrhea, headache, bronchitis, and anemia also reported. In a further open label-study, 44 patients with refractory WG received DSG (0.5 mg/kg/day in six cycles of 21 days with 7 days between cycles) followed by azathioprine [69]. In this study, 20 patients achieved remission (BVAS of 0 for 2 months) and 22 achieved partial remission (BVAS <50% of entry score).

7.5. Alemtuzumab (campath-1H)

The humanized monoclonal antibody, anti-CD52 (alemtuzumab, CAMPATH-1H) depletes circulating lymphocytes and macrophages. It has shown a promising effect in patients with multiple sclerosis and Behçet's disease. It has been studied in a group of patients with relapsing and refractory GPA or MPA in one UK centre [70]. Patients were eligible to receive CAMPATH-1H if they had multiple relapses or life threatening disease despite the standard of care. Prednisolone was continued at 10 mg/day but all other immunosuppressants were discontinued. CAMPATH-1H was administered intravenously on consecutive days at doses of 4, 10,

40, 40 and 40 mg, for a total dose of 134 mg. CAMPATH-1H was readministered for relapsing disease if the initial treatment was tolerated. A total of 71 patients were treated and followed for a mean of 5 years. Sixty-five percent of patients achieved clinical remission, and an additional 20% had a clinically significant improvement in disease activity but still required greater than 10 mg of prednisolone per day or an additional immunosuppressive agent to control disease activity. Almost all subjects relapsed after 9 months, with better renal function and the absence of neurologic involvement protective for relapse. Unfortunately, 44% of the cohort died during the follow-up period, 5 patients were diagnosed with malignancy, and 11% developed Graves disease. These adverse events may limit the use of alemtuzumab in practice to highly selected patients or those with disease refractory to all other agents.

7.6. Antithymocyte globulin (ATG)

The SOLUTION protocol was an uncontrolled prospective open-label study of ATG in 15 subjects with refractory GPA [71]. ATG was given intravenously at a dose of 2.5 mg/kg for a mean of 2 doses. The authors describe partial remission in 9/15 subjects and complete remission in 4/15 with reduced prednisone requirements (mean 49 mg/day to 13 mg/day) and only experiencing relapse after 8 months. However, 2 patients died and 5 others developed severe infections.

8. Treatment of localized vasculitis

8.1. Trimethoprim/sulfamethoxazole (T/S)

There have been case reports and case series of patients with AAV limited to the upper and/or lower respiratory tract treated with T/S for induction of remission with a good outcome [72]. A study of 72 patients with GPA looked at the role of T/S for induction of remission in the localized stage, and maintenance of remission in the generalized stage [73]. Nineteen patients with localized disease received T/S (2×960 mg/day) with 58% achieving complete or partial remission for a median of 43 months. Patients with generalized disease in remission did poorly with T/S, with 42% of those treated with T/S alone relapsing after a median of 13 months compared to a relapse rate of 29% at a median of 23 months in the patients not receiving T/S.

T/S was found to be superior to placebo in maintaining remission in a prospective, placebo controlled study of 81 patients with GPA, 41 of whom received T/S after induction of remission of generalized disease [74]. At 24 months of follow-up 82% of patients in the T/S group were still in remission, as compared to only 60% in the placebo group, with a relative risk of relapse of 0.40 (95%CI 0.17 to 0.98). This reduction was especially evident with respect to relapses involving the upper airways.

Therefore, T/S can be considered for the induction of remission of localized GPA but patients should be monitored carefully for signs of progression to systemic disease. The efficacy of maintenance of remission in generalized disease is controversial and currently not the recommended standard of practice.

9. Treatment of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Most of the studies in AAV include only a small number of patients with EGPA or exclude them altogether. We will discuss trials performed specifically in EGPA.

