Current treatment options in Rheumatology

Clinical trials in vasculitis

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All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Opinion statement:

The systemic vasculitides include a heterogenous group of diseases characterised by inflammation of blood vessels. Evidence for treatment in this group of patients is limited due to rarity of the diseases, incomplete understanding of the pathogenesis and lack of appropriate biomarkers. In the last 20 years international collaboration and networking led to clinical trials in a select sub-group of patients with systemic vasculitis. Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is the most studied sub-group. This article discusses the treatment options of AAV in light of evidence from clinical trials.

Treatment of AAV, which includes an induction and a maintenance phase, is dependent on the severity of the disease. Oral or intravenous cyclophosphamide and high dose glucocorticoids are considered to be standard of care for induction of remission in AAV patients with generalised disease. Latest evidence supports rituximab as an alternative to cyclophosphamide especially in relapsing patients and is increasingly being used in patients who cannot have cyclophosphamide. Plasma exchange, and intravenous immunoglobulins (IVIG) are used as adjunctive therapies for induction.

Azathioprine or methotrexate (in non-renal patients) is considered to be the choice for remission maintenance, whilst mycophenolate mofetil is reserved for patients who cannot tolerate either of them. Rituximab is also being increasingly used for remission maintenance in relapsing patients. Even though an enormous progress has been made in the outlook of patients with AAV, a number of questions remain unanswered with regards to the optimal treatment strategy.

Introduction:

Systemic vasculitis is characterised by inflammation and necrosis of blood vessel walls, leading to occlusion of the vessel lumen, tissue damage and eventually to organ failure. Vasculitis may be primary in origin or secondary to another autoimmune process such as systemic lupus erythematosus or rheumatoid arthritis, infections, neoplasia or drugs. Vasculitides are usually classified according to the predominant size of the blood vessels involved. Research into primary vasculitides has been difficult due to lack of biomarkers except for a sub-group called antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV). AAV is classified under the small vessel vasculitis sub-group of vasculitides in the latest Chapel Hill Consensus classification system[1]. This article will review the treatment options in AAV in light of past, current and future clinical trials.

ANCA associated vasculitis (AAV):

AAV, characterised by the presence of autoantibodies to neutrophil cytoplasmic antigens, proteinase 3 (PR3) and myeloperoxidase (MPO) (ANCA) typically involves small blood vessels of the respiratory tract and kidneys. It encompasses

three distinct clinical syndromes: granulomatosis with polyangiitis (GPA, previously Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (eGPA, previously Churg Strauss Syndrome). GPA is commonly associated with PR3 ANCA (66% of the patients)[2] whilst MPO is associated with MPO-ANCA (58% of the patients)[2]. Only 40% of patients with eGPA are ANCA positive[3].

Patients with GPA typically present with granulomatous inflammation, commonly of the upper airways and lungs. Renal involvement is seen more often in MPA, but can also occur in GPA. Patients with eGPA typically have a prodrome of asthma for few years before presenting with systemic vasculitis symptoms. The pathogenetic mechanisms of eGPA differ significantly from that of GPA or MPA and eGPA is clinically distinct from GPA and MPA.

ANCA vasculitis can present with a wide spectrum of disease activity and it is important to customise the treatment depending on the disease activity. European league against rheumatic diseases (EULAR) recommends (Table 1) [4] using either European vasculitis study group (EUVAS) or Wegener's granulomatosis Etanercept group (WGET) classification of disease states in trial settings.

Table 1 Definitions for disease stages used for subclassification of patients with Wegener's granulomatosis in clinical trials

Study group	Clinical subgroup	Systemic vasculitis outside ENT tract and lung	Threatened vital organ function	Other definitions	Serum creatinine (μmol/l)	Reference
EUVAS	Localised	No	No	No constitutional symptoms, ANCA typically negative	<120	
	Early systemic	Yes	No	Constitutional symptoms present, ANCA-positive or -negative	<120	
	Generalised	Yes	Yes	ANCA-positive	<500	Jayne *et al*[5]
	Severe	Yes	Organ failure	ANCA-positive	>500	Jayne[68]
	Refractory	Yes	Yes	Refractory to standard therapy	Any	Jayne[68]
WGET Research Group/VCRC	Limited	Allowed, but not required	No	Not severe	⩽124, if haematuria, but no red blood cell casts present	WGET Research Group[3]
	Severe	Yes	Yes	Organ- or life-threatening disease, implies need for remission induction with CYC	Any	WGET Research Group[3]

ANCA, anti-neutrophil cytoplasmic antibody; CYC, cyclophosphamide; ENT, ear, nose and throat; EUVAS, European Vasculitis Study Group; VCRC, Vasculitis Clinical Research Consortium; WGET, Wegener's Granulomatosis Etanercept Trial.

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Most clinical trials have not differentiated between the clinical subtypes of AAV disease either based on ANCA specificity or clinical syndrome (GPA and MPA or PR3 and MPO AAV). However this may be important for future studies given the genetic evidence[5] suggesting a robust genetic association in relation to antibody specificity when compared to clinical syndromes (PR3-ANCA disease is associated with HLA- DP, SERPINA1 and PRTN3, while MPO-ANCA disease is associated with HLA-DQ). Also it is known that patients with PR3 disease have a different phenotype associated with increased risk of relapse[6] and patients with renal PR3-AAV are more likely to have a dramatic deterioration in kidney function but respond better to treatment compared to those with MPO-AAV[7].