9.1. EGPA with poor prognosis

A prospective, multicenter, randomized trial of patients newly diagnosed with EGPA and at least 1 poor prognosis factor (creatinine >140 μmol/l (1.58 mg/dl); proteinuria >1 gm/day; or central nervous system, gastrointestinal, or myocardial involvement) was conducted to determine the shortest immunosuppressant duration able to limit the occurrence of side effects and still induce and maintain disease remission by comparing glucocorticoids and 6 compared to 12 intravenous cyclophosphamide pulses [75]. All patients received 3 consecutive intravenous pulses of methylprednisolone (15 mg/kg) followed by oral prednisone (1 mg/kg/day) for 3 weeks followed by a tapering regime. Intravenous cyclophosphamide (0.6 g/m^2) was given every 2 weeks for 1 month, then every 4 weeks, and patients were randomized to receive either 6 or 12 cyclophosphamide pulses. The cumulative cyclophosphamide dose was twice as high in the 12-pulse group than in the 6-pulse group (6.6 g/m^2 versus 3.48 g/m^2). There was a non-significant difference in the proportion of patients achieving complete remission, at 91% for the group receiving 6 pulses and 84% for the group receiving 12 pulses. Relapse frequency demonstrated a trend to significance at 74% for the group receiving 6-pulses compared to 62% in the 12-pulse group (p=0.07), and the mean time to first relapse was 268 days in the 12-pulse group compared to 222 days in the 6-pulse group, although this was not statistically different. Adverse events and deaths were equal between both groups.

9.2. EGPA without poor prognosis factor

One study examined treatment efficacy of corticosteroids as first-line treatment of EGPA without poor prognosis factors, and the use of azathioprine compared to intravenous cyclophosphamide for treatment failure or relapse [76]. Subjects could receive 1 intravenous pulse of methylprednisolone (15 mg/kg) and then oral prednisone (1 mg/kg/day for 3 weeks) followed by a tapering regimen. If the prednisone could not be tapered below 20 mg, or if the patient experienced a relapse, they were randomized to azathioprine (2 mg/kg/day for 6 months) or 6 cyclophosphamide doses (0.6 g/m^2 every 2 weeks for 1 month, then every 4 weeks). Ninety-three percent of subjects achieved remission, with a 1 year survival rate of 100% and 5 year survival rate of 97%. Of the subjects achieving remission, 37% relapsed, and 3% could not reduce their prednisone. A total of 19 subjects went onto randomization with 10 receiving cyclophosphamide and 9 receiving azathioprine. Fifty percent of the cyclophosphamide subjects achieved remission, compared to 78% of the azathioprine subjects. Low-dose corticosteroid therapy was required in 79% of subjects long-term, primarily due to lung disease.

10. Chapter summary

The treatment of AAV is directed at achieving disease control to prevent morbidity and mortality, while minimizing treatment toxicity. Corticosteroid use remains critical in rapidly achieving disease activity suppression, whereas cyclophosphamide and rituximab regimens should be reserved for induction of severe generalized disease, and plasma exchange for severe renal disease. In less severe cases of systemic disease methotrexate is suitable for remission induction. Maintenance of remission is achieved preferably with azathioprine or methotrexate, with leflunomide, mycophenolate mofetil and cyclophosphamide remaining as options. Finally, new discoveries and research will certify the role of alternative agents, such as monoclonal anti-tumor necrosis factor therapy, IVIg, DSG, ATG and CAMPATH-1, in refractory disease.

Author details

Aurore Fifi-Mah and Cheryl Barnabe

Department of Medicine, University of Calgary, Calgary, Canada

References

[1] A. T. Masi, G. G. Hunder, J. T. Lie, B. A. Michel, D. A. Bloch, W. P. Arend, L. H. Calabrese, S. M. Edworthy, A. S. Fauci, R. Y. Leavitt, and et al., "The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis)," *Arthritis and Rheumatism,* vol. 33, pp. 1094-100, Aug 1990.

[2] D. A. Bloch, B. A. Michel, G. G. Hunder, D. J. McShane, W. P. Arend, L. H. Calabrese, S. M. Edworthy, A. S. Fauci, J. F. Fries, R. Y. Leavitt, and et al., "The American College of Rheumatology 1990 criteria for the classification of vasculitis. Patients and methods," *Arthritis and Rheumatism,* vol. 33, pp. 1068-73, Aug 1990.

[3] R. Y. Leavitt, A. S. Fauci, D. A. Bloch, B. A. Michel, G. G. Hunder, W. P. Arend, L. H. Calabrese, J. F. Fries, J. T. Lie, R. W. Lightfoot, Jr., and et al., "The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis," *Arthritis and Rheumatism,* vol. 33, pp. 1101-7, Aug 1990.

[4] R. W. Lightfoot, Jr., B. A. Michel, D. A. Bloch, G. G. Hunder, N. J. Zvaifler, D. J. McShane, W. P. Arend, L. H. Calabrese, R. Y. Leavitt, J. T. Lie, and et al., "The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa," *Arthritis and Rheumatism,* vol. 33, pp. 1088-93, Aug 1990.

[5] J. C. Jennette, R. J. Falk, K. Andrassy, P. A. Bacon, J. Churg, W. L. Gross, E. C. Hagen, G. S. Hoffman, G. G. Hunder, C. G. Kallenberg, and et al., "Nomenclature of systemic vasculitides. Proposal of an international consensus conference," *Arthritis and Rheumatism,* vol. 37, pp. 187-92, Feb 1994.

[6] F. J. van der Woude, N. Rasmussen, S. Lobatto, A. Wiik, H. Permin, L. A. van Es, M. van der Giessen, G. K. van der Hem, and T. H. The, "Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis," *Lancet,* vol. 1, pp. 425-9, Feb 23 1985.

[7] R. J. Falk and J. C. Jennette, "Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis," *The New England journal of medicine,* vol. 318, pp. 1651-7, Jun 23 1988.

[8] E. W. Walton, "Giant-cell granuloma of the respiratory tract (Wegener's granulomatosis)," *British medical journal,* vol. 2, pp. 265-70, Aug 2 1958.

[9] M. Walsh, O. Flossmann, A. Berden, K. Westman, P. Hoglund, C. Stegeman, and D. Jayne, "Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis," *Arthritis and Rheumatism,* vol. 64, pp. 542-8, Feb 2012.

[10] L. Guillevin, F. Lhote, M. Gayraud, P. Cohen, B. Jarrousse, O. Lortholary, N. Thibult, and P. Casassus, "Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients," *Medicine,* vol. 75, pp. 17-28, Jan 1996.

[11] L. Guillevin, C. Pagnoux, R. Seror, A. Mahr, L. Mouthon, and P. Le Toumelin, "The Five-Factor Score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort," *Medicine,* vol. 90, pp. 19-27, Jan 2011.

[12] C. Mukhtyar, L. Guillevin, M. C. Cid, B. Dasgupta, K. de Groot, W. Gross, T. Hauser, B. Hellmich, D. Jayne, C. G. Kallenberg, P. A. Merkel, H. Raspe, C. Salvarani, D. G. Scott, C. Stegeman, R. Watts, K. Westman, J. Witter, H. Yazici, and R. Luqmani, "EULAR recommendations for the management of primary small and medium vessel vasculitis," *Annals of the Rheumatic Diseases,* vol. 68, pp. 310-7, Mar 2009.

[13] D. R. Jayne and N. Rasmussen, "Treatment of antineutrophil cytoplasm autoantibody-associated systemic vasculitis: initiatives of the European Community Systemic Vasculitis Clinical Trials Study Group," *Mayo Clinic proceedings. Mayo Clinic,* vol. 72, pp. 737-47, Aug 1997.

[14] "TREATMENT of polyarteritis nodosa with cortisone: results after one year; report to the Medical Research Council by the collagen diseases and hypersensitivity panel," *British medical journal,* vol. 1, pp. 608-11, Mar 16 1957.

[15] "Treatment of Polyarteritis Nodosa with Cortisone: Results After Three Years: Report to the Medical Research Council by the Collagen Diseases and Hypersensitivity Panel," *British medical journal*, vol. 1, pp. 1399-400, May 7 1960.

[16] K. de Groot, L. Harper, D. R. Jayne, L. F. Flores Suarez, G. Gregorini, W. L. Gross, R. Luqmani, C. D. Pusey, N. Rasmussen, R. A. Sinico, V. Tesar, P. Vanhille, K. Westman, and C. O. Savage, "Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial," *Annals of internal medicine*, vol. 150, pp. 670-80, May 19 2009.