Pathogenesis of AAV:

The pathogenesis of AAV (Figure 1)[8] is not completely known, however there has been progress in our understanding in the last two decades. Genetic

susceptibility along with environmental exposures to agents such as infections (Staphylococcus aureus), silica or drugs is implicated in the disease process. Dysfunctional innate and adaptive immune systems also play a role in its pathogenesis. ANCA produced by B cells may be pathogenic as shown in animal models[9]. B cell activating factor (BAFF) is elevated in AAV patients[10] and this may be an important therapeutic target. Neutrophils activated by ANCA degranulate and release reactive oxygen species (ROS), pro-inflammatory cytokines and complement activators, leading to endothelial damage. Inflammation is also promoted by the presence of increased numbers of pro-inflammatory CD4+ effector memory cells[11], IL17 producing Th17 cells[12], IL21 producing cells and a reduction in the number of regulatory cells. The alternative complement pathway is triggered by activated neutrophils and damaged endothelium[13]. C5a, a by-product of the complement activation is a powerful neutrophil chemo-attractant, which recruits more neutrophils to the site[14]. Therapies in AAV target various aspects of these pathogenic mechanisms in order to re-establish immune homeostasis.

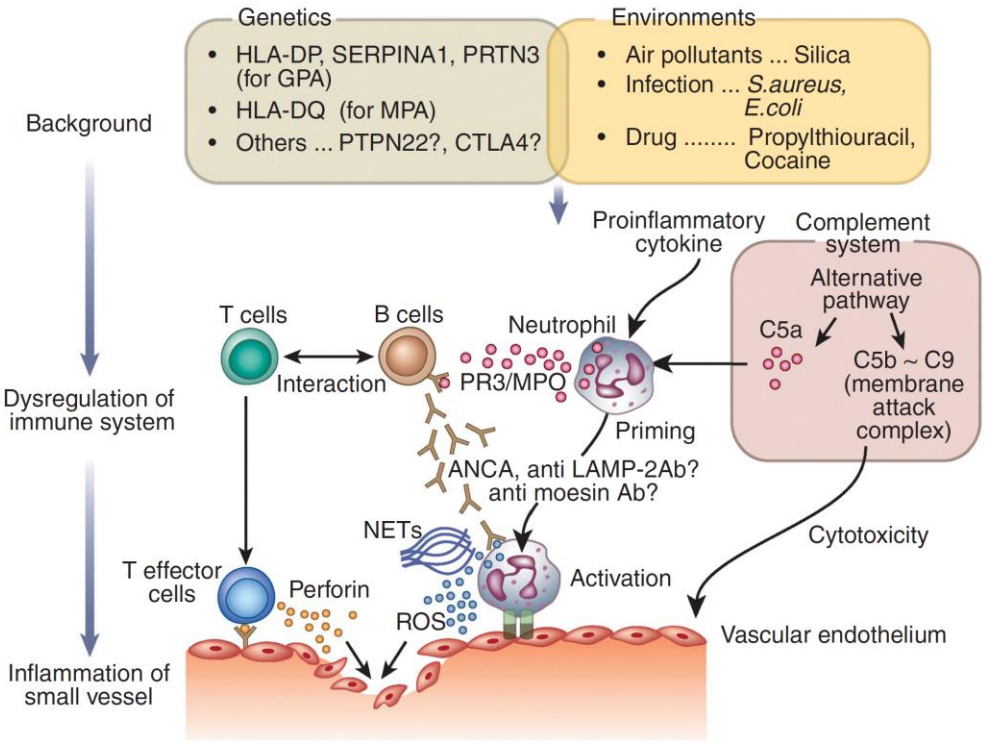

Figure 1 | Mechanism of the onset of antineutrophil cytoplasm antibody (ANCA)–associated vasculitis. LAMP-2, lysome-associated membrane protein-2; MPO, myeloperoxidase; NETs, neutrophil extracellular traps; PR3, proteinase 3; ROS, reactive oxygen species.

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Treatment in AAV:

The use of cyclophosphamide and glucocorticoids as induction therapy for AAV, has improved the survival rates from 20% to well over 80% at 2 years[15]. However, longterm follow up of these patients revealed significant toxicity associated with the use of cyclophosphamide as well as high levels of morbidity associated with chronic glucocorticoid exposure. This, along with a high relapse rate (50%) has provided an impetus to look for less toxic and more efficacious treatment options. Strategies such as pulsed intravenous dosing, switching to less toxic agents after induction of remission and avoidance of cyclophosphamide in less severe disease were used. Rituximab, a B cell depleting agent, in the last decade has been shown to be non-inferior to cyclophosphamide and is now licensed for use of remission induction. Currently strategies to minimise glucocorticoid exposure are also being explored.

Treatment of AAV typically includes two distinct phases, an induction phase (3 to 6 months), to gain rapid control of disease activity and a maintenance phase (18 to 24 months), to maintain remission and prevent relapses, using less toxic agents.

Drugs used for induction of remission:

1. **Cyclophosphamide:**

   Cyclophosphamide, an alkylating agent, inhibits DNA replication by alkylating guanidine nucleotides. Its mechanism of action is poorly understood in vasculitis but it is thought to exert toxic effect on both resting and dividing lymphocytes. Introduction of cyclophosphamide in 1970's has remarkably improved the survival of patients with generalised AAV. Even though it is considered to be standard treatment for induction in generalised AAV, its prolonged use is associated with increased risk of infections, cytopenias, infertility, bladder cancer, cardio-vascular risk and myelodysplasia.