[17] K. De Groot, N. Rasmussen, P. A. Bacon, J. W. Tervaert, C. Feighery, G. Gregorini, W. L. Gross, R. Luqmani, and D. R. Jayne, "Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis," *Arthritis and Rheumatism*, vol. 52, pp. 2461-9, Aug 2005.

[18] "Etanercept plus standard therapy for Wegener's granulomatosis," *The New England journal of medicine*, vol. 352, pp. 351-61, Jan 27 2005.

[19] J. H. Stone, P. A. Merkel, R. Spiera, P. Seo, C. A. Langford, G. S. Hoffman, C. G. Kallenberg, E. W. St Clair, A. Turkiewicz, N. K. Tchao, L. Webber, L. Ding, L. P. Sejismundo, K. Mieras, D. Weitzenkamp, D. Ikle, V. Seyfert-Margolis, M. Mueller, P. Brunetta, N. B. Allen, F. C. Fervenza, D. Geetha, K. A. Keogh, E. Y. Kissin, P. A. Monach, T. Peikert, C. Stegeman, S. R. Ytterberg, and U. Specks, "Rituximab versus cyclophosphamide for ANCA-associated vasculitis," *The New England journal of medicine*, vol. 363, pp. 221-32, Jul 15 2010.

[20] M. Walsh, P. A. Merkel, A. Mahr, and D. Jayne, "Effects of duration of glucocorticoid therapy on relapse rate in antineutrophil cytoplasmic antibody-associated vasculitis: A meta-analysis," *Arthritis care & research*, vol. 62, pp. 1166-73, Aug 2010.

[21] A. S. Fauci and S. M. Wolff, "Wegener's granulomatosis: studies in eighteen patients and a review of the literature," *Medicine*, vol. 52, pp. 535-61, Nov 1973.

[22] A. S. Fauci, B. F. Haynes, P. Katz, and S. M. Wolff, "Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years," *Annals of internal medicine*, vol. 98, pp. 76-85, Jan 1983.

[23] G. S. Hoffman, R. Y. Leavitt, T. A. Fleisher, J. R. Minor, and A. S. Fauci, "Treatment of Wegener's granulomatosis with intermittent high-dose intravenous cyclophosphamide," *The American journal of medicine*, vol. 89, pp. 403-10, Oct 1990.

[24] D. T. Boumpas, H. A. Austin, 3rd, E. M. Vaughn, J. H. Klippel, A. D. Steinberg, C. H. Yarboro, and J. E. Balow, "Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis," *Lancet*, vol. 340, pp. 741-5, Sep 26 1992.

[25] L. Harper, M. D. Morgan, M. Walsh, P. Hoglund, K. Westman, O. Flossmann, V. Tesar, P. Vanhille, K. de Groot, R. Luqmani, L. F. Flores-Suarez, R. Watts, C. Pusey, A.

Bruchfeld, N. Rasmussen, D. Blockmans, C. O. Savage, and D. Jayne, "Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up," *Annals of the Rheumatic Diseases,* vol. 71, pp. 955-60, Jun 2012.

[26] K. de Groot, D. Adu, and C. O. Savage, "The value of pulse cyclophosphamide in ANCA-associated vasculitis: meta-analysis and critical review," *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* vol. 16, pp. 2018-27, Oct 2001.

[27] D. Adu, A. Pall, R. A. Luqmani, N. T. Richards, A. J. Howie, P. Emery, J. Michael, C. O. Savage, and P. A. Bacon, "Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis," *QJM : monthly journal of the Association of Physicians,* vol. 90, pp. 401-9, Jun 1997.

[28] L. Guillevin, J. F. Cordier, F. Lhote, P. Cohen, B. Jarrousse, I. Royer, P. Lesavre, C. Jacquot, P. Bindi, P. Bielefeld, J. F. Desson, F. Detree, A. Dubois, E. Hachulla, B. Hoen, D. Jacomy, C. Seigneuric, D. Lauque, M. Stern, and M. Longy-Boursier, "A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis," *Arthritis and Rheumatism,* vol. 40, pp. 2187-98, Dec 1997.

[29] M. Haubitz, S. Schellong, U. Gobel, H. J. Schurek, D. Schaumann, K. M. Koch, and R. Brunkhorst, "Intravenous pulse administration of cyclophosphamide versus daily oral treatment in patients with antineutrophil cytoplasmic antibody-associated vasculitis and renal involvement: a prospective, randomized study," *Arthritis and Rheumatism,* vol. 41, pp. 1835-44, Oct 1998.

[30] C. Heijl, L. Harper, O. Flossmann, I. Stucker, D. G. Scott, R. A. Watts, P. Hoglund, K. Westman, and A. Mahr, "Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials," *Annals of the Rheumatic Diseases,* vol. 70, pp. 1415-21, Aug 2011.

[31] G. S. Hoffman, G. S. Kerr, R. Y. Leavitt, C. W. Hallahan, R. S. Lebovics, W. D. Travis, M. Rottem, and A. S. Fauci, "Wegener granulomatosis: an analysis of 158 patients," *Annals of internal medicine,* vol. 116, pp. 488-98, Mar 15 1992.

[32] M. A. Little, P. Nightingale, C. A. Verburgh, T. Hauser, K. De Groot, C. Savage, D. Jayne, and L. Harper, "Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis," *Annals of the Rheumatic Diseases,* vol. 69, pp. 1036-43, Jun 2010.

[33] R. Cartin-Ceba, F. C. Fervenza, and U. Specks, "Treatment of antineutrophil cytoplasmic antibody-associated vasculitis with rituximab," *Current Opinion in Rheumatology,* vol. 24, pp. 15-23, Jan 2012.

[34] R. B. Jones, J. W. Tervaert, T. Hauser, R. Luqmani, M. D. Morgan, C. A. Peh, C. O. Savage, M. Segelmark, V. Tesar, P. van Paassen, D. Walsh, M. Walsh, K. Westman,

and D. R. Jayne, "Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis," *The New England journal of medicine,* vol. 363, pp. 211-20, Jul 15 2010.

[35] J. H. Stone, G. S. Hoffman, P. A. Merkel, Y. I. Min, M. L. Uhlfelder, D. B. Hellmann, U. Specks, N. B. Allen, J. C. Davis, R. F. Spiera, L. H. Calabrese, F. M. Wigley, N. Maiden, R. M. Valente, J. L. Niles, K. H. Fye, J. W. McCune, E. W. St Clair, and R. A. Luqmani, "A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. International Network for the Study of the Systemic Vasculitides (INSSYS)," *Arthritis and Rheumatism,* vol. 44, pp. 912-20, Apr 2001.

[36] K. Kessenbrock, M. Krumbholz, U. Schonermarck, W. Back, W. L. Gross, Z. Werb, H. J. Grone, V. Brinkmann, and D. E. Jenne, "Netting neutrophils in autoimmune small-vessel vasculitis," *Nature Medicine,* vol. 15, pp. 623-5, Jun 2009.

[37] C. G. Kallenberg, "Pathogenesis of PR3-ANCA associated vasculitis," *Journal of autoimmunity*, vol. 30, pp. 29-36, Feb-Mar 2008.

[38] D. R. Jayne, G. Gaskin, N. Rasmussen, D. Abramowicz, F. Ferrario, L. Guillevin, E. Mirapeix, C. O. Savage, R. A. Sinico, C. A. Stegeman, K. W. Westman, F. J. van der Woude, R. A. de Lind van Wijngaarden, and C. D. Pusey, "Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis," *Journal of the American Society of Nephrology : JASN,* vol. 18, pp. 2180-8, Jul 2007.

[39] M. Faurschou, K. Westman, N. Rasmussen, K. de Groot, O. Flossmann, P. Hoglund, and D. R. Jayne, "Long-term outcome of a clinical trial comparing methotrexate to cyclophosphamide for remission induction of early systemic ANCA-associated vasculitis," *Arthritis and Rheumatism*, May 21 2012.