   Cyclophosphamide is usually given either as oral or pulsed therapy for three to six months and is replaced by less toxic drugs after achieving remission. Cyclophosphamide when administered intravenously as pulsed therapy may lead to reduction in cumulative dose and consequent reduction in toxicity. This strategy was assessed by the CYCLOPS trial. 149 patients with generalised AAV were randomised to receive intravenous cyclophosphamide [15mg/kg every 2 to 3 weeks] or daily oral cyclophosphamide [2mg/kg], which were continued for 3 months after achieving remission. This trial showed that the time to remission (hazard ratio, 1.098 [95% CI, 0.78 to 1.55]; p = 0.59) and the proportion of patients that achieve remission by 9 months (88.1% vs. 87.7%) was similar in both the groups[16]. The cumulative dose was lower in the pulse group (15.9 g [IQR 11 to 22.5 g] vs. 8.2 g [IQR 5.95 to 10.55 g]; P< 0.001) and this was associated with less incidence of leukopenia (hazard ratio, 0.41 [CI, 0.23 to 0.71]). However longterm analysis of this cohort with a median of 4.3 years, showed that the risk of relapse was lower in the oral

than in the intravenous arm (39.5% versus 20.8%, HR=0.50, 95% CI 0.26 to 0.93; p=0.029)[17]. Nevertheless, there was no difference in terms of mortality, renal function, end stage renal failure or adverse events between the two groups. In this trial, in order to reduce toxicity, the dose of cyclophosphamide was adjusted according to age and renal function (Table 2) and is now considered to be a standard practice.

Table 2: IV pulsed cyclophosphamide dose (per pulse mg/kg)

Age in years	Creatinine <300umol/L	Creatinine >300umol/L
<60	15	12.5
60-70	12.5	10
>70	10	7.5

A retrospective analysis of EUVAS trials[18] showed that oral cyclophosphamide use was associated with lower relapse risk when compared to other agents even though they help to achieve similar primary remission rate.

2. Rituximab:

B cells play an important role in the pathogenesis of AAV. Rituximab, a chimeric monoclonal antibody depletes B cells by ligation with surface expressed CD20 antigens. Two randomised controlled trials, RAVE[19] and RITUXVAS[20] have shown that rituximab is non-inferior to cyclophosphamide for induction of remission in AAV and is now licensed for induction therapy. There was no difference in safety or adverse events.

These two trials had some differences. RITUXVAS (n=44) included new patients with severe renal disease whereas RAVE (n=197) included new as well as relapsing patients with well-preserved kidney function. Oral cyclophosphamide was used as a comparator in RAVE, whilst pulsed cyclophosphamide was used in RITUXVAS. In both trials rituximab was administered as four infusions of 375mg/m^2 body surface area, however in RITUXVAS two or three cycles of cyclophosphamide was given in addition to rituximab. Prednisolone was tapered and stopped by 5 months in RAVE trial whilst it was reduced to 5mg by 6 months and continued for the rest of the trial in RITUXVAS trial. Neither trial continued with maintenance immunosuppression in the rituximab group. The primary endpoint in RAVE was the absence of disease activity (Birmingham Vasculitis Activity score for Wegener's, BVAS/WG of 0) and completion of prednisolone withdrawal by 6 months. In RITUXVAS sustained remission, defined, as absence of any disease activity for at least 6 months was the primary endpoint.

In the RAVE trial (1:1 randomisation), the primary outcome at 6 months was achieved by 64% in the rituximab arm compared to 53% in the control arm and it met the criterion for non-inferiority (p<0.001).

However patients with relapsing disease at baseline achieved better response rate (67% versus 42%, p = 0.01). This effect persisted even after adjusting for ANCA type and clinical site (OR: 1.40, 95% CI, 1.03 to 1.91, p = 0.03). At 18 months 39% in the rituximab arm and 33% in the control arm maintained complete remission[21]. This trial did not show a difference in the number of total or serious adverse events between the two arms.

In the RITUXVAS trial (randomised 3:1 to rituximab or cyclophosphamide), the primary outcome of sustained remission occurred in 76% in rituximab arm compared to 82% in the control arm, p = 0.68. Again no difference in safety was observed between the two groups. Long-term analysis of these patients showed that at 24 months remission was maintained in 61% in rituximab arm compared to 64% in the cyclophosphamide arm[22].

It was evident from the above two trials that the relapse risk after induction of remission with rituximab remains high and most patients would need subsequent maintenance therapy to prevent relapses. Also the adverse event rates in both trials were similar to the conventional therapy with cyclophosphamide suggesting no benefit in choosing rituximab over cyclophosphamide except in patients with relapsing disease. It can be used in patients who are intolerant of cyclophosphamide, patients in the reproductive age group or who had significant exposure to cyclophosphamide in the past with or without associated toxicity. Its role as monotherapy (with glucocorticoids) in severe disease is not established and there is no consensus on the appropriate dosing regimen. These questions need to be addressed in future trials. A post-hoc analysis of the RAVE trial has concluded that PR3-ANCA positive patients were more likely to obtain a remission of their disease with rituximab than cyclophosphamide, but this awaits further confirmation.

3. Methotrexate:

Methotrexate competitively inhibits the dihydrofolate reductase enzyme inhibiting the synthesis of DNA, RNA and proteins. It inhibits T cell activation and down regulates B cells. Methotrexate at a dose of 15mg to 25mg per week (oral or subcutaneously) is used as an alternative to cyclophosphamide and rituximab therapy in patients with early systemic disease without significant renal involvement.

The NORAM trial (n=100) [23] compared oral methotrexate to oral cyclophosphamide for remission induction in newly diagnosed AAV patients with non-severe disease. The remission rate at 6 months in methotrexate arm was not inferior to that in cyclophosphamide arm (89.8% versus 93.5%, p = 0.041). It was shown that in the methotrexate arm, remission was delayed in patients with pulmonary disease or patients with extensive disease. Also the time to remission was longer in the methotrexate arm. 70% of the patients in methotrexate arm relapsed

at 18 months compared to 46% in the control arm. This higher rate of relapse in both arms was influenced by the withdrawal of immunosuppression by 12 months.

Longterm analysis of data from this trial[24] (median 6 years) showed that methotrexate treatment was associated with prolonged use of steroids (p = 0.005) and that was associated with less effective disease control. There was no difference in the adverse event profile between the two treatments. There were less cases of leucopoenia with methotrexate but more cases of liver dysfunction.