[40] J. U. Holle, W. L. Gross, U. Latza, B. Nolle, P. Ambrosch, M. Heller, R. Fertmann, and E. Reinhold-Keller, "Improved outcome in 445 patients with Wegener's granulomatosis in a German vasculitis center over four decades," *Arthritis and Rheumatism,* vol. 63, pp. 257-66, Jan 2011.

[41] D. Jayne, N. Rasmussen, K. Andrassy, P. Bacon, J. W. Tervaert, J. Dadoniene, A. Ekstrand, G. Gaskin, G. Gregorini, K. de Groot, W. Gross, E. C. Hagen, E. Mirapeix, E. Pettersson, C. Siegert, A. Sinico, V. Tesar, K. Westman, and C. Pusey, "A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies," *The New England journal of medicine*, vol. 349, pp. 36-44, Jul 3 2003.

[42] R. A. Luqmani, P. A. Bacon, R. J. Moots, B. A. Janssen, A. Pall, P. Emery, C. Savage, and D. Adu, "Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis," *QJM : monthly journal of the Association of Physicians,* vol. 87, pp. 671-8, Nov 1994.

[43] C. Pagnoux, A. Mahr, M. A. Hamidou, J. J. Boffa, M. Ruivard, J. P. Ducroix, X. Kyndt, F. Lifermann, T. Papo, M. Lambert, J. Le Noach, M. Khellaf, D. Merrien, X. Puechal,

S. Vinzio, P. Cohen, L. Mouthon, J. F. Cordier, and L. Guillevin, "Azathioprine or methotrexate maintenance for ANCA-associated vasculitis," *The New England journal of medicine*, vol. 359, pp. 2790-803, Dec 25 2008.

[44] A. C. Allison, "Mechanisms of action of mycophenolate mofetil," *Lupus,* vol. 14 Suppl 1, pp. s2-8, 2005.

[45] T. F. Hiemstra, M. Walsh, A. Mahr, C. O. Savage, K. de Groot, L. Harper, T. Hauser, I. Neumann, V. Tesar, K. M. Wissing, C. Pagnoux, W. Schmitt, and D. R. Jayne, "Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial," *JAMA : the journal of the American Medical Association*, vol. 304, pp. 2381-8, Dec 1 2010.

[46] C. Metzler, N. Miehle, K. Manger, C. Iking-Konert, K. de Groot, B. Hellmich, W. L. Gross, and E. Reinhold-Keller, "Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis," *Rheumatology,* vol. 46, pp. 1087-91, Jul 2007.

[47] C. Pierrot-Deseilligny Despujol, J. Pouchot, C. Pagnoux, J. Coste, and L. Guillevin, "Predictors at diagnosis of a first Wegener's granulomatosis relapse after obtaining complete remission," *Rheumatology,* vol. 49, pp. 2181-90, Nov 2010.

[48] S. L. Hogan, R. J. Falk, H. Chin, J. Cai, C. E. Jennette, J. C. Jennette, and P. H. Nachman, "Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis," *Annals of internal medicine,* vol. 143, pp. 621-31, Nov 1 2005.

[49] C. Pagnoux, S. L. Hogan, H. Chin, J. C. Jennette, R. J. Falk, L. Guillevin, and P. H. Nachman, "Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts," *Arthritis and Rheumatism,* vol. 58, pp. 2908-18, Sep 2008.

[50] J. H. Stone, J. T. Holbrook, M. A. Marriott, A. K. Tibbs, L. P. Sejismundo, Y. I. Min, U. Specks, P. A. Merkel, R. Spiera, J. C. Davis, E. W. St Clair, W. J. McCune, S. R. Ytterberg, N. B. Allen, and G. S. Hoffman, "Solid malignancies among patients in the Wegener's Granulomatosis Etanercept Trial," *Arthritis and Rheumatism*, vol. 54, pp. 1608-18, May 2006.