4. Mycophenolate mofetil (MMF):

Mycophenolate mofetil (MMF) is used routinely in systemic lupus erythematosus as an induction agent and evidence from a retrospective case series[25] and a prospective pilot trial[26] suggested benefit in AAV as well. The advantages of using MMF include its selective immunosuppressive effect; less toxicity and short duration of action when compared to cyclophosphamide and it can be used in renal failure without dose adjustments.

MYCYC[27], a randomised controlled trial comparing MMF with cyclophosphamide for induction therapy in AAV has finished recruiting. In this trial, newly diagnosed AAV patients were assigned to receive up to 6 months of induction therapy with either MMF 2 to 3g/ day (n=70) or 6-10 pulses of IV cyclophosphamide (n=70). In the preliminary analysis[27] response rates between MMF and cyclophosphamide based regimens were similar at six months but there was an excess of subsequent relapses in PR3-ANCA patients who initially received MMF. Thus MMF may be an alternative induction agent to cyclophosphamide for MPO-ANCA positive patients.

5. Glucocorticoids:

There is little direct evidence to guide glucocorticoid dosing, despite their use in induction therapy for many years. Most physicians give 1mg/kg daily oral prednisolone (after pulsed methyl-prednisolone, e.g. 1g daily for 3 days in patients with severe disease) with an aim to wean to the lowest possible dose by 6 months (e.g. 5mg/day or less by 6 months). Even though steroids help to suppress inflammation and gain rapid control, multiple co-morbidities associated with high dosage, is driving research to reduce or replace their usage.

Two studies are exploring glucocorticoid dosing: PEXIVAS[28], (discussed below), is comparing standard high dose against reduced dose glucocorticoids (0.5mg/kg/day) as a component of the induction regimen for patients with severe AAV. The CLEAR trial[29] is a phase 2 randomised controlled trial (discussed below) designed to evaluate the safety and efficacy of CCX168, an oral C5a inhibitor as a replacement to standard dose steroids in AAV patients with mild to moderate disease activity treated with cyclophosphamide.

Adjunctive therapies:

6. Plasma exchange:

Plasma exchange in AAV may help in rapid induction of severe disease by removing pathogenic ANCA and mediators of inflammation, however its mechanism of action is not clear. Small randomised studies and a larger RCT, MEPEX have shown short-term benefit in reducing the risk of ESRD.

In the MEPEX trial 137 new AAV patients with renal involvement (creatinine >500) were randomised to receive either 7 plasma exchanges (PLEX arm) or three doses of IV methylprednisolone in addition to standard therapy. At 3 months, 69% in the PLEX arm were independent of dialysis compared to 49% in the IV methylprednisolone arm (RR: 20%, 95% CI: 18 to 35%, p = 0.02). At 12 months the risk for progression to ESRD was lower in the PLEX arm (RR: 24%, 95% CI: 6.1 to 41%).

Long-term data analysis of this cohort at a median of 3.95 years showed that the advantage of better kidney function at 12 months with plasma exchange was not carried forward. The hazard ratio for PLEX compared to IV methyl prednisolone was 0.81(95% CI 0.53 – 1.23, p = 0.32) for a composite outcome of death or ESRD[30].

The MEPEX study was not powered to detect this change and the larger PEXIVAS trial currently recruiting patients will hopefully provide more answers. This trial has a two-by-two factorial design to answer two important questions: 1) does adjunctive plasma exchange improve the time to composite endpoint of all-cause mortality and end stage renal disease? 2) Is a more rapid glucocorticoid reduction as efficacious, but safer than a standard regimen? In this open label study, 700 AAV patients with severe disease will be randomised to receive 1) adjunctive plasma exchange or no plasma exchange and 2) high dose steroids or reduced dose steroids, in addition to standard induction therapy with cyclophosphamide or rituximab. Patients are followed up for a maximum of 7 years and a minimum of 1 year.

7. IV methylprednisolone:

Most patients presenting with severe disease receive up to 3g of intravenous methyl prednisolone over a period of 3 days. There is no established evidence for the same. MEPEX trial tested intravenous methylprednisolone against plasma exchange, however in reality both are used simultaneously.

8. Intravenous immunoglobulins (IVIG):

IVIG is used as an adjuvant therapy in patients with severe disease, refractory disease or patients in whom standard therapy is contraindicated such as with severe infections where immunosuppression is deemed unsuitable. A Cochrane review[31] identified only one randomised placebo controlled trial[32] in 34 previously treated AAV patients with persistent disease activity. 17 patients in the

IVIG arm received 1 course of 2g/kg IVIG and the other group received placebo. Even though IVIG caused reduction in disease activity (MD 2.30; 95% Confidence interval (CI) 1.12 to 3.48, P < 0.01), the effects did not last for more than 3 months. Also there were more adverse events in the IVIG group (relative risk (RR) 3.50; 95% CI 1.44 to 8.48, P < 0.01). Given the lack of robust evidence for its use IVIG should not be routinely used.

Maintenance therapy:

Relapses are common without maintenance therapy. In a prospective study, conducted by National Institute for Health, treatment with oral steroids and oral cyclophosphamide for prolonged periods, even though resulted in 75% complete remission rate had a 50% relapse rate[33]. The optimal duration of maintenance therapy is not known but conventionally given for a period of 18 to 24 months[34]. The high relapse rate seen in the NORAM trial (relapse rate of 69.5% in the methotrexate arm and 46.5% in the cyclophosphamide arm) where maintenance therapy was stopped by 12 months, suggests that prolonged therapy may be needed. The REMAIN trial[35], has reported a reduced relapse risk after 24 months if azathioprine and prednisolone are continued. ANCA positivity at 24 months was a predictor of subsequent relapse.

1. Azathioprine:

Azathioprine is an anti-metabolite and a purine analogue that blocks the synthesis of DNA inhibiting the proliferation of cells. Before the introduction of azathioprine, treatment with oral steroids and cyclophosphamide for prolonged periods was the norm. 42% of these patients had treatment related side effects such as serious infections, leucopoenia, haemorrhagic cystitis, risk of bladder cancer, infertility and amenorrhoea.

The CYCAZAREM trial (n=155) [36] demonstrated that after remission induction, cyclophosphamide can be switched to azathioprine maintenance at a dose of 2mg/kg/day for relapse prevention (relapses in azathioprine versus oral cyclophosphamide groups at 18 months: 15.5% versus 13.7%, p = 0.65). This strategy may reduce the adverse affects seen with prolonged use of cyclophosphamide. Serious adverse events in both groups were similar (11% versus 10%, p = 0.94) in the short term. Long term follow up of these patients showed that there is a trend towards poorer outcomes (relapse risk, ESRD and death) in the azathioprine group but this was not statistically significant[37]. Azathioprine use is associated with myelosuppression, increased risk of infections, hepatotoxicity, increased incidence of skin cancers and lymphoma but is considered safer than cyclophosphamide and, along with methotrexate, is the first choice for maintenance therapy.

2. Rituximab:

Rituximab is being increasingly used for remission maintenance in selected AAV patients who are at high risk of relapse or who relapsed on

other maintenance therapies. MAINRITSAN trial (n=115)[38] that compared rituximab maintenance therapy with azathioprine in new or relapsing AAV patients after cyclophosphamide induction, has confirmed the superiority of rituximab for maintenance therapy. Patients in the rituximab arm received 1000mg rituximab at 6 months then 500mg every six months for three further doses whilst patients in the azathioprine arm received 2mg/kg/day azathioprine for 22 months. At 28 months, there were relapses in 5% of the patients in the rituximab arm compared to 29% in the azathioprine arm (hazard ratio of 6.61 [95% CI 1.56 to 27.96, p = 0.002]). The frequencies of adverse events did not differ between the two groups.

The RITAZERAM trial (n=190)[39] is testing the hypothesis that rituximab is superior to azathioprine in patients with relapsing disease who achieve remission following rituximab induction. Rituximab 1g is administered every 4 months from randomisation until month 20 (5 doses) in the rituximab arm whilst the other arm receives oral therapy (azathioprine, methotrexate or mycophenolate mofetil).

A retrospective analysis[40] of patients that received six monthly repeat dose rituximab maintenance for a two year period, showed that 42% of the patients who were in remission at the end of the treatment period relapsed at a median of 34.4 months after the last dose. The risk of relapse was predicted by PR3-ANCA positive disease, return of B cells within 12 months after the last dose of rituximab and a switch from ANCA negativity to positivity.

The optimal maintenance regimen using rituximab is not known and is the subject of current investigations. MAINRITSAN 2 trial[41] is testing two different dosing regimens for maintenance, one based on fixed dosing every six months and the other based on the return of B cells and/or re-appearance of ANCA or rise in ANCA titres. The MAINRITSAN 3 trial[42] is comparing the effect of rituximab therapy for 46 months against the conventional therapy for 18 months, as the relapse rate after discontinuing therapy at 18 months was high at 30% in the MAINRITSAN trial.

The long-term affects of rituximab therapy are not known and registry data would enable us to garner this information. Rituximab use may be associated with increased risk of infections (serious including PML), acquired hypogammaglobulinaemia and late onset neutropenia. These risks should be weighed against potential benefit before embarking on prolonged maintenance therapy.

3. Methotrexate:

Methotrexate can be used as an alternative to azathioprine to maintain remission in patients with adequate renal function (creatinine <150umol/L or 1.8mg/dl). WEGENT trial (n= 126)[43] compared

methotrexate (at a dose of 0.3mg/kg/week progressively increased to 25mg/week) against azathioprine (2mg/kg/day) for maintenance therapy in AAV patients that achieved remission with cyclophosphamide and steroids. These two agents were shown to be similar in terms of remission maintenance (relapses seen in 33% in methotrexate arm compared to 36% in azathioprine arm, p = 0.71) and adverse events (hazard ratio for methotrexate, 1.65 [95% confidence interval, 0.65 to 4.18; P = 0.29]). Methotrexate use can be associated with myelotoxicity, hepatotoxicity, nephrotoxicity, pulmonary toxicity and hypersensitivity reactions.

4. **Mycophenolate mofetil:**

Mycophenolate mofetil, an anti-proliferative agent is another alternative to azathioprine to maintain remission in AAV patients. However it was shown to be less effective than azathioprine in maintaining remission and is used as a second line agent.
IMPROVE trial (n=174)[44] compared mycophenolate mofetil (2g/day) against azathioprine (2mg/kg/day) in maintaining remission after induction of remission with cyclophosphamide and steroids. Relapses were more common in the mycophenolate arm (55% versus 37.5%, hazard ratio for mycophenolate 1.69, 95% CI [1.06-2.70, p=0.03]). Adverse events did not differ between the two arms. In view of this result mycophenolate is considered in patients in whom azathioprine and methotrexate are contra-indicated.

5. **Co-trimoxazole:**

As respiratory tract infections may predispose patients with GPA to relapses, co-trimoxazole is used in some patients to maintain remission. In a randomised placebo controlled trial (n=81) [45] conducted in GPA patients who are in remission, 24 months treatment with co-trimoxazole (960mg bd) was compared against placebo in preventing relapses. Co-trimoxazole use resulted in less relapses (18% versus 40%; relative risk of relapse 0.40) especially in upper airways disease and was also identified as an independent factor associated with prolonged disease-free survival. As this drug is well tolerated and given it's anti-staphylococcal action it would seem logical to use this drug in remission maintenance of patients with GPA and upper airway disease.