[51] A. Booth, L. Harper, T. Hammad, P. Bacon, M. Griffith, J. Levy, C. Savage, C. Pusey, and D. Jayne, "Prospective study of TNFalpha blockade with infliximab in anti-neutrophil cytoplasmic antibody-associated systemic vasculitis," *Journal of the American Society of Nephrology : JASN*, vol. 15, pp. 717-21, Mar 2004.

[52] M. D. Morgan, M. T. Drayson, C. O. Savage, and L. Harper, "Addition of infliximab to standard therapy for ANCA-associated vasculitis," *Nephron. Clinical practice,* vol. 117, pp. c89-97, 2011.

[53] S. Laurino, A. Chaudhry, A. Booth, G. Conte, and D. Jayne, "Prospective study of TNFalpha blockade with adalimumab in ANCA-associated systemic vasculitis with

renal involvement," *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association,* vol. 25, pp. 3307-14, Oct 2010.

[54] R. M. Smith, R. B. Jones, M. J. Guerry, S. Laurino, F. Catapano, A. Chaudhry, K. G. Smith, and D. R. Jayne, "Rituximab for remission maintenance in relapsing ANCA-associated vasculitis," *Arthritis and Rheumatism,* Jun 21 2012.

[55] M. D. Kazatchkine and S. V. Kaveri, "Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin," *The New England journal of medicine,* vol. 345, pp. 747-55, Sep 6 2001.

[56] D. R. Jayne, V. L. Esnault, and C. M. Lockwood, "ANCA anti-idiotype antibodies and the treatment of systemic vasculitis with intravenous immunoglobulin," *Journal of autoimmunity,* vol. 6, pp. 207-19, Apr 1993.

[57] F. Rossi, D. R. Jayne, C. M. Lockwood, and M. D. Kazatchkine, "Anti-idiotypes against anti-neutrophil cytoplasmic antigen autoantibodies in normal human polyspecific IgG for therapeutic use and in the remission sera of patients with systemic vasculitis," *Clinical and Experimental Immunology,* vol. 83, pp. 298-303, Feb 1991.

[58] D. R. Jayne, M. J. Davies, C. J. Fox, C. M. Black, and C. M. Lockwood, "Treatment of systemic vasculitis with pooled intravenous immunoglobulin," *Lancet,* vol. 337, pp. 1137-9, May 11 1991.

[59] P. Tuso, A. Moudgil, J. Hay, D. Goodman, E. Kamil, R. Koyyana, and S. C. Jordan, "Treatment of antineutrophil cytoplasmic autoantibody-positive systemic vasculitis and glomerulonephritis with pooled intravenous gammaglobulin," *American journal of kidney diseases : the official journal of the National Kidney Foundation,* vol. 20, pp. 504-8, Nov 1992.

[60] C. Richter, A. Schnabel, E. Csernok, K. De Groot, E. Reinhold-Keller, and W. L. Gross, "Treatment of anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis with high-dose intravenous immunoglobulin," *Clinical and Experimental Immunology,* vol. 101, pp. 2-7, Jul 1995.

[61] D. R. Jayne and C. M. Lockwood, "Pooled intravenous immunoglobulin in the management of systemic vasculitis," *Advances in experimental medicine and biology,* vol. 336, pp. 469-72, 1993.

[62] Y. Levy, Y. Sherer, J. George, P. Langevitz, A. Ahmed, Y. Bar-Dayan, F. Fabbrizzi, J. Terryberry, J. Peter, and Y. Shoenfeld, "Serologic and clinical response to treatment of systemic vasculitis and associated autoimmune disease with intravenous immunoglobulin," *International archives of allergy and immunology,* vol. 119, pp. 231-8, Jul 1999.

[63] T. Ito-Ihara, T. Ono, F. Nogaki, K. Suyama, M. Tanaka, S. Yonemoto, A. Fukatsu, T. Kita, K. Suzuki, and E. Muso, "Clinical efficacy of intravenous immunoglobulin for

patients with MPO-ANCA-associated rapidly progressive glomerulonephritis," *Nephron. Clinical practice,* vol. 102, pp. c35-42, 2006.

[64] A. Hot, L. Perard, B. Coppere, M. Simon, F. Bouhour, and J. Ninet, "Marked improvement of Churg-Strauss vasculitis with intravenous gamma globulins during pregnancy," *Clinical rheumatology,* vol. 26, pp. 2149-51, Dec 2007.