6. **Glucocorticoids:**

Glucocorticoid dosing practices vary widely and there is no consensus. Typically prednisolone dose is tapered to 15mg/day by 3 months and to 5mg/day or less by 6 months. A meta-analysis[46] of 13 heterogenous vasculitis studies showed that patients on longer courses of steroids are likely to have fewer relapses (14% in the prolonged steroid group versus 43% in the other group). This study was limited by the fact that the comparability of the trials was poor and there may have been many factors other than steroid dose that lead to relapses.

TAPIR[47] is a randomized controlled trial in patients with a diagnosis of GPA who are in remission to evaluate the effects of using low-dose

glucocorticoids (5 mg/day of prednisolone) as compared to stopping glucocorticoid treatment entirely (0 mg/day of prednisolone) on rates of disease relapse/disease flares. LoVAS trial[48] is comparing low dose prednisolone (0.5mg/kg/day tapered to 0mg within six months) with rituximab induction against standard dose prednisolone (1mg/kg/day tapered to 10mg/day within six months) with rituximab induction in patients with a new diagnosis of AAV.

7. **Anti-TNF agents:**

   The WGET trial[49] did not show benefit in adding etanercept (soluble TNF receptor) to standard therapy with cyclophosphamide and steroids in maintaining remission. Its use was associated with increased incidence of solid cancers. This treatment option is not recommended. A phase IIb trial of infliximab as a component of remission induction therapy for new or refractory patient subgroups had acceptable safety and suggested a steroid sparing effect of infliximab.

Treatment of eosinophilic granulomatosis with polyangiitis (EGPA):

Eosinophilic granulomatosis with polyangiitis (EGPA) shares many clinical features with GPA and MPA but has received much less clinical trial activity. The French Vasculitis study group has identified five prognostic factors: 1) creatinine >140umol/L 2) proteinuria (>1g/day) 3) gastrointestinal tract involvement 4) cardiomyopathy 5) central nervous system involvement. These five factors together make five factor score (FFS)[50]. Patients with less severe disease (FFS=0) do well compared to patients with more severe disease (FFS ≥ 1).

A European taskforce on EGPA has issued consensus guidelines for evaluation and management of EGPA[51]. Glucocorticoids are the primary choice of therapy to treat EGPA. Patients with severe disease receive methylprednisolone. Steroids are tapered over a period of 6 months to about 0.15mg/kg/day or lowest dose possible to maintain remission. There are no trials looking at the best dosing strategy for steroids in EGPA.

In a prospective randomised controlled trial[52], patients with less severe disease (Five factor score, FFS = 0), who were treated with steroids alone remission was achieved in most patients (93%) but relapses were common (35%). Azathioprine or cyclophosphamide was effective in treating steroid resistant disease. Cyclophosphamide is considered first line agent to treat severe disease. In a trial[53] in EGPA patients with poor prognosis factors (FFS ≥ 1), it was shown that 12 cyclophosphamide pulses were better at controlling the disease when compared to 6 pulses (relapses 62% in 12 pulses versus 85.7% in 6 pulses). Current strategies to maintain remission are similar to those of GPA and MPA. There is little evidence to recommend one treatment over others. Rituximab was shown

in a retrospective study[54] to be effective in achieving remission even in refractory and relapsing patients and is used for induction and maintenance of remission. EGPA is considered classically to be a Th-2 mediated disease with elevated levels of IL-4, IL-13 and IL-5[55]. Mepolizumab is a humanized monoclonal antibody against IL-5, which was recently licensed for use in chronic eosinophilic asthma, is being tested to treat EGPA (see below).

Current studies using newer drugs in vasculitis:

CLEAR trial (CCX168):

CCX168 is an oral inhibitor of C5a, an anaphylotoxin produced as a by-product of complement system activation. C5a primes neutrophils for ANCA induced activation[14]. The CLEAR trial is a phase 2 randomised controlled trial designed to evaluate the safety and efficacy of CCX168 compared to standard dose steroids and cyclophosphamide in AAV patients with mild to moderate disease activity and an eGFR >20ml/minute[29]. The purpose of this trial is to see if CCX168 can induce remission by reducing or avoiding glucocorticoids from the regimen. Preliminary results did show an improvement in renal function (eGFR improved by 6.8 mL/min/1.73 m2 over 12 weeks), urinary albumin creatinine ratio (mean decrease up to 63% over 12 weeks), and urinary MCP-1 to creatinine ratio (up to 72% decrease over 12 weeks)[56]. This was against a background of reduced or no oral glucocorticoids..

BREVAS trial (Belimumab):

Belimumab is a monoclonal antibody directed against B cell activating factor (BAFF). BAFF, a member of TNF family is a crucial factor that promotes the B cell survival and transition from immature to mature B cells. Elevated levels of BAFF are found in patients with GPA and there is accruing data to support that neutralization of BAFF would help to control the autoimmune process. Belimumab has been approved recently for use in the treatment of lupus. Currently BREVAS[57] trial (n= 400) comparing belimumab with azathioprine against standard therapy for maintenance of remission is on going.

ABROGATE trial (Abatacept):

Abatacept is a fusion protein with CTLA-4 domain, which binds to CD80 molecule on antigen presenting cells, thereby inhibiting the co-stimulatory pathway needed for activation of lymphocytes. A non-randomised trial in GPA suggested an improvement on disease control and glucocorticoid sparing. The ABROGATE trial[58] (n=150) is testing abatacept for glucocorticoid free remission induction in relapsing patients with non-severe GPA.

MIRRA (Mepolizumab in EGPA)

MIRRA (A Study to Investigate Mepolizumab in the Treatment of Eosinophilic Granulomatosis With Polyangiitis) trial (n=130) is currently recruiting patients with relapsing or refractory EGPA receiving standard of care therapy including background corticosteroid therapy with or without immunosuppressive therapy. Patients are randomised to receive either mepolizumab (300mg administered subcutaneously every 4 weeks) or placebo. Primary outcome is the total accrued duration of remission.

Conclusions:

Improved understanding of the disease processes in the last decade has identified multiple new targets and strategies to treat this otherwise fatal disease. The development of tools to assess disease in vasculitis and experience with a sequence of clinical trials has established a foundation on which newer agents can be evaluated. Strategies to reduce toxicity associated with treatment whilst not compromising on the efficacy remains a key goal for future research. There is a need to optimise and customise the treatment for patients depending on disease severity and risk of relapse. This can be achieved by gaining further understanding of the pathogenesis and developing robust biomarkers. Subgrouping of patients according to ANCA serotype or disease severity may also help optimise the risk to benefit ratio of vasculitis therapy.

REFERENCES:

- * Of importance
- ** Of major importance

1.* Jennette, J. C. *et al.* 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* **65,** 1–11 (2013).

This article provides a framework for the current nomenclature system of systemic vasculitis

2. Hagen, E. C. *et al.* Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int.* **53,** 743–753 (1998).

3. Sable-Fourtassou, R. *et al.* Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. *Ann. Intern. Med.* **143,** 632–638 (2005).

4. Hellmich, B. *et al.* EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. *Ann. Rheum. Dis.* **66,** 605–617 (2007).

5**. Lyons, P. a *et al.* Genetically distinct subsets within ANCA-associated

vasculitis. *N. Engl. J. Med.* **367,** 214–23 (2012).

A landmark paper confirming the genetic association of ANCA associated vasculitis with ANCA specificity.

6. Pierrot-Deseilligny Despujol, C., Pouchot, J., Pagnoux, C., Coste, J. & Guillevin, L. Predictors at diagnosis of a first Wegener's granulomatosis relapse after obtaining complete remission. *Rheumatology (Oxford).* **49,** 2181–2190 (2010).

7. Franssen, C. F. *et al.* Antiproteinase 3- and antimyeloperoxidase-associated vasculitis. *Kidney Int.* **57,** 2195–2206 (2000).

8. Furuta, S. & Jayne, D. R. W. Antineutrophil cytoplasm antibody-associated vasculitis: recent developments. *Kidney Int.* **84,** 244–9 (2013).

9. Xiao, H. *et al.* Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. *J. Clin. Invest.* **110,** 955–963 (2002).

10. Sanders, J.-S. F., Huitma, M. G., Kallenberg, C. G. M. & Stegeman, C. A. Plasma levels of soluble interleukin 2 receptor, soluble CD30, interleukin 10 and B cell activator of the tumour necrosis factor family during follow-up in vasculitis associated with proteinase 3-antineutrophil cytoplasmic antibodies: associations with di. *Ann. Rheum. Dis.* **65,** 1484–9 (2006).

11. Abdulahad, W. H., Kallenberg, C. G. M., Limburg, P. C. & Stegeman, C. A. Urinary CD4+ effector memory T cells reflect renal disease activity in antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* **60,** 2830–8 (2009).

12. Abdulahad, W. H., Stegeman, C. a., Limburg, P. C. & Kallenberg, C. G. M. Skewed distribution of Th17 lymphocytes in patients with Wegener's granulomatosis in remission. *Arthritis Rheum.* **58,** 2196–2205 (2008).

13. Xiao, H., Schreiber, A., Heeringa, P., Falk, R. J. & Jennette, J. C. Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. *Am. J. Pathol.* **170,** 52–64 (2007).

14. Schreiber, A. *et al.* C5a receptor mediates neutrophil activation and ANCA-induced glomerulonephritis. *J. Am. Soc. Nephrol.* **20,** 289–298 (2009).

15. Flossmann, O. *et al.* Long-term patient survival in ANCA-associated vasculitis. *Ann. Rheum. Dis.* **70,** 488–494 (2011).

16. Groot, K. De *et al.* Pulse Versus Daily Oral Cyclophosphamide for Induction of Remission. *Ann Intern Med* **150,** 670–680 (2009).

17. Harper, L. *et al.* Pulse versus daily oral cyclophosphamide for induction of remission in ANCA-associated vasculitis: long-term follow-up. *Ann. Rheum. Dis.* **71,** 955–60 (2012).

18. Westman, K., Flossmann, O. & Gregorini, G. The long-term outcomes of systemic vasculitis. *Nephrol. Dial. Transplant* **30,** i60–i66 (2015).

19.* Stone, J. H. *et al.* Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis — NEJM. *The New England journal of medicine* 221–32 (2010). at <http://www.nejm.org/doi/full/10.1056/NEJMoa0909169>

This study established the non-inferiority of rituximab to cyclophosphamide in induction of remission in AAV patients.

20.* Jones, R. B. *et al.* Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. *N. Engl. J. Med.* **363,** 211–20 (2010).

This study established the non-inferiority of rituximab to cyclophosphamide in induction of remission in AAV patients with severe renal disease.

21. Specks, U. *et al.* Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N. Engl. J. Med.* **369,** 417–27 (2013).

22. Jones, R. B. *et al.* Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis: 2-year results of a randomised trial. *Ann. Rheum. Dis.* 1–5 (2015). doi:10.1136/annrheumdis-2014-206404

23. De Groot, K. *et al.* Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum.* **52,** 2461–9 (2005).

24. Faurschou, M. *et al.* 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.* **64,** 3472–3477 (2012).

25. Draibe, J. *et al.* Use of mycophenolate in ANCA-associated renal vasculitis: 13 years of experience at a university hospital. *Nephrol. Dial. Transplant* **30 Suppl 1,** i132–7 (2015).

26. Silva, F. *et al.* 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,** 445–453 (2010).

27. Jones, R. *et al.* A randomized trial of mycophenolate mofetil versus cyclophosphamide for remission induction of ANCA-associated vasculitis : ‘‘ MYCYC ’’. On behalf of the European vasculitis study group Assessment of patients with Takayasu ’ s arteritis in a routine clini. *Presse Med.* 678–69 (2013).