[65] D. R. Jayne, H. Chapel, D. Adu, S. Misbah, D. O'Donoghue, D. Scott, and C. M. Lockwood, "Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity," *QJM : monthly journal of the Association of Physicians,* vol. 93, pp. 433-9, Jul 2000.

[66] V. Martinez, P. Cohen, C. Pagnoux, S. Vinzio, A. Mahr, L. Mouthon, L. Sailler, C. Delaunay, A. Sadoun, and L. Guillevin, "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 and Rheumatism,* vol. 58, pp. 308-17, Jan 2008.

[67] K. Maeda, Y. Umeda, and T. Saino, "Synthesis and background chemistry of 15-deoxyspergualin," *Annals of the New York Academy of Sciences,* vol. 685, pp. 123-35, Jun 23 1993.

[68] R. Birck, K. Warnatz, H. M. Lorenz, M. Choi, M. Haubitz, M. Grunke, H. H. Peter, J. R. Kalden, U. Gobel, J. M. Drexler, O. Hotta, R. Nowack, and F. J. Van Der Woude, "15-Deoxyspergualin in patients with refractory ANCA-associated systemic vasculitis: a six-month open-label trial to evaluate safety and efficacy," *Journal of the American Society of Nephrology : JASN,* vol. 14, pp. 440-7, Feb 2003.

[69] O. Flossmann, B. Baslund, A. Bruchfeld, J. W. Tervaert, C. Hall, P. Heinzel, B. Hellmich, R. A. Luqmani, K. Nemoto, V. Tesar, and D. R. Jayne, "Deoxyspergualin in relapsing and refractory Wegener's granulomatosis," *Annals of the Rheumatic Diseases,* vol. 68, pp. 1125-30, Jul 2009.

[70] M. Walsh, A. Chaudhry, and D. Jayne, "Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H)," *Annals of the Rheumatic Diseases,* vol. 67, pp. 1322-7, Sep 2008.

[71] W. H. Schmitt, E. C. Hagen, I. Neumann, R. Nowack, L. F. Flores-Suarez, and F. J. van der Woude, "Treatment of refractory Wegener's granulomatosis with antithymocyte globulin (ATG): an open study in 15 patients," *Kidney International,* vol. 65, pp. 1440-8, Apr 2004.

[72] R. A. DeRemee, "The treatment of Wegener's granulomatosis with trimethoprim/sulfamethoxazole: illusion or vision?," *Arthritis and Rheumatism,* vol. 31, pp. 1068-74, Aug 1988.

[73] E. Reinhold-Keller, K. De Groot, H. Rudert, B. Nolle, M. Heller, and W. L. Gross, "Response to trimethoprim/sulfamethoxazole in Wegener's granulomatosis depends on

the phase of disease," *QJM : monthly journal of the Association of Physicians,* vol. 89, pp. 15-23, Jan 1996.

[74] C. A. Stegeman, J. W. Tervaert, P. E. de Jong, and C. G. Kallenberg, "Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granu-lomatosis. Dutch Co-Trimoxazole Wegener Study Group," *The New England journal of medicine,* vol. 335, pp. 16-20, Jul 4 1996.

[75] P. Cohen, C. Pagnoux, A. Mahr, J. P. Arene, L. Mouthon, V. Le Guern, M. H. Andre, M. Gayraud, D. Jayne, D. Blockmans, J. F. Cordier, and L. Guillevin, "Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients," *Arthritis and Rheumatism,* vol. 57, pp. 686-93, May 15 2007.

[76] C. Ribi, P. Cohen, C. Pagnoux, A. Mahr, J. P. Arene, D. Lauque, X. Puechal, P. Letelli-er, P. Delaval, J. F. Cordier, and L. Guillevin, "Treatment of Churg-Strauss syndrome without poor-prognosis factors: a multicenter, prospective, randomized, open-label study of seventy-two patients," *Arthritis and Rheumatism,* vol. 58, pp. 586-94, Feb 2008.