28. Walsh, M. *et al.* Plasma exchange and glucocorticoid dosing in the treatment of anti-neutrophil cytoplasm antibody associated vasculitis (PEXIVAS): protocol for a randomized controlled trial. 1–7 (2013).

29. Clinical Trial to Evaluate Safety and Efficacy of CCX168 in ANCA-Associated Vasculitis (CLEAR). *Clin. NCT02222155* (2014).

30. Walsh, M. *et al.* Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int.* **84,** 397–402 (2013).

31. Fortin, P. M., Tejani, A. M., Bassett, K. & Musini, V. M. Intravenous immunoglobulin as adjuvant therapy for Wegener’s granulomatosis. *Cochrane database Syst. Rev.* **1,** CD007057 (2013).

32. Jayne, D. R. W. *et al.* Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. *QJM* **93,** 433–439 (2000).

33. Hoffman, G. S. *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann. Intern. Med.* **116,** 488–498 (1992).

34. Mukhtyar, C. *et al.* EULAR recommendations for the management of primary small and medium vessel vasculitis. *Ann. Rheum. Dis.* **68,** 310–317 (2009).

35. Randomised trial of prolonged remission-maintenance therapy in systemic vasculitis, REMAIN. www.vasculitis.org/trials/active/REMAIN. at <http://www.vasculitis.org/images/documents/remain jan 2006.pdf>

36. Jayne, D. *et al.* A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N. Engl. J. Med.* **349,** 36–44 (2003).

37. Walsh, M. *et al.* Long-term follow-up of cyclophosphamide compared with azathioprine for initial maintenance therapy in ANCA-associated vasculitis. *Clin. J. Am. Soc. Nephrol.* **9,** 1571–6 (2014).

38.* Guillevin, L. *et al.* Rituximab versus Azathioprine for Maintenance in ANCA-Associated Vasculitis. *N. Engl. J. Med.* **371,** 1771–1780 (2014).

This study established the efficacy of rituximab in ANCA associated vasculitis remission maintenance.

39. Rituximab Vasculitis Maintenance Study (RITAZAREM). *ClinicalTrials.gov* **NCT0169726,**

40. Alberici, F. *et al.* Long-term follow-up of patients who received repeat-dose rituximab as maintenance therapy for ANCA-associated vasculitis. *Rheumatology* 1–8 (2014). doi:10.1093/rheumatology/keu452

41. Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis (MAINRITSAN 2). ClinicalTrials.gov Identifier: NCT01731561. at <MAINRITSAN 2>

42. Comparison Between a Long Term and a Conventional Maintenance Treatment With Rituximab (MAINRITSAN3). ClinicalTrials.gov Identifier: NCT02433522.

43. Pagnoux, C. *et al.* Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. *N. Engl. J. Med.* **359,** 2790–2803 (2008).

44. Hiemstra, T. F. *et al.* Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody – Associated Vasculitis. *JAMA* **304,** 2381–2388 (2011).

45. Stegeman, C. A., Tervaert, J. W. C., Jong, P. E. DE & Kallenberg, C. G. M. Trimethoprim-sulfamethoxazole (Co-trimoxazole) for the Prevention of Relapses of Wegener ' S Granulomatosis. *N. Engl. J. Med.* 16–20 (1996).

46.* Walsh, M., Merkel, P. a & Mahr, A. The effects of duration of glucocorticoid therapy on relapse rate in anti-neutrophil cytoplasm antibody associated vasculitis: A meta-analysis. **62,** 1166–1173 (2010).

A meta-analysis suggesting reduced relapse risk with prolonged administration of glucocorticoids.

47. The Assessment of Prednisone In Remission Trial (TAPIR) - Patient Centric Approach. ClinicalTrials.gov Identifier: NCT01933724.

48. Low-dose Glucocorticoid Vasculitis Induction Study (LoVAS). ClinicalTrials.gov Identifier: NCT02198248.

49. The Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N. Engl. J. Med.* **352,** 351–61 (2005).

50. Guillevin, L. *et al.* Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. *Medicine (Baltimore).* **75,** 17–28 (1996).

51. Groh, M. *et al.* Eosinophilic granulomatosis with polyangiitis (Churg–Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur. J. Intern. Med.* **26,** 545–553 (2015).

52. Ribi, C. *et al.* Treatment of Churg-Strauss syndrome without poor-prognosis factors: A multicenter, prospective, randomized, open-label study of seventy-two patients. *Arthritis Rheum.* **58,** 586–594 (2008).

53. Cohen, P. *et al.* Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. *Arthritis Rheum.* **57,** 686–693 (2007).

54. Mohammad, A. J. *et al.* Rituximab for the treatment of eosinophilic granulomatosis with polyangiitis (Churg–Strauss). *Ann. Rheum. Dis.* (2014). doi:10.1136/annrheumdis-2014-206095

55. Jakiela, B. *et al.* Increased production of IL-5 and dominant Th2-type response in airways of Churg–Strauss syndrome patients. *Rheumatology* **51,** 1887–1893 (2012).

56. Bekker, P., Jayne, D. & Brukfeld, A. CCX168, an Orally Administered C5aR Inhibitor for Treatment of Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis - ACR Meeting Abstracts. *2014 ACR/ARHP Annual Meeting* (2014). at <http://acrabstracts.org/abstract/ccx168-an-orally-administered-c5ar-inhibitor-for-treatment-of-patients-with-antineutrophil-cytoplasmic-antibody-associated-vasculitis/>

57. Belimumab in Remission of VASculitis (BREVAS), ClinicalTrials.gov Identifier: NCT01663623. (2012).

58. Abatacept for the Treatment of Relapsing, Non-Severe, Granulomatosis With Polyangiitis (ABROGATE). ClinicalTrials.gov Identifier: NCT02108860. (2014).